

Reviewing Clinical Trials: A Guide for the Ethics Committee

Editors

Johan PE Karlberg and Marjorie A Speers

**Clinical Trials Centre, The University of Hong Kong
Hong Kong SAR, PR China**

**Association for the Accreditation of Human Research
Protection Programs, Inc.
Washington, DC, USA**



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Preface

The idea for this manual came from Pfizer in the US, which provided the Clinical Trials Centre at The University of Hong Kong, Hong Kong SAR, PR China with a nonbinding grant for its development. The general project layout protocol was accepted by Pfizer in July 2009. Pfizer has not in any way interfered with the project, except for providing nonbinding comments to the final product.

The entire text of this manual was written by Johan PE Karlberg. Marjorie A Speers provided considerable and essential comments on the contents and the first and subsequent drafts. A group of international human research protection experts mostly working in non-profit institutions or organisations – see Contributors for details – reviewed and provided important comments on the contents and final draft. It was solely created with the intention to promote human research protection of participants in clinical trials.

This manual will be translated into numerous languages and is provided free of charge as an electronic file over the Internet (<http://www.ClinicalTrialMagnifier.com>) and offered in print for a fee. The objective beyond this project is to establish educational activities, developed around the manual, and jointly organised with leading academic institutions worldwide.

Marc B Wilenzick – Chief Compliance Counsel, Pfizer R&D, New York, USA – contacted Johan PE Karlberg in May 2009 and proposed the project for an ethics guide. The first question raised was: *“Why approach The University of Hong Kong and not a leading medical institution in the US or in Europe?”* The reply was: *“Because of the monthly newsletter that you produce, i.e., the Clinical Trial Magnifier,”* (<http://www.ClinicalTrialMagnifier.com>), which may be a valid reason, after all. The project has been a great challenge but also an honour. The final product fits well with the mission of the Clinical Trials Centre as one of the leading academic research organisations in Asia, in line with the mission of the Association for the Accreditation of Human Research Protection Programs, Inc., Washington, DC, the sole non-profit human research accreditation organisation in the US.

Once we agreed to consider the invitation, we arranged a phone conference with ten senior Pfizer global staff to discuss the overall objective of the project. It became clear that there was a large worldwide demand for educating ethics committee members on how to review clinical trial protocols, especially in health care organisations outside the leading academic institutions in emerging clinical trial locations, including Brazil, China, India and Russia, but also in other emerging regions such as Argentina, Bulgaria, Chile, Colombia, Croatia, the Czech Republic, Estonia, Hong Kong, Hungary, Latvia, Lithuania, Malaysia, Mexico, Peru, the Philippines, Poland, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, South Korea, Taiwan, Thailand, Turkey and Ukraine. In 2009 around 25% of all sites involved in industry-sponsored clinical trials were located in emerging countries, corresponding to 12,500 sites annually – or 50 ethics committee reviews of clinical trials every working day.

Although the publication is entitled *Reviewing Clinical Trials: A Guide for the Ethics Committee*, it was developed mindfully to be relevant and useful to all other categories of professionals entering the clinical trial research area. We highly recommend anyone, whether a novice in the clinical trials research area or experienced, wishing to learn more about the basic modern concepts of human research ethics and clinical trial research methodology to study this manual. The audience can equally be professionals acting as investigators, research nurses, research support staff, ethics committee

administrators, contract and budget development administrative staff, monitors, project managers, biostatisticians, clinical data managers, regulators or inspectors.

We must stress that *nothing in this manual overrules local laws, regulations and guidance*. It was developed to provide an overall, theoretical background of clinical trials following the general principles spelt out in the Declaration of Helsinki and the ICH GCP E6 Guideline. The final chapter includes about 50 ethics committee scenarios covering most ethical areas in human research. Many of those scenarios have been utilised in educational activities for ethics committee members and have proven exceptionally helpful in translating theory into practice, especially for novice clinical trial research professionals.

Our gratitude goes to the advisors for their valuable comments and positive criticism on the final version of this manual, and to Mr. Marc B Wilenzick at Pfizer R&D, for acting as the sponsor's representative, and also as the catalyst for the project. All contributors who participated as individuals do not represent the institution, organisation or company where they are employed.

While all the advisors agreed with overall content of this Guide, some occasionally disagreed with specific content. Each advisor reserves the right to make such differences of opinion public at any time.

March 2010

Hong Kong SAR, PR China and Washington, DC, USA

Johan PE Karlberg and Marjorie A Speers

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Comments from the Contributors

What is your background/experience within clinical research, human research ethics, research design, Good Clinical Practice (GCP) and quality assurance?

Is this Manual a better choice over other books covering research ethics and/or good clinical practice?

Mark Barnes - Harvard University, USA

"For many years, I have advised academic medical centers, medical schools and pharmaceutical and medical device companies on issues related to clinical trials. I also have directly supervised trials and have helped to establish clinical trial centers in various parts of the developing world.

This guide provides to the 'learned layperson' a wealth of information about clinical trials – what they are and how they are designed and conducted – to allow such laypersons to become confident members of research ethics committees and IRBs. Such a publication, learned and yet accessible, is, in my experience, unprecedented."

Ames Dhai - University of the Witwatersrand, South Africa

"I have close to eight years of experience in review activities including chairing of research ethics committees. I am the Head of the Research Ethics Unit and of the Masters in Bioethics and Health Law program at the university. I am also a researcher.

The Manual will complement other readings in the field."

David G Forster - Western Institutional Review Board, USA

"15 years as an IRB member and staff, JD and Masters in medical ethics.

It is a good manual in that it is widely applicable to IRB review and is not wed to one country's regulatory requirements."

Edwin C Hui - The University of Hong Kong, China

"I'm a medical ethicist and I have been a member of many human research committees in the last 20 years.

YES, because it is comprehensive and condense enough to be read in an afternoon."

Juntra Karbwang - World Health Organization, Switzerland

"I have coordinated the development of the WHO operational guidelines for the establishment of ethics committees in biomedical research in 2000 and I have been working with the national and regional ethics forums since 2000.

I believe that this Manual is a better choice over other similar books, since the EC members should have at least an overview of product R&D and different study designs to do a better risk assessment and better identify the ethics issues within different study designs."

Johan PE Karlberg - The University of Hong Kong, China

"I have been involved in clinical research in Asia for some 26 years and have been the Director of the Clinical Trials Centre at The University of Hong Kong since its establishment in 1998.

I believe the Manual is a better choice over other books covering this topic, because it is simple to digest and also because it covers the general fundamental nature of clinical trials."

Boleslav L Lichterman - Russian Academy of Medical Sciences, Russia

"I did my Ph.D. on head injury in the 1980s. At that time I had no idea about informed consent or GCP. When starting my part-time work as a science editor of the Russian National Medical Periodical "Meditsynskaya Gazeta" in 1997, I became interested in medical ethics and wrote several papers on the subject.

The book is concise, clearly written and has many visual aids - tables and figures - and a chapter on typical EC scenarios. These are evident advantages over other numerous publications on research ethics and GCP."

Ulf Malmqvist - Lund University Hospital, Sweden

"I am a clinical pharmacologist and I have been working within both pre- and clinical research for more than 25 years. I have been a board member of the regional ethics committee in Lund. I am at present head of the Regional Competences Centre for Clinical Research in the county of Skåne at Skåne University Hospital, where among many tasks, I am responsible for giving courses in GCP and providing quality assurance to investigator-initiated studies.

This manual is a good introduction to practical ethics in clinical trials and is a complement to books covering ethics or good clinical practice."

Carlo Petrini - National Institute of Health, Italy

"I am a member of both the national and local Ethics Committees: Italian National Institute of Health; National Agency for New Technologies, Energy and the Environment; and others.

I think that the Manual is clear, complete and provides a synthetic overview."

Mildred Z Solomon - Harvard Medical School, USA

"I teach research ethics to physician-investigators and believe that good materials can always enhance practice.

This Ethics Guide is a comprehensive introduction to the conduct of clinical trials, and will be very useful to investigators new to clinical research methods and the complicated web of ethical and regulatory issues that guide that research."

Marjorie A Speers - Accreditation of Human Research Protection Programs, USA

"Twenty-five years ago I started conducting epidemiologic studies. While at the U.S. Centers for Disease Control and Prevention (CDC) I oversaw all domestic and international human research for the agency. In 1999 I was asked to join the National Bioethics Advisory Commission to lead the project on reviewing the U.S. oversight system. Since 2001, I have been the President and CEO of AAHRPP, the only international accrediting agency of human research protection programs.

I highly recommend this Manual. It is thorough, easy to read, and offers case examples which can be so helpful to ethics committees with limited experience in reviewing research."

Marc B Wilenzick - Pfizer, USA

"I am a lawyer at Pfizer, serving as the Chief Compliance Counsel for R&D. In that role, I spend a good deal of time working with development teams, quality assurance, and study managers on issues related to regulatory compliance and in developing corporate policies for our trials. Many of these policies reflect not just legal norms and regulatory requirements but ethical norms and generally accepted research standards (CIOMS, ICH, etc.).

At a large pharma company that is doing an ever increasing number of multi-regional trials, with more and more of these involving sites from the developing world and well as sites in the developed world, we see that the need to ensure resources for independent ethics committees is strong. This ethics manual should be an invaluable resource for many ethics committees, across both high resource and low resource regions. It ties international standards, like CIOMS and the Declaration of Helsinki, into the overall scientific and statistics framework for trial design, in a way that will be useful for any ethics committee member that doesn't already have a deep background in clinical trial design and ethics committee operations. We appreciate the effort made by Drs. Karlberg and Speers, and their board of international advisors, in taking the idea for such a manual and making it into what promises to be a must-have resource for ethics committee members."

John R Williams - University of Ottawa, Canada

"I was the coordinator of the most recent (2006-7) revision of the Declaration of Helsinki. I am a member of the Advisory Board of the Training and Resources in Research Ethics Evaluation for Africa (TRREE for Africa) project and Chair of the Canadian Institutes for Health Research Stem Cell Oversight Committee.

This Guide fills a niche between short statements and book-length treatments of research ethics. The method of distribution will be important for its usefulness, e.g., if electronically, it should be easy to download section by section."

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Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRFs	Case Report Forms
CRO	Clinical Research Organisation
DSMC	Data Safety and Monitoring Committee
EC	Ethics Committee
EMA	European Medicines Agency
ERB	Ethics Review Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HRPP	Human Research Protection Programmes
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH GCP	ICH Good Clinical Practice E6
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
NDA	New Drug Application
QoL	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOPs	Standard Operating Procedures
WMA	World Medical Association

Chapter 1. Introduction

This introductory Chapter presents the clinical trial landscape with a brief overview of ethics and bioethics, the introduction of the current internationally recognised and applicable ethical codes, a definition of an ethics committee, a position of where clinical trials stand within biomedical research, an introduction of the risks associated with clinical trial participation and presentation of the various players involved in clinical trials. The following Chapters provide a more in-depth understanding of issues related to clinical trials. To clarify a few points: Ethics and bioethics represent large domains of their own, both theoretically and practically, and have a long history of advancement. We do not go into detail, but only introduce a few practical and currently valid human research ethical issues.

Today, there are two internationally recognised human research guidelines that form the basis for the conduct of ethical clinical trials. We have chosen to use the term Ethical Codes rather than Ethical Guidelines, since we consider them more than just guidelines. A code of practice defines professional rules according to which people in a particular profession are expected to behave. Other human research guidelines/codes of practice have emerged over the past century, such as the Nuremberg Code – a set of research ethics principles for human experimentation set forth as a result of the Nuremberg Trials at the end of the Second World War. The principles of that code and other earlier guidelines are covered in the two current applicable international ethical codes, as introduced in this Chapter.

1.1 Ethics and Bioethics

Ethics – also known as moral philosophy – seeks to address philosophical questions about morality. Its history goes back to philosophy and religious writings. Bioethics is the philosophical study of ethical controversies brought about by advances in biology and medicine. Bioethics concerns ethical issues that arise in relationships among life sciences, biotechnology, medicine, politics, law, philosophy and theology. The modern field of bioethics first emerged as an academic discipline in the 1960s.

Ethical Codes – The Declaration of Helsinki

The first set of ethics rules for research in humans formulated by the international medical community was established in 1964 by the World Medical Association (WMA), in the Declaration of Helsinki (Declaration). The WMA is an international organisation representing physicians and was founded in 1947. The organisation was created to ensure the independence of physicians and to work for the highest possible standards of ethical behaviour and care among them, at all times.

The Declaration includes a number of important human research ethics codes of practice. However, the Declaration is still a very short document, covering only five pages. It defines ethical principles, but provides little guidance on the governance, operation and responsibilities of a human ethics committee (Ethics Committee, EC). The Declaration is not a legally binding instrument in international law. Rather, its authority is drawn from the degree to which it is codified or influences national or regional legislation and regulations. The Declaration should be seen as an important human research guidance document, but it cannot overrule local regulations and laws. There have been several updated versions – with the last accepted at the 59th WMA General Assembly in Seoul, South Korea in 2008.

Declaration of Helsinki:

<http://www.wma.net/en/30publications/10policies/b3/index.html>

Ethical Codes – The ICH GCP Guideline

The ICH GCP E6 Guideline (ICH GCP) was published in 1996. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use brought together the European Union, Japan and the United States. The objective of the harmonisation is to eliminate unnecessary delay in the global development and availability of new medicines, while maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. The ICH GCP has so far only one version – the original version launched in 1997.

ICH GCP: *“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 participants. Compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible (see text boxes).”*

The ICH GCP has become the leading international guideline for the conduct of clinical trials. It is not so much a policy document, rather an operational guideline, spelling out operational matters and responsibilities surrounding clinical trials. The ICH Guideline refers to the ethical principles of the Declaration, but does not specifically mention which version of the Declaration should apply. The ICH also refers to GCP and the applicable regulatory requirements. The ICH GCP has had a significant impact on the globalisation of industry-sponsored clinical research, since clinical trial data collected in one region in compliance with ICH GCP can today be used to file new drug applications in other regions.

ICH GCP E6: <http://www.ich.org/LOB/media/MEDIA482.pdf>

The ICH GCP E6 Guideline

“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. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide 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.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that might have an impact on the safety and well-being of human subjects.

The Principles of ICH GCP

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 requirement(s).

Ethical Codes – Ethics Committee

The Declaration of Helsinki includes a paragraph addressing the role of an EC in human research: *“The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the trial begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research participants set forth in this Declaration.”* The statement that a country is not allowed to *“reduce or eliminate any of the protections”* is not a legal enforcement, rather a strong recommendation.

The ICH GCP provides guidance on how an EC should operate and describes the responsibilities of the committee. It covers topics such as composition, function, operations, procedures, responsibilities, record keeping, contents of informed consent, and adverse event reporting. Based on the ICH GCP, an EC must develop its own written standard operating procedure (SOP). EC SOPs often refer to the ICH GCP as well as to local legal requirements and guidelines.

No Universal Ethical Code for Ethics Committees

In the ethics review of human research projects and conduct of research, researchers and EC members must be aware of both the institutional requirements and the applicable laws. Legal rules and ethical principles are not always consistent, and both differ greatly over jurisdictions. No single human research ethics guide can provide universal answers to all the ethical issues of research involving humans or reflect the broad diversity

2.2 Before a trial is initiated, 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 investigational 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 institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

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.

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, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.”

of legal requirements worldwide. The aim of this Guide is to point out the cornerstones of the design, conduct and oversight of ethical human research, with a focus on clinical trials. Nothing in this Guide should overrule local ethical concepts, concerns or legislations. We will at some places refer to specific guidelines or legal documents as illustrations, especially some of the more recognised regulatory guides. However, the intention is not in any way to endorse specific documents as opposed to others.

Any EC must learn all the details of the local laws and requirements. Most applicable international and local laws, regulations and guidelines for human research protections are included in the *International Compilation of Human Research Protections, 2010 Edition*, compiled by the Office for Human Research Protections, US Department of Health and Human Services. It lists approximately 1,100 laws, regulations, and guidelines that govern human participant research in 96 countries. It was developed for ECs, investigators and sponsors involved in international research. Its purpose is to help these groups familiarise themselves with the laws, regulations and guidelines in effect wherever research is conducted, to ensure that those standards are followed appropriately. See for instance: China (MOH: Guidelines on Ethical Review of Biomedical Research Involving Human Subjects (2007)), Brazil (CONEP: Resolution 196/96: Rules on Research Involving Human Subjects (1996)), India (ICMR: Ethical Guidelines for Biomedical Research on Human Participants (2006)), and Russia (FSSHSD: Order No. 2314-Pr/07 17 on August 2007, About the Ethics Committee). The list is updated annually.

Compilation of Human Research Protections:

<http://www.hhs.gov/ohrp/international/HSPCompilation.pdf>

Ethics Committee Definition

An EC reviews and subsequently approves or rejects research protocols submitted by investigators/researchers (investigators). There are different kinds of ECs. Some review protocols for animal studies, some for human studies in social sciences such as psychology and education, and others for clinical trials in patients or healthy volunteers. In this Guide, we address only the principles of ethics review of protocols involving interventional studies or clinical trials in humans. Many countries require and legally enforce approval by an EC before clinical trials can be initiated for testing new drugs or vaccines, medical devices, diagnostics and medical procedures referred to as test article in this Guide.

As stated in the Declaration of Helsinki: *“The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins.”*

The ICH GCP states: *“A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.”*

Different names are used for ethics committees reviewing human clinical trial protocols, such as ethics committee (EC), research ethics committee (REC) or institutional review board (IRB). For simplicity in this Guide, we use the term Ethics Committee and the corresponding abbreviation EC. Regardless of the term chosen for an individual EC, each operates in accordance with applicable laws and regulations.

We also need to clarify that most ECs review study protocols for a single institution, such as a hospital, with or without academic affiliation, while some are centralised, and review protocols from more than one institution/clinic. Central ECs are designed to help reduce administrative burdens on local ECs and investigators, while maintaining a high

level of protection for human research participants. This arrangement is especially useful when the investigator works from a single physician's private practice or when multiple sites are involved in the same geographical or judicial region. However, whether local or centralised, ECs should all operate at the same standard.

A human research ethics committee – EC – should not be confused with any hospital ethics committee (HEC) reviewing ethical or moral questions that may arise during a patient's standard care. The EC reviews clinical research protocols, while the HEC acts as the patients' advocate, defining the ethical principles of clinical procedures and management within a hospital.

1.2 Clinical Trials in the Context of Biomedical Research

Biomedical research can be sub-classified as basic/pre-clinical research and clinical research (*see illustration*).

Pre-clinical biomedical research is important for expanding the knowledge of basic biological mechanisms. Studies are commonly conducted in pre-clinical departments or institutions in fields such as anatomy, biochemistry, cellular biology, immunology, microbiology, molecular biology, neuroscience, pharmacology and physiology. Pre-clinical research can contribute to the discovery of new medical treatments.

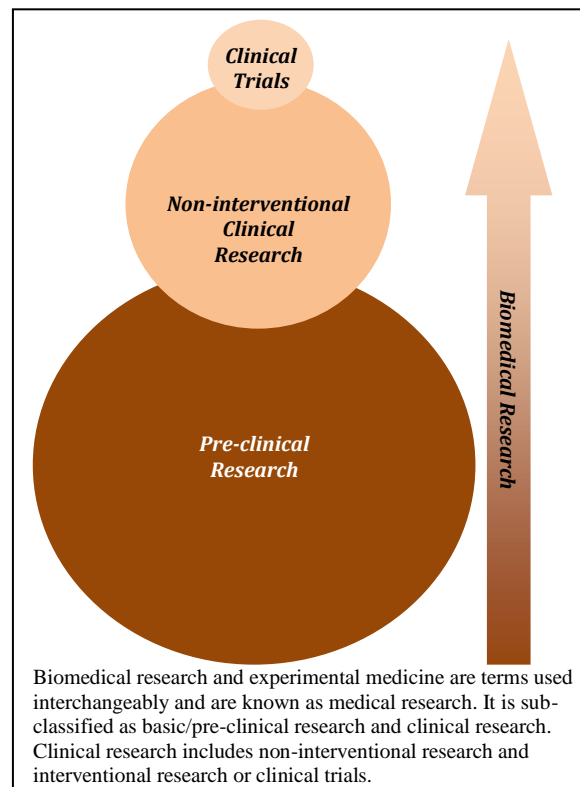
Clinical research ranges from clinical laboratory or investigational studies to testing of new clinical procedures, new clinical diagnostic tools and new medicinal products in humans.

Clinical Trials on Medicinal Products

There is a persistent demand, in addition to a great need, to develop new medical treatments that are as effective and safe as, or more effective or safer for specific types of patients than, treatments already on the market. Research also enables discovery of new therapeutic uses for currently available medications, as well as enabling development of innovative treatments for currently untreated conditions. New medicinal products are commonly discovered by means of laboratory research and animal studies before they can be tested in humans – through clinical trials – and eventually used in medical care.

Clinical trials are the mandatory *bridge* between pre-clinical discovery of new medicinal products and their general uses. This means that clinical trials *must* take place before new research treatments can be made available to the public, whether for prescription, over-the-counter sale or for use in a clinic.

Pre-clinical testing of new medicinal products can only forecast their treatment and side-effects in humans. On average, only one out of 14 new drugs that enter clinical testing programmes is eventually introduced for clinical use. The main reasons for the high drop-out rate are unforeseen side-effects or insufficient treatment effects. Pre-clinical laboratory and animal studies thus only partially indicate effects in humans.



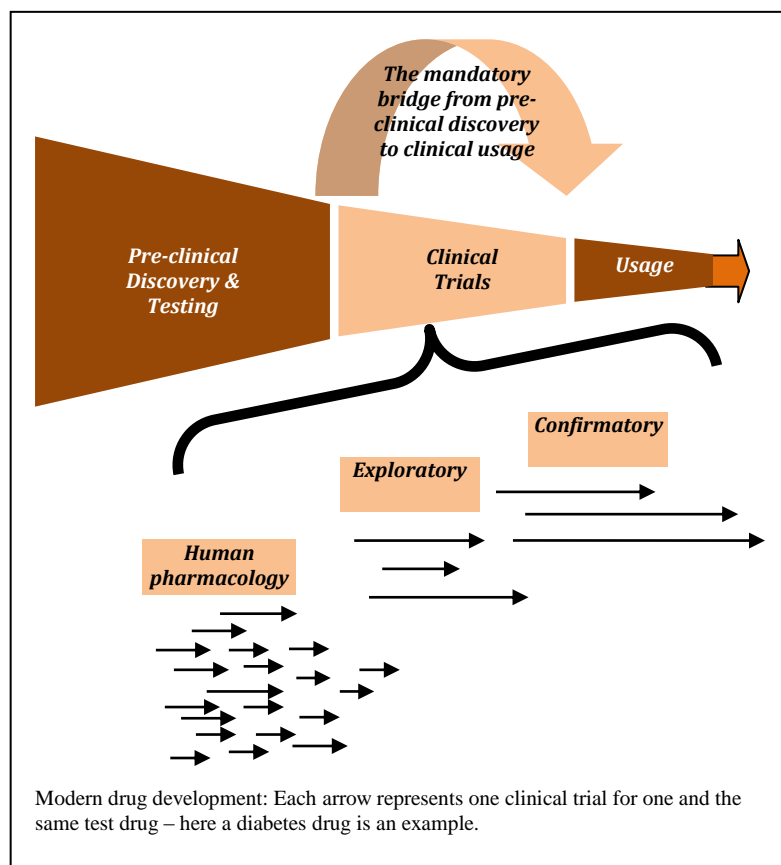
During the clinical testing period, data are collected to support a subsequent marketing application for the new medicinal product (test article), whether a drug, vaccine, medical device or diagnostic tool. A new drug application, for instance, will include all aspects of the test article, from pre-clinical information about the molecular structure and action, manufacturing information, formulation and animal studies to test results in humans depicting the pharmacological action, dosage, preventive or curative effects, and potential side-effects.

Pre-clinical and clinical developments are carefully monitored under strict government regulations in most countries to ensure that all aspects of the compound have been studied – and that research has used proper trial designs in a high-quality manner, in accordance with international and local human research ethical standards.

Clinical testing of the product passes through different phases, from human pharmacology to exploratory research in participants with the target disorder, and eventually large-scale trials where the product's safety and effects are compared to the best current treatment on the market (*see illustration*).

On average, there are 25-30 different trials conducted on the same compound, each adding some essential information to the existing body of knowledge. The trials are conducted in a close to sequential manner, although the clinical development plan is altered and adjusted according to results obtained at certain points in time.

Most (about 85%) approved medicinal products are developed and tested by the pharmaceutical and biotechnology industries, not academic institutions or non-profit organisations. The link between pre-clinical and clinical research is thus more obvious in for-profit rather than non-profit clinical trial research.



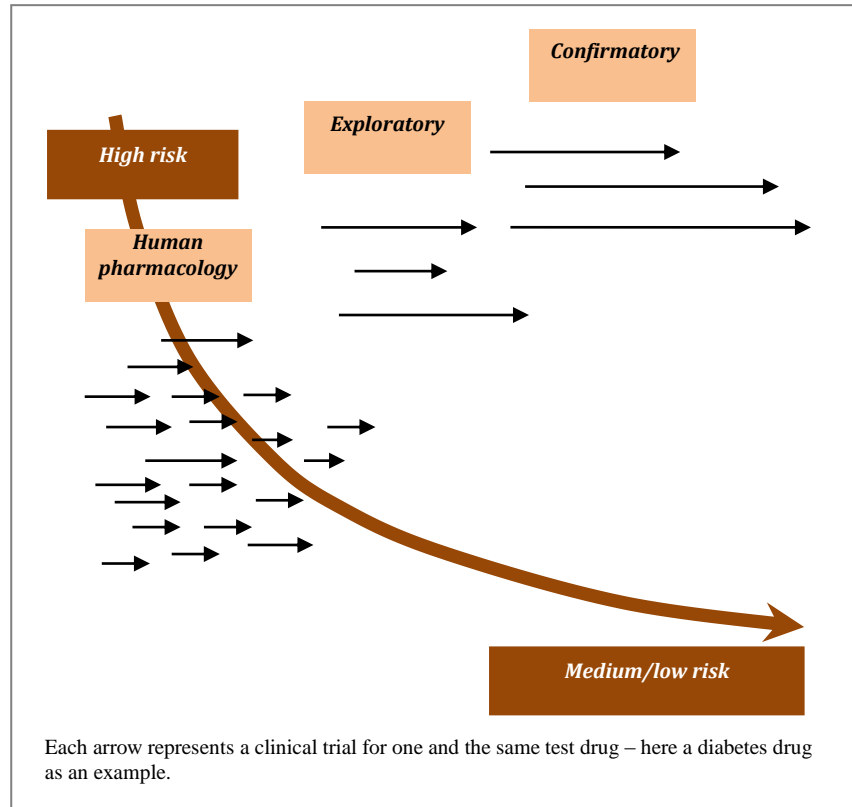
Low and High Risk Clinical Trials

Three essential factors echo the risk of harm level of a clinical trial: cumulative clinical experiences of the test article, targeted participant population and biological characteristics of the test article.

As clinical testing proceeds, more and more participants are exposed to the test article. The information gathered is used to evaluate the effects – negative as well as positive – of the product in humans. Accordingly, it follows that risk of harm in general is much higher during the initial clinical testing phase, i.e., human pharmacology, than during

later stages. Thus early phase clinical trials often need more oversight than later phase trials.

The highest level of risk arises when the product is first tested in humans (first-into-human trials), followed by trials with dose escalation and multiple dosing. Most of these trials are conducted in healthy volunteers, not participants with the target disease. Initial human pharmacology clinical trials, conducted mostly on healthy volunteers, are followed by exploratory trials where the test article is administered on target participant groups for the first time. The reactions from these participants may differ from those in healthy volunteers, so first-into-human trials are also often regarded as having a higher risk of harm and therefore need extra oversight (*see illustration*).



Clinical testing of medicinal products that are ineffective and/or have unreasonable side-effects is terminated early. This means that late exploratory and confirmatory clinical trials are performed on a subsample of products confidently expected to have a reasonably low risk of inducing side-effects in relation to the treatment effect, since the safety profile is acceptable.

The targeted patient population may also influence the degree of risk of a medicinal product. For instance, life-threatening diseases such as cancer usually call for stronger and thus potentially more toxic drugs with a different risk of harm acceptance from, for instance, anti-flu drugs. Likewise, young children may have a higher risk of side-effects than adults, due to their ongoing organ growth and the body's functional development in early life. Participants in need of multiple drug treatments, such as psychiatric patients or drug abusers, have a risk of harm from drug-to-drug interaction, which may be higher than for participants given the test drug who have no other significant medical conditions.

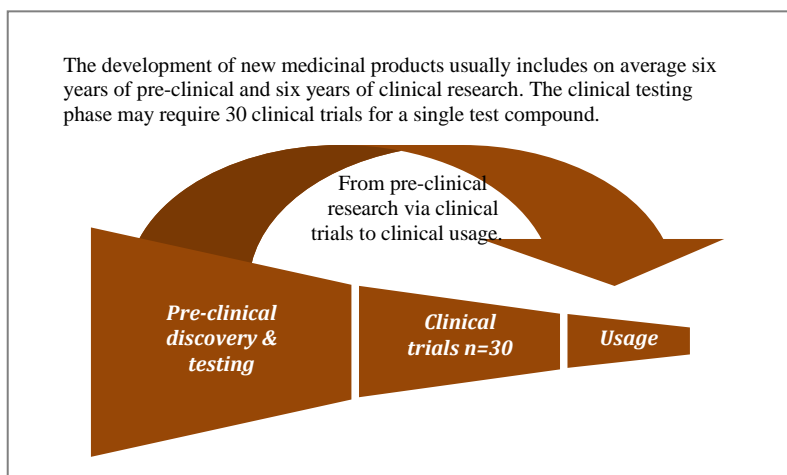
Proper risk assessment of a trial can be made only with detailed access to the results of previous testing of the product, in animals and humans, as well as details of the target population and knowledge about the characteristics of the test article. Such information should be included in any trial protocol. For trials overseen by a regulatory authority, additional details are documented in a mandatory investigator's brochure. Both the trial protocol and the investigator's brochure for a trial, if present, should be submitted to an EC for review.

Sponsors of Clinical Trials

Sponsors of a clinical trial can be either a commercial company (industry-sponsored trial) or a clinical investigator/physician (non-industry trial). The former comprises pharmaceutical and biotechnology companies, while the latter comprises medical schools, biomedical research institutes, government institutions or clinical trial networks. Depending on the body, non-industry trials are referred to as non-profit, non-industry-sponsored, investigator-initiated, or institutional-initiated trials.

The large majority of industry-sponsored clinical trials are registered with the US national clinical trials registry (<http://www.ClinicalTrials.gov>), because registration is a mandatory requirement by the US government for filing a new drug application in the US. The US trials registry includes more investigator-initiated than industry-sponsored trials, although the former are registered predominantly by US investigators. Globally, there are many more investigator-initiated than industry-sponsored clinical trials.

The overall objective of a commercial life-science company in conducting clinical trials on a medicinal product is to collect information about the safety and efficacy of the product in human participants, i.e., to take the test article from pre-clinical discovery and testing to usage (*see illustration*). The data collected and analysed from trials eventually represent an important and mandatory body of information for the application to a government drug regulatory authority for market acceptance of the product. The commercial company is therefore concerned that the trial follows international and local regulations – from scientific, ethical and quality assurance viewpoints – so government market approval can be achieved in a timely and undisputed manner. The main objective here is thus primarily commercial.



In contrast, an investigator acting as sponsor of a clinical trial may primarily be involved for scholarly reasons, rather than to bring a new medicinal product to the market. Often, the investigator's motive is scientific achievement, leading to published findings, advancing knowledge among peers, and many times also improvement of patient care, health care or population health. Such trials may compare new surgical procedures, health interventional programmes or clinical diagnostic tools. They may also test combination therapies or new indications of already approved commercial medicinal products. A smaller number of investigator-initiated trials test new medical products that an investigator or institution has invented, with the primary objective being commercial.

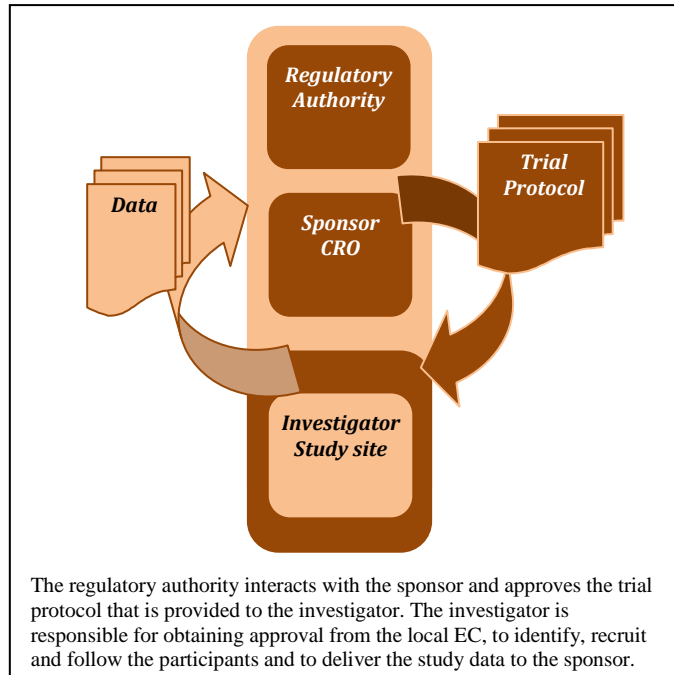
Whether the sponsor of a clinical trial is a commercial or non-commercial body, the same scientific, ethical and quality standards should apply, and the EC review process should be identical. Industry-sponsored trial protocols have commonly been subject to third-party review because the clinical development plan of products is continuously monitored by drug regulatory authorities. Investigator-initiated trials, on the other hand, may lack the review of an independent third party before they are submitted to

the EC. The EC may request details of the third-party review and details of the protocol development team.

Regardless of who the sponsor may be, the clinical trial protocol should detail the same aspects: the scientific rationale behind the protocol, the rationale behind the trial design and sample size, treatment blinding, the risk-benefit balance, participant compensation, informed consent, insurance/indemnity, any conflicts of interest that may influence the collection of data or results, and essential quality assurance measures.

1.3 Clinical Trial Players and Their Responsibilities

There are four major players in the clinical trial arena: the drug regulatory authority, the trial sponsor (*sponsor*), the clinical researcher (*investigator*) and the ethics committee (EC). Together the key players work in harmony within a strict pattern of interaction, defining their responsibilities and enabling collection of high-quality trial data in a safe and ethical manner. The sponsor interacts continuously with both the regulatory authority and the investigator before, during and after the trial, while the investigator interacts with the EC generally without involvement from other parties (*see illustration*). With rare exceptions, the trial participants – patients or healthy volunteers – are not clinical trial players by means of actively planning or monitoring a trial, or reporting the trial results. The sponsor or its representative shall not have knowledge of participants' identity and does not usually have direct contact with them; an exception is a Phase I unit owed by a sponsor.



Drug Regulatory Authority

Each country has its own drug regulatory authority with its own regulations for approving clinical trial protocols and also for conducting clinical trials when testing and approving new medicines and other medicinal products. A clinical trial of a new medicinal product can be overseen by one or several drug regulatory authorities. In addition, the drug regulatory authority has important quality assurance responsibilities in the development of new medicines, as well as the production, distribution, labeling and safety monitoring of medicines, including medicines already registered. There are a number of local and international regulations/guidelines that must be followed when new medicines are developed and tested.

Drug regulatory authorities come under different names in different countries. For instance, in the US the authority is the Food and Drug Administration, or FDA; in the European Union it is called the European Agency for the Evaluation of Medicinal Products (EMA); and in Japan, the Ministry of Health, Labor and Welfare, or (MHLW). Other examples are Health Canada (Canada), the State Food and Drug Administration (SFDA, China), the Therapeutic Goods Administration (TGA, Australia), the Drugs

Controller General of India (DCGI, India), the National Health Sanitary Surveillance Agency (ANVISA, Brazil), and the Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor, Russia).

Responsibilities of the regulatory authority (examples):

- Reviewing and approving clinical trial protocols.
- Ensuring that clinical trials comply with national regulations of a country and international guidelines.

Sponsor

A clinical trial sponsor is an individual, company, institution or organisation that takes responsibility for the initiation, management, and financing of a clinical trial. A sponsor can be a pharmaceutical or biotech company, a non-profit organisation such as a research fund, a government organisation or an institution where the trial is to be conducted, or an individual investigator. The sponsor initiates a clinical trial and has a number of responsibilities such as protocol development, financing the trial and quality assurance. The sponsor will seek permission for trial initiation from the drug regulatory authority or authorities if more than one country is involved in conducting the trial.

A clinical trial project manager acts as a coordinator among the activities of clinical trials, e.g., protocol development, regulatory applications, auditing, clinical data management, laboratory testing, courier transport and managing monitors.

A trial monitor (monitor), or clinical research associate (CRA), is a person employed by a sponsor or by a clinical research organisation (CRO, *see pages 26-27*) who acts on a sponsor's behalf and monitors the progress of investigative sites participating in a clinical trial. The monitor interacts regularly with the investigator and his/her team members, while monitoring the participant informed consent process, participant recruitment rate, test drug presence, protocol compliance and payment schedules. The monitor visits the trial site approximately every month and reports findings to the project manager coordinating the trial.

Responsibilities of the sponsor (examples):

- Submitting a plan for the clinical trial to the regulatory authority for approval.
- Providing complete information to investigators about the test article, its safety and instructions for proper use, as well as making sure there is appropriate training for staff and appropriate facilities are available.
- Ensuring the trial protocol is properly reviewed by an experienced EC.
- Monitoring the trial to ensure the protocol is being followed, data collection is accurate, adverse events are reviewed and reported and all regulations are complied with.

Investigator

Often, there is an investigative team, consisting of the investigator (principal investigator), one or several co-investigators, one or several study nurses (clinical research coordinators, CRCs), and, where necessary, other study support staff. The investigative team can belong to academic medical centres, public hospitals or outpatient clinics, private health care organisations, private practices or commercial research sites. The sponsor identifies a potential principal investigator for the trial and communicates with the investigative team throughout the course of it, usually by way of a project manager and a trial monitor. In a non-commercially-initiated clinical trial, the

investigator, government institution, or another funding body takes on the role and responsibilities of the sponsor.

An investigator is a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team. A more formal definition of an investigator is *“under whose immediate direction the test article is administered or dispensed to, or used involving, a participant, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.”*

A co-investigator or sub-investigator is any individual member of the clinical trial team – such as an associate, resident or research fellow – designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions. A clinical research coordinator (CRC) handles most of the administrative responsibilities of a clinical trial, acting as liaison between the investigative site and sponsor, and also reviewing all data and records before a monitor’s visit. Synonyms are trial coordinator, study coordinator, research coordinator, clinical coordinator, research nurse and protocol nurse.

Responsibilities of the investigator (examples):

- Protecting the rights and well-being of the participants.
- Following GCP and other guidelines.
- Having access to all necessary facilities.
- Following the protocol.
- Ensuring the clinical trial is reviewed by an EC.
- Informing the EC of any adverse events.
- Ensuring an ongoing informed consent process for the participants.
- Protecting participants’ identity.
- Proper handling of all trial medications/supplies.
- Reviewing and reporting adverse events during the trial.

Ethics Committee

The EC’s responsibility is to ensure the protection of the rights, safety, and well-being of potential participants as well as those participants involved in a trial. The EC provides public assurance of that protection by, among other things, reviewing and approving or rejecting the protocol and ensuring the investigator(s) are suitable to conduct the trial, the facilities are adequate, and the methods and materials to be used in obtaining and documenting informed consent of the trial participants are appropriate.

The legal status, composition, function, operations, and regulatory requirements pertaining to independent ECs differ among countries, but should allow the EC to act in accordance with GCP.

Responsibilities of the EC (examples):

- Safeguard the rights, safety and well-being of all trial participants; special attention should be paid to trials that may include vulnerable participants, such as children and participants who may have the capacity to make a decision but are unable to exercise that capacity, because prior consent could not be obtained in an emergency situation.
- Review the protocol and associated documents and provide opinions within a reasonable time, documenting its views in writing in a timely manner.

- Consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the EC requests.
- Conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human participants, but at least once a year.
- Reviewing certain types of adverse events and any harm that happens as a result of the trial.

During an EC meeting it is important for the chair to take the lead, ensuring that all members have the opportunity to express their views and concerns, all opinions are summarised and any potential dissenting opinions are clearly presented for voting. Some ECs vote on actions while others use consensus to determine action.

Many have pointed out a number of problems with consensus decision-making. It may require giving a small self-interested minority group veto power over decisions; it may take an extremely long time and it may encourage *groupthink*, where members modify their opinions to reflect what they believe others want them to think. It can also lead to a few dominant individuals making all the decisions, and may even fail altogether in a situation where there is simply no agreement possible and where interests are irreconcilable.

The EC membership should be composed of one or more institutional members, one or more members representing the viewpoint of the participants, one or more members who do not have scientific expertise, and one or more members who have scientific expertise. As for research that involves vulnerable participants, there should be one or more members who are knowledgeable about or experienced in working with such participants. Diversity in the EC members' knowledge and experience is important for ensuring a comprehensive EC review.

Trial Participant

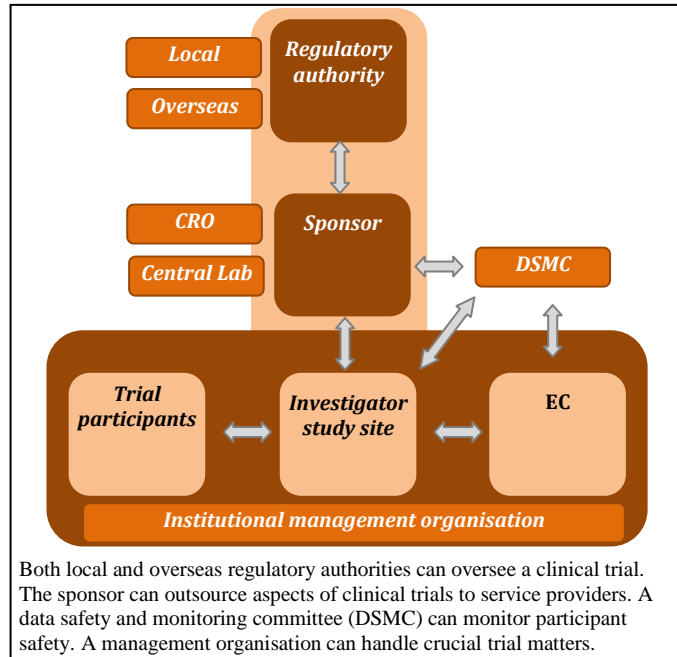
Most clinical trials include participants with a specific disease that is the target for the test drug, device or diagnostic tool, such as cancer or allergy. Participants are usually recruited from an ordinary pool of patients at a trial site, but sometimes by referral from other clinics or through local advertisements. Trial participation is voluntary, and participants do not normally have to pay any hospital fees during the duration of a trial.

However, some clinical trials are conducted on healthy participants or healthy volunteers. Examples are studies on preventive medicinal products such as vaccines, or when the product is tested for the first time in human participants, for drug safety and dosage to be determined. Healthy volunteers are commonly paid for participation because they receive no direct benefit, and may have to take leave from their ordinary work during the trial. Some procedures may also cause discomfort and pain.

Clinical Trial Services Provider

Outsourcing of tasks related to clinical trials has increased substantially over the past two decades. Today there are thousands of clinical research organisation (CROs) acting as service providers worldwide. CROs are independent companies providing research services for the pharmaceutical and biotech industry. Such outsourcing services can be related to the pre-clinical testing phase, such as animal studies. During the clinical phase, a CRO's services can take the form of project management, trial monitoring and medical statistics work. When a CRO is contracted by a sponsor, it takes on many and sometimes all the sponsor's trial responsibilities.

Central laboratory services have also become an important ingredient of clinical trials, conducting work such as processing blood samples and reading electrocardiograms (ECGs). Sponsors and sometimes also drug regulatory authorities require that one single central laboratory should process all trial blood samples – or in the case of ECGs, read all the ECGs – from study sites, whether they are in Europe, the US, Asia, South America or Australia (*see illustration*). There are three major reasons for using a single central laboratory, rather than local laboratories, for the same trial. One laboratory can standardise the processing or reading procedures, so that results are reliable and reproducible. Results can also be processed at any time, because a central laboratory usually operates 24 hours a day, and perhaps more important, because tests such as blood samples and ECG constitute important safety measures when test articles with unknown side-effects are administered in healthy volunteers or patients. Since results from all sites from the same trial are stored in a centralised computer, with a database updated several times a day, the data can be continually analysed to detect side-effects from all study sites.



Site Supporting Organisation

Another emerging clinical trial organisation – a for-profit or non-profit institutional management organisation – acts as an interface between the investigator and the sponsor. It can be located either at an academic institution or at a non-academic health care organisation (*see illustration*). These organisations often operate from centres commonly called offices of clinical trials or clinical trials centres. The supporting organisation assists the sponsor or CRO to identify potential investigators and assists the investigator to estimate the trial budget, prepare the contract, provide GCP training, establish research pharmacy services and prepare EC applications, and other administrative tasks.

Data Safety and Monitoring Committee

A data safety and monitoring committee (DSMC), data and safety monitoring board (DSMB), independent data monitoring committee (IDMC), or independent data safety committee (IDSC), may be established by the sponsor to assess, at intervals, the progress of a clinical trial, safety data and critical efficacy endpoints, and recommend to the sponsor whether to continue, modify or stop a trial (*see illustration*). The IDMC usually consists of international clinical research experts, together with representatives of the sponsor and a medical statistician to provide results to the IDMC based on statistical analyses of accumulated data from all sites. The EC can gain much useful information from regular feedback from the IDMC, ensuring that risks trial participants are kept to a minimum. The EC can also insist that certain high risk for harm or complex trials have an IDMC in place – usually established within the institution, but independent of the investigative site.

Chapter 2. Features of Clinical Trials

Chapter 2 describes the essential features of clinical trials. The text is quite lengthy, providing readers with detailed insight into the various aspects of clinical trial design. Without this understanding it would be very difficult for a novice or any EC member to take part in discussions surrounding a clinical trial protocol, since the selected research design should be scrutinised during the EC review.

The following chapter – Chapter 3 – covers Science, Ethics and Quality Assurance of Clinical Trials, which means that the contents of Chapter 2 and 3 partially overlap. Some readers may feel that certain aspects detailed in Chapter 2 might more appropriately be covered in Chapter 3, and vice versa. For instance, some aspects of Chapter 2 deal both with research design issues and ethics, e.g., the utilisation of placebo treatment control groups. When a topic is essential for the understanding of research design, it is detailed in Chapter 2, and subsequently only partially addressed in Chapter 3, using cross-references when appropriate.

Biostatistics also forms an important part of clinical trial design and statistical analyses of clinical trial data. With regards to this topic, readers are suggested to explore the many existing excellent text books in biostatistics. The Internet also serves as a good library of resources in this respect.

2.1 Objectives of Clinical Trials

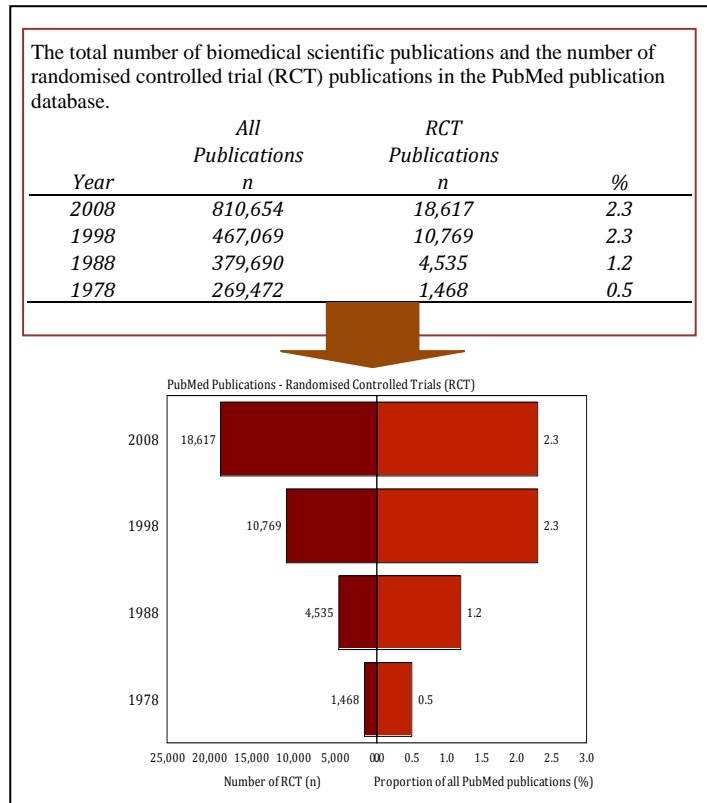
Clinical trials are conducted to test new medicinal products and medical procedures in humans. The earliest recorded clinical trial is documented in the Old Testament, and describes how Daniel followed a diet of pulses and water instead of the meat and wine recommended by King Nebuchadnezzar II. James Lind is seen as the father of clinical trials. As the first to introduce control groups in 1747, he documented that citrus fruits in diet could prevent scurvy. From 1800 onwards, clinical trials became more and more common, with more attention paid to trial design. Placebos were first used in 1863. The idea of randomisation was introduced in 1923. The first trial using properly randomised treatment and control groups was carried out in 1948 by the Medical Research Council, UK. This trial also adopted blind assessment enabling unbiased analysis of the results. The three cornerstones of clinical trial design are still *controls*, *randomisation* and *blinding*. This chapter describes the three cornerstones in more detail, along with other important clinical trial features.

Although clinical trial design has been around for decades, it was not until around 1990 that it was given status as the trial design of choice for clinical interventional studies. Today, it would be difficult to have results of an interventional clinical trial accepted by journals without utilising the modern concepts of clinical trial research methodology. Using controls, randomisation and blinding is the optimum way to ensure that results are not influenced in a non-random way by external factors. Although external factors – such as the extra attention and medical care that usually come with trial participation – most certainly will influence trial participants in one way or another, these should not influence treatment groups any differently. But without using controls, randomisation and blinding, the conclusions may not reflect the reality.

The objective of clinical trials is to evaluate the efficacy and safety of medicinal products or medical procedures in humans so new medical treatments can be identified for medical practice. In 2008, randomised controlled clinical trials (RCT) accounted for only 2.3% of all biomedical scientific publications identified in the PubMed publication database; 18,617 publications from a total of 810,654. But the volume of such trials has increased by more than twelve times over the past three decades, while the total

number of PubMed publications has increased by three times over the same period (*see illustration*). It may be argued that this number is not an accurate measure of the level of research activity. Clinical trials, in fact, last over a long period, even years, while many other biomedical research studies are much shorter – and are conducted in a research laboratory, not in humans. However, it is clear from these illustrated statistics that clinical trials have become increasingly popular and that we can expect a further rapid increase in clinical trial activities.

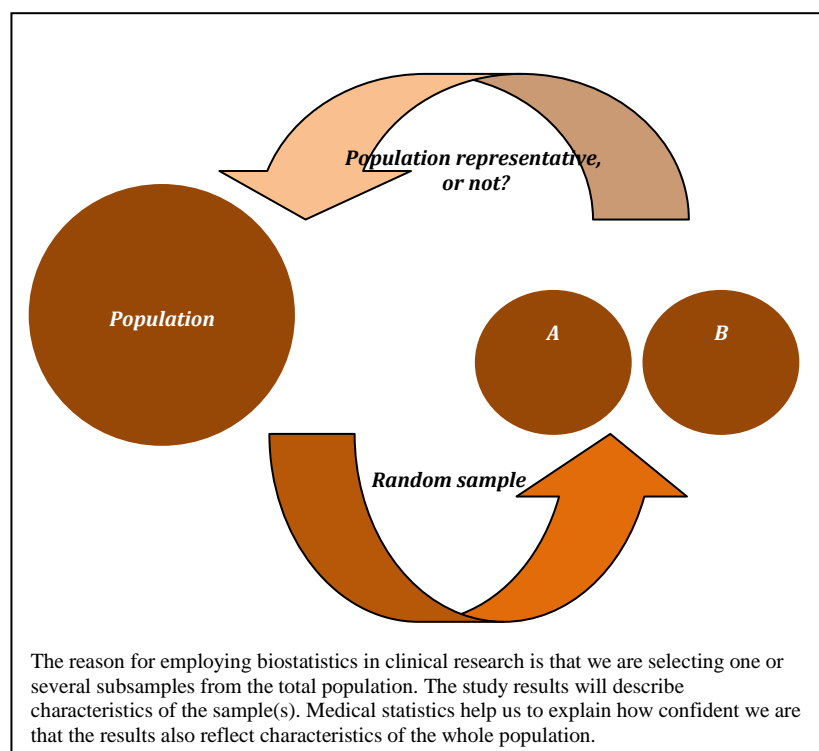
On the surface, clinical trial research methodology is not complicated, but there are many factors to be considered in designing a good trial. The most important and crucial single clinical trial design feature is the primary trial outcome/endpoint; selection of a wrong trial outcome/endpoint renders the trial worthless, since it would be difficult to correctly and solidly interpret results and get general acceptance of them.



2.2 Clinical Trial Design

The Importance of Clinical Trial Design

The overall objective in designing a clinical trial is to be able to provide the best possible and most reliable estimate of the effect and/or safety of a certain test article. Now, this estimate will never be absolutely conclusive, since it only observes a subsample of the entire participant population (*see illustration*). There is always the possibility that the sample in question does not, in fact, fully represent the underlying population. With this come two potential



mistakes or errors: (I) we concluded there was a difference between two treatment groups when there was, in fact, no difference (*false positive result*), or (II) we concluded there was no difference between two treatment groups when there was, in fact, a difference (*false negative result*). The objective is to identify the optimum trial design for the purpose of reducing the probability of false results; this is dependent on many factors, such as trial objectives, therapeutic area, treatment comparison and phase of clinical testing.

Biostatistics is an important science of clinical trials, since it provides an estimate of probability for making any of those two *false* conclusions. For example: when we flip a fair coin 100 times, we *expect* 50 heads and 50 tails – but we can also get different numbers such as 60 and 40. In clinical trials the same variation arises because the random selection of participants typically involves a large number of difficult or easy participants to one treatment over the other. Treatment A, which has a true treatment success rate of say 50%, could show 30 successes in 100 participants, while treatment B, which has a true rate of say 40%, could show 50 successes in 100 participants. Based on our total combined sample of 200, we could come to the wrong conclusion that treatment B is better than treatment A (a *false result*).

The basic problem is that the important characteristics of the random sample may or may not match the reality of the world, namely the entire participant population. And we rarely know how representative a subsample is of the real world. The point of clinical trial design and interpretation is to control the risk of making an error in order to discover the truth. We have to decide what level of risk we can afford and rationally justify. Note that a *false negative* trial result will in practice end a particular development programme. This is costly not only to the trial sponsor, but also to society, which loses out on finding a potentially useful treatment.

Four different interpretations can be made from a clinical trial: either the two aforementioned errors or correct interpretations that reflect the real world, i.e., the treatment is either effective or ineffective (*see illustration*), where a *false positive* result is termed *type I error* and a *false negative result* is termed *type II error*. The level of risk that we are prepared to take in reaching a wrong conclusion can also be measured by the cost of the trial. If we can afford a very large sample size – say, 10,000 rather than 10 participants – the risk of making type I/II errors will be reduced to a very small fraction. However, the cost of conducting the trial will increase by a factor of 1,000. From a research ethics point of view, we may also unnecessarily put a large number of trial participants at risk by increasing the sample size without making a proper risk assessment.

The four types of interpretations that can be made from a clinical trial			
		Trial interpretation	
		Effective	Ineffective
Real life	Effective	Success	False "negative" type II error
	Ineffective	False "positive" type I error	Success

So the main objective of a clinical trial design is to give the decision makers a probability measure for taking certain risks, weighed against the financial cost that must be invested in order to decrease the risk. The EC must have this information to be in a position to approve or reject a clinical trial protocol.

Clinical Equipoise

Equipoise can be defined as “balance” or “equability of distribution.” In the context of clinical trials, “clinical equipoise” relates to the state of uncertainty regarding whether one of the alternative interventions, of, for instance, two study treatment arms, will give a more favourable outcome than the other. Under the principle of equipoise, a participant should be enrolled in a randomised controlled trial only if there is substantial uncertainty about which intervention will likely benefit the participant more than the other intervention(s). Clinical equipoise is a part of the EC review process, because it is critical to the research design – for instance, by setting up the research hypothesis and statistical testing and, perhaps, the number of participants to be recruited into one treatment group. It can also be the rationale behind interim data analysis during the course of a trial, to identify findings that might change the clinical equipoise picture.

Superiority, Non-inferiority and Equivalence Clinical Trials

The E9 ICH Guideline – “*Statistical Principles for Clinical Trials*” – that brings up the basic principles of designing and analysing clinical trials is highly recommended to be studied by any person involved in clinical trials (<http://www.ich.org/LOB/media/MEDIA485.pdf>). It is in fact surprisingly easy to understand.

This guidance contains a section addressing the type of comparisons made in certain clinical trials. The most common type of comparison trial is the so-called *superiority trial*, whereby efficacy is most convincingly established by demonstrating superiority to a placebo in a placebo-controlled trial or by showing superiority to an active control treatment.

However, sometimes an investigational product is compared to a reference treatment without the objective of showing superiority. Some active control trials are designed to show that the efficacy of an investigational product is no worse than that of the active comparative treatment, i.e., *non-inferiority* trials.

Other trials – *equivalence* trials – have the primary objective of showing that the response to two or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and upper equivalence margin of clinically acceptable differences.

The choice of the type of comparison will influence some technical aspects of the study design, sample size and statistical analysis, but this will not be further elaborated in this Guide, where superiority trials are generally assumed to be the design of choice.

Types of Clinical Trial Designs

The vast majority of clinical trials use a fixed design that remains virtually unchanged during the duration of the trial. In those cases, the design is defined prior to trial initiation, which makes life easier for the EC. But some trials might not have enough information to correctly estimate the sample size beforehand. Here, the protocol might spell out that the sample size will be reassessed and revised at a certain point in time – it usually happens after a specific number of participants have completed a certain

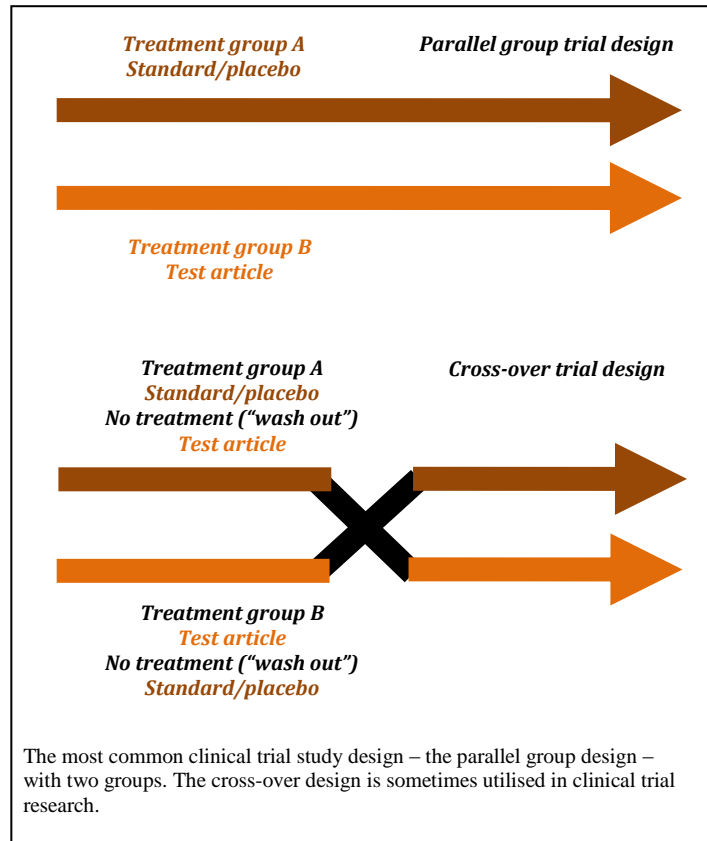
number of study visits. Increasing the number of visits or duration of the follow-up is also quite common with protocol amendments. Such changes will not usually affect the sample size and trial design in general, but an EC review is needed for any protocol amendments that may influence the risk of harm to participants.

A clinical trial design has many features and some of them are covered in other sections of this Chapter, i.e., controls, outcomes, randomisation, blinding, sample size and trial phases. Here, we address a few general, common trial design characteristics based on the number of groups and treatment alternatives. The most common type uses two parallel groups – *parallel group design* (see illustration). In most cases, trial

participants are randomised to one of the two treatment groups, with randomisation commonly giving each participant the same possibility or chance to be allocated to either treatment section. One group – say group B – is given the test article, and the other group frequently given placebo (*dummy*) treatment, or the current best available treatment on the market (*standard treatment*). It is also possible to give both groups the standard treatment with the addition – as an *add-on* treatment or as a combination therapy – of the test article for one of the two treatment groups.

Another type of trial design is the *cross-over trial design* (see illustration). Here, the trial participants receive both treatments in sequence. The cross-over design represents a special situation where there is not a separate comparison group. In effect, each participant serves as his/her own control. Some participants will receive the standard therapy or the placebo first, followed by the new therapy (AB). Others will receive the new therapy first, followed by the standard therapy or the placebo (BA). A cross-over design has the advantage of eliminating individual participant differences from the overall treatment effect. On the other hand, it is important in a cross-over trial that the underlying condition – for instance, a disease – does not change over time, and that the effects of one treatment disappear before the next is applied. With this, it follows that cross-over design is utilised much less commonly than parallel group design. The cross-over design is also more sensitive to drop out during the course of the trial, since participants act as a control as well as active treatment participants.

An *open-label trial* – though less common – is when both the investigators and participants know which treatment is being administered, with trial participants still commonly randomised to one of two treatment groups. Using *historical controls* is nowadays seen as a sub-standard research design, since standard medical treatments change over time and randomisation to treatment cannot apply. Sometimes a trial has



more than two *concurrent treatment* groups, for instance when different doses are to be compared.

Adaptive Clinical Trial Design

A few, but an increasing number of trials use the so-called *adaptive clinical trial design* – empowering sponsors to respond to data collected during the trial.

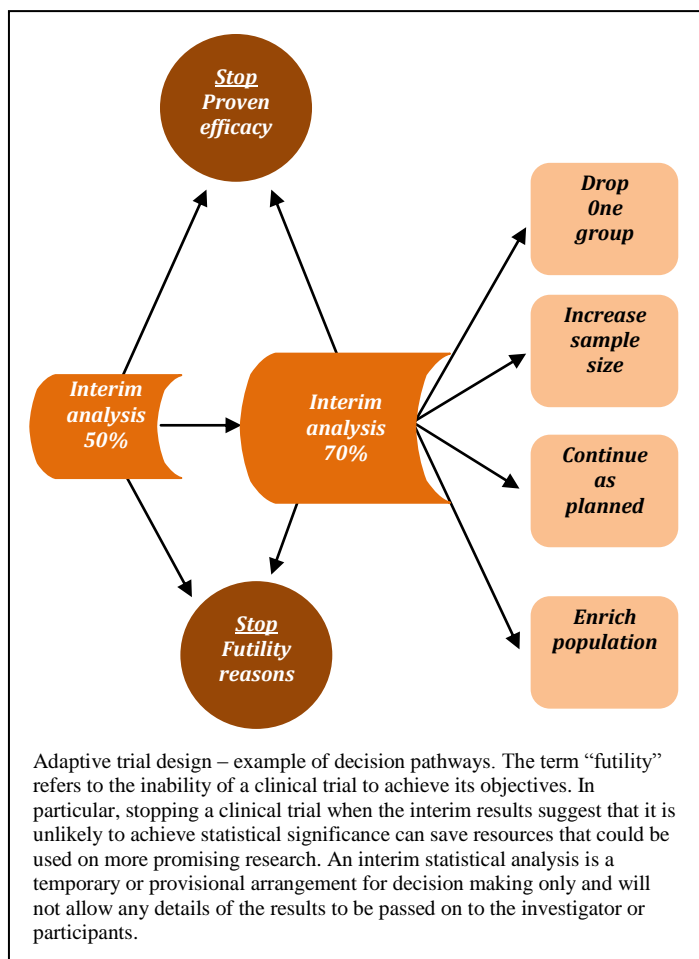
Examples of adaptive trial designs include dropping a treatment group, modifying the sample size, balancing treatment assignments using adaptive randomisation, or simply stopping a trial early due to success or failure (*see illustration*). In a standard trial, safety and efficacy data are collected and reviewed by a data safety and monitoring committee during scheduled interim analyses. However, aside from stopping a trial for safety reasons, very little can be done in response to these data. Often, a whole new trial must be designed to further investigate key trial findings.

In an adaptive trial, the sponsor might have the option of

responding to interim safety and efficacy data in a number of different ways, including narrowing the trial focus or increasing the number of participants. An example of narrowing the trial focus includes removal of one or more of the treatment groups based on predetermined *futility rules* – the inability of a clinical trial to achieve its objectives. Alternatively, if data available at the time of the review do not allow for a clear decision between utility and futility, it might be decided to expand the enrolment of participants to one or more treatment groups beyond the initially targeted sample size.

Another example of adaptive design is *response-adaptive*. In this setting, participants are randomised to treatment groups based on response to treatment of previous participants. Real-time safety and efficacy data can be incorporated into the randomisation strategy to influence subsequent adaptive randomisation decisions on a participant-by-participant basis. An example of response-adaptive randomisation is *play-the-winner*, which assigns participants to treatment groups that have resulted in fewer adverse events or better efficacy.

As these examples demonstrate, the adaptive design concept can be utilised in a number of different ways to increase trial flexibility. In a well-designed adaptive trial, that flexibility can result in lower drug development costs, reduced time to market and improved participant safety. Cost reduction is achieved by identifying successful trials sooner, dropping unnecessary treatment groups or determining effective dose regimens



faster. Participant safety is improved because adaptive trials tend to reduce exposure to unsuccessful treatment groups and increase access to effective treatment groups.

Adaptive trial design requires modern data collection technologies to provide the research team with real-time information, and enables them to plan and quickly implement seamless changes in response to that information. Key enabling technologies for adaptive trial design are, for instance, real-time electronic data capture over the Internet to a central database.

The general impression is that utilising adaptive clinical trial design will become more and more popular. The ECs will play a crucial role in this process, since they will be required to respond within a very short time to design changes so trials can be adjusted in a real-time manner. This calls for ECs to also become adaptable to change. The adaptive trial design is still in its infancy and may become generally accepted in the future.

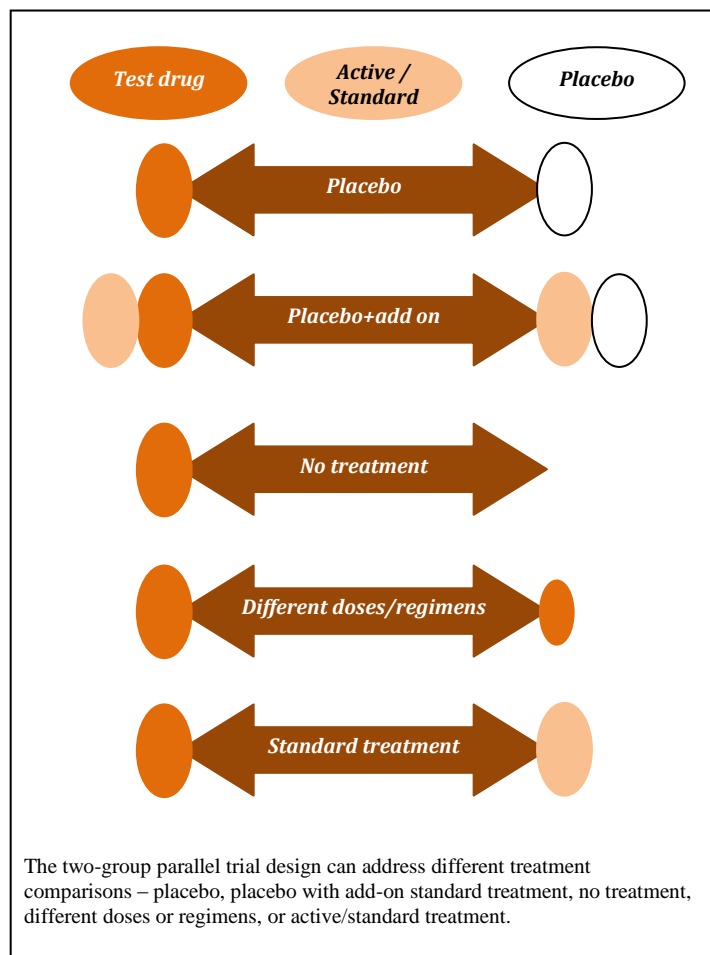
2.3 Controls of Clinical Trials

The control group experience tells us what would have happened to participants if they had not received the test treatment – or if they had received a different treatment known to be effective. A control group is chosen from the same population as the test group and treated in a defined way as part of the same trial studying the test treatment. Test and control groups should be similar at the initiation of the trial on variables that could influence outcome, except for the trial treatment. Otherwise, bias can be introduced into the trial.

The ICH Topic E10 Choice of Control Group in Clinical Trials states: *“The choice of control group is always a critical decision in designing a clinical trial. That choice affects the inferences that can be drawn from the trial, the ethical acceptability of the trial, the degree to which bias in conducting and analyzing the trial can be minimized, the types of participants that can be recruited and the pace of recruitment, the kind of endpoints that can be studied, the public and scientific credibility of the results, the acceptability of the results by regulatory authorities, and many other features of the trial, its conduct, and its interpretation.”*

The type of control can be (1) placebo, (2) no treatment, (3) different dose or regimen of the trial test treatment, or (4) the standard treatment (see illustration):

- In a placebo-controlled trial, participants are randomly assigned to a test



treatment or to an identical-appearing treatment that does not contain the test drug. Such trials are almost always double blind.

- In a no treatment-controlled trial, participants are randomly assigned to test treatment or to no trial treatment. Here, participants and investigators are not blind to treatment assignment. This design is needed and suitable only when it is difficult or impossible to use blinding.
- In a randomised, fixed-dose, dose-response trial, participants are randomised to one of several fixed-dose groups. Dose-response trials are usually double-blind.
- In an active control trial, participants are randomly assigned to the test treatment or to an active control treatment. Such trials are usually double-blind, but this is not always possible as blinding to the two treatments may be impossible. Active control trials can have two objectives with respect to showing efficacy: to show efficacy of the test treatment by showing it is as good as the standard treatment, or by showing superiority of the test treatment to the known effective treatment.

An externally controlled trial compares a group of participants receiving the test treatment with a group of participants external to the trial. The external control can be a group of participants treated at an earlier time (historical control) or a group treated during the same time period but in another setting. Such trials are usually considered uncontrolled. It is possible to use more than one kind of control in a single trial. Trials can, for instance, use several doses of a test drug and several doses of an active control, with or without placebo.

Choice of participants – trial sample – should mirror the total participant population for which the drug may eventually be indicated. However, this is not the case for early phase trials, when choice of participants is influenced by research questions such as human pharmacology. However, for confirmatory late phase trials, the participants should closely mirror the target patient population. However, how much the trial participants represent future users may be influenced by the medical practices and level of standard care of a particular investigator, clinic or geographic region. The influence of such factors should be reduced and discussed during interpretation of the results.

Placebo Treatment

The Declaration of Helsinki states: *“The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the participants who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.”*

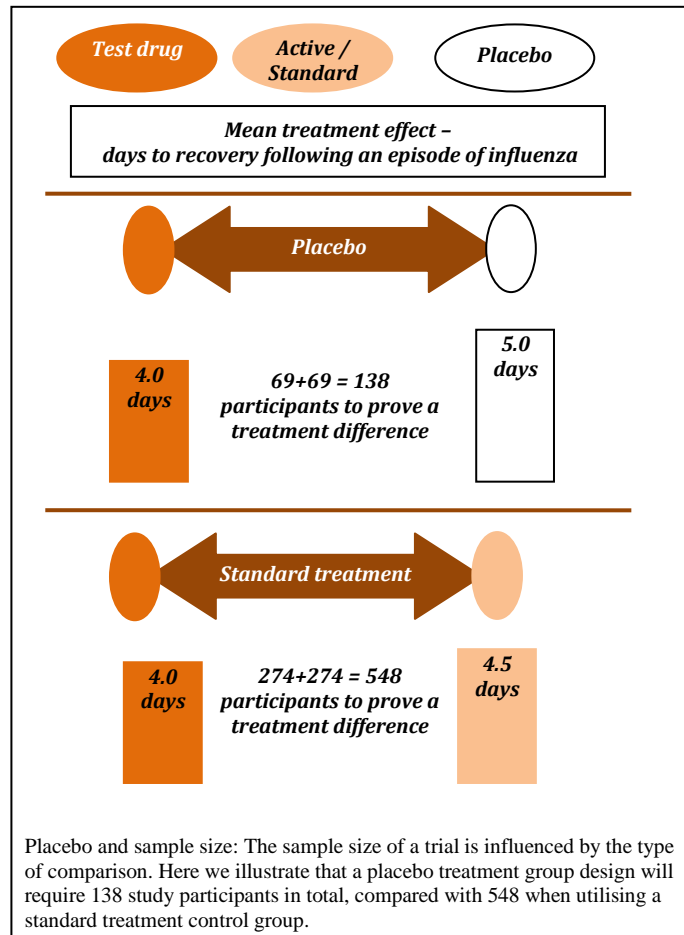
There is no ethical problem in using a placebo group if a new treatment is being tested for a disease for which there is no known effective treatment. However, using a placebo control may pose ethical concerns if an effective treatment is available. When the available treatment is known to prevent serious harm, such as death or irreversible morbidity, it is most often inappropriate to use placebo control. An exception is, for instance, when the standard therapy has such severe toxicity that participants will not accept it. When a placebo-controlled trial is not associated with serious harm, it is by and large ethically sound to use a placebo-controlled trial design, even with some discomfort, assuming that the participants are fully informed about available therapies and the consequences of delaying treatment. Opinions on the acceptability of using

placebo controls are in any event controversial. In the end, it is up to investigators, participants and ECs to decide. Placebo or no-treatment control does not mean a participant does not receive treatment at all. The best supportive available care will normally be provided, plus the same clinical follow-up as the active treatment group. Placebo-controlled trials can also be conducted as add-on trials where all participants receive a standard therapy.

Placebo-controlled trials measure the total mediated effect of treatment while active control trials, or dose-comparison trials, measure the effect relative to another treatment. They also make it possible to distinguish between adverse events caused by both the drug and underlying disease. Placebo-controlled trials can detect treatment effects with a smaller sample size (*see example below*). However, it is also arguable that they represent an artificial environment, producing results different from *real-world* effects. It should also be noted that they provide little useful information about the comparative effectiveness of standard treatment.

Placebo and sample size: Assume that “normal” recovery from influenza – without any specific influenza treatment – takes on average 5.0 days (*see illustration*). However, when standard treatment is used, the mean duration to symptom recovery is 4.5 days. A drug company has developed a promising new anti-influenza drug and would like to proceed with a

first-into-human, exploratory, proof-of-concept phase II trial. Theoretically, the new test article is more effective, being able to reduce the average number of days to recovery to 4.0 days. If the comparison is against standard treatment, to show a statistical difference between the two treatment groups, we need to recruit 274 participants for each (the calculation is based on certain assumptions not described in detail). But only 69 participants are needed per group if no treatment – placebo – is used as a comparison. In this scenario, 410 *extra* participants are put at risk of harm when standard treatment is used as a comparison. Yet in fact we do not know whether the test article has any effect at all or is safe when given to participants. So three times more participants are put at risk of harm, and the trial budget may increase by as much as US\$4 million.



2.4 Clinical Trial Outcome/Endpoint

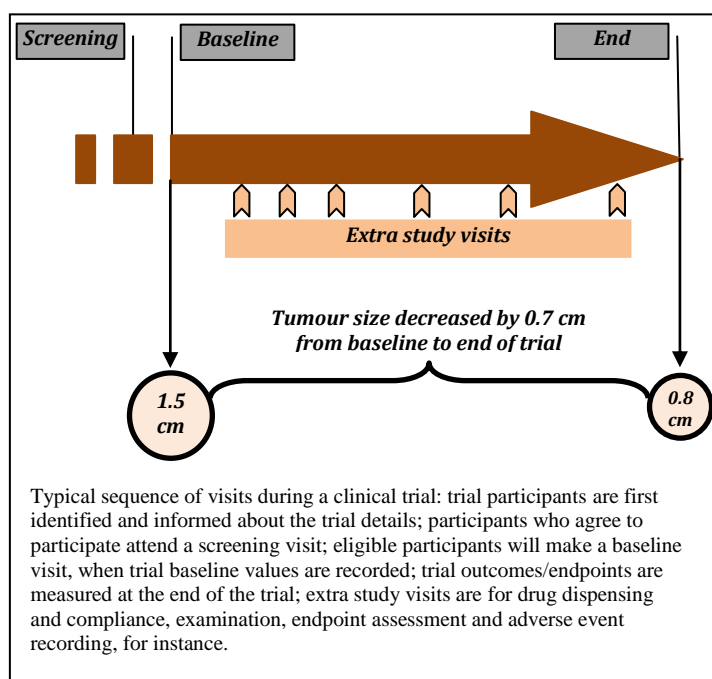
Defining Clinical Trial Outcome/Endpoint

A clinical trial outcome/endpoint is an indicator measured in a participant or in a sample taken from the participant to assess the safety, efficacy or other objective of a clinical trial. The endpoint measure of a trial can be of various types. Efficacy, safety and quality of life are the most common and widely accepted indicators:

- *Efficacy* is simply an estimate of how effective the test medicinal product is in eliminating/reducing the symptoms or long-term endpoints of the condition under trial. Efficacy measures can be of many kinds, such as blood pressure, tumour size, fever, liver function test or body mass index.
- *Safety* of the test treatment is as important to the trial as the treatment efficacy. All negative adverse reactions or events that a trial participant experiences during the conduct of the trial should be documented. The investigators monitor for adverse reactions or events to determine safety during a clinical trial. The information is used to describe the safety profile of the test treatment. Adverse events can be mild, such as local short-term reactions and headaches, or serious such as stroke and death.
- The measurement generally referred to as *quality of life* (QoL) in clinical trials is now a well-established term. QoL includes physical, mental and social well-being, and not just the absence of disease or illness. There are broad QoL measurements that are not very specific for the disease or condition – *general well-being* – and there are *disease-specific* questionnaires that are more sensitive to treatment and disease influences. All questionnaires must be validated properly before they are used as a valid trial endpoint.

Trial participants are usually assessed at a minimum of three different time points (*see illustration*):

- **Screening:** Trial participants are commonly examined before a trial starts to assess their health status in relation to certain trial inclusion/exclusion criteria. Such screening values can be established from the results of laboratory test samples, for instance.
- **Baseline:** Once a participant has met the inclusion/exclusion criteria, a baseline value of the trial endpoint measures is recorded. Baseline is the time point when a clinical trial starts, just before any treatment begins.



- **End of Trial:** The trial endpoint measure is repeated at the end of the trial. Often the research team compares the baseline endpoint values to those made at the end of the trial to see how well the treatment worked.

A trial endpoint is usually estimated as the difference between the end value and baseline value of the endpoint measure; in some trials, follow-up continues for the participants after the end-of-treatment visit. For example, the tumour diameter was measured to be 1.5 cm at baseline and 0.8 cm at trial end (*see illustration*). The cancer diameter thus decreased by 0.7 cm. The participants will visit the study site several times during the course of a trial to collect trial medication or other medications, for instance, or to be given a physical examination and follow-up test(s) (*see illustration*). Adverse events – side-effects – and test article dispensing/compliance information is often accumulated continuously throughout the trial, by means of laboratory tests, for example, or home log-books. Such accumulated information is commonly used in the final safety statistical analysis. *Primary and secondary endpoints* (see below) are commonly recorded or assessed at each or some of the extra site visits as well. One reason for this is that if a participant drops out during the active trial period, the data can still be used for some of the statistical endpoint analyses. All details about trial endpoints – how they are assessed, at what time points, how they are analysed, etc – must be clearly spelled out in the clinical trial protocol.

Primary and Secondary Outcome/Endpoint

The *primary endpoint* of a trial represents the variable providing the most relevant and convincing evidence related to the prime objective of the trial. Generally, there is only one primary variable – usually an efficacy variable. Safety may occasionally serve as the primary variable, but safety is always an important consideration, even if it serves as a secondary set of endpoints. It is also possible that QoL is the primary variable. *Selecting the primary variable is one of the most important tasks when designing a clinical trial, since it is the gateway for acceptance of the results.* We must produce evidence that the primary variable represents a valid and reliable measure reflecting clinically relevant and important treatment benefits.

The primary endpoint is taken into account when estimating the sample size. It should be well defined in the protocol, along with the rationale for why it was selected, when it will be measured during the course of the trial and how the statistical analysis will be carried out. Redefining the primary endpoint after the trial has been completed is unacceptable since it violates the trial design and may be unethical, especially when the original, real primary endpoint was statistically insignificant between the treatment groups.

Secondary endpoints can be supportive measurements of the primary objective or measurements of effects related to other secondary objectives. These should also be pre-defined in the protocol, explaining their importance and role in interpreting trial results.

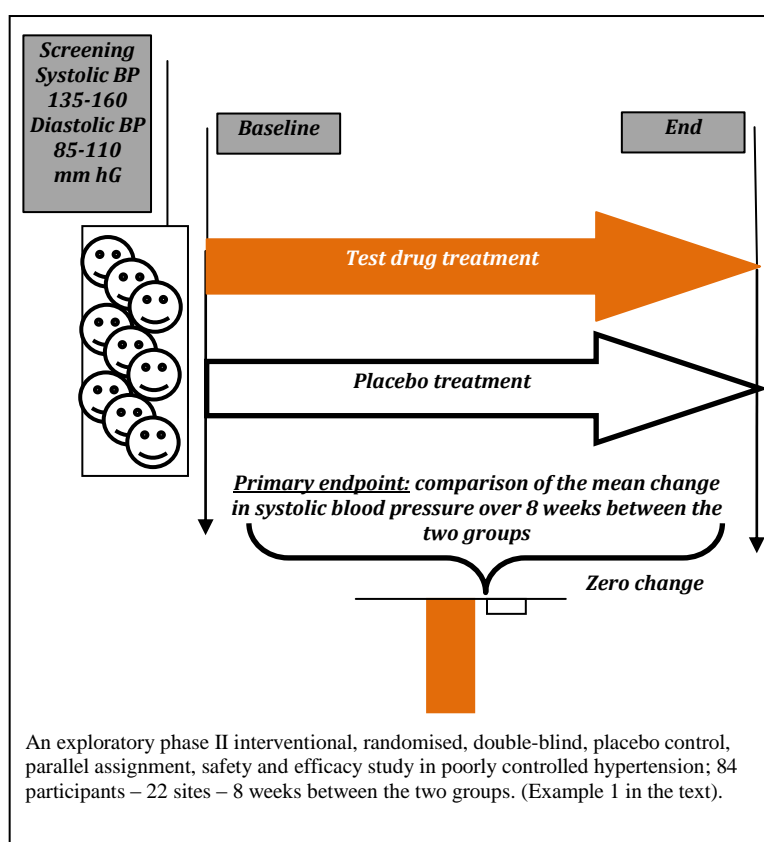
Below are two illustrations based on actual trial protocols from the US clinical trials registry. The first is a hypertension phase II trial using a placebo control group, and the second a phase III cancer trial with an active treatment control. Both primary and secondary endpoints are clearly defined, both with an efficacy estimate as the primary endpoint and safety as the secondary endpoint. The cancer trial also listed QoL and health economics as secondary endpoints.

Example 1 – hypertension, exploratory phase II, sample size 84 (42/group), 22 study sites (*see illustration on the following page*)

- Objective: To determine whether drug XX is safe and effective in the treatment of poorly controlled hypertension.
- Trial design: Treatment, randomised, double-blind, placebo control, parallel assignment, safety/efficacy trial.
- Primary endpoint: Change from baseline in arterial systolic blood pressure after 8 weeks of treatment in participants with poorly controlled hypertension.
- Secondary endpoint: Change from baseline in arterial diastolic blood pressure after 8 weeks; change from baseline in eNOS activity and endothelial dysfunction after 8 weeks and safety assessments.

Examples 2 – colorectal cancer, confirmatory phase III, sample size 102 (51 per group), 39 study sites

- Objective: To compare overall survival in participants with previously treated metastatic, epidermal growth factor receptor (EGFR)-positive colorectal cancer treated with drugs XX1+XX2+ XX3 and drugs XX1+ XX3 alone.
- Trial design: Treatment, randomised, open label, active control, parallel assignment, safety/efficacy trial.
- Primary endpoint: Compare the overall survival between the two treatment groups.
- Secondary endpoint: Compare the response rates; compare progression-free survival; time to response; compare the safety profiles; compare the QoL; conduct an economic assessment comparing healthcare resource utilisation.



Surrogate or Clinical Outcome/Endpoint

A trial endpoint of a clinical trial should fulfill three criteria: (1) be *measurable* and *interpretable*, (2) *sensitive* to the objective of the trial, and (3) *clinically relevant*. The endpoint can be either clinical or surrogate in nature.

- A *clinical endpoint* directly measures substantial clinical benefit to participants, for example survival or reducing the effect of a disease.
- A *surrogate endpoint* is a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a participant feels, functions or survives. Changes induced by a therapy on a

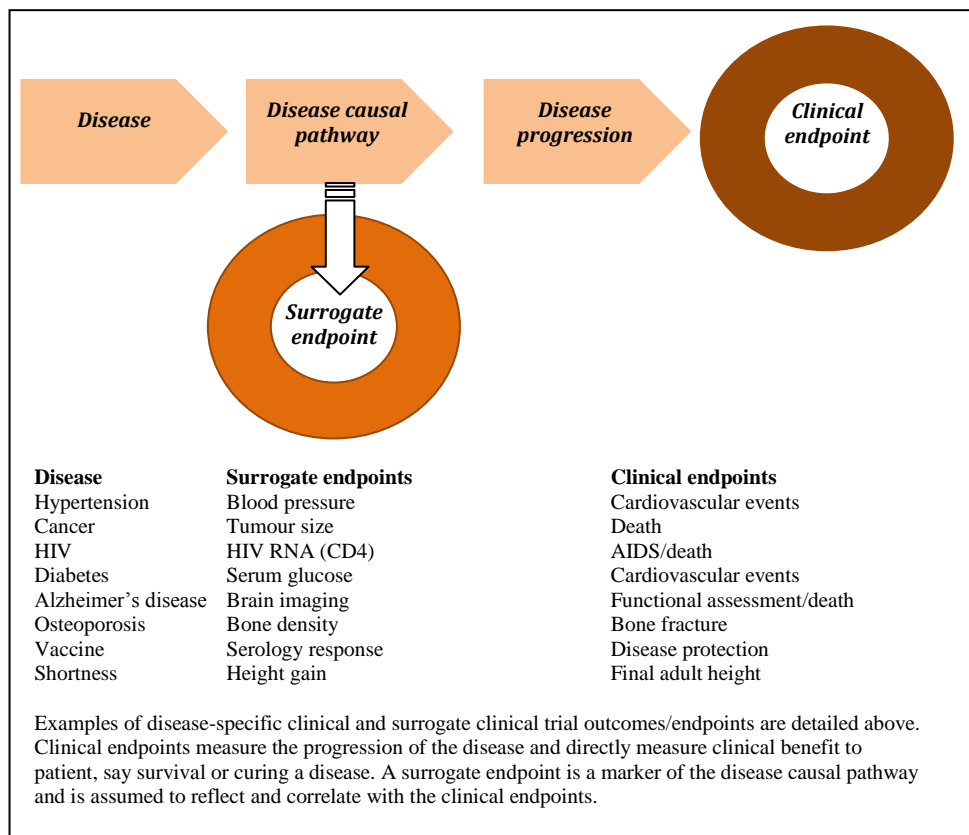
surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint: i.e., there should be an association between the response of surrogate measures and the response of clinical endpoints.

Press report, 2008: *“The US FDA is considering requiring diabetes drugs to show efficacy on cardiovascular safety and increased life expectancy rather than the control in blood sugar. Diabetes patients will eventually die from cardiovascular complications and the FDA is therefore considering insisting on more direct clinical measures of participant benefit rather than relying on surrogate endpoints as the control of blood sugar. For instance, one diabetes drug that has been approved based on surrogate markers has in fact been linked with an increased risk of myocardial infarction.”*

Surrogate endpoints are used because they can be measured earlier, are convenient or less invasive, can be measured more frequently and can accelerate the approval process.

Additional advantages are that their utilisation can very likely reduce the sample size of clinical trials, shorten their duration and thus reduce their cost. Using surrogate endpoints also put fewer trial participants at risk from adverse reactions to the test article. Examples of clinical and surrogate endpoints in clinical trials are various (*see illustration*). For instance, in cardiovascular trials, blood pressure and cholesterol levels are commonly used as surrogate measures, while the true clinical endpoints are myocardial infarction and death.

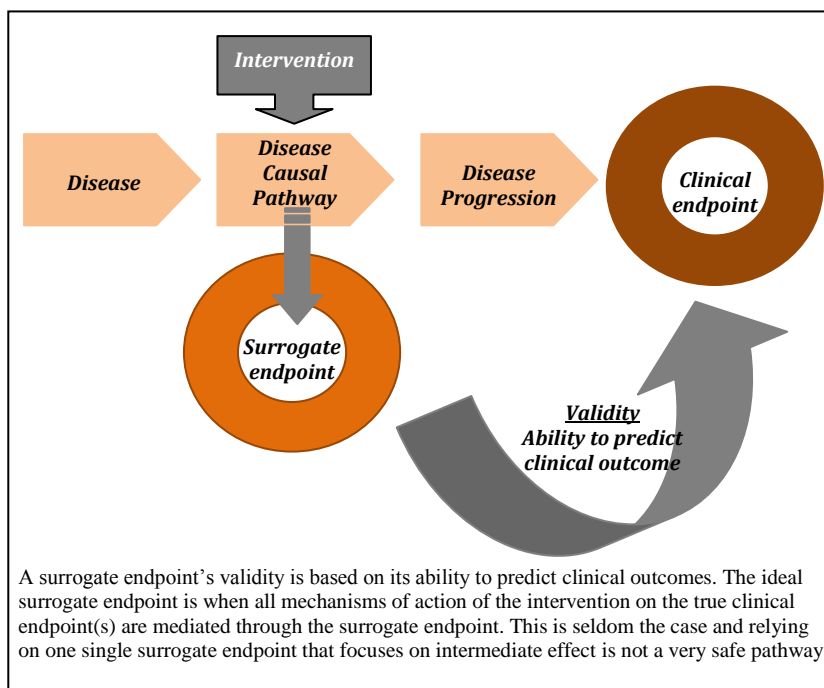
Generally, a clinical endpoint is adopted in the final, large-scale confirmatory clinical trial (phase III) of a new medical therapy, while a surrogate endpoint is more commonly used in initial, exploratory trials (phase II) of a test article. The drug regulatory authority may request the use of a clinical endpoint, rather than a surrogate endpoint as the most important health indicator in a clinical trial for a specific disease. But such events are rare, and many participants need to be studied in confirmatory trials. However, in the exploratory early phase of a new therapy, it is common to use a surrogate endpoint. This reduces the sample size as well as the duration of the trial.



Disadvantages of Using Surrogate Outcome/Endpoint

The ideal surrogate endpoint is when all mechanisms of action of the intervention on the true clinical endpoints are mediated through the surrogate endpoint (*see illustration*). It is essential to have a comprehensive understanding of causal pathways of the disease process. For instance, do changes in measures from brain imaging precede changes in the true clinical endpoint in Alzheimer's disease? The main reason for the failure of surrogate endpoints is that the surrogate does not play a crucial role in the pathway of the effect of the intervention. For example, an intervention could affect the surrogate endpoint,

but not the clinical endpoint. Ultimately, test articles approval based on effects on a surrogate involves an extrapolation from experience with existing products to an untested test article. There have been many instances where treatments showing a highly positive effect on a proposed surrogate have ultimately been shown to be detrimental to the participants' clinical endpoint outcome. Conversely, there are cases of treatments conferring clinical benefit without measurable impact on proposed surrogates.



Example: Surrogate Outcome/Endpoint in the Cardiovascular Area

The following is a classical example of a failed surrogate: A Cardiac Arrhythmia Suppression Trial (CAST) sought to evaluate the efficacy and safety of arrhythmia suppression therapy in participants with asymptomatic or mildly symptomatic ventricular arrhythmia after myocardial infarction. A pilot trial evaluated four active drugs (Encainide, Ethmozine, Flecainide, Imipramine) against a placebo using the surrogate endpoint – asymptomatic arrhythmia – in 500 participants. Based on the results of this pilot trial, a full-scale trial began enrolling participants in 1987, and after less than one year of follow-up the Encainide and Flecainide groups of the trial were stopped because of a three-fold increase in mortality compared to the placebo. This example illustrates that a drug can mitigate disease symptoms – representing a surrogate endpoint – but over the long term can be associated with a negative clinical outcome (here, death).

Cardiovascular disease is the number one reason for premature death among adults. Many large-scale clinical trials have sought effective new treatments where the clinically important endpoint – such as cardiac arrest or death – is expected to be prevented. A trial of lipid-lowering therapy using a surrogate – serum lipid level – endpoint will need around 100 participants over 3 to 12 months. However, if the endpoint is the incidence of cardiovascular events, thousands of participants need to be

studied over many years. Most drug therapies have multiple effects, and, therefore, relying on a single surrogate endpoint that focuses on an intermediate effect is not a very safe pathway. One approach is to require new drug therapies in large, long-term clinical trials to assess their effects on clinical endpoints. The use of surrogate endpoints is in this way avoided, and major health endpoints are known prior to marketing. But such an approach slows the time to test article approval and clinical usage, which is a problem especially for severe diseases with no effective standard treatment and can be very expensive. An alternate approach, which is adopted more and more frequently after regulatory authority approval of a new test article has been obtained, based only on the surrogate endpoints, is to conduct long-term phase IV trials on the clinical usage and experience of that new drug. Phase IV, high-quality trials are designed to assess the effects of test article therapies on clinical endpoints.

Often, these are called “*large simple trials*.” When new drugs enter the market, their safety and efficacy profile may vary considerably from that measured in carefully conducted clinical trials. In daily clinical practice, such drugs are prescribed not only for the relatively healthy and usually younger patients who enter clinical trials but also for patients with multiple diseases and for older patients. Rare, unexpected, serious side effects might not be detected during the course of clinical trials. When they, in fact, are detected, their frequency may not be exactly defined. Thus, the factual clinical effectiveness and/or safety may not be mirrored by clinical trials. The post-marketing of “*large simple clinical trials*” aims to identify such factual discrepancies between observations made in clinical practice and those made during clinical trial conduct. A large simple trial is characterized by a large sample size that randomises thousands or tens of thousands of participants into two or several treatment groups. Those trials are simplified by being conducted in, for instance, established general practitioner medical clinics or outpatient clinics using simple, measurable clinical outcomes. The data quality is not seen as the prime concern, rather the representativeness of the target population. For instance, a large simple trial can be used in comparing the survival of HIV/AIDS patients receiving different types of anti-retroviral therapies. The trial requires a large number of patients, conducted in a community-based primary care setting. Baseline data can be communicated over the phone or through the Internet, and similarly the randomisation and treatment allocation. Study drugs can be mailed overnight to the treating physician. The follow-up is limited to deaths, and any serious adverse event is, again, reported over the phone/Internet.

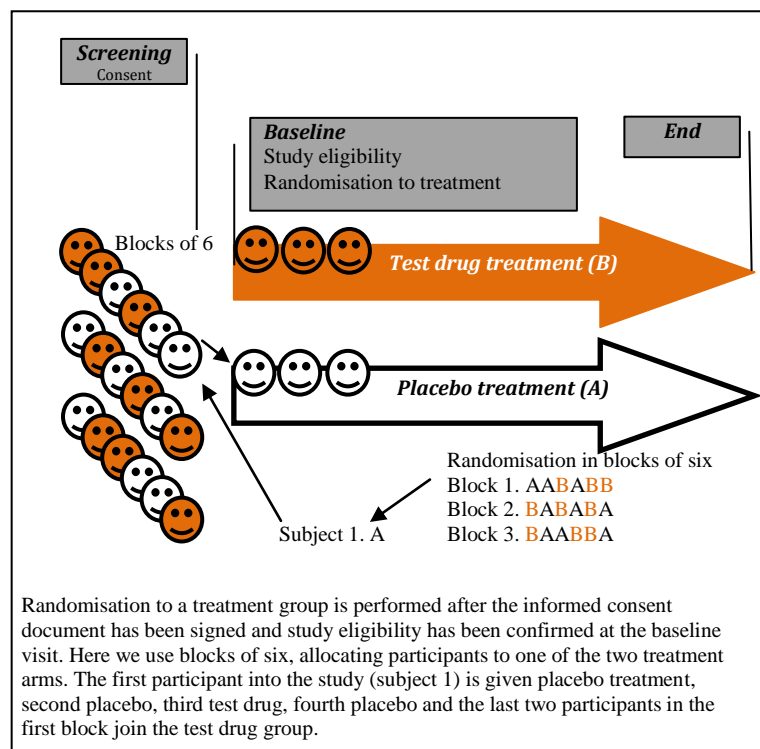
2.5 Randomisation

There are many ways that results of a clinical trial can be biased in favour of one or other test treatment regimes. The most important design techniques for avoiding bias are *randomisation and blinding*, which usually come hand-in-hand during preparation of the trial. Most trials follow a double-blind approach – blind to the investigator and participants – in which treatments are pre-packed, for instance, by a pharmacist, following the randomisation schedule. The test article supplied to the study site is labeled only with a participant number and treatment period and looks identical for all treatment groups. Study site staff are, thus, in this way, unaware of the specific treatment allocated to any particular participant.

The randomisation list is prepared during the trial planning stage and is given to the person responsible for preparing the test article. The test article is sent – usually by courier – to study sites and stored at a hospital pharmacy, at a dedicated institutional research pharmacy or in a locker at the study site. When a new participant has been enrolled and has signed the informed consent document, he/she is given the next

sequence of participant number and the test article labeled with the participant's corresponding number. This test article dispensing procedure is usually repeated several times for each participant during the course of a trial.

Randomisation of trial participants reduces selection bias, which is a result of preferential enrolment of specific participants into one treatment group over another. For example, *healthier participants* are more likely to be assigned the new treatment. Participants less likely to respond may be enrolled only when the next treatment to be assigned is known to be the control. Randomisation is a method to assign participants to various groups or arms of a trial based on chance. This leads to groups that are generally comparable and it minimises bias. In most trials, participants are given an equal 50% chance of being given the active or control treatment (*see illustration*). Randomisation is commonly computer generated prior to initiation of the trial, for example, in blocks of six. When using blocks of six, there are three participants allocated to the active treatment group and three to the control group. This procedure ensures a well-balanced number of participants between the two groups.



Randomisation should be performed by a third party not involved in the conduct of the trial or monitoring source data and case report forms. The randomisation list is kept secret from all parties during the entire trial, with the exception of the person responsible for preparing the trial drugs and the DSMC (in case of adverse events). A copy of the treatment code should be available at all times in case there is a need to break the code for a participant, such as, by unblinding a sealed envelope or through an electronic telephone-based unblinding procedure.

Randomisation can be performed in various ways; for instance, by allocating an unequal number of participants to different treatment groups, ensuring that similar characteristics of importance are present in every treatment group. Stratified randomisation is a method used to ensure that the number of males/females is similar for the groups, or that the number of participants at a certain disease stage is similar for each trial group.

2.6 Blinding

The term blinding refers to keeping trial *participants, investigators or evaluators* uninformed of the assigned intervention. Blinding should be maintained throughout the conduct of a trial; therefore, treatments applied should remain indistinguishable. There can be difficulties in achieving a double-blind environment: treatments may vary, such

as surgery and drug therapy; two drugs may have different formulations; the daily pattern of administration of two treatments may differ; and there may be various treatment-induced effects. In such cases, blinding may be improved by blinding study site staff to certain test results.

Breaking the blind for a single participant should be considered only when knowledge of the treatment assignment is deemed essential by the participant’s physician for the participant’s care. Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence. Some clinical trial professionals may however know the actual treatment given to each participant such as the pharmacist preparing the treatments or the members of a DSMC.

There are different levels of blinding:

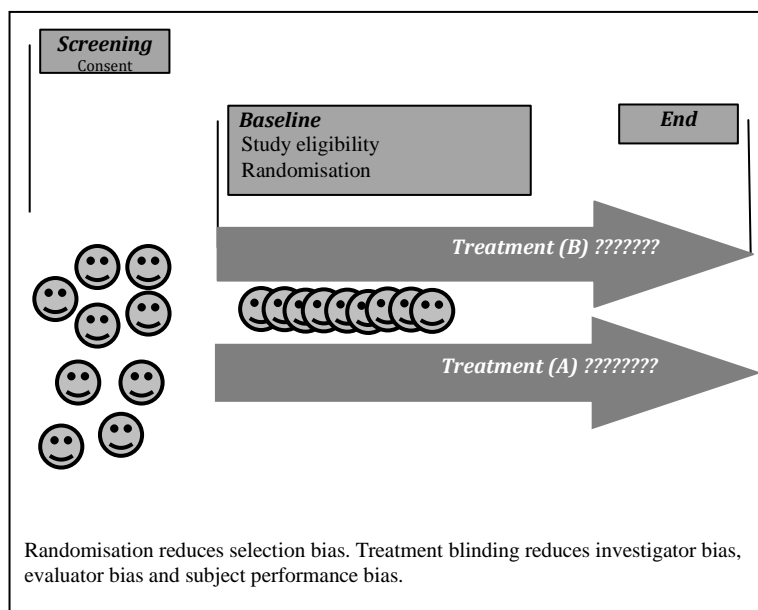
- The terminology *single blind* usually means one of the three categories of individuals remains unaware of intervention assignments throughout the trial.
- In a *double-blind* trial, participants, investigators and assessors usually all remain unaware of the intervention assignments throughout the trial. In medical research, however, an investigator frequently also makes assessments, so in this instance, the terminology accurately refers to two categories.
- *Triple blind* usually means a double-blind trial that also maintains a blind data analysis.

Blinding or masking is intended to limit occurrence of bias in the conduct and interpretation of a clinical trial. Knowledge of treatment may have an influence on:

- Recruitment of participants.
- Treatment group allocation of participants.
- Participant care.
- Attitudes of participants to the treatment.
- Assessment of endpoints.
- Handling of withdrawals.
- Exclusion of data from analysis.
- Statistical analysis.

Three of the more serious biases that may occur in a clinical trial – *investigator bias, evaluator bias and performance bias* – are reduced by *blinding* (see illustration):

- *Investigator bias* occurs when an investigator either consciously or subconsciously favours one group at the expense of others. For example, if the investigator knows which group received the intervention,



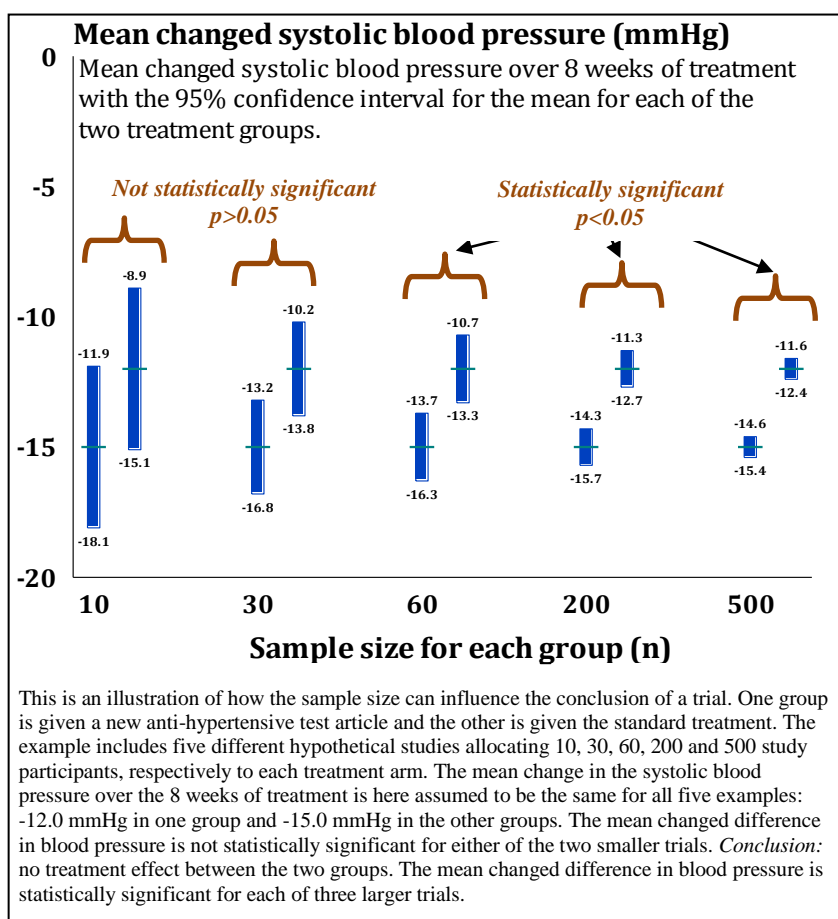
he/she may follow that group more closely and thereby treat that group differently from the control group, in a manner that could seriously affect the endpoint of the trial.

- *Evaluator bias* can be a type of investigator bias in which the person taking measurements of the endpoint variable intentionally or unintentionally shades the measurements to favour one intervention over another. Studies that have subjective or quality of life endpoints are particularly susceptible to this form of bias.
- *Performance bias* occurs when a participant knows that he or she is exposed to a certain therapy, be it inactive or active. For instance, self-reported disease symptoms may be seen as higher in the placebo group because the participant knows the treatment is inactive. The same group is also more inclined to quit the trial, thus producing a drop-out bias between the two groups.

2.7 Sample Size

In the early days – before the establishment of modern concepts of clinical trials research methodology – many clinical trials involved a relatively small number of participants. The problem with small trials is that despite indicating a true difference of clinical importance in the treatment effect between trial groups, the difference could not always be proven to be statistically significant. Many early trials with a small sample size were subject to false negative results, namely type II error, and no conclusive interpretation could be made from them. Today, we accept results only when the number of trial participants is large enough to provide a reliable answer to the questions addressed.

The necessary pre-determined sample size – especially for late phase trials – is usually determined based on the primary endpoint of the trial. Sample size calculation is usually performed by a biostatistician after the clinical investigator has developed a trial protocol. That protocol provides essential information, namely the clinical hypothesis, the primary endpoint and the statistical distribution representing, for instance, a continuous variable such as blood pressure or a percentage such as mortality. The equation selected to calculate the sample size is based on the values for each of the two types of statistical errors. The



probability of type I error – a false positive result – is commonly set at 5% and the *probability of type II error – a false negative result* – is conventionally set at 10% or 20%. The statistician also needs to know the minimum treatment difference of clinical importance that the trial should be able to prove to be statistically significantly different. If, for example, we want to show a mean change difference of at least 5 mmHg blood pressure between two treatment groups, the estimated sample size should be adjusted – increased – for any potential participant drop out, e.g., 5% or 10%.

Sample size calculation is essential in the planning stage of a trial since it forms the basis for the trial cost estimation and the number of sites needed to complete the trial within a certain time frame. We do not want an insufficient number of trial participants to reach a conclusive interpretation of the results; yet, neither do we want to spend unnecessary resources or put an unnecessarily large number of participants at risk of harm. The method for calculating sample size should be given in the protocol, together with all assumptions that have been made, so anyone who wishes can re-compute and confirm the sample size.

A hypothetical example can be found (*see illustration* on opposite page). With a sample size of 10 or 30 for each of the two groups, the mean changed difference in systolic blood pressure is not statistically different between the two groups. We thus conclude that we could not confirm any treatment difference when one trial included 20 (10+10) participants and the other 60 participants. However, the other three hypothetical trials with larger sample sizes all support the interpretation that the treatment difference is statistically different between the two groups. The total sample size is very different, ranging from 120 to 1,000.

A sample size calculation will be able to identify the optimum or close to optimum sample size for the scenario “*that an additional reduction in the systolic blood pressure with at least 3 mmHg is regarded as clinically meaningful by having an impact on the risk of getting adverse events caused by high blood pressure.*” The estimated sample size required to reach a statistically significant treatment difference would then be around 60 for each group.

2.8 Trial Phases

Drug Development at Large

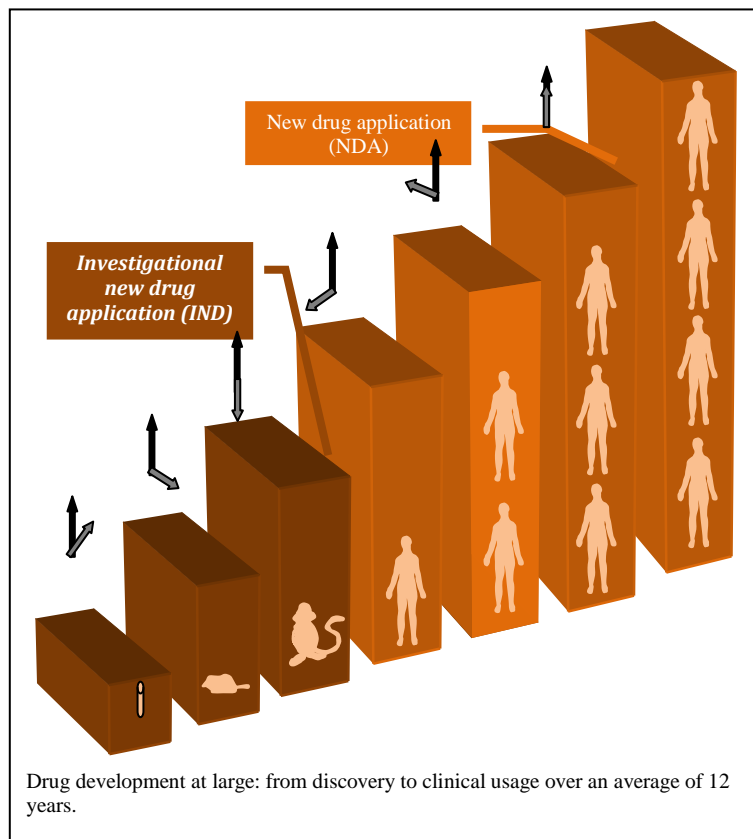
There is a rather fixed pattern in the stages of drug development process which a test treatment must pass before it can reach the market. Before a new drug application can be filed with drug regulatory authorities, it needs to go from pre-clinical stage to the clinical stage with three phases of clinical trials. The fourth and final trial phase represents post-marketing research.

A clinical trial is one of the final stages of a long and careful research process. The search for new treatments begins in the laboratory, where scientists first develop and test new ideas. The next step is to try a test article – molecules, vaccines or medical devices – in animals to see how it affects, for example, cancer in a living being and whether it has harmful effects. During pre-clinical drug development, a sponsor evaluates the test article’s toxic and pharmacologic effects through *in vitro* (Latin meaning *within the glass*), such as test tube testing, and *in vivo* (Latin meaning *within the living*) such as animal testing. It includes investigations on drug absorption and metabolism, toxicity of the drug's metabolites, and the speed at which the drug and its metabolites are excreted from the body.

At the pre-clinical stage, the regulatory authority will generally ask the sponsor to:

- Develop a pharmacological profile of the drug.
- Determine the acute toxicity of the drug in at least two species of animals.
- Conduct short-term toxicity studies ranging from 2 weeks to 3 months, depending on the proposed duration of use of the substance in the proposed clinical trials.

After completing pre-clinical testing, the company files an investigational new drug application (IND) with the drug regulatory authority in the country where the product will be marketed (*see illustration*). The IND provides the results of pre-clinical experiments, the chemical structure of the compound, how it is believed to act in the body, any toxic effects discovered during the animal studies and how the compound is manufactured. The IND should also describe how and where the compound will be tested in humans. Approval is needed from an independent EC to undertake human studies.



In a clinical trial, results from a limited sample of participants are used to infer how treatment will work in a general population of participants requiring treatment in the future. Most clinical trials are carried out in steps called phases. Each trial phase is designed to discover different information. Participants may be eligible for studies in different phases, depending on their general condition, the type and stage of their disease, and what therapy, if any, they have already received. The participants are seen regularly to determine the effect of the treatment, and treatment is always stopped if side-effects become too severe. After completion of the clinical testing, the company reports all the findings from all pre-clinical and clinical trials on the specific test article. If the results clearly demonstrate safety and effectiveness, the company files a new drug application (NDA) with the drug regulatory authority. The application includes all the results obtained. It takes a year or more to learn the endpoint of the review of an NDA submission.

The Basics of Trial Phases

The trial phase classification proposed by ICH – in the ICH E8 Guide – is based on the objective of the trial and not just a sequential number ranging from I-IV: human pharmacology, therapeutic exploratory, therapeutic confirmatory and therapeutic use.

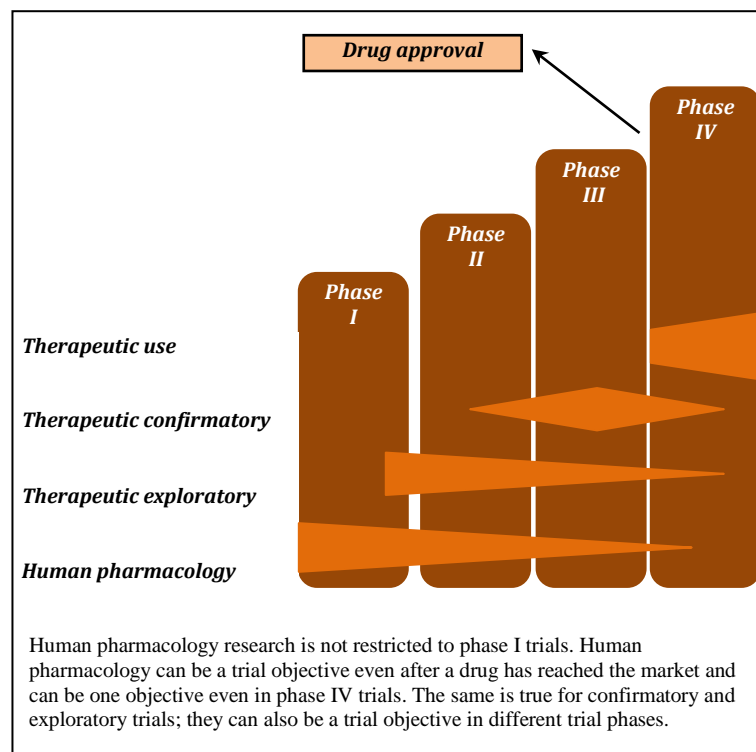
On the other hand, drug development traditionally consists of four different phases (phases I-IV), (*see illustration*). But it is important to understand that those four phases do not necessarily have to follow a sequence and they are not mandatory for inclusion in a medicinal product development plan. In addition, sometimes the phase of development provides an inadequate basis for the classification of clinical trials, because one trial may combine several phases with different fundamental objectives. Despite this, the phase I-IV classification is still the only one generally recognised and adopted on a global basis.

Because of their multi-objective characteristics, trials are often labeled not just as phase I, for instance, but alternatively early phase I (IA) or late phase I (IB), or perhaps phase I/II or phase II/III, since they aim to study several different fundamental aspects.

Human pharmacology research is not restricted to phase I trials. It can be a trial objective even after the drug has reached the market or an objective even in phase IV trials (*see illustration*). The same is true for confirmatory and exploratory trials; they can also be a trial objective in different trial phases.

The number of phase I-IV trials per test article varies vastly from compound to compound and especially between therapeutic areas. An average of 25 and 35 trials are conducted for a single test article, with more early than late phase trials. The variation between drugs and therapeutic areas is large so it is not easy to picture all possible scenarios, but a realistic average estimate is conducting 20 phase I trials, four phase II trials, three phase III trials and two phase IV trials – making a total of 29 individual trials for one test article. The average number of participants included in all trials for one and the same test article is 2,000, with around 10% healthy volunteers and the rest mostly patients with the disease under trial; those figures are based on the GlaxoSmithKline publicly available clinical trial database.

It is estimated that the industry needs to identify around 50,000 sites for some 2,500 trials annually. The majority of these trials are phase I. They can be associated with higher risk of harm than late phase trials and are therefore conducted in dedicated phase I units in established clinical trial regions. It should be noted that the majority of phase I trials are simple and involve a low risk of harm. Phase III trials are confirmatory and have the largest sample size and consequently the largest number of investigators/sites. They are the predominant type of trials in both established and emerging clinical trial regions, frequently conducted in outpatient clinics or wards. The ECs of emerging regions will usually review trials of predominantly late phase characteristics – the confirmatory type of trial aiming at comparing a test article with standard treatment. These trials also frequently have other objectives including human pharmacology and exploratory research in new age groups or diseases. They may also



address therapeutic usage based on safety endpoints, quality of life improvement and health economic comparisons with standard available treatments.

Phase 0 Trials

In recent years, a new trial phase term has emerged – the so-called phase 0 (*zero*) or micro-dosing trials (*see illustration*). They are not yet frequently utilised, but may become an important instrument for studying some essential elements of human pharmacology towards the latter part of the pre-clinical drug development phase. Such studies thus precede the traditional human pharmacology dose escalation, safety and tolerance phase I trials that ordinarily initiate a clinical drug development programme. The concept of a phase 0 trial is an interim step between *pre-clinical* research and

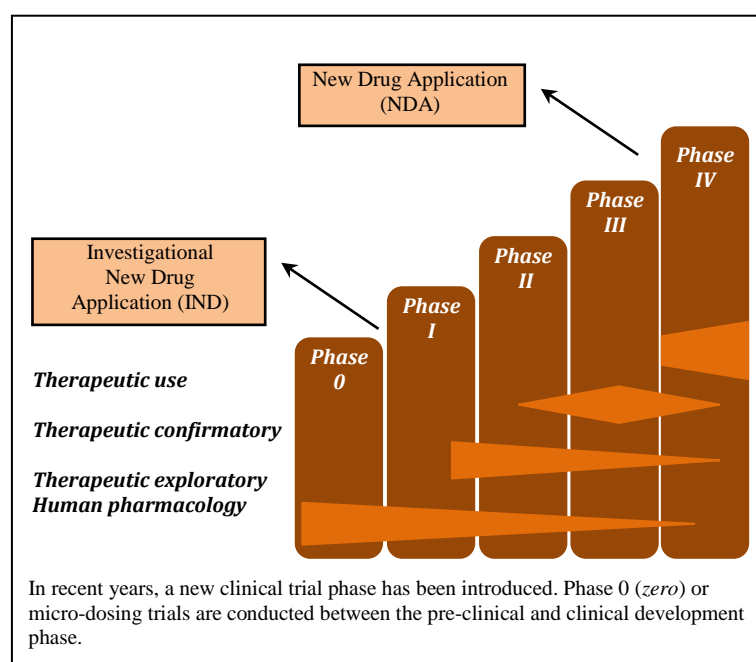
Press report, 2006: “Good news for researchers since FDA has approved testing of small quantities of experimental drugs in human beings. Approval of small quantity drug clinical trials will be very helpful for researchers to understand the path of the drug in the body and its efficacy. If the test article is proved effective in small quantities, researchers can continue with a phase I clinical trial.”

phase I studies, where a small number of human volunteers take small doses of experimental test article so there is little risk of toxicity. A phase 0 trial has no therapeutic intent; the objective is human pharmacology, rather than identifying any toxic effects. Because participants receive sub-therapeutic doses, this means their risk of harm is much less than in conventional phase I trials, but they still need close monitoring.

The scientific rationale for phase 0 trials is to find out whether a new drug is capable of modulating its intended target in humans, identifying its distribution in the body, or describing the metabolism of a drug. This knowledge is often critical in drug development and may avoid larger phase I and II trials for drugs shown to have unfavourable pharmacologic properties. However, the results of phase 0 trials do not always predict the human pharmacology for the intended dosage. This is probably the main reason that micro-dosing has yet to become very popular, since it may incorrectly terminate the development of a test article.

Utilisation of micro-dosing is claimed to reduce overall drug development costs because the microgram amounts of compounds required do not need to be scaled up to an expensive and time-consuming manufacturing level. Other arguments in favour of its usage are that fewer animal studies are needed to support micro-dosing studies, compared to phase I trials, so there are ethical as well as financial advantages.

Given the design and purpose of phase 0 trials, there can be



little expectation of either direct or indirect benefits from them, as is the case with phase I trials. Phase 0 trials should be reviewed by experts in clinical pharmacology and toxicology. Also, they should be conducted only at dedicated and experienced research units, such as high-quality inpatient phase I units.

The ICH recently (June 2009) released a guideline – *M3(R2)* – that has also been accepted by the European Union. It includes some guidance on micro-dosing trials, spelling out that the aim of micro-dosing, or rather “*exploratory studies,*” is to collect human data early in development, as well as information about the characteristics of the candidate compound. These studies do not seek to investigate therapeutic effects or safety, and the dosage should have limited human exposure, namely less than 100 µg or less than 1/100th of the pharmacological active dose.

Human Pharmacology/Phase I Clinical Trials

A human pharmacology trial is typically a phase I trial, representing the first stage of testing in human participants. Phase II-IV clinical trials can also have components of human pharmacology, but these are not addressed in this section. As elaborated elsewhere in this Guide, certain phase I trials are generally associated with a higher risk of harm than any other trials, especially the so-called *first-into-man* trials and *dose escalating* trials. These studies are usually conducted on small populations of healthy humans to specifically determine a *drug's toxicity, absorption, distribution, metabolism, excretion, duration of action, drug-to-drug interaction and drug-to-food interaction.*

Although the treatment will have been thoroughly tested in laboratory and animal studies, side-effects in participants cannot be completely known ahead of time. For this reason, phase I studies may involve significant risks. These trials are often conducted in a dedicated inpatient clinic, where the participant can be observed by full-time staff, usually until several half-lives of the drug have passed (*see illustration*).

About 20% of all phase I trials are conducted in patients rather than in healthy volunteers. The reason for this is that some drugs are too toxic – e.g., anticancer drugs – to be given to healthy participants. Such phase I trials may provide some early information about efficacy based on surrogate endpoints.

An example: A drug under development by a German company was tested in 2006 in a commercial phase I unit in London. The *pre-clinical* data – including high dosing studies in primates – did not indicate any safety concerns, but the test drug was targeting the immune system, which should have raised concerns. But in this *first-into-human* trial, six healthy volunteers were simultaneously dosed with the test drug and within minutes they all experienced systemic inflammatory

Example of sequential dosing in high risk Phase I trial

Day 1	Day 2	Day 3	Etc
One active	Review of data	Review of data	
One placebo	Two active	Three active	
In phase I unit*	One placebo	One placebo	
	In phase I unit*	In phase I unit*	

Sequential dosing

*Phase I trials should be undertaken in dedicated centres with appropriate facilities for emergency treatment and intensive care. The first study participant should be dosed in a hospital ward near the intensive care unit with a trial physician present.

response. All suffered from multiple organ failure and required machine support. Fortunately, everyone recovered or recovered with sequelae after weeks of hospital care. The review of the incident revealed that the sponsor and the commercial phase I unit provider had followed all regulations at the time with respect to *pre-clinical* testing and phase I trial operation. The side-effects could not have been predicted, and no misconduct was identified that could have caused the event. The event triggered much press coverage and eventually also led to a new regulation in Europe for the conduct of phase I trials. The new regulation stresses sequential dosing – namely, start the dosing in one participant alone. It also insists on using a dedicated hospital ward or intensive care unit (ICU) for very high risk of harm phase I trials.

The London incident was very rare. Most established phase I test units do not experience serious adverse events (SAEs) requiring ICU medical care of trial participants. However, since unforeseen risks are always present during the early clinical testing phase, the EC should be sure that all possible safety aspects are in place in the event of an unexpected SAE reaction.

Risk Assessment/Management of Human Pharmacology/Phase I Trials

The risks of harming participants must be fully assessed before each phase I trial, especially during the transition from the pre-clinical stage to the first-into-human trial. The trial sponsor must have the pre-clinical data reviewed by experts with technical, scientific and clinical background. In assessing the risk of harm, the sponsor's designated expert(s) must take into account all aspects of the test article, such as its class, novelty, species specificity, mode of action, potency, dose- and concentration-response relationship for efficacy and toxicity, and route of administration. The following types of phase I trials are generally regarded as a *higher-risk*:

1. *First-into-human* trials
2. Trials in a new population, new dosage or new formulation of a test article regarded as *higher-risk biological product* are elaborated below:
 - Any agent that might cause severe disturbance of vital body systems.
 - Agents with agonistic or stimulatory action.
 - Novel agents or mechanisms of action for which there is no prior experience.
 - Species specificity, making pre-clinical risk assessment difficult or impossible.
 - High potency, e.g., compared with a natural ligand.
 - Multifunctional agents, e.g., bivalent antibodies.
 - Cell-associated targets.
 - Targets that bypass normal control mechanisms.
 - Immune system targets.
 - Targets in systems with potential for large biological amplification *in vivo*.

Clinical Risk Management: The Association of the British Pharmaceutical Industry (ABPI) published a guideline for phase I clinical trials in 2007, which includes detailed guidance on risk management of various trial aspects. The aspects include, but are not limited to:

- Starting dose, increases in the dose, administration of doses.
- Safety records of phase I trials.
- Requirements of a protocol.
- Trial procedures.
- Administrations such as contracts between the sponsor and investigator
- Location, construction, space, facilities and staff.

- Trial participant-related issues: recruitment, obtaining informed consent, screening.

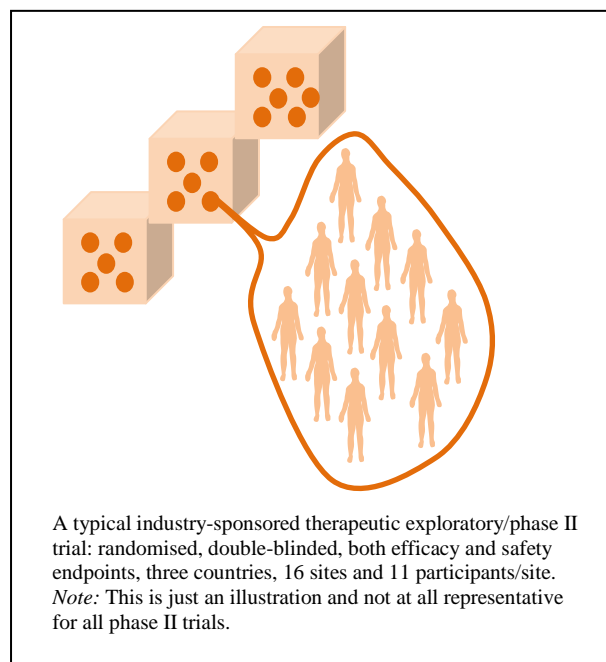
Apart from the ABPI Guideline, some additional risk management issues should be considered, such as:

- An independent data safety and monitoring committee should be established by the sponsor to assess at intervals the safety data and to recommend to the sponsor whether to continue, modify or stop a trial.
- The first participant to be tested in a hospital ward close to the ICU.
- Dosing usually to be made in the morning, e.g., 8:00 am.
- A doctor should stand by in the hospital ward or phase I unit during the first 24 hours from the start of each trial.
- Night-shift back-up of the hospital resuscitation team should be available in the hospital ward or phase I unit. The resuscitation team should anticipate stabilising the participant before transportation to ICU.

After the phase I incident in London, the European Medicines Agency developed a guideline for phase I trials (EMA/CHMP/SWP/294648/2007). This guide addresses the essence of phase I. *“It identifies factors influencing risk for new investigational medicinal products and considers quality aspects, non-clinical and clinical testing strategies and designs for first-in-human clinical trials. Strategies for mitigating and managing risk are given, including the calculation of the initial dose to be used in humans, the subsequent dose escalation, and the conduct of the clinical trial.”* *“Key aspects of the trial should be designed to mitigate those risk factors, including: study population; trial sites; first dose; route and rate of administration; number of participants per dose increment (cohort); sequence and interval between dosing of participants within the same cohort; dose escalation increments; transition to next dose cohort; stopping rules; allocation of responsibilities for decisions with respect to subject dosing and dose escalation.”*

Therapeutic Exploratory/Phase II Clinical Trials

After the successful completion of phase I, an experimental drug is next tested for safety and efficacy in a larger population of individuals afflicted with the disease or condition for which the drug was developed. If a significant portion of participants in the phase II trial respond to the treatment, the treatment is judged active. The aim is to assess the drug's effectiveness in about 3 to 6 phase II trials involving around 200 to 600 participants. The studies are fairly short, usually lasting several weeks or months. In addition to effectiveness, they consider the drug's safety and require close monitoring of each participant. Often intermediate endpoints – surrogate endpoints – are used, rather than clinical endpoints, since the objective is to show some sign of efficacy – *proof-of-concept* – rather than demonstrate efficacy.



Phase II trials primarily aim to *explore* therapeutic efficacy in target patients. They also aim to estimate the *proper dosage* for subsequent studies and provide the basis for confirmatory trial design, endpoints and related methodologies. Initial phase II trials use various trial designs, while subsequent trials are usually randomised using concurrent controls to evaluate the efficacy of the test drug and its safety for a particular therapeutic indication. Phase II trials are typically conducted in a small, well-defined group of participants, leading to a relatively homogeneous population.

An important objective of exploratory trials is to *define the dose(s)* and formulation for subsequent phase II/III trials. Dose escalation trial designs can be used for this purpose, and later studies may confirm the dose response relationship for the specific indication. Phase II trials are also important for evaluating *potential trial endpoints*, therapeutic regimens, concomitant medications and target populations – e.g., age, gender, disease stage/degree.

Based on 3,295 industry-sponsored phase II clinical trials registered with the US clinical trials registry (October 2005 to July 2009), the mean sample size was 179.1, mean number of sites 16.2 and mean number of countries involved 2.7 (*see illustration* on previous page). Randomisation was adopted in 72.6% of all phase II trials, double blinding was used in 55.9% and both safety and efficacy were studied in 66.5%. A placebo control group was used in 31.8% and an active control in 13.8%. About one-third of the trials did not supply information about trial design, but were included when computing the above percentages.

Therapeutic Confirmatory/Phase III Clinical Trials

After a drug is shown to be reasonably effective, it must be compared with current standard treatments for the relevant condition in a large trial involving a substantial number of participants. Phase III trials – major randomised controlled trials – usually involve 500 to 3,000 participants. Some, such as prevention trials – e.g., vaccine, osteoporosis and cardiovascular trials – may require as many as 20,000 participants.

There is usually more than one phase III trial owing to different indications. The duration can vary from a week to many years. For instance, an influenza treatment phase III trial may last for less than a week for an individual trial participant, while a growth promotion trial in children can last for 10 years, i.e., until final adult height has been reached.

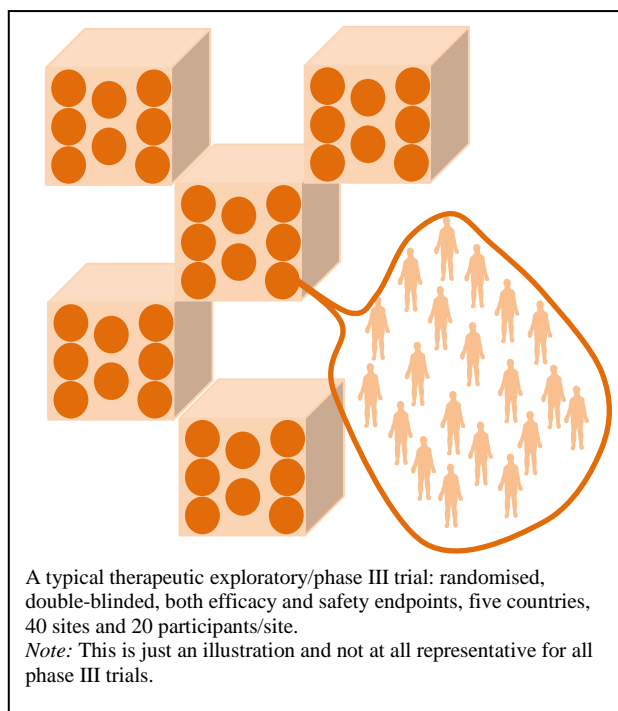
Press report, 2009: “Array BioPharma Inc. today announced its preliminary analysis of results from a study examining a MEK inhibitor in a 12-week phase II clinical trial with 201 participants. The participants had active rheumatoid arthritis that was not completely responsive to methotrexate. This study included a placebo group and three different dose groups of the test drug, all on a stable background of methotrexate. None of the treatment groups demonstrated a statistically significant response rate compared to the placebo group at 12 weeks.”

Press report, 2009: “Auxilium Pharmaceuticals, Inc. today announced that *The New England Journal of Medicine (NEJM)* has published the Company's pivotal CORD I phase III clinical trial of a novel, first-in-class, biologic for the nonsurgical treatment of Dupuytren's contracture. The CORD I study is the largest prospective clinical trial ever conducted in the field of Dupuytren's contracture. The test treatment significantly reduced the angle of contracture for participants with Dupuytren's contracture in both their metacarpophalangeal and proximal interphalangeal joints, with clinically meaningful responses in both less severe and more severe contractures.”

The primary objective of a confirmatory phase III trial is to *demonstrate or confirm the therapeutic benefit* from using important clinical endpoint(s), rather than surrogate endpoint(s). Those trials are designed to confirm preliminary evidence collected during the exploratory phase of clinical testing, i.e., that the drug is safe and effective for use in the specific indication and patient population. These studies provide the basis for marketing approval.

Other aims could be to study the test article's *extended patient populations*, in *different disease stages*, or as a *combination therapy* with another drug.

Based on 3,357 industry-sponsored phase III clinical trials registered with the US clinical trials registry (October 2005 to July 2009), the mean sample size was 783.2, the mean number of sites 40 and the mean number of countries involved 4.7 (*see illustration*). Randomisation was adopted in 77.6%, double blinding was used in 57.8% and both safety and efficacy were studied in 67.6%. A placebo control group was used in 28.3% of the trials and an active control in 23.8%. About one-third of the trials did not supply information about the trial design, but they were included when computing the above statistics.



Therapeutic Use/Phase IV Clinical Trials

Therapeutic use/phase IV trials begin after a drug has been approved for distribution or marketing. In phase IV trials or post-marketing surveillance trials, safety surveillance – *pharmacovigilance* – is conducted and ongoing technical support of that drug is provided. Other phase IV trials aim to study the effectiveness of treatment after approval. Such trials are becoming more and more common and represent an area of *outcome research*. In the past, phase IV trials were frequently *marketing trials* with the aim of introducing a new drug to a new market. Such trials had little scientific value owing to the lack of good study design as well as quality assurance, and would not today be seen as ethically sound trials.

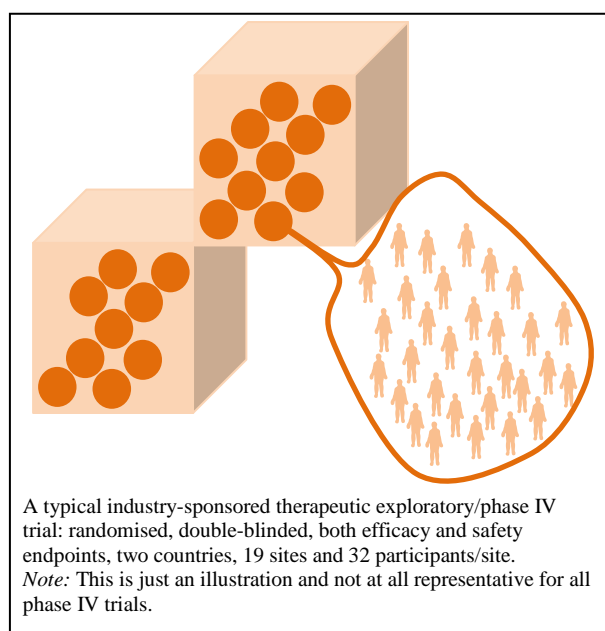
Medications such as cerivastatin under the brand names Baycol and Lipobay, and the medications troglitazone and rofecoxib, known respectively as Rezulin and Vioxx, were approved for sale, but later recalled due to the severe health risks they posed on patients. As such, these phase IV trials are usually required by regulatory authorities or they may be carried out voluntarily by the sponsor.

Therapeutic use trials are not necessary for approval, but are regarded as important for optimising usage of the drug. Examples are additional drug-drug interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g., mortality/morbidity studies.

Post-marketing trials can also be critical for exploring *new uses* for a therapy, as well as acquiring a full understanding of the capability and uses of a drug. After initial approval, drug development may continue with studies of *new or modified indications, new dosage regimens, and new routes of administration or additional patient populations*. If a new dose, formulation or combination is studied, additional human pharmacology studies may be indicated, necessitating a new development plan. These new therapeutic use studies of an approved drug are under the drug regulatory authority's area of responsibility, likewise pre-marketing phase II or III trials.

Based on 1,221 industry-sponsored phase IV clinical trials registered with the US clinical trials registry (October 2005 to July 2009), the mean sample size was 605.7, mean number of sites 18.7 and mean number of countries involved 2.3 (*see illustration*). Randomisation was adopted in 64.8% of them, double blinding was used in 35.6% and both safety and efficacy were studied in 54.5%. A placebo control group was used in 14.9% of the trials and an active control in 24.2%. About one-third of the trials did not have information about the trial design, but they were included when computing the above statistics. Please note that not all phase IV trials were registered, leaving some concerns about the validity of the data presented in this paragraph.

Press report, 2006: *"The role of independent clinical research in phase IV testing should be encouraged and supported by the FDA. Too many pharmacologic agents have entered into clinical practice for which considerable and potentially life-threatening outcomes were recognized only after a large number of participants had been treated. The recent example of cyclooxygenase-2 inhibitors is a high-profile case in point. Recognition of drug-induced toxic effects in certain participant populations or with increased dosing regimens must be reflected in clinical practice as early as possible in order to optimize participant safety."*

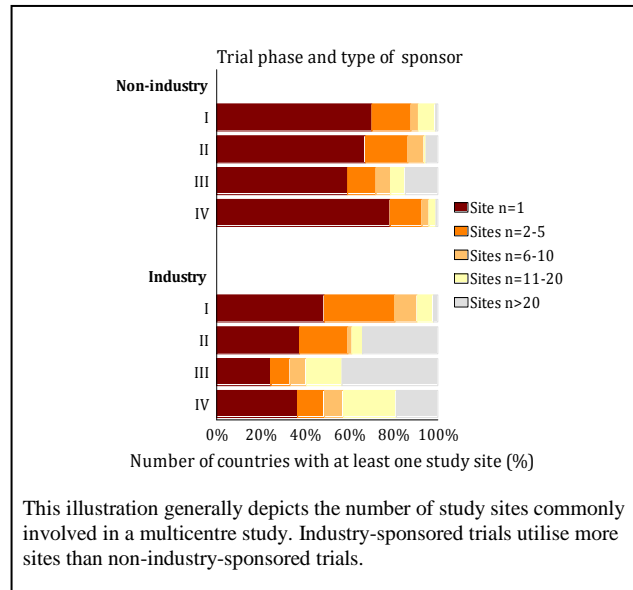


2.9 Multicentre Trials

Multicentre trials are carried out for two reasons. First, they help *accrue sufficient number of participants* to satisfy the trial objective within a reasonable time frame. Second, they produce more *general findings*, with participants recruited from a wider population and a broader range of clinical settings, i.e., representing a situation that is more typical of future use. Allowing a larger number of investigators early experiences in using a test article may be of interest. Access to potentially new, effective and safe

treatments is a leading incentive for an investigator to participate in an industry-sponsored clinical trial, along with increasing scientific knowledge.

The *illustration* on the right generally depicts the number of study sites commonly involved in a multicentre protocol study. Industry-sponsored trials utilise more sites than non-industry-sponsored trials; 59.4% of all industry-sponsored phase III trials have at least eleven sites or more, compared with 42.6%, 33.4% and 9.3% for phase IV, II and I trials, respectively. The corresponding figures for non-industry-sponsored trials are 26.7% for phase III trials and 4.8%, 6.2% and 8.8% for phase IV, II and I trials, respectively (based on US trials registry data between October 2005 and July 2009).

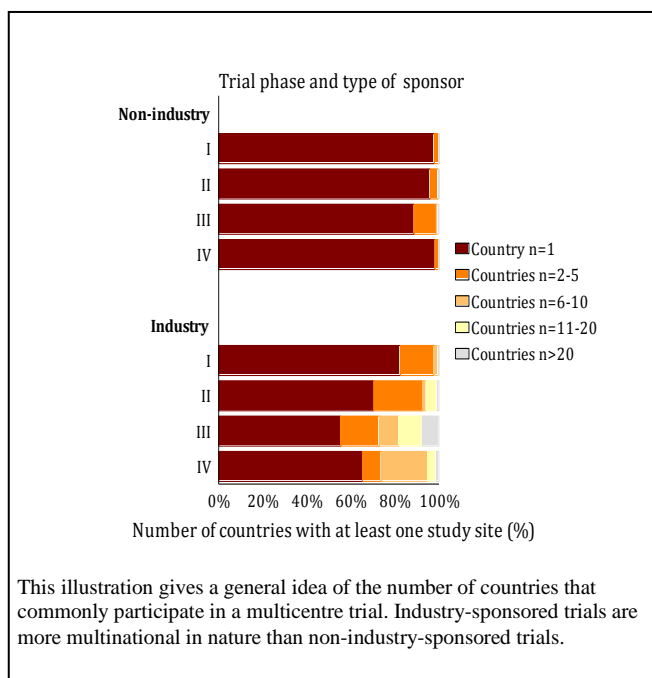


If a multicentre trial is to be meaningful, then it must be conducted in the same way at all study sites. *Procedures must be standardised, as well as evaluation criteria.*

Investigator selection, investigator meetings, site staff training and monitoring are the tools to ensure protocol compliance and trial conduct standardisation. The trial protocol should be designed with this background in mind, and the EC should understand how this important quality assurance issue is addressed and that it can be difficult to alter the trial design or protocol parameters. However, the EC can still reject the protocol.

With the rapid globalisation of clinical trials, other factors must also be taken into consideration in designing a trial protocol. The level of *standard medical care diversity* and *medical practice diversity* is becoming increasingly important.

The *illustration* on the right gives a general idea of the number of countries that commonly participate in a multicentre trial. Industry-sponsored trials are more multinational in nature than non-industry-sponsored trials; 44.6% of all industry-sponsored phase III trials are multinational, being conducted in at least two countries, compared with 34.7%, 29.6% and 17.5% for industry-sponsored phase IV, II and I trials, respectively. The corresponding figures for non-industry-sponsored trials are 11.3% for phase III trials and 1.9%, 4.2% and 2.1% for phase IV, II and I trials, respectively (based on the US trials registry data between October 2005 and July 2009).

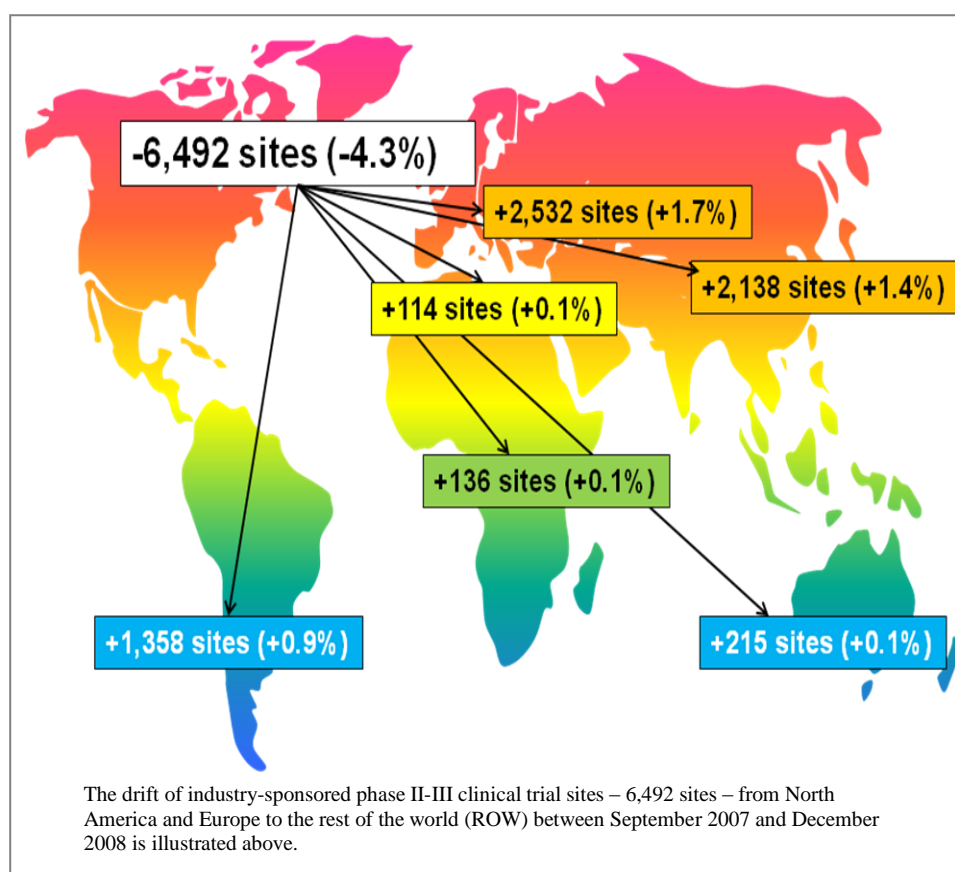


Uninterrupted Globalisation of Industry-Sponsored Clinical Trials

The globalisation process of industry-sponsored clinical trials is growing. More and more study sites are located outside North America and Europe, especially phase III trials. From the latest analysis, there are now more phase II-III trial sites in the rest of the world (ROW) than Europe; 27.0% versus 24.6%, respectively. Between 2008 and 2009, North America and Europe together lost 4.3% of study sites to the ROW, which in absolute numbers corresponds to some 6,500 sites.

The major emerging regions are still Eastern Europe, Asia and Latin America. Several of the emerging countries have, in fact, evolved into established countries with more clinical trial sites than many established countries (*see illustration*). Clearly, it can be concluded that some of the previously emerging countries for clinical trials have evolved into established countries.

It is estimated that the industry needs to identify about 50,000 new study sites/investigators annually for its clinical trials. About 25% of the sites are located to emerging regions thus representing 12,500 sites per year. *On average, 50 industry-sponsored clinical trials are reviewed every working day by an EC located in an emerging region.*



Chapter 3. Science, Ethics and Quality Assurance of Clinical Trials

Chapter 3 highlights the essence of the EC review process of clinical trial protocols. As previously mentioned, some elements have already been included in Chapter 2 and are not detailed in Chapter 3. However, some repetition is necessary for clear understanding.

The EC review process of a trial protocol includes three different considerations: science, ethics and data quality. Any clinical trial with poor science, poor ethics or poor data quality puts participants at unnecessary risk of harm and is likely to be rejected by regulatory authorities or by the international biomedical scientific community. The EC should thus review all three aspects, ensuring that a trial is not conducted without adding any new information to our body of knowledge and putting participants at risk without any reason.

The last few pages of Chapter 3 – describing the US Association for Accreditation of Human Research Protection Programs, Inc. (AAHRPP) accreditation standards – was independently written by the author (JK) without initially consulting the co-editor (MS) of this Guide, since MS is the present President and CEO of AAHRPP. JK found it crucial to demonstrate that an EC is commonly not a stand-alone entity, rather an entity under an organisation/institution. For that reason, several aspects of human research protection are the responsibility of the institution, not primarily the EC. By seeing the AAHRPP standards for the Organization, EC and Researcher and Research Staff, readers gain a comprehensive and clear view of the modern requirements of a human research protection programme (HRPP). It must be emphasised that there are several other EC accreditation programmes in countries other than the US, so the objective here is not at all to promote one accreditation programme over another.

3.1 Research in Humans

Research in humans represents our aspiration to know and to advance our society. Research has improved our lives and will continue to do so, and we must acknowledge that good research can benefit society. Research seeks to understand the unrevealed, which means that it may come with risks. There have been examples of trial participants needlessly harmed by research. But on the other hand, there have been tens of thousands of ethically sound and successful research studies. Human research ethics is about the balance between recognising potential benefits and the need to protect participants from research-related risks – in other words, the *risk-benefit balance*. The balance is about ensuring that participants are not exposed to unnecessary risk of harm, while at the same time avoiding unnecessary barriers or postponement of research. Those personnel involved in reviewing human research projects must keep in mind that research design should be structured so that risks are minimised.

Any ethics review of human research projects and conduct of research must be evaluated, taking into account both the institutional requirements and the applicable laws. Laws establish rules regulating the conduct of human research by, for instance, assuming an acceptable risk-benefit balance, addressing privacy, confidentiality and intellectual property. Legal rules and ethical principles are not always consistent, and they can differ greatly over jurisdictions. No single human research ethics guide can provide universal answers to all ethical issues; nor can a single guide reflect the large diversity of legal requirements. The aim of this Guide is to point out the cornerstones of the design, conduct and oversight of ethical human research, with a focus on clinical trials. This should not overrule local ethical concepts, concerns or legislations.

However, clinical trials should act in accordance with the general principles of the Declaration of Helsinki as being a statement of ethical principles (*see text box*) for medical research involving human participants, including research using identifiable human material and existing data.

Declaration of Helsinki Principles

In short: "In medical practice and in medical research, most interventions involve risks and burdens. Medical progress is based on research that ultimately must include studies involving human subjects. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments)."

Principles for all medical research, in short:

- *Protection of life, health, dignity, integrity, right to self-determination, privacy, and confidentiality.*
- *Acceptable scientific principles.*
- *Described in a protocol.*
- *Protocol must be reviewed by an EC.*
- *Consideration of local laws and regulations.*
- *Assessment of predictable risks, burdens and importance.*
- *Appropriate training and qualifications of investigator.*
- *Participation must be voluntary.*
- *Participants must give consent.*

Essential Clinical Trial EC Review Topics

Several important ethical issues have to be correctly addressed for EC approval, including the risk-benefit balance, vulnerable participants, sensitive privacy concerns, contents of informed consent, advertising for recruitment of participants, the investigator's qualifications, conflicts of interest and tissue/blood sampling. Each EC has its own operational framework, while views on ethical matters vary among EC members and different ECs.

Both the Declaration of Helsinki and the ICH GCP Guideline clearly define aspects of the scientific requirements of a clinical trial. For instance, medical research involving participants must conform to generally accepted scientific principles, conducted in an adequate laboratory, and be based on thorough knowledge of the scientific literature and other relevant sources of information including, when appropriate, animal experimentation. Clinical trials should be described in a clear, detailed protocol. When an EC reviews a trial protocol, it should discuss the scientific soundness of the protocol. To enable an informed, detailed discussion, EC members must be able to understand the scientific and clinical rationale behind the protocol. This is why EC members should be provided with a detailed trial protocol. A protocol that is unsound from either a scientific and/or clinical viewpoint should not be conducted – and thus not be approved by the EC.

A clinical trial that will not advance knowledge about a certain medical test article should not be conducted, since the risk-benefit balance for participants will be unacceptably high. With any trial there comes a certain risk of harm – e.g., expected adverse events – ranging from accidents when traveling to the study site, to catching an infectious disease in a health care setting or encountering an adverse event during a routine practice that is an unnecessary, rather than standard, treatment-related medical procedure. But even if the results are negative – ultimately showing no beneficial effect of the test article – the trial still advances our knowledge.

All data collected during a clinical trial must be free of errors. It is intended for use as an important body of evidence when a new medicinal product is reviewed by the government drug regulatory authority. Before a product can be used in medical care, the regulatory authority reviews the results from all trials of the product. After approval is granted, the product will be given to a large patient population. For this reason, the regulatory authority must be sure that all supporting data included in the new drug application file are trustworthy and reliable, so the efficacy and safety profile of the product can be accurately established. This is why quality assurance is an important issue in clinical trials.

Human Research Protection Assurance

An appropriate governance structure for an EC is crucial to ensure that the EC operates with a well-defined mandate and authority, with responsibilities clearly defined. In fulfilling this responsibility, an institution is required to develop the necessary structure of an independent EC for ethical review of research involving humans. The highest appropriate body within an institution shall establish the EC, and the EC shall report directly to the highest level of the institution. The institution mandates the EC to review the ethical acceptability of human research on its behalf.

The operation and responsibilities of the EC must be defined in a detailed set of written standard operating procedures (SOPs) that comply with GCP, the general principles of the Declaration of Helsinki and applicable local guidelines and regulations. The contents of SOPs should cover topics such as the EC's goal, role, membership and meetings, participants of research, informed consent, tissue sampling, initial review, continuing review, amendments, adverse event reporting, progress reporting, trial monitoring, expedited and full review, educational activities and record keeping.

Clinical Trials of Today – Only One Standard

Over the past decade or so, we have seen a remarkable change in our view of how a clinical trial is conducted. Today, the benchmark for decision making in clinical practice is an amalgam of decades of governmental regulatory involvement and legal enforcement in the development of medicinal products and the emerging academic paradigm of evidence-based medicine. Modern concepts of clinical trial research methodology and evidence-based-medicine reflect the same perception; individually and combined, they both stand for one and the same standard. We no longer test a medical product or procedure on a few participants and see what happens.

Today both industry-sponsored and non-industry-sponsored clinical research must follow the same standards. Both have to defend their research on the same grounds for acceptance by regulatory authorities or international medical scientific journals. Research must be scientifically sound, follow basic ethical principles for the conduct of

human research, and prove data are of high quality. If a clinical trial does not meet these standards, the results will not be accepted, rendering the trial pointless.

Thus, ECs should not only review ethical aspects of a research protocol, such as the informed consent process, participant recruitment and advertisement, research staff suitability and the risk-benefit balance, but ECs must also understand the scientific rationale behind the protocol, the research design, and quality assurance measures. A clinical trial must not be initiated if there is a possibility that the trial results will not be accepted, or not completed according to pre-set plans due to such factors as insufficient participants or lack of financial or human resources.

The following pages address the three areas – science, ethics and quality assurance – that an EC should consider when reviewing a clinical trial protocol. Though not all aspects are covered, some of the most important are listed. Some aspects belong to more than one area, but they have only been listed once to avoid repetition. Some may hold different views on one or several highlighted issues. We all have our own personal views on human research ethics, but an EC should listen to all of them. If a consensus is not reached, voting should follow.

3.2 Science of Clinical Trials

Both the Declaration of Helsinki and the ICH GCP Guideline clearly define aspects of the scientific requirements of a clinical trial. For instance, medical research involving human participants must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature and other relevant sources of information, and be performed with an adequate laboratory and, when appropriate, animal experimentation. Clinical trials should be described in a clear, detailed protocol. The sponsor should utilise qualified individuals – e.g., biostatisticians, clinical pharmacologists and physicians, as appropriate – throughout all stages of the trial process, from designing the protocol and case report forms (CRFs) and planning the analysis to analysing and preparing interim and final clinical trial reports. The ICH GCP also provides detailed guidance on clinical trials research design issues and the kind of pre-clinical data that should be disclosed in a trial protocol.

When an EC reviews a trial protocol, it needs to discuss the scientific soundness of the protocol. To enable an informed, detailed discussion, EC members *must* be able to understand the scientific and clinical rationale behind the protocol. This is why EC members should be provided with a detailed trial protocol covering all issues listed in the ICH GCP Guideline and, if available, also a copy of the investigator's brochure covering the current knowledge of the test article to date.

A protocol that is unsound from either a scientific or clinical viewpoint should not be conducted – and thus not be approved by the EC. Examples follow:

- A protocol that lacks sufficient pre-clinical research information should not be accepted, since it might put participants at a higher risk of harm than necessary.
- A protocol that has no obvious clinical value should not be approved, since it will not advance knowledge, participants will be at risk of harm and the trial will consume financial and human resources for no reason.
- A protocol using sub-optimal trial design such as the incorrect endpoint measure or a sample size that is too small should not be approved, since the results will not be conclusive or useful, and will not be accepted for registration or publication by the international research community. The same is true if there are no controls, no randomisation or no blinded treatment allocation, when they could in fact be utilised.

- A multinational trial that is confirmatory in nature should not use a surrogate or primary endpoint or a control group that is not provided with current best treatment available, since such a trial is not designed to confirm that the test article is a better choice than the current best treatment.
- A protocol aiming to study the effects of a test article that is manufactured without evidence of good manufacturing practice (GMP) should not be approved, because only consistently produced test articles can be used to correctly predict treatment efficacy and safety.
- The utilisation of placebo control group(s) must be justified (*see pages 36-37*).

An EC constitutes members with different areas of expertise so that trial protocols are scientifically reviewed from different perspectives. Committee members should jointly identify and discuss the main scientific aspects of each clinical trial to be reviewed. The *next page* lists some of the main scientific essentials – but not all – that should be made clear before the EC makes a final decision of approval or rejection on a clinical trial application.

3.3 Issues of Ethics of Clinical Trials

A clinical trial that will not advance knowledge about a certain treatment should not be conducted, because the risks compared with the potential benefits for the participants will be infinitely, unacceptably high. An EC will always have difficulty predicting the final outcome of a well-designed clinical trial; that, of course, is the reason for conducting the research in the first place. But even if the results are negative – ultimately showing no beneficial effect of the test article – the trial still advances our knowledge. However, in some cases the EC can predict – e.g., for scientific reasons – that the results are unlikely to be useful. In such cases, the EC should consider the protocol unethical and unacceptable.

The EC should be focused on the science, ethics and quality assurance of a clinical trial protocol. For instance, clinical trials agreements and budgets are usually not a matter for the EC, but rather a responsibility of the investigator, the department involved and the institution. One common practice is that the agreement and budget must always be signed by an appointed institutional representative.

Risk-Benefit Balance

Risk-benefit ratio or *risk-benefit balance* are interchangeable terms in the concept of risk and benefit analysis of clinical trials. *Ratio* is Latin for *calculation*. From a mathematical viewpoint, ratio is a relationship between two quantities, normally expressed as the quotient of one divided by the other. Clearly, it is virtually impossible to set a realistic numerical value for the anticipated risk in participating in a clinical trial, as well as a numerical value on the benefit of a trial, either to participants or society. Still, the term *risk-benefit ratio* is commonly used, even though no calculation is made.

Scientific Evaluation of a Clinical Trial Protocol

Any protocol raising many minor concerns or a few major concerns should either be rejected or subject to revision and subsequently re-assessed. The following lists some – but not all – essential information needed for a proper evaluation of the scientific soundness of a clinical trial protocol:

Matters of concern

Third party review:

Potential questions

Have any regulatory or scientific bodies reviewed and formally accepted the current version of the protocol?
Have any other ECs reviewed the protocol?

Protocol development:

Are the names of the persons involved in the protocol development, their qualifications and responsibilities provided?

Pre-clinical information:

What is the safety and efficacy profile of the test article?

Test article manufacturing:

Is the product evidently manufactured according to GMP?

Study objective:

What is the scientific rationale behind the study?

Clinical rationale:

What is (are) the expected benefit(s) of the test article in normal clinical care?

Study design – treatment:

If placebo comparison is used rather than the best standard treatment, what is the justification?

Study design – outcome:

Is the study exploratory or confirmatory in nature?
Is the primary outcome of the trial a clinical outcome or a surrogate outcome?
Is the outcome the current and most valid internationally accepted outcome?
Does the trial use the best possible comparison groups for its purpose?

Study design – randomisation:

Does the trial use randomisation to treatment groups?
If randomised, how will this be performed?

Study design – blinding:

Are the investigator, participants and the trial outcome evaluator blinded?
If blinding is utilised, how is this ensured?

Study design – sample size:

Has a proper sample size calculation been made?
Who calculated the sample size?
What were the assumptions behind the sample size calculation?

Participant availability:

Are there enough participants available?
What is the anticipated duration of patient recruitment?
Are there other clinics or hospitals available to secure the anticipated sample size?

Resources:

Are enough financial and manpower resources available for completion of the trial?

Balance is the state of being in *equipoise* or *equilibrium*, meaning the condition of a system in which competing influences – such as risk and benefit – are balanced. For these reasons, we feel that *risk-benefit balance* is a much more appropriate term than *risk-benefit ratio* when evaluating risk in clinical trial proposals.

Determining risk-benefit balance is seen by many as the single most difficult ethical issue to be addressed by an EC. In general terms, it compares the risk of harm from participating in a trial to its related potential benefits. Generally, for research involving more than minimal risk of harm to participants, the investigator must ensure that the potential benefit clearly outweighs the risk of harm: “*In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.*” “*Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.*” (Declaration of Helsinki).

The benefit is not strictly related to the participants, but in fact it is more related to the benefit of society, i.e., accumulation of new knowledge and the advancement of science. Obviously, both risk of harm and potential benefits are highly dependent on the phase of a clinical trial, the type of therapeutic agent tested, the disease under trial, the current best treatment and the standard of care provided. The number of study visits, type and number of clinical investigations and number of participants can all also add weight to the equation. The risks of a clinical trial are usually determined by the risks of expected serious or non-serious adverse reactions, ranging from very mild to worst-case scenarios. Estimates of risk of harm are determined from both earlier clinical experiences of the test article and pre-clinical experiences. It is mandatory that all previous experiences in using the test article are summarised in the trial protocol and usually also detailed in the investigator’s brochure.

It is the responsibility of the EC to decide whether a clinical trial has an ethically acceptable risk-benefit balance, while it is up to potential participants to decide whether it serves their interests and welfare to participate or not. The EC must determine that the research is appropriately designed and conducted, while at the same time ensuring that participants are not unjustifiably or unnecessarily exposed to risks.

Potential harm to participants is usually translated as a risk assessment. Both the degree of potential harm, such as headache or death, and the probability of its occurrence – e.g., one in a million or one in five – are assessed, and together they provide an estimate of the overall risk of harm. Clinical trials with a risk of harm above a minimum level should be subject to a higher degree of ethics review. The concept of minimal risk raises special issues, especially when new medicinal products are studied in interventional studies. Such research often involves uncertainties about the precise magnitude and kind of harm that can occur, which limits a solid prior identification of risk of harm. It is often hard to predict the exact nature and magnitude of the benefits and harm of a research project; thus, a need for data and safety monitoring exists.

Risks of harm should be assessed systematically, considering factors such as physical harm (bodily harm or simple inconvenience, for example), psychological harm (emotional suffering or breach of confidentiality), social harm (employment or social discrimination) and economic risks (financial costs related to participation). Similarly, potential benefits should be assessed systematically in terms of physical benefit (for instance, improvement of disease), psychological benefit (comfort from suffering or feeling of helping others in the future), economic benefit (financial benefits related to

research participation), or benefit to science/society (general knowledge, effective interventions in the future, or change in practice standards decreasing morbidity or mortality). Finally, the assessment should determine both the magnitude and the duration of the potential risk of harm as well as the benefits.

Clinical trials inevitably have uncertainties concerning both risks and potential benefits. It must be emphasised that the potential benefits are always for the good of society and for the advancement of knowledge. A new medicinal product under clinical testing is a test article, not a recognised medical treatment, so the beneficial value for participants is uncertain. Most participants become involved in clinical trials because they are in need of treatment, while others participate because they assume there is therapeutic value. The EC must ensure the procedures for recruitment and informed consent stress the differences between research and standard clinical care that participants might otherwise receive. The participants may benefit by, for instance, being examined and followed up more frequently than might otherwise be the case, which is especially beneficial for those in locations with sparse publicly funded health care. However, such trials need to be carefully evaluated in terms of risks because individuals can be coerced or unduly influenced to enroll for the benefits of free examination.

Risk-Benefit Balance and Phase I Trials: The highest risk-benefit balance arises in phase I trials where there is virtually no benefit at all for the participants, whether they are healthy volunteers or patients. There are virtually no health-related incentives to participate, since any potential treatment effect is unknown and the curative dosage of the test article is not yet defined. In addition, the treatment is usually short – over just a few days or weeks – so any factual therapeutic benefit will be less than marginal.

On the other hand, phase I trials hold the likelihood of gaining the most important knowledge. For this reason, it is argued that society will benefit greatly from those trials, since they are crucial to the development of new effective and safe medical therapies.

Today, about 80% of phase I trial participants are healthy volunteers who, by definition, receive no therapeutic benefit from trial participation. However, both healthy volunteers and patients enrolled in phase I trials can be given a stipend based on the level of discomfort and trial duration.

The major safety concern in phase I trials is the occurrence of immediate serious adverse reactions after dosing, such as anaphylactic shock or cardiac arrhythmia. An EC reviewing phase I trials should have an expert panel set up, because the risk of harm is highly dependent on the type of compound, pre-clinical trial results and the clinical testing environment. For an EC review of phase I trials, a medical institution should thus consult its own expert sub-committee or outside expert opinion.

Predicting potential serious adverse reactions for the first-in-human use of a test article involves identifying the risk factors. Concerns may arise from particular knowledge or lack thereof regarding: (1) the proposed dosing, (2) the mode of action, (3) the nature of the target, or (4) the relevance of animal models. Estimation of the first dose in humans is an important element to safeguard the participants in those studies. Dosing may be done in a sequential manner, with one participant dosed on day one, and the remaining participants dosed subsequently after a review and a go-ahead decision by a data safety monitoring committee.

Phase I trials should take place in appropriate clinical facilities and be conducted by trained investigators with the necessary expertise and experience in conducting early phase trials, together with medical staff who have appropriate training and previous

experience in handling phase I human studies. All involved should also understand the test article, its target and its mechanism of action (European Medicines Agency, 2007).

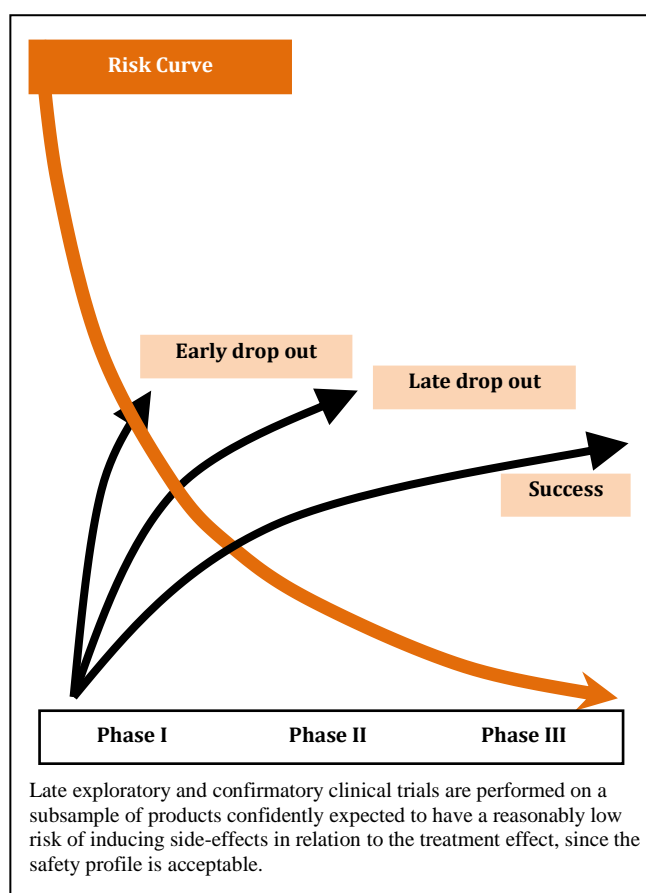
Risk-Benefit Ratio and Phase II-III Trials: Initial human pharmacology clinical trials, mostly on healthy volunteers, are followed by exploratory trials where the test article is administered on target group patients for the first time. The reaction of these participants – sometimes severely diseased – may differ from that of healthy volunteers, so these *first-into-patient* trials are also regarded as high risk. However, once the first group of participants has been exposed to the test article, it becomes easier to predict any treatment-related risks and benefits.

It is important to note that clinical testing of medicinal products that are ineffective or have unreasonable side-effects is terminated early. This means that late exploratory (phase II) and confirmatory (phase III) clinical trials are performed on a subsample of products confidently expected to have a reasonably low risk of inducing side-effects in relation to the treatment effect, since the safety profile is acceptable (*see illustration*).

The targeted patient population may influence the risk of harm assessment of a medicinal product. For instance, life-threatening diseases such as cancer may call for stronger and thus potentially more toxic test articles with different risks of harm acceptance from, say, anti-flu treatment products. Likewise, children may have a higher risk of side-effects than adults, due to their ongoing organ growth and the body's functional development in early life. Patients in need of multiple product treatments – such as psychiatric patients or drug abusers – may run the risk of drug-to-drug interaction, which may be at a higher risk level than that of participants given only the test article.

Once the test article enters phase II-III trials there are some clear benefits from trial participation. Standard medical care is enhanced, since the trial commonly requires additional medical examinations and clinical investigations. Furthermore, the medical care provided in a trial should in principle be free of charge, an additional incentive, especially in countries with little or no free public health care.

With the ongoing globalisation process of industry-sponsored clinical trials, there are more incentives for trial participation. For instance, a strong incentive in developing countries is access to health care. Many developing countries lack an efficient public health care sector, and a large proportion of the population cannot afford private health care. Therefore, clinical trials offer access to health care services that would otherwise not exist.



Informed Consent Process

One cornerstone of human research ethics is that individuals who participate in clinical research should do so voluntarily. The voluntary aspect is important, since it is the participant's choice to participate according to his or her own preferences and wishes. To maintain the voluntary air, participants should be free to withdraw from the research at any time.

EC members must be aware of the methods used for participant recruitment, i.e., the person responsible for the recruitment, when the participants will be approached and how they will be approached. Those are crucial elements in either ensuring or undermining the voluntary element. Undue influence and exploitation may happen when potential participants are approached by persons in a position of authority. Any relationship of dependency – including even between a physician and a participant – may give rise to unjustified influence. Intentional financial compensation for participation is primarily related to the lost time and inconvenience of participation. Compensation should not be so attractive as to constitute an overwhelming incentive to take higher risks than would otherwise be the case. This is particularly true for participants in early phases of clinical trials. Some potential participants, such as young children, lack the capacity to decide for themselves whether to participate, and a special set of rules apply here, involving authorised third-party decision-makers.

The decision to participate in a research trial involves weighing the risk of harm and potential benefits prior to agreeing to participate. Both the informed consent discussion between the investigator or his/her delegate and the participants, and the written informed consent document and any other written information provided to participants, should include explanations of important issues. These include, for instance, that the trial involves research; purpose of the trial; treatment(s) and procedures; expected duration of the trial; participant's responsibilities; foreseeable risks or inconveniences; reasonably expected benefits; compensation and/or treatment available in the event of trial-related injury; payment, if any; anticipated expenses, if any; and acknowledge that participation is voluntary, with the possibility of withdrawal (*see text box on this page and following pages*).

The ICH GCP also addresses a set of rules that should apply when consent of the participant's legally acceptable representative is needed, such as when the participant is a minor, or is an adult who has impaired decision-making. There are also ICH GCP informed consent rules in emergency situations, when prior consent of the participant is impossible.

In general, clinical trials should begin only after written informed consent has been obtained and documented.

ICH GCP and Informed Consent

Section 4.8 Informed Consent of Trial Participants addresses the essentials of informed consent. Briefly, it clarifies that:

"The Investigator should have the EC's written approval of the written informed consent document, and any other written information to be provided to participants; any revised written informed consent document and written information should receive the EC's approval in advance of use; it should not contain language that causes the participant to waive any legal rights, or release the investigator, institution or sponsor from liability for negligence; and language used during the informed consent process should be as non-technical as practical. Prior to participation in a trial, the written informed consent document should be signed and personally dated by the participant, or their legally acceptable representative, and also by whoever conducted the informed consent discussion."

The informed consent document provides a synopsis of the clinical trial protocol, from its purpose, treatment, risk of harm, potential benefits, alternative treatments and voluntary participation. It also explains the participant's rights by taking part.

The document is designed to initiate the informed consent process or the conversation between the participant and the research team. If the participant subsequently decides to be involved in the trial, he/she will provide consent by signing the informed consent document. The participant should be offered a copy to keep for future use.

Informed consent is not designed to protect the legal interests of the research team – rather to protect participants by providing essential information about the trial and informing them about their rights as participants. But investigators should realise that the written document alone may not ensure that participants fully understand the consequences of trial participation. Therefore, the investigator or another team member should discuss all aspects of the trial with the potential participants. The study team should also continue to provide updates to the participants when new information arises that may influence their participation. Informed consent is a process that should continue over the entire course of a trial, and a copy of the valid informed consent form should be given to the (potential) participant.

The EC is only able to review and approve the written informed consent and any other written information to be provided to participants. But the EC is not able to ensure the informed consent process is in fact performed in a proper manner at the study site; the EC has the right to conduct site visits and audits, although this is not commonly practiced. When a trial is monitored by an independent body, such as a commercial trial sponsor, there will be assurance that the participant/legally

Informed Consent Contents

The ICH GCP specifies that the following 20 issues should – if applicable – be properly addressed, using layman's language, in the written informed consent form. In short the 20 points are:

- *The trial involves research.*
- *Purpose of the trial.*
- *Trial treatment(s).*
- *Trial procedures.*
- *The participant's responsibilities.*
- *Experimental trial aspects.*
- *Foreseeable risks or inconveniences.*
- *Expected benefits.*
- *Alternative procedure(s) or treatment (s).*
- *Compensation and/or treatment available in the event of trial-related injury.*
- *Payment to participant.*
- *Expenses for participant.*
- *Participation is voluntary, and the participant may refuse to participate or withdraw from the trial at any time.*
- *The monitor(s), the auditor(s), the EC, and the regulatory authority(ies) will be granted direct access to the participant's medical records.*
- *Records identifying the participant will be kept confidential.*
- *The participant or representative will be informed if information becomes available that may be relevant to their willingness to continue participating in the trial.*
- *Person(s) to contact for further information regarding the trial, rights of trial participants, and in the event of trial-related injury.*
- *Circumstances and/or reasons under which participation in the trial may be terminated.*
- *Expected duration of trial participation.*
- *Approximate number of participants involved in the trial.*

authorised representative has signed the informed consent document prior to trial participation. Yet, US FDA site inspections of industry-sponsored trials have revealed that 8.9% of all sites inspected had inadequate informed consent.

The EC will also have problems in making certain the informed consent document is updated with previously unknown information essential for trial participation during the course of a trial, except when there is an amendment of the trial protocol that needs EC approval. The EC should be informed continuously about any SAEs identified at any sites involved in a specific trial. New knowledge on the safety profile of a test article should be amended to the written informed consent. The common reporting pathway is that the investigator at a certain study site reports any SAE identified at his/her site to the sponsor. The sponsor will subsequently report each SAE to all investigators involved in the particular trial. Each investigator will finally report such SAEs to his/her local EC.

In summary, the EC has only partial oversight of the informed consent process and is only able to ensure that the written information provided to participants is correct and to some extent appropriately updated. But the factual consent process itself is normally not verified by ECs.

Human Tissue: Clinical trial human tissue samples add much information to the outcome of the trial. Ethical issues here focus on access and consent to the use of tissue and on potential privacy concerns. Human tissue is any biological material, including body fluids such as blood. It is defined based on knowledge of the donor: identified, de-identified or anonymous tissue. It can also be defined according to the way it is collected; specific research purpose, incidentally collected, or for future as yet undefined research. The latter two categories may face an ethical dilemma, since *secondary* use for future research may not have been considered at the time of collection.

Participation Information Example

“Clinical trials are an important part of health care research. Clinical trials are often used to determine whether new drugs, procedures, or other treatments are safer or more effective than drugs or treatments currently being used.

Often there is a control group that receives the current standard of care or best treatment available. One or more groups receive the test treatment.

There are usually no costs associated with participation in a study. In some cases participants may receive payment, medications, tests, or follow-up care at no cost.

Written and verbal informed consent is needed before you may be enrolled in clinical research trials to allow you to decide whether or not to participate. Informed consent for a clinical research study should include the following information:

- *Why the trial will be conducted?*
- *What will the investigator hope to achieve?*
- *What will be done during the trial?*
- *How long will the trial last?*
- *What risks are there from participation?*
- *What benefits are there from participation?*
- *Other treatments available if you decide not to participate?*
- *The right to leave the trial at any time?*

The informed consent form must be signed before you enroll into the trial. It is also important to know that informed consent process continues throughout the trial. You may ask questions at any time – before, during, or after the trial.

It is advisable to discuss the informed consent with your family or friends before deciding whether to participate or not.”

Unpublished information, Clinical Trials Centre, The University of Hong Kong (2009).

Initial research involving tissue collection requires an EC review and consent of the tissue donor or representative. Consent should address several aspects, such as type and amount of tissue to be taken; the manner at which it will be taken; safety and invasiveness of the procedures; potential uses including commercial purposes; measures to protect privacy and maintain confidentiality; length of time of storage; method of preservation; and plan for disclosure of clinically relevant information. To make possible subsequent use of the tissue, consent documents should provide choices concerning future usage issues, such as refusing any future use, permitting only anonymous use, permitting identified use, permitting future contact to seek consent for other studies, and permitting coded use for any kind of future trial.

Usually the EC approves secondary use of identifiable human tissue. The investigator must declare that use of the tissue is essential to the research; that appropriate measures will be taken to protect privacy, minimise harm and ensure confidentiality; and that donors did not object to secondary use at the initial stage of tissue collection.

Tissue Sampling in Standard Care: Consent forms for routine tissue sampling are commonly used in most clinical settings. The wording of those forms is usually general and open, and permission is given to use, conserve and destroy samples, depending on the needs of the clinical laboratory, without participant notification. ECs are often unaware that routine tissue samples are secondarily used for research purposes.

Human Reproductive Tissue: Specific ethical concerns arise from research involving human fetuses and fetal tissue, embryos, stem cells and gametes (egg/sperm). Stem cells are characterised by their ability to renew themselves through division and differentiation. Many believe that human reproductive tissue research may hold the key to curing diseases such as diabetes, Parkinson's disease and Alzheimer's disease. Ethical opinion on human reproductive tissue research is highly diverse, with religious beliefs a major factor in the ongoing debate. Some countries have for the time being banned such research, while others consider it morally acceptable and beneficial in achieving long-sought medical gains. Each country has its own guidelines for human reproductive tissue research, so those specific ethical issues are not addressed here.

Human Genetic Research: Human genetic research aims to understand genetic contributions to health and diseases and identify new approaches to preventing and treating diseases. The genetic predispositions of an individual can be used to prevent or moderate disease. Individuals respond differently to drugs, and sometimes the effects are unpredictable. Differences in genetic influence on the expression or function of proteins targeted by drugs can contribute significantly to variation in the responses of individuals. This intersection of genetics and medicine has the potential to yield a new set of clinical laboratory diagnostic tools to individualise and optimise drug therapy.

Human genetic research should comply with general ethical principles of human tissue research. It is especially ethically crucial to develop a plan for managing information that may be revealed, both through approval by the EC and in obtaining informed consent from participants. In addition, participants should have the opportunity to receive the genetic information revealed about themselves and decide whether such information is disclosed to any person. If genetic research information is disclosed to a participant, genetic counseling should be available.

Secondary Analysis of Clinical Database

Secondary database analysis refers to the use in research of data contained in previously created data sets, whether they have been collected retrospectively or prospectively, or represent normal clinical data or research data.

Database projects often use the same data set to answer several related research questions. Secondary use of already collected data, where the participants have not been given their consent for such use, is regulated differently in various regions/countries. Analysis of clinical databases for hospital administrative purposes does usually not require any EC review or approval. However, as a requirement for publication in many international biomedical journals, an EC must review and accept secondary analysis of clinical database studies.

Most ECs require that investigators submit a description of a secondary database analysis project, including such elements as the scope and purpose of the database; expected types of studies that will use information from the database; anticipated benefits; anticipated harms and how they will be minimized; patient information sources that will be accessed; data abstraction information; any linkage of data; measures that will ensure security of the personal identifiers; and details if the data will be sent elsewhere. Whether each participant should be contacted and whether each should give his/her consent for the usage of the data, depends on local regulations and guidelines, the nature of the research question and the sensitivity of the data.

Vulnerable Participants

The key issue of vulnerability is to assess the potential participants' *mental capacity* to give consent. There are many different types of vulnerability (*see text box*). Of concern to ECs is vulnerability to coercion or undue influence. This type of vulnerability occurs when participants have diminished mental capacity to give consent, such as adults with dementia or children. Others who have diminished capacity to provide consent are students, prisoners, women in certain cultures, and employees. We should note that pregnant women themselves are not vulnerable unless the trial occurs when the woman is in labor or delivery; the vulnerability is with the fetus.

The EC plays an important role in overseeing clinical trials, ensuring that the rights, safety and well-being of participants are protected, especially for vulnerable participants who are most in need of such protection. Local implementation of the EC's protection function is through its operational procedures; and they are usually unique to each institution. As clinical trials are conducted more frequently in emerging clinical trial regions, all

What makes a participant vulnerable?

The ICH GCP definition of vulnerable participants is as follows: *“Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include participants with incurable diseases, persons in nursing homes, unemployed or impoverished persons, those in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.”*

stakeholders should be aware of the new challenges – and solutions that can improve protection for vulnerable people around the world.

Clinical trials conducted in emerging regions face a unique common problem, compared with trials conducted in established regions: That is a relative shortage of experienced clinical researchers to form the composition of an EC. In conjunction with high illiteracy rates and sparse public healthcare services, this creates a uniquely sensitive environment for vulnerable individuals. For instance, should illiterate people not be allowed to participate in clinical trials, or should the informed consent process be altered? Limited or no access to public health care increases the incentives for trial participation, because of lack of any alternative treatment. This also triggers an ethical dilemma for participants living with chronic disease, since study treatments are frequently withdrawn when trials are completed. Definition and protection of vulnerable participants are issues driven by local regulations and guidelines – and this is undoubtedly a major, growing concern about trials conducted in emerging regions. Emerging clinical trial regions are here defined as regions/countries outside North America and former Western Europe, excluding some already established countries such as Israel, South Africa, Australia, New Zealand and Japan.

A conflict: Currently, the regulatory authorities want both to protect and include vulnerable participants in clinical trials, which places some pressure on the EC. For instance, children are seen as a vulnerable trial population, since they may not fully understand the concept of risks, benefits and responsibilities of trial participation; therefore, they may also be more vulnerable to various kinds of external pressures. On the other hand, very few new medicinal products are tested in children, thus leading to labeling of medicinal products based on the trials in adult populations.

Privacy and Confidentiality

Privacy encompasses being free from interference by others – especially in relation to personal information, thoughts and opinions, and personal communications with others.

Confidentiality includes the responsibility to protect such personal information from unauthorised access, use, disclosure, modification, loss or theft. Investigators must maintain confidentiality of personal information of participants and must describe procedures taken to meet confidentiality obligations for all stages of the research life cycle. In using individual data already collected for a new – secondary – research project, approval from the EC needs to be obtained, and informed consent from the relevant individual participants may also be needed, as requested by the EC.

Safety Monitoring

The EC must ensure that a clinical trial incorporates a plan to assess the safety of participants. The EC should have and follow written policies and procedures for reviewing the plan and determine that the data and safety monitoring plan provides adequate protection for participants. The EC may initially suggest enrolling a small number of participants into the trial, after which data collection by an independent monitor takes place. A review of the data by a biostatistician follows, before the remainder of the trial proceeds. For high risk or complex trials, it may be necessary to establish a multi-disciplinary institutional or external data safety and monitoring committee (DSMC). A DSMC must be autonomous in the trial, and the EC should receive copies of all DSMC reports and recommendations. Normally, the DSMC will report its

findings to the sponsor and the DSMC has the mandate to make recommendations to suspend or terminate if there are strong emerging safety concerns. However, the final decision lies with the sponsor.

While it is recommended that a DSMC be considered for all clinical trials, there are few instances where this is not necessary. Clinical trials differ in nature, where some clinical trials may have predictably higher risk of harm, while other trials continue over a long period of time. Therefore, it may be desirable to continuously monitor various aspects of such trials for both safety and other reasons (*see text box*).

An independent DSMC is represented by a group of experts external to a trial that reviews accumulating data from an ongoing clinical trial. Commonly, safety monitoring is the main concern of the DSMC, but other aspects of a clinical trial, such as trial design, may also be its responsibility. This monitoring work is normally done on treatment blinded accumulated data from an ongoing trial. Occasionally, the DSMC may also need to have access to un-blinded treatment information. If so, it is important to ensure the scientific integrity of the trial so that, for instance, the un-blinded information is kept within the DSMC.

External Parties Overseeing Clinical Trials: In practice, there is often more than one external party monitoring the progress of a clinical trial, although the ultimate responsibility for its conduct lies with the sponsor and the investigator. Examples of external parties monitoring various aspects of a clinical trial are the EC and DSMC. Some trials also have a steering committee, especially large multicentre trials. These committees usually oversee areas such as the scientific value of the protocol, quality assurance and scientific quality of the final trial report.

Establishment of a DSMC: In life-threatening disease trials it is common to have a DSMC in the first instance from an ethical point of view. Apart from ethical and safety concerns, there are other factors that bring about the establishment of a DSMC, including the need for early stopping at the pre-planned interim analyses or need for modification to the trial design based on unblinded interim data analysis for adaptive trial designs, which tend to be more complex (*see page 34*). However, major design modifications need regulatory authority advice and EC review and acceptance.

The establishment of a DSMC should be finalised during the planning phase of the trial, and the DSMC should be in full function prior to the initiation of the trial. The composition of the DSMC, the members' qualifications and the independence of the members should be addressed. Within the committee, a qualified clinician(s), a medical statistician and an ethics expert are needed. For practical reasons, the number of members of a DSMC should be limited.

For avoidance of conflicts of interest, the DSCM members should, for instance, not be employees of the sponsor, and should not be involved as authors of any subsequent scientific output of the trial. The DSMC is usually not completely independent of the sponsor, since the sponsor is responsible for the establishment of the committee and provides financial support for the operation of the DSCM. The DSCM members act rather as independent consultants of the sponsor.

ICH GCP and DSMC

In the ICH GCP Guideline, the data safety and monitoring committee (DSMC), formally referred to as the independent data-monitoring committee (IDMC), is described as:

“An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.”

Responsibility of a DSMC: The sponsor and investigators should promptly provide the DSMC with the information it needs for trial monitoring purposes, documented in writing prior to the onset of the trial. A critical point of the DSMC's work is to ensure the integrity of the ongoing trial, and the sponsor must have appropriate policies in place to ensure that integrity.

The DSMC is responsible for proper communication of its recommendations. If any changes in the trial conduct are recommended by the DSMC, sufficient information should be provided to allow the sponsor to decide whether and how to put into practice these recommendations. Implementation of any DSMC recommendation is solely the responsibility of the sponsor.

DSMC Working Procedures: Because of the DSMC's involvement in overseeing clinical trials, sensitive details pertaining to the trial – unblinded treatment information, for instance – will be made available. As such, transparency is important when it comes to the procedures used by the DSMC. The following aspects should be documented and described: responsibilities, members and qualifications, declaration of possible conflict of interest, frequency and format of meetings, communication procedures, data flow, statistical analysis plans, procedures to interact with the sponsor or other parties, timelines and format for analysis to be assessed by the DSMC and its meetings (open as well as closed).

Investigator-Initiated Research Studies: It may also be decided that a DSMC should be established for investigator-initiated trials. In that case, it operates along the same lines as described above. The duties of a trial sponsor are here taken up by the principal investigator of the trial.

EC and DSMC Communication: Interaction between the EC and the DSMC varies according to individual trials and settings. The EC application should include essential information about the existence of a DSMC for a certain trial. The EC may request that information that might influence the safety profile or other essential elements of the trial, will be provided by the DSMC through the investigator to the EC.

Participant Recruitment Procedures

Recruitment procedures: Recruitment of participants for a trial can take place through the patient pool at the study site, referral of participants from other clinics or by advertisement or directly approaching or screening the public. Regardless of the recruitment method used, this information should be clearly defined in the EC application including advertisements and other recruitment information (*see text box*).

An investigator is allowed to consult the hospital records of his/her patients before the EC application has been submitted in order to screen potential participants in relation to the protocol-specific inclusion/exclusion criteria. However, the participant should have been informed beforehand and approved that their medical history can be reviewed and used for this

ICH GCP Guideline states the EC should obtain the following documents:

- *Trial protocol.*
- *Amendment(s).*
- *Written informed consent form.*
- *Participant recruitment procedures, e.g., advertisements.*
- *Investigator's brochure.*
- *Information about payments and compensation available to subjects.*
- *Investigator's current curriculum vitae.*

purpose. Other physicians can refer their patients to a trial site, but it should be made clear that those participants have been informed beforehand and granted approval that their medical history can be reviewed and used for this purpose. However, those are not strict rules since they vary by country. In some countries the referring physician is allowed to receive a *finder's fee*, which should be described in the EC application. A finder's fee should be reasonable and reflect the work involved in screening the potential participants and any reduction in income during the course of the trial. Some bioethicists regard *finder's fees* or *referral fees* categorically unethical. Using health care computer systems to identify potential participants is not allowed in some countries without the individual participant's consent.

Advertisements for participant recruitment – e.g., newspapers, radio, posters, etc – are subject to EC review and approval. If participants are identified from the public, it is important to inform the treating physician – after obtaining his/her consent for the contact – about the trial and also to ensure that the participant does not have any undiscovered health problems and medical treatments that may violate the inclusion/exclusion criteria.

Inclusion/Exclusion of Trial Participant Categories: There should be a fair distribution of the benefits and burdens in research. Special individuals or groups should neither take up more of the burden of participating in research, nor be wrongly excluded from potential benefits of participation. For instance, research should not exclude individuals on the basis of culture, lack of certain language skills, religion, race, disability, sexual orientation, ethnicity, sex or age – unless there is a scientifically valid reason for the exclusion. Where a trial involves individuals without the capacity to provide informed consent, the EC should ensure that the research question can be addressed only with the participation of those individuals.

Participant Advertisements: The EC should review and approve all advertisement(s) to be used for recruitment of participants for all clinical trials. There is well-defined acceptable and unacceptable information that can be included in an advertisement. Statements that should not be used are implied or expressed claims of safety or efficacy; undue emphasis on reimbursement (although mention of reimbursement is permitted); any express or implied claim that the research is government approved; use of the term *new*, i.e., *new research medicine*, *new investigational medicine*; the test article's name; or promotion of the medicine concerned.

Advertising for participants for clinical trials is practiced and allowed in many countries, with media increasingly used. There are several guidelines for how an advertisement should be presented. Here is the guidance developed by the Medical Affairs Department of the Association of the British Pharmaceutical Industry (ABPI) in 2002. It states that:

An EC should be invited to review all materials used to recruit subjects for all phases of clinical trials, including, but not limited to:

- Television and radio advertisements.
- Letters, posters and newsletters.
- Newspaper advertisements.
- Internet web sites.

The essential information for an advertisement:

- A statement indicating that the trial involves research.
- A contact name and phone number for the participant to use.
- Some of the eligibility criteria.

- The likely duration of the participant's participation for a specific trial.
- That the advertisement has been approved by an EC.
- That the participant's general practitioner will be informed that he/she is taking part in the clinical trial.
- That any response to the advertisement will be recorded but will not indicate any obligation.

Additional permitted content:

- The purpose of the research may be described.
- The location of the research.
- The company or institution involved may be named if appropriate.

Statements that should not be used:

- Implied or expressed claims of safety or efficacy.
- Undue emphasis on reimbursement, but mention of reimbursement is permitted.
- Any expressed or implied claim that the research is approved by regulatory authority.
- The term *new* unless qualified, i.e., *new research medicine, new investigational medicine*.
- The compound's name.
- Care should be taken to ensure that advertisements are in no way promotional for the medicine concerned.

Qualification of Investigator and Research Staff

Neither the ICH GCP Guideline nor the Declaration of Helsinki provides a complete definition of the qualification of an investigator (*see text box*).

It is not clear from those two definitions if the investigator needs to be a medical doctor with a valid medical license, specialised in the specific therapeutic area. The two investigator qualification definitions do not make any distinction between human intervention studies, e.g., clinical trials and observational studies.

However, the widespread definition of qualified investigators refers, in fact, to either of the two kinds: investigators for clinical trials of medicinal products regulated by a local or overseas governmental regulatory authority, or for other human studies.

ICH GCP - investigator qualifications:

"The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies)."

Declaration of Helsinki, 2008 - investigator qualifications:

"Medical research involving human participants must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent."

The EC must judge the qualification of the investigator by means of his/her education, training, and experience to assume responsibility for the proper conduct of the trial, and the EC should determine whether the investigator is qualified or not. For clinical trials of medicinal products regulated by a local or overseas government regulatory authority, a qualified physician entitled to provide health care under the laws of the country/province where the clinical trial site is located must normally act as the investigator. For other clinical trials, the investigator does not always need to be a qualified physician. But on the EC application there must be a named, qualified physician as a co-investigator, who is willing to accept clinical responsibilities including supervision of clinical team members during the entire course of the trial.

Financial Conflict of Interest

A conflict of interest can be defined as any situation in which an individual or corporation is in a position where personal or corporate interests could interfere with a professional obligation. The existence of a conflict of interest is not evidence of wrongdoing, and for many professionals it is virtually impossible to avoid having conflicts of interest. Someone accused of engaging in a conflict of interest may deny that a conflict exists because he/she did not act improperly. However, a conflict of interest can exist even if there are no improper acts as a result of it.

The influence of the pharmaceutical industry on medical research has been a major cause for concern. In 2009 a study found that "*a number of academic institutions*" do not have clear guidelines for relationships between their ECs and the industry. Disclosing any financial conflict of interest to the EC is to ensure reasonable expectation that the design, conduct or reporting of research funded will not be biased by any conflicting financial interests of an investigator. Conflict of interest examples include but are not limited to:

- Salary or other payments for services, e.g., consulting fees or honoraria.
- Equity interests, e.g., stocks, stock options or other ownership interests.
- Intellectual property rights, e.g., patents, copyrights and royalties from such rights.

Financial conflicts of interest that may compromise the truthfulness of research and protection of participants are never welcomed, but they are now and again exposed in media reports. The investigators, institutions and the EC's members should identify and address potential conflicts of interest and how they can be managed to ensure accountability for all parties involved. Institutions should have financial conflicts of interest policies and procedures in place to identify, prevent, disclose and manage conflict of interest. EC members must also disclose known conflicts of interest and, if necessary, withdraw from EC discussions and decisions. Investigators should also disclose to the EC real, potential individual financial conflicts of interest that may have an impact on their research. A clinical trial investigator is allowed to receive a reasonable financial compensation for the conduct of the trial itself.

In General – How to Mitigate Significant Conflicts of Interest: Avoid them entirely or abstain from decisions where such a conflict exists; identify conflicts of interest by disclosing financial information; minimise problems with conflicts of interest through codes of ethics and peer review.

Clinical Trial Insurance and Indemnity

The purpose of an indemnity arrangement is to provide legal protection for the participants in the event of an unforeseen adverse circumstance arising during the course of a clinical trial. Indemnity is a form of contract to compensate an individual for loss or damage. To cover the costs that may be incurred as a result of providing indemnification, the indemnifier can obtain clinical trial insurance. It is important that clinical trial participants are insured to provide treatment for adverse events linked to participation in a clinical trial (*see text box*). Often health plan policies define clinical trials as *experimental* or *investigational*. Under this scenario, normal health insurance may not cover the costs of what is actually routine care, i.e., costs for doctor visits, hospital stays and tests or treatments that would be covered even if the participant were not taking part in a clinical trial.

Press report, 2009: "A lawyer who helped win a multimillion settlement from a university after the death of a study participant has since been known as an expert on how clinical trials go wrong; the settlement is undisclosed but is believed to be around US\$10 million. The lawyer's pending US cases, observers say, will be much bigger challenges. Among them was a case against a university on behalf of a woman that suffered temporary liver toxicity in a trial; a lawsuit against a cancer research center for allegedly harming subjects in a study aimed at making bone-marrow transplantation safer; against a university on behalf of a patient and her husband who claim they were harmed by an experimental medication to aid nerve regeneration; a suit against four university scientists that alleges participants were harmed in a melanoma cancer vaccine trial; and a suit against a university for a schizophrenic patient who committed suicide after researchers deliberately stopped his medication."

Clinical trials insurance should cover the following liabilities:

- Professional negligence in the course of conducting clinical trials.
- Product liability, in case a product under investigation causes injury.
- No-fault liability – intended to provide compensation to research participants, regardless of liability, in the event of their suffering a significant and enduring injury (including illness or disease) which, on the balance of probabilities, is attributable to their involvement in the clinical trial.

An industry-sponsored clinical trial should generally have clinical trial insurance, and the EC may request to be provided with a copy of the valid insurance policy unless the sponsor is a large company able to guarantee coverage. Some ECs will not review an application without having a copy of the clinical trial insurance or indemnification. The insurance coverage will commonly be granted only when the EC has appropriately reviewed and accepted the application.

For non-industry-sponsored clinical trials, the institution or any other non-profit sponsor is responsible for the insurance coverage or indemnification. Clinical trial insurance or a guarantee of indemnification from the sponsor protects the institution from legal liability to pay damages or compensation as a result of any claims made by participants for bodily injury caused by any act, error or omission in connection with clinical trials approved by the EC. Injuries caused by the misconduct of the institutions may not be covered by the insurance or sponsor's guarantee. However, there are

exceptions when non-industry sponsors are unwilling to take up the indemnity responsibility, which must be addressed in the informed consent.

In some regions such as the European Union and Australia there is a basic requirement that no clinical trial may be held without providing both insurance and indemnification to cover the liability of the investigator and the sponsor. But this is not the case everywhere. In some countries, the EC may impose a liability so great that many insurers are unwilling to bear, and in others a sponsor is liable for damage, even without fault.

The basic principle is that clinical trial insurance/indemnity should be in place whether there is an industry or non-industry sponsor, but there are large geographic and local variations in liability/insurance policies, laws and requirements.

Elements of the Insurance Policy: An original or certified copy of the original policy, along with a notarised translation if needed, may be requested to be submitted to the EC. The insurance can be trial specific or cover more than one trial. The following must usually be explicitly identified in a clinical insurance policy as submitted to an EC:

- Name, surname, trade name and address of the insurance company.
- Covered risks for treatment expenses, illness, disability and death.
- Date of commencement and termination of coverage.
- Liability limit – per person and total.
- Premium amounts, due dates and place of payment.
- Date of issuance of the policy.
- Original signature.
- Special conditions.
- Any additional coverage.
- Countries for which the policy provides cover.
- Deductibles or the existence of co-insurance.

Declaration of Helsinki and ICH GCP: Neither the Declaration of Helsinki nor the ICH GCP Guideline addresses liability and insurance matters surrounding clinical trials.

Essential Clinical Trial Documents

Essential documents are those enabling evaluation of the conduct of a trial and quality of the data. They serve to demonstrate the compliance of the investigator, sponsor and monitor with GCP and applicable regulatory authority requirements. Filing essential documents at the investigative sites and sponsor sites also enables successful management of a trial. They are also those usually audited by the sponsor and inspected by the regulatory authority(ies). The EC should have access to and review some of the essential documents as listed below:

- Investigator's brochure: to document that relevant and current scientific information about the test article has been provided to the investigator.
- Signed protocol and amendments: to document investigator and sponsor agreement to the protocol/amendment(s).
- Questionnaire(s) for participants.
- Informed consent documentation.
- Other written information that participants will be given.
- Advertisements for recruitment of participants.
- Curriculum vitae and other documents showing qualifications of investigator(s) and co-investigator(s).
- SAE reports and related reports.

- Interim or progress reports.
- Final report.

In addition to those essential documents, as recommended in the ICH GCP Guideline, the EC may require other documents as exemplified below:

- Clinical trial insurance statement.
- Case report forms (CRFs) and other data forms used to collect data.
- Indemnity statement signed by the sponsor.
- Conflict of interest statement signed by the investigator.
- Statement signed by the department head that the investigator is qualified for the trial and that resources are available in the department.
- Statement from the institution about sponsor agreement(s).
- Statement from the institution about clinical trial insurance.
- Finder's fees: payment to physicians or other health care professionals for referring participants to investigators.
- Bonus payments: payment either to the investigator or the institution for enhanced enrollment.
- Bonus payments to study coordinators or enrollers: payment made to study coordinators for enhanced enrollment.

Clinical Trial Registration

Some countries and institutions have mandatory rules enforcing the registration of clinical research projects/clinical trials in a publicly available trials registry prior to the initiation of a trial. For instance, free web-based access to information about ongoing clinical trials is regarded as important for the public. It also provides a complete picture of past research, whether negative or successful. The EC may be requested to monitor compliance of clinical trial registration according to local regulations and policies.

The past decade witnessed a clear trend that called for clinical trials to be registered. Two different organisations have enforced this development: regulatory authorities and scientific journals.

Regulatory Authorities and Trial Registration: Since the late 1990s, drug regulatory authorities have put more emphasis on the need to publish essential information about ongoing clinical trials on publicly searchable trial registries. This has been an explicit concern for those with life-threatening diseases, such as HIV/AIDS and cancer, since it would increase the possibility for patients to identify trials for participation. Since 2007, the US FDA has enforced trial registration by law for any phase II/III trial – though not phase I trials – since the data collected are planned to be used for a new drug application. Each trial must be registered before its onset, and there is a penalty system in place for non-compliance.

Jurisdictions outside the US have also adopted trial registration procedures and requirements, and the trial registration landscape is rapidly changing. An EC should be familiar with the local clinical trial registration requirements and include those in its operational procedures.

Scientific Journals and Trial Registration: Since 2004, the international Committee of Medical Journal Editors (ICMJE) has set up a policy enforcing the registration of interventional trials – phases II-IV – in an accepted public trials registry in order to be considered for publication in its journals. The policy became mandatory in July 2005,

and the registration must take place before the onset of patient enrollment. This policy has been extended to include phase I trials. The policy accepts only a few specific trial registries accredited by the World Health Organization (WHO). The main reason for introducing this policy is related to the so-called *publication bias* phenomenon; successful trials have a much higher likelihood to be published in a scientific journal than unsuccessful trials. The impact of publication bias is that the scientific literature is over-represented by “success stories” providing a distorted picture. Trial registries therefore allow identification of all trials, including those never published.

The consequence of this trial registry publication policy is that an investigator may have a manuscript rejected on the grounds that it has not been properly registered before the initiation of the trial. It is the investigator’s prime responsibility to adhere to the publication policy. We should, however, mention that only a few journals have adopted this policy. Most medical journals do not mention the policy in their instructions to authors. Only a few journals demand using the few WHO-accredited trial registries. Each EC should refer to local trial registration regulations and institutional guidelines as these dictate the role of an EC in monitoring trial registration compliance.

ICH GCP/Declaration of Helsinki and Trial Registration: The ICH CGP Guideline does not address this topic, but a short sentence added to the 2008 version of the Declaration of Helsinki states: *“Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.”*

Trial Registration and Current Practice: Virtually all for-profit trial sponsors register their phase II/III trials with the US national trials registry (<http://www.clinicaltrials.gov>) regardless of the country their headquarters are located in, be it Israel, Japan, Europe or North America, for instance. Some sponsors register phase IV trials, while other sponsors do not. The US trials registry has become the sole registry of choice for the multinational pharmaceutical and biotech industry because of US FDA legal references for registration and the fact that the US life-science market is the largest worldwide.

Investigator-initiated clinical trials – with the prime sponsor being a non-profit organisation – exceed the number of industry-sponsored trials. Many but not all investigator-initiated trials are subject to US FDA review, and those trials need to be registered with the US national trials registry; an investigator-initiated trial that is subject to US FDA review is called a “sponsor-investigator” trial. Many countries/regions have established their own trial registries, which may be preferred by some investigators. For instance, there are local trial registries in China, Australia and New Zealand, Germany, Hong Kong, The Netherlands, Iran, Japan, Pan Africa and Sri Lanka.

Some of those registries have become part of a WHO Primary Registry, merged on a regular basis into a single trial database – the so-called International Clinical Trial Registry Platform (<http://www.who.int/ictrp/en/>). However, there are registries not included in the WHO Primary Registry, and they are thus not included on the WHO Trial Registry Platform.

Dissemination of Trial Results

The sponsor, investigator and institution have an ethical responsibility to make reasonable efforts to publicly disseminate the results of clinical research in a timely manner. However, it has to be accepted that negative research results are less often submitted and accepted for publication in international medical journals. The investigators must anyhow submit a final report of the trial to the EC for review and approval, providing details about major outcomes of the trial. It is becoming

increasingly required for final reports to be posted in juxtaposition with the registration of the trial in a public clinical trials registry. In some countries, this has been enforced by law. Proper dissemination of the trial results is, in the first instance, an institutional responsibility.

Operation of an EC

An EC must develop a set of written standard operating procedures (SOPs) for a large range of issues, such as its composition, members' roles, preparations for meetings, meeting frequency, application procedures and forms, safety monitoring, sub-committees, education of EC members and archiving (*see textbox*). The EC's SOPs should include the critical elements spelt out in the ICH GCP Guideline and in any national or local EC Guide. Some further general details are provided on the following pages.

Each EC must develop its own set of unique SOPs applicable for the local situation because there are no generic or typical EC SOPs in place.

ICH GCP

EC Responsibilities - Examples

- *An EC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.*
- *The EC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the EC requests.*
- *The EC 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.*
- *Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible, the EC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).*
- *The EC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.*
- *The EC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.*

Continuation of ICH

EC's

Composition, Functions & Operations

Procedures

Records

3.4 Issues of EC Procedures

Local Laws and Institutional Guidelines

International human protection research guidelines, such as the Declaration of Helsinki and the ICH GCP Guideline, unfold the basic concepts and principles of research ethics of clinical trials. However, the interpretation and implementation of those and other guidelines are highly dependent on local laws and guidance. The EC and its members must therefore be well-versed and know the applicable local laws and guidance.

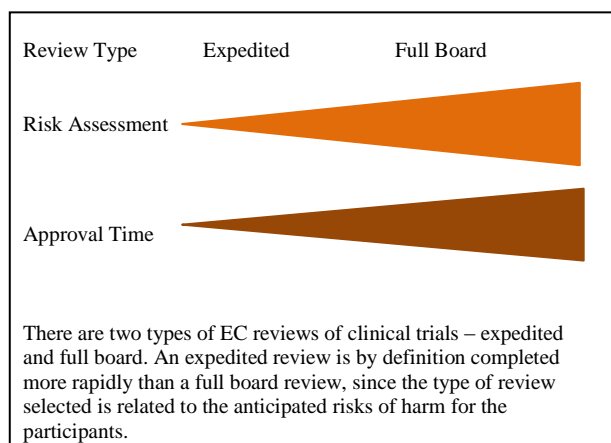
Proportionate EC Review: Expedited/Full

All human research projects must be reviewed sufficiently, but ethics review should be proportionate to the level and nature of the risks. A balanced ethics review approach starts with assessment of the risk of harm and potential benefits associated with the research (*see illustration*).

The concept of “*minimal risk*” provides the foundation for a balanced review, and in deciding whether a “*full board review*,” conducted by the convened EC, or an “*expedited review*” using expedited procedures should be adopted. A “*minimal risk*” situation is where the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The decision to conduct an expedited review may be made by the chair of the EC. The chair is required to adopt a method of keeping all members advised of research studies that have been approved by expedited review.

Virtually all clinical trials are at least initially subject to a full EC review, and usually the continuing review of trials must be conducted by the full EC. Views differ among ECs whether, for instance, scheduled continuing reviews, safety reports or protocol amendments are acceptable for expedited review or not, and this is driven by local laws and institutional guidelines (*see text box*).



The US FDA and Type of EC Review

In 1998 the US FDA spelt out when an expedited or a full EC review can/should be adopted. Parts of the text are included as they are related to clinical trials on drugs and devices. The following refers to the list of research categories pertaining to both initial and continuing IRB review.

“Research Categories accepted for expedited review

Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application is not required. Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

(b) Research on medical devices for which (i) an investigational device exemption application is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.”

Declaration of Helsinki and Type of EC review:

The Declaration of Helsinki does not specify when an expedited or full EC review can/should be adopted. However, it does specify that each protocol must be reviewed by an EC, that the EC should be informed about the trial progress, and that the EC should review serious adverse events and protocol amendments.

ICH GCP and Type of EC Review: The ICH GCP Guideline spells out more details about the operation, constitution and responsibilities of an EC but does not explicitly or specifically address expedited and full EC review.

Acceptability of Trial

The EC should deem that all clinical trials are subject to scientific review, and thus avoid putting participants at unnecessary risk of harm. A scientific review judges the importance of the research question and validity of the methodology; this can only be assessed by those familiar with the disciplines and methods of the proposed research. Traditionally, clinical trials undergo scientific review as part of the EC review process, using appropriate expertise among EC members. Clinical trials overseen by regulatory authorities will have already been subject to scientific review prior to the EC review. It is thus good practice to collect information from the EC application about the types of scientific reviews a particular trial has been subject to *prior* to the EC review, for instance, by regulatory authorities or granting agencies.

Any protocol raising many minor concerns or a few major concerns should either be rejected or subject to revision and subsequently re-assessed. Results from a trial not based on or adhering to current scientific knowledge, lacking important pre-clinical information and/or using sub-standard trial design will, in most cases, not be conclusive and therefore not be useful. Such trials could also put participants at

**Continuing Progress Report to EC
Template Example**

The following information is usually required to be included in the continuing progress report.

Details of the Investigator and Research Staff:

Details of the study: Title of study; EC reference number; date of favourable ethical opinion; sponsor.

Commencement and termination

dates: What is the expected start date? Has the study finished? What is the expected completion date? If you do not expect the study to be completed, give reason(s).

Site information:**Recruitment of participants:**

Number of participants recruited as proposed in original application; actual number of participants recruited; number of participants who completed the trial; number of withdrawals from trial to date, due to (a) withdrawal of consent, (b) loss to follow-up, (c) death; total study withdrawals; number of treatment failures to date, due to (a) adverse events, (b) lack of efficacy; total treatment failures; have there been any serious difficulties in recruiting participants? If yes, give details; do you plan to increase the planned recruitment of participants into the study?

Safety reports: Have there been any unexpected serious adverse reactions in this trial?

Amendments: Have any substantial amendments been made to the trial during the year? If yes, please give the date and amendment number for each substantial amendment made.

Serious breaches of the protocol or Good Clinical Practice: Have any serious breaches of the protocol or GCP occurred in relation to this trial during the year?

Other issues: Are there any other developments in the trial that you wish to report to the Committee? Are there any ethical issues on which further advice is required?

Declaration: Signature of principal investigator; print name; date of submission.

risk of harm without any scientific reason, while also consuming financial and human resources that might be more purposefully directed to other more important research projects.

Continuing Review

After initial review of a clinical trial protocol, the EC must also review ongoing research during the life of the trial. The primary goal of continuing ethics review is to ensure continued ethical acceptability of the research. As with initial review, continuing ethics review should be based on a proportionate approach. The EC has the authority to determine the level and frequency that continuing ethics review occurs, frequency and type of information. Commonly, continuing review is performed once yearly, and the project is not allowed to proceed without renewed approval by the EC.

National regulations and/or institutional requirements require clinical trial progress reports – also called annual progress reports, re-approval or renewal of research studies – approved by the EC. The renewal must describe current enrolment, ongoing enrolment, adverse events, withdrawals, progress of the trial, and any amendments/changes (*see text box on previous page*).

The review of the suitability of a clinical trial design includes many aspects, and they should be evaluated as an amalgam rather than in isolation, as elaborated in a special section of this Chapter.

Trial Amendments

Following approval of a clinical trial protocol by the EC, it is the responsibility of the principal investigator to inform the EC of any proposed changes made to the project, namely amendments. There are two types of possible amendments, i.e., major and minor.

Major Amendments: Major amendments are defined as any changes that affect the safety or physical or mental integrity of the participants for the conduct or management of the trial. Examples of major amendments are changes in the purpose or design of a trial, substantive changes in procedures used, changes to the trial population such as estimated numbers, age range, inclusion/exclusion criteria, a change of the principal investigator, and changes to trial documentation, such as participant information sheets or consent forms. Where a major amendment to a trial is to be introduced, it must be approved by the EC before implementation.

Minor Amendments: Minor amendments are defined as any changes that do not involve a more than minimum risk for participants or the conduct of the trial. Examples of minor amendments are correcting typographical errors, minor clarifications of the protocol, etc. Where a minor amendment is to be introduced, there may be local requirements for notifying the EC.

An EC must review all the amendments made to a previously approved protocol – whereby such protocol changes cannot be applied until the EC has given its approval. A substantial amendment is defined as an amendment to the terms of the application, to the protocol, or to any other supporting documentation likely to affect the trial to a significant degree, i.e., the safety or physical or mental integrity of the participants of the trial; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of any test article used in the trial. If in doubt, the investigator and sponsor should seek advice from the EC. The concept of “*minimal risk*” also provides the foundation for a proportionate review of a protocol amendment, i.e., if an expedited or full EC review should be adopted.

Full Review of Minor Amendments: Some sponsors – industry or granting bodies – require a full EC review for amendments. Researchers must familiarise themselves with the requirements of the sponsor to ensure that the appropriate review is conducted. Major amendments to the trial design, inclusion/exclusion criteria or trial interventions that involve additional risk of harm(s) to trial participants generally require a full EC review. The EC chair will make the final decision regarding whether a full EC review is required or not.

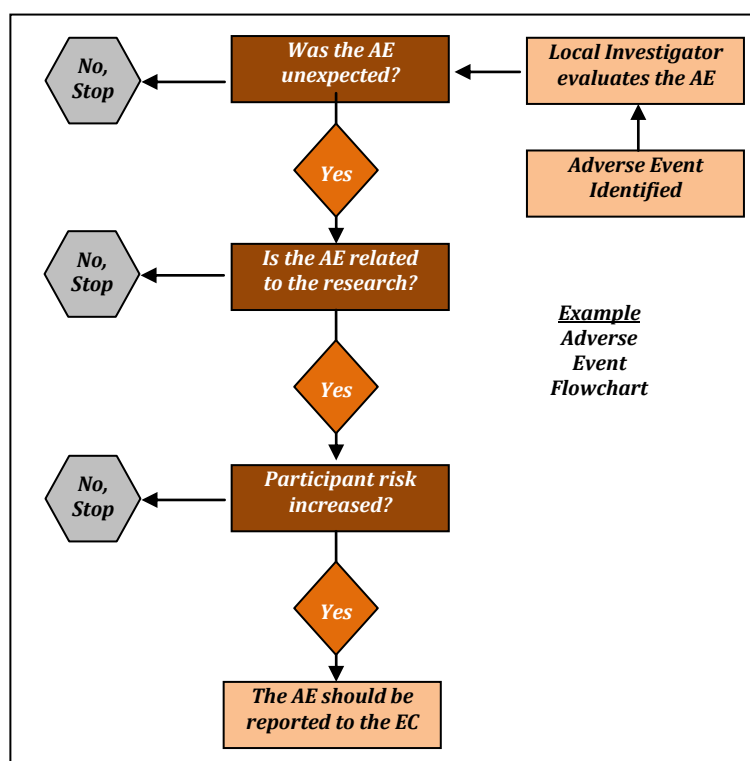
Adverse Event Reporting

An adverse event (AE) is any unfavourable and unintended sign, abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

A serious adverse event (SAE) is defined as any adverse test article experience, at any dose, that results in any of the following outcomes: death, life-threatening adverse test article experience, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, but are life threatening or require hospitalisation, may be considered serious adverse test article experiences when, based upon medical judgment, they may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Adverse Events Grading and Attribution: Local investigators have the primary responsibility for AE identification, documentation, grading, and assignment of attribution. The grading includes six categories: no AE, mild AE, moderate AE, serious and undesirable AE, life-threatening or disabling AE, and fatal AE. The attribution of an AE – relationship with the test article – is defined as unrelated, unlikely, possible, probable and definite.

Reporting of AE to EC: Only a subset of adverse events needs to be reported to the EC, i.e., AEs that may represent unanticipated problems involving risks to participants or others (*see illustration*). The definition of AEs and SAEs that need to be reported to the EC varies. For instance, some ECs request to be provided with a report pertaining to all SAEs, while others request reports pertaining to all AEs and SAEs that are unexpected – not previously defined – and related to the research.



All multi-site trials are expected to forward summary reports of adverse events to each EC involved in the trial at the time of continuing review. An EC has the authority to suspend or terminate approval of research at sites that are associated with unexpected serious harm to participants. When an EC takes such action, it is required to provide a statement of reasons for the action and to promptly report this action to the investigator, appropriate institutional officials, and regulatory authority(ies), if applicable.

AE and SAE reports represent a particular challenge for ECs because they often lack details and explanation of their significance to the safety of participants. Therefore, most reports cannot be accurately evaluated, and the EC decision based on the reports may not be the most favorable or correct one. To avoid this regrettable situation, there is a need to develop a more efficient and correct way of reporting adverse events to the EC. One option would be requiring the sponsor of a specific trial to provide all the ECs overseeing this specific trial with a report to update the status of the safety profile – say, every three months. This is in fact a current trend that may become the general practice in the near future – i.e., a summary adverse event report rather than reports for each individual adverse event.

Unanticipated Problems

A participant protection issue that is often ignored is how investigators identify and manage problems that develop during the course of a trial that are unexpected, related to the research and involve risks to the participants. Investigators and ECs are very good at identifying expected problems such as adverse events and serious adverse events, but these events are expected and known. Having knowledge of unanticipated adverse events or other problems can change the risk-benefit balance in a trial. Therefore, ECs should specify the types of problems the investigators should report to the ECs. For example, rather than reporting known and expected adverse events, unexpected adverse events that are related to the research and involve increased risks should be reported. This will be a subset of all adverse events. In addition, other types of unanticipated problems can occur, such as test tube mislabeling, breaches in confidentiality, or administration of the wrong dose, even if it results in no harm to participants. The EC should have written policies and procedures to identify, manage, and report as required these types of unanticipated problems.

Complaints

While trials are designed to take into account the interests as well as the safety of research participants, sometimes participants become dissatisfied and wish to file a complaint. To ensure that investigators address the complaints of participants, the EC should have a mechanism separate from the investigator for participants to voice their concerns or complaints and provide input about the trial.

Appeals

Whenever the EC disapproves part of a trial or the entire trial, the EC notifies the investigator of the disapproval and provides reasons for the disapproval. In addition, the EC should have a process for the investigator to make an appeal to the EC. In the end, the EC has the final authority to approve or disapprove a trial, but the EC should be willing to hear the investigator's point of view. Under some countries' laws, appeal processes established must be independent of the EC. In these situations, the institution should ensure that the appeal process does not take the authority away from or place undue influence on the EC.

Non-compliance

Once the EC approves a clinical trial protocol, it is the responsibility of the investigator and research staff to conduct the trial according to the terms of reference in the protocol and the determinants of the EC. However, this does not always happen. The EC should have mechanisms to identify non-compliance such as through reporting by investigators and research staff, reports by the sponsor's monitors, and internal audits. When non-compliance is detected, it should be evaluated and appropriate actions should be taken to prevent occurrences of non-compliance to ensure that research participants are protected. Under some laws, serious or continuing non-compliance must be reported to regulatory authorities.

Suspension or Termination of a Trial

The sponsor, investigator or EC can suspend a part or all parts of a trial or terminate a trial entirely. The EC is likely to suspend or terminate its approval when there are unanticipated problems, serious or continuing non-compliance, or study results that cause the EC to question and re-evaluate the risk-benefit balance. The EC should have procedures for determining when it will suspend or terminate a part or all parts of a trial, how it will take into consideration the rights and welfare of enrolled participants, and whether the suspension or termination must be reported to regulatory authorities and others.

Based on the US trials register, there were 9,878 industry-sponsored trials completed or halted over a four-year period, for trials registered from 2006 to 2009; 109 have been suspended, 990 terminated and 142 redrawn, thus together representing 12.7% of all such trials. In comparison, 18.0% of all non-industry-sponsored trials were not completed as planned.

A suspension of a clinical trial can be related to unexpected events such as the death of a participant; an unaccepted change in the duration, severity, or frequency of AEs, or non-compliance of the investigator. Such suspensions should take into account a review of all scientific information as well as the safety and welfare of the enrolled trial participants.

Several factors can also influence the decision to prematurely terminate an ongoing clinical trial, including ethical concerns, alterations in standard clinical practise, or reaching a positive or negative statistical end point earlier than anticipated.

Termination of a trial can be prompted by the investigator, sponsor, or both. This decision can be reached with or without the influence of DSMC. Termination can also be for financial reasons, such as change of the sponsor's lead compound priority or diminishing financial resources, including bankruptcy. An individual study site can also terminate its involvement in a trial, owing to factors such as poor recruitment rate, change among site staff, change in research interest, or maybe financial or contractual issues.

3.5 Quality Assurance of Clinical Trials

Quality Assurance Guidance and Legal Enforcements

Clinical research has globalised over the past decade because of international recognition of a single guideline for conducting industry-sponsored clinical trials on new medicinal products – the ICH GCP Guideline. The ICH defines it this way: *“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 participants. Compliance with this standard provides public assurance that the rights, safety and well-being of trial participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.”*

Conforming to the guideline requires full compliance by many parties, not only regulatory authorities, sponsors and investigators but also study site staff, EC members, project managers, monitors, clinical laboratory technicians, data managers and medical statisticians. However, very few aspects of clinical research are enforced by mandatory educational requirements or quality assurance/control measures as defined by human research protection programmes (HRPPs). Most aspects of HRPPs are regulated by voluntary enforcement, and often according to requirements of an organisation, not the regulatory authority.

By definition, quality assurance programmes should include both educational activities and regular periodic audits to ensure that written standard operating procedures (SOPs) are followed. However, there is no mention of educational activities and SOPs either in the ICH GCP Guideline or the Declaration of Helsinki. For example, the ICH GCP Guideline states:

- *“The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.”*
- *“The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s).”*

Yet, the two requirements mentioned do not define what a qualified clinical investigator needs to know, and leave individual organisations to determine their own definition of procedural issues. Mandatory educational activities of investigators, staff and EC members are also difficult to implement, because of the lack of standard requirements, or indeed legal enforcements.

Quality assurance (QA) is an important aspect of clinical trials, because the data collected must be valid and free of errors and the trial conduct must comply with the protocol. The data are intended for use as an important body of evidence when a test article new medicinal product is reviewed by a government regulatory authority. In this and the next couple of sessions, the most important QA steps of industry-sponsored clinical trials, required by various independent parties, will be described, from regulatory authority inspections of pre-clinical test laboratories to inspections of clinical trial sites. If these authorities identify quality deficiencies during the course of product development, the application may very well be rejected, or parts of the data collected may not be considered good enough – and may be deleted from the body of evidence. The industry is absolutely clear about this condition and complies with the

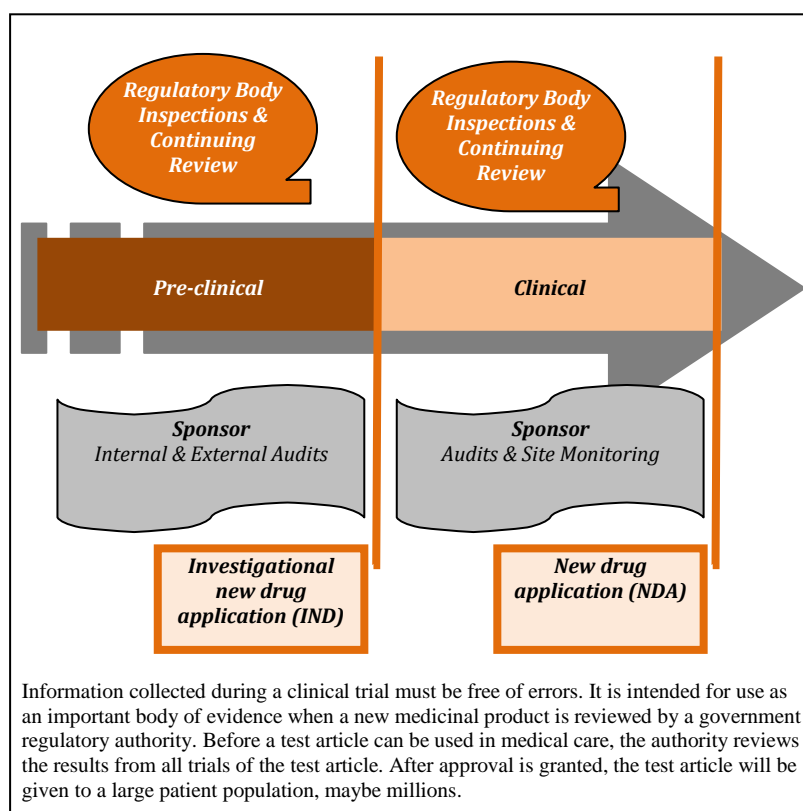
regulated quality assurance steps to ensure marketing approval is granted in a timely and undisputable way.

On the other hand, non-industry-sponsored clinical trials are not usually subject to monitoring, third-party audits or inspections, since the data less commonly support a new medical product application requiring regulatory approval. However, many non-industry-sponsored trials provide important knowledge about the safety and efficacy of an existing approved medicinal product in participants with other diseases or age groups than the product has been labeled and accepted for. Many such trials study the combination therapies of approved drugs, modification of diagnostic or prognostic laboratory tests or medical devices such as ultrasound and X-ray. Various medical procedures, for instance surgical operations, are also subject to clinical trials. Investigator-initiated trials may not be scrutinised in the same way as industry-sponsored trials, but this has been given attention in some regions. For instance, the European Union (EU) Clinical Trials Directive of 2004 makes it clear that any sponsor of a clinical trial must by law adhere to the ICH GCP principles; the directive specifies that a single “sponsor” – whether a person, company or organisation – must take overall responsibility for the initiation, management and financing of a trial, plus all data quality assurance aspects. The US FDA has a similar regulation. However, those are European or American regulations and are therefore not internationally applicable.

Assurance at Large

The following pages address various essential quality assurance steps that should be in place in medicinal product development. There are some differences in this respect – among drugs, vaccines, medical devices and diagnostic/prognostic tools – but the major issues are similar. Since drugs are the dominant type of product developed by the industry, they are the focus here. Governmental regulatory authorities are deeply involved in the drug development program, both pre-clinically and clinically, through a continuous review of each step of the testing, and also by providing advice and permission for the next step of studies.

Regulatory authorities perform onsite inspections that include pre-clinical testing laboratory facilities and drug manufacturing plants (*see illustration*). The data collected from pre-clinical testing facilities are the source of the main body of evidence for the development program, so it is very important that they are conducted in a high-quality way in full compliance with good



laboratory practice (GLP). All pre-clinical laboratories have to be accredited by an independent, non-regulatory and recognised accreditation organisation that carries out inspections at regular intervals. GLP embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived.

Another essential quality assurance aspect is in the manufacturing of the test article. The test article must be produced in a consistent manner – i.e., in line with good manufacturing practice (GMP) – so it is not contaminated or adulterated. Manufacturing processes are clearly defined and controlled; all critical processes are validated to ensure consistency and compliance with specifications.

During the pre-clinical and the clinical testing phase, the sponsor undertakes numerous internal and external audits of the facilities, of contracted service providers and study sites involved.

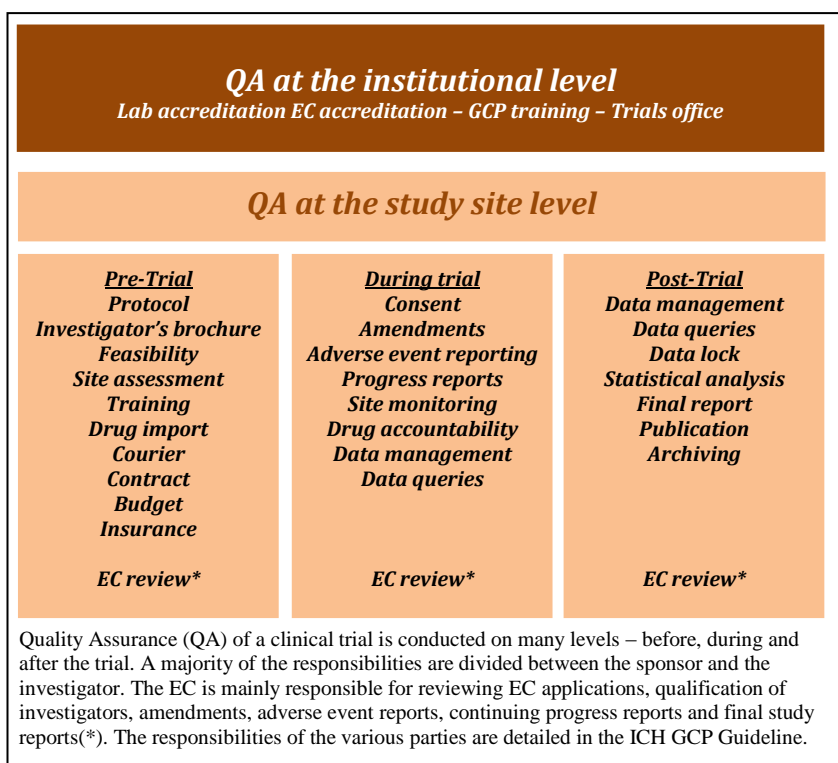
The pre-clinical test article dropout rate is high. Perhaps only four out of an initial one hundred compounds enter animal testing. Of those, maybe only seven out of one hundred will ultimately enter a clinical testing program. Toxicity, lack of tolerance and lack of efficacy are the main dropout reasons. A stringent pre-clinical quality assurance program is crucial because the information collected forms the body of evidence in an investigational new drug application (IND) for entering the clinical testing phase.

Pre-clinical and Clinical Quality Assurance

Quality assurance of a clinical trial is conducted on many levels – before, during and after the trial (*see illustration*).

Pre-trial QA Activities: During the preparation period of a trial, the sponsor is responsible for ensuring its protocol is scientifically sound and ethical, and approved by the appropriate regulatory authority(ies). The sponsor is also responsible for ensuring GMP of the test article and that the investigator’s brochure is updated.

The sponsor will identify suitable investigators and undertake feasibility studies to ensure the site can produce enough participants, that the investigator is qualified, and that the site has sufficient infrastructure in place. The infrastructure on an institutional level can consist of clinical laboratory accreditation, EC accreditation, GCP educational activities, archiving facilities and pharmacy services. Some institutions have established a



centralised office – a “*Clinical Trials Office/Clinical Trials Centre*” – to handle all administrative matters surrounding trials, including quality assurance.

Once the site has been identified, the sponsor is responsible for ensuring that study staff members are knowledgeable about GCP, the protocol and essential regulations, so that the site will comply with applicable regulations. Training will cover protocol-specific tasks to enable the site to conduct the trial in compliance with the protocol. The sponsor also commonly carries out onsite assessment, both at the institutional level – clinical laboratory, pharmacy, EC and clinical investigational facilities – and at the study site level, to ensure staff suitability for the task and to make certain that case report forms and test articles are safely stored. Prior to initiation of the trial, the sponsor will send an application to the regulatory authority for a license for the test article and put in place insurance or a guarantee of indemnification, in the event of any adverse test article reactions. In most trials, tissue samples are sent overseas by means of a courier, so the sponsor also needs to contract courier services for this purpose. Most countries request an import/export certificate for human tissues samples, while some countries do not even allow such export. Before the trial can start, the sponsor and the site must also negotiate contractual and budget issues, spelling out that the trial will be conducted in full compliance with the ICH GCP Guideline and any local requirements and that the investigator will ensure full compliance with the protocol. The investigator is responsible – usually assisted by the sponsor – for submission of the EC application for approval before the trial is finally initiated.

QA activities during the trial: There are a number of QA activities during the conduct of a trial. The most important activity is adverse event reporting by the investigator to the sponsor and, as appropriate, to the EC, verification of data against source documents, resolution of data queries and drug accountability. The sponsor should expedite the safety reporting to all concerned investigator(s) and to the regulatory authority of all adverse drug reactions – both serious and unexpected. Those safety reports should comply with the applicable regulatory requirements. ECs should be informed about any unexpected and related adverse events that can influence the overall risk-benefit balance.

The purpose of trial monitoring is to verify that the rights and well-being of the participants are protected; the trial data are accurate, complete, and confirmable from source documents; and the conduct of the trial is in compliance with the protocol, with GCP, and also with the applicable regulatory requirements. Monitors appointed by the sponsor should be appropriately trained and be familiar with the test article(s), the protocol, the written informed consent document, the sponsor’s SOPs, GCP, and the applicable regulatory requirement(s). The monitor is the main line of communication between the sponsor and the investigator. The monitor should follow the sponsor’s established written SOPs as well as those procedures specified by the sponsor for monitoring a specific trial. The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

Data management of clinical trials is important and highly regulated, since the data collected will be used for statistical analysis and report writing and will subsequently be subject to regulatory review. The data must reflect the reality, i.e., the source data as collected and stored at the study site. Data collection can be made electronically via Internet or by data entry on case report forms. All the data collected will be checked for missing, outlying or inconsistent values. The data management team will forward data

queries to the study site and the resolutions will be returned to the data management team by the monitor.

Post-trial QA activities: Most post-trial QA activities should be handled by the sponsor with the exception of resolution of remaining data queries, summary of the trial outcome, publication and archiving of trial documents. The latter is mandatory since a regulatory authority may decide to make an onsite inspection at a later stage in order to review all the trial source data.

Monitoring of Site Performance

Although trial requirements are carefully set forth in such trial documents as an approved trial protocol, a data management plan, and an accompanying project plan, expectations and requirements can change during the course of a trial. This calls for revising mechanisms and communicating these revisions clearly to all investigators and support staff.

Internal audits of the site selection and management processes require suitable staff and ensure that the trial was conducted in compliance with the protocol and appropriate regulations. Site performance is evaluated by an internal process assessment after the trial has begun, taking into account such trial-related items as percentage of monitoring visits completed on time, percentage of participants capable of being evaluated (no protocol violations), percentage of serious adverse events reported within 24 hours, percentage of properly executed informed consent documents, number of queries/case report form pages and the number of missing data entries/case report form pages.

The QA group conducts site assessments throughout the course of a trial to review protocol and regulatory compliance, to ensure that the safety and welfare of participants are addressed, and to confirm that problems reported by trial monitors have been resolved. The QA criteria for site selection include high participant enrollment, high staff turnover and/or abnormal number of adverse events (high/low).

To be successful as a monitor, it is important to develop a sense for what should be monitored at each site and how much attention should be given to each activity. It helps to be aware of where problems are most likely to arise during the conduct of a trial. The following items receive the most deficiencies during site audits/inspections: failure to follow the protocol; failure to keep adequate and accurate records; problems with the informed consent form; failure to report adverse events as required by law, regulation, or the sponsor and failure to account for the disposition of study drugs. Most sponsors have developed a set of generic monitoring SOPs. However, in addition, the protocol dictates the conduct of the study by establishing the procedures that participants must undergo and a schedule of assessments. The more activities that are required during a study visit, the more monitoring will be required and the more likely the monitor is to find deficiencies.

Site monitoring visits are made on a regular basis – from daily for phase I trials to monthly or less seldom for simple trials such as phase II/III vaccine trials. The monitor finalises a report after each visit, and each report is submitted to the monitor's supervisors – usually a project manager of the sponsor/CRO – and to the investigator. In a recent trend, the institution asks the sponsor to provide the EC with a copy of each monitoring report for the institution's research sites when the findings of the monitor can affect the safety of the trial participants or the conduct of the trial. Some institutions have added this request into the clinical trial agreement, as it forms a part of the institution's/organisation's quality assurance policy.

3.6 Human Research Protection Programme Accreditation

One way to ensure that clinical trials are conducted ethically is to join an accreditation programme to make sure the organisation follows modern concepts of clinical research. An example highlighted here is the Association for the Accreditation of Human Research Protection Programs in the US (AAHRPP, <http://www.AAHRPP.org>). AAHRPP was established in 2001 to advance accreditation as a means of ensuring excellent and ethically sound research. The AAHRPP is a voluntary, peer-driven and educationally based model of accreditation. It seeks to recognise high-quality HRPPs of research organisations.

The accreditation standards meet or exceed international and local regulatory requirements for protection, and are also reasonable, attainable and representative of current best practices. The organisation/institution/company/EC seeking accreditation, referred to as the “organisation,” must have a “human research protection program,” as defined by the accreditation standards (*see text box*).

As of December 2009, a total of 200 organisations had obtained the accreditation; 176 of them are research or health care organisations, along with 12 ECs, one clinical trial services provider and one pharmaceutical company. Of the top 26 medical schools in the US, 14 are accredited.

The initial step in the accreditation process is for an organisation to engage in a thorough self-assessment. This enables it to identify and remedy programme weaknesses. Prior to seeking accreditation, the organisation should develop a clear concept of the programmatic unit that will seek accreditation. The results of the internal review are submitted to AAHRPP in the form of an application.

AAHRPP Accreditation Standards

Domain I: Organization

STANDARD I-1: The Organization has a systematic and comprehensive Human Research Protection Program that affords protections for all research participants. Individuals within the Organization are knowledgeable about and follow the policies and procedures of the Human Research Protection Program.

- Element I.1.A. The Organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.
- Element I.1.B. The Organization delegates responsibility for the Human Research Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program.
- Element I.1.C. The Organization has and follows written policies and procedures that allow the Institutional Review Board or Ethics Committee to function independently of other organizational entities in protecting research participants.
- Element I.1.D. The Organization has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate.
- Element I.1.E. The Organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.
- Element I.1.F. The Organization has and follows written policies and procedures for reviewing the scientific or scholarly validity of a proposed research study. Such procedures are coordinated with the ethics review process.
- Element I.1.G. The Organization has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws.

STANDARD I-2: The Organization ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that the Organization conducts or oversees.

STANDARD I-3: The Organization's transnational research activities are consistent with the ethical principles set forth in its Human Research Protection Program and meet equivalent levels of participant protection as research.

The following part of this Chapter lists the key elements of the AAHRPP self-assessment recommendations for the three domains of assessment: (I) Organisation, (II) EC and (III) Researchers. This exercise enables two important aspects of human research protection assurances to be addressed. Are your organisation and your EC up to an acceptable standard? What are the key elements of the EC's governance, operation and responsibilities?

3.7 The AAHRPP Accreditation Standards

Organisation

This domain describes the structural characteristics of the entity that assumes responsibility for the HRPP and applies for accreditation. The organisational structure is the means by which the organisation meets the range of responsibilities of the HRPP (*see text boxes*). The organisation applies its HRPP to all research regardless of funding source, type of research, or location of the conducted research. The organisation exercises these responsibilities through relationships with investigators and staff, ECs, sponsors, participants and the community.

An organisation has the responsibility not only to protect the rights and welfare of human research participants but also to involve them in the research. The involvement of research participants at every stage helps everyone to achieve the ethical principle of respect for persons. In addition to enhancing the appropriate safeguards and protecting the rights and welfare of research participants, involving them in the research process can improve recruitment and retention and also improve the overall quality of research.

The conduct of research is highly dependent upon the partnership between organisations and sponsors. A sponsor is the company, institution, donor or government agency responsible for the initiation, management or financing of a trial. Sponsors may enter into agreements

conducted in the Organization's principal location while complying with local laws and taking into account cultural context.

STANDARD 1-4: The Organization responds to the concerns of research participants.

- Element 1.4.A. The Organization has and follows written policies and procedures that establish a safe, confidential, and reliable channel for current, prospective, or past research participants or their designated representatives that permits them to discuss problems, concerns, and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research protocol or plan.
- Element 1.4.B. The Organization conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement.
- Element 1.4.C. The Organization promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results.

STANDARD 1-5: The Organization measures and improves, when necessary, compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization also measures and improves, when necessary, the quality, effectiveness, and efficiency of the Human Research Protection Program.

- Element 1.5.A. The Organization conducts audits or surveys or uses other methods to assess compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization makes improvements to increase compliance, when necessary.
- Element 1.5.B. The Organization conducts audits or surveys or uses other methods to assess the quality, efficiency, and effectiveness of the Human Research Protection Program. The Organization identifies strengths and weaknesses of the Human Research Protection Program and makes improvements, when necessary, to increase the quality, efficiency, and effectiveness of the program.
- Element 1.5.C. The Organization has and follows written policies and procedures so that Researchers and Research Staff may bring forward to the Organization concerns or suggestions regarding the Human Research Protection Program, including the ethics review process.
- Element 1.5.D. The Organization has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements. The Organization works with the Institutional Review Board or Ethics Committee, when appropriate, to ensure that participants are protected when non-compliance occurs. Such

with intermediaries that act as agents, such as clinical trial services providers or coordinating centres. In sponsored research, both the sponsor and the organisation have obligations to protect human participants. In this domain, the focus is the obligations of the organisation. In seeking accreditation, the organisation must address human research protection requirements with all sponsors, and apply its HRPP to all sponsored researches.

Commentary: In summary, the AAHRPP accreditation standards spell out that the **ORGANISATION** is responsible for developing a number of written procedures addressing very crucial and essential aspects of an HRPP.

The most important issues addressed here are that the organisation must develop written procedures for an independent EC, as well as written procedures addressing the review of the scientific value of a research protocol.

The organisation should also establish procedures ensuring that the research complies with applicable laws and regulations, by developing written procedures for educational activities, internal audits and conflict of interest policies. Other topics to be addressed in written procedures are safe storage and accountability of test articles as well as HRPP issues built into sponsor agreements.

Summary: The ORGANISATION is responsible for developing written human research protection programme procedures addressing, for instance:

- EC operation.
- Scientific review.
- Educational activities.
- Applicable laws.
- Resources.
- Transnational research.
- Participants' concerns.
- Compliance audits.
- Conflict of interest.
- Investigative products.
- Sponsor agreements.

policies and procedures include reporting these actions, when appropriate.

STANDARD I-6: The Organization has and follows written policies and procedures to ensure that research is conducted so that financial conflicts of interest are identified, managed, and minimized or eliminated.

- Element I.6.A. The Organization has and follows written policies and procedures to identify, manage, and minimize or eliminate financial conflicts of interest of the Organization that could influence the conduct of the research or the integrity of the Human Research Protection Program.
- Element I.6.B. The Organization has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of Researchers and Research Staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. The Organization works with the Institutional Review Board or Ethics Committee in ensuring that financial conflicts of interest are managed and minimized or eliminated, when appropriate.

STANDARD I-7: The Organization has and follows written policies and procedures to ensure that the use of any investigational or unlicensed test article complies with all applicable legal and regulatory requirements.

- Element I.7.A. When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.
- Element I.7.B. The Organization has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.
- Element I.7.C. The Organization has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article.

STANDARD I-8: The Organization works with public, industry, and private Sponsors to apply the requirements of the Human Research Protection Program to all participants.

- Element I.8.A. The Organization has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate.
- Element I.8.B. In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, the Organization has a written agreement with the Sponsor that the Sponsor promptly reports to the Organization findings that could affect the safety of

Ethics Committee

Within an HRPP, responsibilities must be delegated for providing ethical review and oversight of research. These responsibilities are assigned differently in different organisations; in many, the EC, along with support personnel and systems, provides these functions. In more complex organisations, there might be multiple ECs and a general oversight office. This domain of standards sets forth requirements for the ethical oversight of research.

An EC is a body established generally under laws, regulations, codes, and guidance to protect the rights and welfare of human participants. The HRPP must have mechanisms in place to ensure the independence of its ethics review and oversight functions from other units within the organisation, particularly with respect to decision-making regarding the ethics of research involving human participants (*see text boxes*). EC structure, composition, operations and review standards are set forth in laws, regulations, codes and guidance. The following are the accreditation standards related to the EC used by AAHRPP.

Commentary: In summary, the AAHRPP accreditation standards clearly spell out that **ETHICS COMMITTEES** should operate according to written procedures addressing very crucial and essential aspects of an HRPP.

Summary: The ETHICS COMMITTEE is responsible for developing written human research protection programme procedures addressing, for instance:

- EC structure.
- EC membership and composition.
- Scientific review.
- Research exempted from review.
- Expedited/full review.
- Risk-benefit review.
- Privacy and confidentiality.
- Consent process.
- Vulnerable participants.
- Archiving.

participants or influence the conduct of the study.

- Element I.8.C. When the Sponsor has the responsibility to conduct data and safety monitoring, the Organization has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to the Organization.
- Element I.8.D. Before initiating research, the Organization has a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that Researchers and Sponsors will play in the publication or disclosure of results.
- Element I.8.E. When participant safety could be directly affected by study results after the study has ended, the Organization has a written agreement with the Sponsor that the Researcher or Organization will be notified of the results in order to consider informing participants.

AAHRPP Accreditation Standards

Domain II: Institutional Review Board or Ethics Committee

Standard II-1: The structure and composition of the IRB or EC are appropriate to the amount and nature of the research reviewed and in accordance with requirements of applicable laws, regulations, codes, and guidance.

- Element II.1.A. The IRB or EC membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB or EC roster. The IRB or EC has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB or EC regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.
- Element II.1.B. The IRB or EC has qualified leadership (e.g., chair and vice chair) and qualified members and staff. Membership and composition of the IRB or EC are periodically reviewed and adjusted as appropriate.
- Element II.1.C. The Organization has and follows written policies and procedures to separate competing business interests from ethics review functions.
- Element II.1.D. The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.

- Element II.1.E. The IRB or EC has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan.

Standard II-2: The IRB or EC evaluates each research protocol or plan to ensure the protection of participants.

- Element II.2.A. The IRB or EC has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB or EC. Such policies and procedures indicate that exemption determinations are not to be made by Researchers or others who might have a conflict of interest regarding the studies.
- Element II.2.B. The IRB or EC has and follows written policies and procedures for addressing protection of participants in research that is exempt from applicable laws and regulations. These functions may be delegated to an entity other than the IRB or EC.
- Element II.2.C. The IRB or EC has and follows written policies and procedures for conducting meetings by the convened IRB or EC.
- Element II.2.D. The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB or EC.
 - Element II.2.D.1. – Initial review
 - Element II.2.D.2. – Continuing review
 - Element II.2.D.3. – Review of proposed modifications to previously approved research
- Element II.2.E. The IRB or EC has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used.
 - Element II.2.E.1. – Initial review
 - Element II.2.E.2. – Continuing review
 - Element II.2.E.3. – Review of proposed modifications to previously approved research
- Element II.2.F. The IRB or EC has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate.
- Element II.2.G. The IRB or EC has and follows written policies and procedures for suspending or terminating IRB or EC approval of research, if warranted, and for reporting these actions, when appropriate.
- Element II.2.H. The IRB or EC has and follows policies and procedures for managing multi-site research by defining the responsibilities of participating sites that are relevant to the protection of research participants, such as reporting of unanticipated problems or interim results.

Standard II-3: The IRB or EC approves each research protocol or plan according to criteria based on applicable laws, regulations, codes, and guidance.

- Element II.3.A. The IRB or EC has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society.
- Element II.3.B. The IRB or EC has and follows written policies and procedures for reviewing the plan for data and safety monitoring, when applicable, and determines that the data and safety monitoring plan provides adequate protection for participants.
- Element II.3.C. The IRB or EC has and follows written policies and procedures to evaluate the equitable selection of participants.
 - Element II.3.C.1. The IRB or EC has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate.
- Element II.3.D. The IRB or EC has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research.
- Element II.3.E. The IRB or EC has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data, when appropriate, preliminary to the research, during the research, and after the conclusion of the research.
- Element II.3.F. The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process.
- Element II.3.G. The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.

Standard II-4: The IRB or EC provides additional protections for individuals who are vulnerable to coercion or undue influence and participate in research.

- Element II.4.A. The IRB or EC has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.
- Element II.4.B. The IRB or EC has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making

Virtually all the points addressed by the AAHRPP accreditation scheme have been elaborated in other Chapters of this Guide, and several are addressed in the ICH GCP Guideline. This strongly emphasises that an EC must have written operational procedures in place addressing the essential elements of research participant protection, as defined both by AAHRPP and by many other local or national directives about an EC's governance, operation and responsibilities. The organisation is, however, responsible for making sure that the EC's written operating procedures comply with institutional, local and international guidance and regulations on human research. The organisation must also warrant – by internal audits for instance – that the EC fully complies with its written operational procedures.

Investigator and Staff

The environment in which investigators and staff conduct research and the type of research they perform influence their roles and responsibilities. Competent, informed, conscientious, compassionate and responsible investigators and staff provide the best possible protection for human participants. This domain of standards sets forth requirements for investigators and staff involved in research involving human participants (*see text boxes*). As part of its HRPP, an organisation can improve its protection of participants if it has arrangements ascertaining and enhancing the competence of investigators and staff.

Commentary: In summary, the AAHRPP accreditation standards clearly spell out that the **INVESTIGATOR** and **STAFF** should operate according to all aspects of human research protection programme procedures.

capacity is in question.

- Element II.4.C. The IRB or EC has and follows written policies and procedures for making exceptions to consent requirements for planned emergency research and reviews such exceptions according to applicable laws, regulations, codes, and guidance.

Standard II-5: The IRB or EC maintains documentation of its activities.

- Element II.5.A. The IRB or EC maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, Sponsor requirements, and organizational policies and procedures.
- Element II.5.B. The IRB or EC documents discussions and decisions on research studies and activities in accordance with legal and regulatory requirements, Sponsor requirements, if any, and organizational policies and procedures.

AAHRPP Accreditation Standards

Domain III: Researcher and Research Staff

Standard III-1: In addition to following applicable laws and regulations, Researchers and Research Staff adhere to ethical principles and standards appropriate for their discipline. In designing and conducting research studies, Researchers and Research Staff have the protection of the rights and welfare of research participants as a primary concern.

- Element III.1.A. Researchers and Research Staff know which of the activities they conduct are overseen by the Human Research Protection Program, and they seek guidance when appropriate.
- Element III.1.B. Researchers and Research Staff identify and disclose financial interests according to organizational policies and regulatory requirements and, with the Organization, manage, minimize, or eliminate financial conflicts of interest.
- Element III.1.C. Researchers employ sound study design in accordance with the standards of their discipline. Researchers design studies in a manner that minimizes risks to participants.
- Element III.1.D. Researchers determine that the resources necessary to protect participants are present before conducting each research study.
- Element III.1.E. Researchers and Research Staff recruit participants in a fair and equitable manner.
- Element III.1.F. Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary

Quality Assurance and Quality Control

Over the past few decades, we have seen a welcome development of guidance and regulations surrounding human research projects as a result of our improved understanding of the strong need to protect human research participants – no longer tolerating poor science and research ethics.

Non-institutional guidance by the Declaration of Helsinki and the ICH GCP Guideline represents general ideas regarding human research. These internationally recognised documents have been developed by a core group of international professionals representing investigators, industry and regulatory authorities. As they stand, they have no legal power. However, many countries, sponsors and/or organisations have adopted those internationally valid, ethical documents as deemed mandatory.

In addition, each jurisdiction has developed its own legal framework for the protection of human research participants. Such non-institutional HRPPs provide the international and national framework of human research operation, but they do not enforce quality control to keep an individual organisation, EC or investigator and staff in full compliance. Similarly, regulatory authorities are never or seldom responsible for quality control at an institutional level, even though they establish legally valid quality assurance structures. Once in a while, regulatory authorities may perform an inspection at a study site for a specific clinical trial. But these are not full “*audits*” of an organisation, EC or investigators and staff, ensuring overall compliance with either national and organisational regulations, or applicable written SOPs.

There has been an increase in demand – though not yet legally enforced – that the organisations must take steps to make sure that trial participants’ well-being, privacy and confidentiality are handled appropriately. The operation of an EC is now well defined and generally accepted. However, in the end, it is the investigator and the site staff that have control over the participants’ well-being during the course of a clinical trial.

participation to foster informed decision-making by participants.

- Element III.1.G. Researchers and Research Staff have a process to address participants’ concerns, complaints, or requests for information.

Standard III-2: Researchers and Research Staff meet requirements for conducting research with participants and comply with all applicable laws, regulations, codes, and guidance; the Organization’s policies and procedures for protecting research participants; and the IRB’s or EC’s determinations.

- Element III.2.A. Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization’s policies and procedures regarding the protection of research participants.
- Element III.2.B. Researchers maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions.
- Element III.2.C. Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to the policies and procedures of the Organization and to the requirements or determinations of the IRB or EC.
- Element III.2.D. Researchers and Research Staff follow reporting requirements in accordance with applicable laws, regulations, codes, and guidance; the Organization’s policies and procedures; and the IRB’s or EC’s requirements.

Chapter 4. Scenarios of Ethics Committee Review

4.1 Introduction to Practical EC Review

This last Chapter includes several specifically themed sets of EC scenarios that cover a wide range of topics in relation to ethics in human research, from expedited or full EC review to clinical trials registry. Please accept that these are simplified scenarios, although most reflect real cases. Also, since the information is only briefly provided, it is impossible to undertake an in-depth narrative review. Each set of scenarios addresses a specific ethics issue that should be identified and addressed. At the end of each set, comments are also provided. Most of the scenarios have been utilised in educational activities for EC members and have proven helpful in translating theory to practice, especially for novice EC members.

If this Guide is used for educational purposes of EC members or groups of clinical research professionals, the scenarios and their commentaries can be studied by participants and thereafter discussed to seek a consensus. Now and again, you will almost certainly find that your views differ both from those reflected here and from those of fellow participants. This is, in fact, what a meaningful review process should reflect: diversity in one's thinking, searching and arguing for a general consensus.

The scenarios deal with:

Issues of Ethics of Clinical Trials:

- Risk-benefit balance.
- Informed consent process.
- Vulnerable participants.
- Privacy and confidentiality.
- Data safety monitoring.
- Participant recruitment procedures.
- Qualification of investigators.
- Conflict of interest.
- Clinical trial insurance and indemnity.
- Essential clinical trial documents.
- Clinical trial registration.
- Dissemination of trial results.

Issues of EC Procedures:

- Local laws and institutional guidelines.
- Proportionate EC review.
- Expedited/full board review.
- Continuing review.
- Acceptability of trial.
- Trial amendments.
- Adverse event reporting.
- Anticipated problems.
- Suspension or termination of a trial.
- Complaints.
- Appeals.
- Non-compliance.

Risk-Benefit Balance - Scenarios

The following pages include scenarios about risk-benefit balance. Does the protocol in each scenario illustrate an acceptable risk-benefit balance situation or not? Write your comments, and view ours.

Risk-Benefit Balance - Scenario 1

Dr. Kristianna Haugen - consultant oncologist - has been approached by a research organisation that is handling a phase I clinical trial of a novel drug for the treatment of acute small cell carcinoma of the lung for a multinational pharmaceutical company based in the US. The drug under evaluation will be tested in a small group of patients with late stage cancer and requires the investigator to draw regular quantities of blood amounting to no more than 800 ml in total over a two-week period, so that a full range of haematological, biochemical, pharmacokinetic and pharmacodynamic parameters can be assessed. The size of the tumour will also be measured. Dr. Haugen has background pre-clinical information concerning the drug from some publications she read several months ago, and thinks the new drug being evaluated will be a breakthrough in the treatment of cancer. She is naturally very keen to be an investigator for the trial and duly submits an application to her hospital's EC for consideration.

Risk-Benefit Balance - Scenario 2

Professor Chandra Sekaran - an eminent pediatrician at a university medical institution - has a keen interest in children's vaccination. He has worked in collaboration for some time with a colleague in the US for the development of a new vaccine for a certain infection in children. Professor Sekaran's colleague, who is employed by an international vaccine research group, is now seeking suitable investigators willing to undertake the clinical trial. The risk of mild adverse events associated with the vaccine such as swollen arms and glands is 5 in 100, and the risk of serious adverse events related to the vaccine, such as the occurrence of convulsions and permanent brain damage, is 1 in 5,000. However, Professor Sekaran is aware that if a child does not receive the vaccine and contracts the disease as a result of becoming infected, about 1 in 500 will develop severe, life-threatening and persistent complications as a result of the infection. Professor Sekaran submits an application to his EC for review.

Risk-Benefit Balance - Scenario 3

Professor Greta Garbo - a paediatric endocrinologist - has received a small research grant to undertake a clinical trial that aims to identify the age at onset of the effect of growth hormone in children in relation to two different infant formulas. She has written a trial protocol and intends to ask mothers with babies, who gave birth in the department of obstetrics and gynecology, if they would permit their child to take part in the trial. The trial protocol that Professor Garbo wrote states she will follow the children from birth until they are 12 months of age. She will also take a sample of blood (4 ml) from each of the children at 0, 6, 8, 10 and 12 months, in order to perform growth factor assays, with an aim to determine the age at onset of the effect of growth hormone in children. After preparing the necessary documentation, Professor Garbo submits her application to the university's EC for review.

Comments to Risk-Benefit Balance - Scenario 1

Dr. Haugen plans to become the investigator of a lung cancer phase I clinical trial. The trial requires her to draw regular quantities of blood, amounting to no more than 800 ml in total over a two-week period. The EC chair was surprised when he read the protocol, i.e., that as much as 800 ml of blood would be drawn from terminally ill cancer patients. Being a specialist in haematology, he knows that a normal blood donation of healthy individuals varies from 200 to 550 ml, depending on the country, and a full blood donation should in principle not be repeated over an eight-week period. The chair noted that the protocol had listed a well-known medical university in the United Kingdom as a potential trial site, so he simply sent an email to the EC chair at that university and asked for comments on the protocol in question. It took just a few hours before the email reply: *“No, we did not accept the protocol, since it is harmful and unethical to collect 800 ml in terminally ill patients – no gain, just pain for very sick participants.”* The EC chair could not disapprove the protocol, since that can only be done by during a full EC review meeting.

Note: This scenario in fact represents a true case; sponsors may assume that even if one EC does not accept a protocol, maybe another will. Consulting other ECs involved in the review of the same protocol is in fact good practice and should be encouraged.

Comments to Risk-Benefit Balance - Scenario 2

Professor Sekaran is considering participating in a new vaccine trial for a certain infection in his area of expertise. The EC review is focused on the risk of serious adverse events associated with the vaccine; the occurrence of convulsions and permanent brain damage for the vaccine is 1 in 5,000. On the other hand, if a child does not receive the vaccine and contracts the disease as a result of becoming infected, the risk is about 1 in 500 of children developing severe, life-threatening and persistent complications. The EC members reached consensus that the development of an efficient vaccine would be very beneficial, since as many as 10 in 5,000 children will develop severe complications from the disease itself. Although serious side-effects occur in 1 in 5,000 children vaccinated, the EC determined that the benefits outweighed the risk of harm. An additional piece of information was that the disease is quite prevalent in the community where the trial was to be conducted, providing potential societal benefits and maybe protection to those participating in the trial.

Note: This scenario is common where the risk of disease complications is evaluated against the risk of vaccine-induced complications. There is an ongoing debate about the general benefit of vaccinating populations, so our views diverge here.

Comments to Risk-Benefit Balance - Scenario 3

Professor Garbo plans to conduct an infant formula clinical trial that aims to identify the age at onset of the effect of growth hormone in children. The trial protocol specifies that she will follow the children from birth until they are 12 months of age and that she will take a sample of blood (4 ml) from each of the children at 0, 6, 8, 10 and 12 months, in order to perform growth

factor assays. The EC chair understood that this is an intervention trial involving more than minimal risk, but he also realised that the trial population is vulnerable in nature. The EC application was thus subject to a full EC review. The EC members did not identify any major risks of concern and accepted the application as it stood. The trial was regarded as scientifically valid. Another important factor was that the investigator would perform a full physical examination at each visit, inform the parents about the blood sample test results, and also be available for consultation for any health-related issues during the course of the trial. The EC members took this as being of significant benefit for the children and their parents.

Note: Taking blood samples is not associated with a risk more than the minimal level, although there may be some degree of sudden and short-term discomfort.

Informed Consent Process – Scenarios

The following pages include scenarios about the informed consent process. Write your comments, and view ours.

Scenario Informed Consent Process - Workshop

Today is Friday, July 13th and the institutional EC has scheduled an educational workshop for 13 novice study site staff and three new EC members. The focus of the entire workshop is on the informed consent process. There are five scenarios that the EC deputy chair will discuss with the workshop participants.

The deputy chair - Dr. William Wang - presents the first scenario. *“The first scenario represents a recent EC application of an influenza treatment clinical trial. The potential participants were recruited from the hospital’s emergency department, as they turned up for treatment of acute influenza symptoms. The participants were informed about the trial by the ward manager. Those who agreed to participate met the investigator for a full physical examination, took some laboratory tests, and received further information about the trial prior to signing the informed consent form and starting the test treatment. Do you see any problems with this informed consent process?”* None of the workshop participants showed the slightest interest in responding to the question, so Dr. Wang continued: *“Well, my dear friends, this scenario is about the duration between conducting the consent interview and signing the informed consent form - the so-called waiting period. The potential participants should have sufficient time to read the informed consent, ask questions and consult relatives or friends. So the waiting period should normally not be less than a day. In some countries, I have heard that it may take even weeks before the participant is ready to make a decision. In the present scenario, we dealt with a relatively mild disorder - influenza. More importantly is that influenza is an acute disease that may last only five days, so the waiting period cannot be too long since the illness would have passed. What we suggested to the investigator of the current trial was to see that the participants were given enough time to study the consent form, be able to consult a relative or friend – maybe by phone – and then meet the investigator again before deciding whether to participate or not.”*

Note: It is important for EC members not only to study the informed consent form, but also to understand the informed consent *process*. One important factor of this process is the *waiting period*. In principle, the waiting period should be long enough to ensure that the potential participants understand all aspects of the consent form.

Dr. Wang continues with the second scenario. *“The first scenario told us that we need to give the potential participant enough time and enough support to be able to reflect and understand the contents of the informed consent form. One important aspect of achieving this objective is to have clear messages in the informed consent form, using layman’s language. The consent form should be as short as possible without compromising the understanding of the consent form contents. From time to time, our EC comes across informed consent forms of 15-20 pages, using language that only lawyers really understand; written by lawyers for other lawyers, and not for the potential participants. Can anyone please tell me how we can avoid such consent forms?”* Dr. Wang looks around

at the workshop participants, and his eyes stop at a young woman with small, round spectacles. She fumbles with her glasses and looks at Dr. Wang and answers: *“Well, first I suggest that the informed consent be written by the investigator or a person with in-depth knowledge about the protocol and the science behind the trial. And second, I do not think a lawyer should be involved in writing an informed consent form primarily since it is not a legal document, rather a standardised document that will facilitate the process of obtaining consent from the participant. It is always risky that a document becomes technical and long when legal aspects are aimed to be covered.”* Dr. Wang looks surprised and continues: *“Yes, you are absolutely correct. However, it may be a good practice to have some legal advice on the last informed consent version. Also, many phrases in an informed consent form are standard phrases, and that is the reason we have posted many such phrases on our EC’s homepage. The length of an informed consent form can be restricted to 3-4 pages, which will still allow for the 20 mandatory points listed by the ICH GCP E6 Guideline to be appropriately addressed. One additional piece of information – it is better to have a clear consent form covering all aspects of the trial than to have participants dropping out simply because they were not well informed about their responsibilities, treatment regimes and types of examinations.”*

Note: Rule number one for the EC in ensuring that the informed consent process will be up to acceptable standards is to make clear that technical and scientific terms should not be included and that the form is kept as short as possible.

“So we can now conclude that the potential participant should be given enough time to reflect on the information about the trial and that the information should be factual and relatively easy to understand for a layperson. Now let us address another important aspect of the informed consent process,” Dr. Wang continues. *“Let’s address the language to be used in the consent form. As you may all know, many people in our society have an excellent command of English, but the vast majority do not understand or only vaguely understand English. This is the reason that we have to translate the informed consent from English into Chinese, so that all or most of our peers in society can have the possibility of participating in a clinical trial. Do you think it is easy to do provide the translation, and who would be the best person to do this?”* The young woman with the small, round spectacles again suggests: *“The most qualified person must be the investigator.”* *“Well, this time, young lady, you may not be fully correct. You see, from our experience, investigators are sometimes poor translators. To my understanding, the best consent form translation can only be provided when two certified translators are consulted; one translates from English to Chinese and the other re-translates from Chinese to English, and thereafter they have a meeting to discuss any differences between the original English and the re-translated English version. In fact, a large portion of EC review meeting discussions are focused on the disparities between the English and the Chinese consent forms, and this can be avoided by using certified translators.”*

Note: A correctly translated informed consent form makes certain that the original informed consent information is correctly presented to non-native-English-speaking potential participants.

“Dear colleagues, now we have set aside a reasonable waiting time for the potential participants to digest a professionally translated short and easily understandable informed consent form before deciding whether to participate or not. Do you reckon that we have done enough?” Dr. Wang asks the participants. One of the workshop delegates – a young male doctor with a red stethoscope dangling around his neck in a very stylish manner – raises his arm. *“Well, Dr. Wong, I would just like to know how we can be sure that the potential participants are in fact subject to a fair informed consent process? I mean, in theory, it may look good on paper, but what about in practice? The risk is that a very busy investigator rushes up to a participant and smartly convinces him or her to participate, without going through the whole consent process as it has been detailed in the EC application and approved by the EC. The participants may not like to upset the doctor and will therefore not ask any difficult questions, nor refuse participation.”* Dr. Wang looks content and points his finger to his head: *“You got it, but you got my name wrong – Dr. Wang, not Dr. Wong. The EC has little or no possibility of ensuring a fair, factual informed consent process. Can I please have suggestions on how to approach this delicate problem?”* Dr. Wang sits down in the EC chair at the end of the conference table and stretches his arms over his head. *“No proposal? I will probably surprise you by stating that I would rather anyone other than the investigator to seek consent from potential participants. This is what I always practice in my own research, since in the past I have made the same mistake myself – i.e., rushing the informed consent process. Today, I always delegate the informed consent process to my research nurse as she is regarded more as a friend by the potential participants, and they know that they can ask ‘stupid’ questions that otherwise would not be heard.”*

Note: A staff member of the research team other than the investigator is often more suitable for administering the informed consent process. However, some countries have legally enforced that only qualified physicians can obtain informed consent.

“Only 10 minutes are left of this workshop, so please, ask me one or two questions in turn,” Dr. Wang says. One of the delegates who was playing with his mobile phone during the entire workshop wakes up and wonders: *“What about potential participants who cannot grasp the consent information. They simply do not understand what a test article or what an informed consent is. Can we just skip the informed consent process for those individuals and without wasting any time, simply enroll them in the trial?”* Dr. Wang reflects on the question without showing any sign of annoyance. *“Some individuals never get it,”* he mutters. *“When a potential participant is unable to understand the contents of the informed consent, we need to engage a representative for the potential participant in the whole consent process. Children and participants with impaired decision-making capabilities are examples of potential participants that need to have a representative – a parent, relative or a caretaker, for instance. The informed consent process in such trials should be scrutinised in detail by the EC, so that it is absolutely certain that each participant has a representative that has taken part in the informed consent, and subsequently makes the decision to participate, or not.”*

Note: For informed consent involving vulnerable potential participants, a representative must be present and must engage in the whole consent process.

Finally, Dr. Wang declares: *“Time’s up. Please sign the workshop participation list, and we will forward a certificate of participation, as required for new EC members and inexperienced investigators.”*

Informed Consent Process - Scenario 1

Can participants be charged a fee during the course of a trial?

Dr. Olle Bo is a specialist surgeon in a university hospital. One of his areas of expertise is the surgical treatment of snoring. Some anti-snoring devices can be very simple but others very complex. The majority of similar devices are available in drug stores or through direct mail. However, severe snoring can lead to the onset of breathing problems in patients, thus making them good candidates for surgical procedures. At the hospital where Dr. Bo is employed, the participant has to cover some of the cost of the snoring device surgery – US\$700 for part of the cost for the surgery, and US\$500 for the entire cost of the snoring device. An American medical device company has now asked Dr. Bo if he would like to be involved in a trial to test the safety and efficacy of its new soft palatal implant procedure for reduction of palatal snoring. The soft palate is the middle part of the roof of the mouth. The anti-snoring device is an implant braided of polyester filaments. Dr. Bo agrees to act as the investigator and starts to draft the informed consent form. *“There will be a participation fee in this clinical trial of US\$700 in total. This fee corresponds to the fee for the surgery that you have to pay even if you choose not to participate in the study but instead have a normal non-trial associated operation. However, you will not be charged for the cost of the test snoring device as a trial participant, a cost that would otherwise be US\$500.”* Upon finishing the consent form, Dr. Bo submits it together with all other application documents to the local EC.

Informed Consent Process - Scenario 2

Can the informed consent text be improved?

Dr. Elisabeth Crown has just graduated from medical school and has taken up a residential post at the same university hospital. Professor Jonathan Boss has decided to involve Dr. Crown in an investigator-initiated clinical trial harvesting bone marrow from healthy volunteers. Professor Boss asks Dr. Crown about her interest in being a co-investigator. Dr. Crown is not that keen because she is not familiar with the procedures involved in taking bone marrow biopsies, and is in fact more interested in conducting research in the elderly. Still, she finds it difficult to refuse the invitation, so she replies: *“Of course. Thank you for considering me.”* Professor Boss answers: *“Good. Please prepare an informed consent form that outlines the details of the trial. We have no funding, and the hospital will not be able to cover any costs for side-effects that may occur during the biopsy. Also, ensure participants are informed they will not be able to claim any property rights over their harvested cells, since we will certainly file a patent ourselves.”* Dr. Crown has no experience at all in writing an informed consent form, but is much too proud to let anyone know about her lack of knowledge. So she writes up the informed consent form, including the following two sentences: *“I waive any possibility of compensation for injuries that I may receive as a result of participation in this research. By giving consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples*

obtained in the course of the research.” Professor Boss did not read through the informed consent form before the EC application was submitted.

Comments to Informed Consent Process - Scenario 1

Can participants be charged a fee during the course of a trial?

Dr. Bo is planning to initiate a snoring device surgical trial. In the participant informed consent form, he states: *“There will be a fee for you as a participant in this clinical trial of US\$700 in total. This fee corresponds to the surgery you have to pay even if you choose not to participate in the study, but instead have a normal non-study-associated operation. However, you will not be charged for the cost of the test snoring device as a study participant, a cost that would otherwise be US\$500.”* The EC members thought that charging trial participants was controversial. After some discussions, the EC chair summarised: *“It may be seen as appropriate by some, but not by others. In this scenario, the participant will be charged exactly the same amount for the surgery as for standard care. However, there will be no fee charged for the test snoring device, while there is such a charge when the surgery is performed within the framework of standard care. The charging arrangement seems to be reasonable since it has clearly been declared upfront in the informed consent form and the patient has a choice of participation. However, charging for the test snoring device would not be regarded as ethically sound by many, since it is still a test article that has yet to be proven safe and effective and is provided free of charge by the sponsor.”*

Note: One rule of thumb is that a study participant should not be charged for any examination, investigation or treatment that has been covered by the budget for the trial – in this instance, provided by a sponsor. Double charging is not acceptable.

Comments to Informed Consent Process - Scenario 2

Can the informed consent text be improved?

Professor Boss has asked Dr. Crown, a residential doctor, to be a co-investigator in an investigator-initiated trial related to bone marrow harvesting. Dr. Crown is asked to draft the informed consent form. She writes up the informed consent form, including the following two sentences as implied by Professor Boss: *“I waive any possibility of compensation for injuries that I may receive as a result of participation in this research. By giving consent to participate in this research, I give up any property rights I may have in bodily fluids or tissue samples obtained in the course of the research.”* The EC chair read the consent form and reflected: *“This was a very unusual informed consent form submitted by Professor Boss. The consent should not contain any language that causes the participant to waive any legal rights, or release the investigator, institution or sponsor from liability for negligence. It could be better worded as: ‘This hospital is not able to offer financial compensation or absorb the costs of medical treatment should you be injured as a result of participating in this research. Tissue obtained from you in this research may be used to establish a cell line that could be patented and licensed by the university.’”*

Note: Ethical aspects of not providing compensation for injury caused as a result of trial participation are addressed elsewhere in this Guide.

Vulnerable Participants – Scenarios

The following pages include scenarios involving vulnerable participants. Does the protocol described in each scenario include vulnerable participants? Write your comments, and view ours.

Vulnerable Participants - Scenario 1

The knock on the door was loud and demanding. *"Come in please,"* said Dr. Gregoris Markantonis. *"Come in, come in; take a seat. Would you like a cold drink?"* Stefanos was anxious to get down to business and discuss the new trial with Dr. Markantonis, but he accepted the kind offer of some cold water. *"Now, what have you come to discuss with me?"* Dr. Markantonis asked. *"I've got another vaccine study, as you know already, and I have just stopped by to see if you were interested in taking this one on,"* said Stefanos. *"Can we go into it in a bit more detail?"* asked Dr. Markantonis. Stefanos reached inside his briefcase for the trial protocol. *"It's all here in the protocol,"* he said. *"Have you had time to go through the one I sent to you earlier?"* *"Oh, yes, yes,"* said Dr. Markantonis. *"But I just want to briefly go through the protocol with you again before I submit it to the EC for their review."* Stefanos turned to the synopsis of the protocol. *"Let's see now, we are looking for babies for this trial, and they must be between 12 and 18 months."* Dr. Markantonis replied: *"It might be a bit difficult persuading the mothers to allow their infants to participate, but I have an excellent research nurse who has a lot of experience in these types of studies."* Both Stefanos and Dr. Markantonis continued to review the rest of the synopsis of the protocol together. Finally, Dr. Markantonis said: *"I'll submit the application to the EC in time for the next meeting. I have checked the informed consent documentation and it appears fine to me. I will be in touch once I have received a reply from them."*

Vulnerable Participants - Scenario 2

Dr. Jacqueline Dupont, an oncologist, wishes to be the investigator of a phase I trial to assess the pharmacodynamic and pharmacokinetic properties of a new drug for the treatment of terminally ill patients with small cell carcinoma of the lung. Pre-clinical trials of the new drug have proven to be very effective in animal studies conducted by the company developing the drug, but the company has little information about how it is metabolised, and the safe dosage to use in humans. As this is a phase I trial of a new drug, it is extremely important that all samples of blood drawn from each of the trial participants are taken at specific time intervals so that various parameters can be calculated accurately. This being the case, it has been estimated by the sponsor that approximately 300 ml of blood would be required from each subject over a two-week period. The protocol and participant information sheet for the trial are clearly written and, in lay terms, point out to the trial participants what will happen to them during their participation in the trial. The sponsor has provided Dr. Dupont with the trial protocol, the investigator's brochure outlining all the pre-clinical data and studies conducted in animals to date, the informed consent form and insurance documentation. The sponsor has also signed the hospital indemnity documentation and furthermore provided the necessary equipment to conduct the trial. Dr. Dupont therefore submits an application

to her hospital EC to conduct the trial.

Vulnerable Participants - Scenario 3

Dr. Jane Higgins is a consultant psychiatrist who works in a psychiatric unit of a local community hospital. She specialises in the treatment of patients with psychiatric illnesses, particularly those with dementia. As a result of her research work in this area of medicine, she receives a telephone call from the medical director of a multinational pharmaceutical company. *“Dr. Higgins, this is Dr. Tim Lewis. I’m the medical director of a biotechnology company called Neuropharm Limited,”* he said cheerfully. *“We are an international biotechnology company with research headquarters in North Carolina in the US. I am wondering if you would be interested in undertaking a clinical trial for us as an investigator?”* *“Please, tell me a bit more about the study,”* replied Dr. Higgins. Dr. Lewis went on to describe the trial: *“Basically, we want to examine the blood of groups of participants – senior citizens with mild senile dementia – taking a small amount of blood from them and then analysing it for genetic markers related to dementia and two treatment regimes. I’ll send you a copy of the protocol that we have written and also the informed consent documentation.”* *“Thanks, I look forward to receiving it,”* replied Dr. Higgins. She subsequently receives the documents from the biotechnology company and is very interested in conducting the trial, so she duly submits an application to her EC.

Comments to Vulnerable Participants - Scenario 1

Dr. Markantonis is going to be the investigator of a vaccine trial involving healthy infants of 12-18 months of age. In the EC review, members of the committee initially discuss the ethical aspects of conducting vaccine trials in infants, not adults. One of the EC members is a specialist in infectious diseases, and she makes it clear that vaccine trials are most commonly conducted in infants or children since they serve as the target population. Therefore, it would be an ethical problem not to include infants or children in such vaccine trials. The second issue raised is related to the vulnerability of the participants and the informed consent process. The EC chair reads from the EC’s standard operating procedure:

“Because children cannot legally provide consent for research on their own behalf, permission by at least one parent or legal guardian is required prior to enrollment of a minor in a research study; (1) Research involving no more than minimal risk requires permission from at least one parent (or guardian); (2) Research that involves more than minimal risk but presents the prospect of direct benefit to individual participants requires permission from at least one parent (or guardian); (3) Research that involves more than minimal risk and presents the prospect of no direct benefit to individual participants, but generalisable knowledge (societal benefit) requires permission from both parents; (4) Research that presents an opportunity to understand, prevent or alleviate a serious problem affecting the health or welfare of children but does NOT provide direct benefit to the subject or societal (indirect) benefit requires permission from both parents.”

The EC decides to approve the application. Since all members agree that the research in question involves more than minimal risk, but presents the prospect of direct benefit to individual participants, the EC determines that

permission from at least one parent/guardian is sufficient.

Note: Children are considered a vulnerable research population because their intellectual and emotional capacities are limited, and they are therefore legally incompetent to give valid informed consent.

Comments to Vulnerable Participants - Scenario 2

Dr. Dupont, an oncologist, plans to act as the investigator of a phase I trial of a new drug for the treatment of terminally ill patients with small cell carcinoma of the lung. Although the trial population is vulnerable because the patients are terminally ill, the EC review concludes that it is important to allow terminally ill patients to participate in relevant clinical trials, even though the possibility of receiving curative treatment is zero, or close to zero. The scientific rationale behind this trial is seen as acceptable, since the cancer drugs are too toxic to be given to healthy volunteers; there is no other option to advance our knowledge in finding better treatments for future cancer patients.

Note: Vulnerable populations should not automatically be omitted from being invited to participate in a clinical trial. The final decision will always rest with the participant and in this scenario, also with the parent(s) or legally authorised representative.

Comments to Vulnerable Participants - Scenario 3

Dr. Higgins is a consultant psychiatrist specialising in the treatment of patients with psychiatric illnesses, particularly dementia. She has been invited to participate in a trial that aims to examine the blood of senior citizens with mild senile dementia, looking for genetic markers related to the illness, as well as examine two established treatment regimes. The EC quickly identifies the potential vulnerability of the trial population, but it also finds the trial scientifically sound and of low risk. The protocol has addressed the informed consent process for tissue sampling and genetic makers, so these are not issues of concern. However, the informed consent document is to be signed by the trial participants only, not by a third-party representative. The EC would accept the protocol under the condition that at least one legally authorised representative signs the informed consent form together with the participant, to ensure voluntary trial participation.

Note: Diagnosis of dementia does not automatically confer decisional incapacity on affected individuals. Especially in the earliest stages of dementia, many remain capable of making a wide variety of decisions, including deciding whether to participate in the research. The views here on the informed consent process in this dementia trial are diverse.

Privacy and Confidentiality – Scenarios

The following pages include one scenario about a discussion between the investigator of a genetics trial and a potential trial participant. Please try to respond to the questions raised by the potential participant.

Privacy and Confidentiality – Scenario 1

Dr. Maria Lucia is a clinical biochemist at a university-affiliated hospital, and is currently planning her first genetic treatment trial. She plans to take blood samples and perform DNA analysis on 100 elderly females diagnosed with osteoporosis and include it in an industry-sponsored trial to relate the DNA analysis with the treatment response. Osteoporosis, in simple terms, is diagnosed by studying the results of skeletal X-rays, laboratory tests and bone density tests. In the planning phase of this trial, Dr. Lucia asks one of her colleagues, Dr. Eugenio Bennato, to act as a potential trial participant in order to identify key points for the informed consent process. Dr. Lucia asks Dr. Bennato, *“So, you have now heard about the details of the genetic study that you have been invited to participate in. Do you have any concerns or questions that I can help you clarify?”* Dr. Bennato silently looks out the window for a moment and then declares in his razor-sharp voice, *“Yes, in fact I have six major concerns. How will my confidentiality and privacy be protected? What are my rights to my DNA? Can I withdraw my DNA from the study? How long do you plan to keep the DNA? What will I find out about my DNA results? Will you use my DNA for other purposes?”* Dr. Lucia looks with great surprise at her colleague and whispers: *“Mamma Mia. How on earth did you come up with those difficult questions?”* Dr. Bennato points to a book on his desk: *“I just finished reading that book entitled “Reviewing Clinical Trials: A Guide for the Ethics Committee.”*

Comments to Privacy and Confidentiality – Scenario 1

Dr. Bennato is a potential participant in a genetics clinical trial that Dr. Lucia is currently planning. Dr. Lucia is embarking on her first genetics trial, and she has now been faced with six difficult questions raised by Dr. Bennato, who says: *“I will help you with the replies.”* He reaches for the book on his desk and reads:

“How will my confidentiality and privacy be protected?” Reply: *“Your DNA will be stored and kept confidential in my laboratory. There is a possibility that Dr. Lucia and the company sponsoring this research will study your DNA.”*

“What are my rights to my DNA?” Reply: *“Dr. Lucia will be responsible for deciding how it will be used. She may use your DNA in additional research. The DNA may be proven to have therapeutic or commercial value. Do you give permission for this use?”*

“Can I withdraw my DNA from the study?” Reply: *“Yes, you may tell Dr. Lucia about this, and she will try to stop additional studies. However, it may be impossible to locate and stop some future research once the materials have been shared with other researchers.”*

“How long do you plan to keep the DNA?” Reply: *“Dr. Lucia or her collaborators will keep your DNA specimen for not more than 50 years.”*

“What will I find out about my DNA results?” Reply A: “There will be no direct benefit to you from this study since you will not be provided with any results regarding your DNA test.” Reply B: “If we obtain information that will affect your health, we will inform you of the existence of this information. You can then decide if you wish to know the details.”

“Will you use my DNA for other purposes?” Reply: “Your DNA may be used by Dr. Lucia or the other scientists for additional research.”

Dr. Maria Lucia follows the wording exactly in writing up the informed consent form and submits it along with the other documents to the local EC. In the reply letter, the EC chair states that the informed consent information is perfect and that Dr. Lucia is invited to the next institutional research ethics educational workshop to give a short presentation on how DNA study participants should be informed.

Note: Detailed local guidelines have been developed for DNA studies, and they should be consulted for better understanding. For instance, some countries request an EC review for each genetics study when the identities of the participants are known.

Data Safety Monitoring – Scenarios

This scenario covers data safety monitoring. What action should be taken by the EC? Write your comments, and view ours.

Data Safety Monitoring - Scenario 1

The EC is to review a 36-participant, single-centre, phase I sepsis trial sponsored by an overseas biotech company. The EC chair, Dr. Ping Wang, is concerned about the safety aspects of this trial, since the mortality rate is normally high in sepsis patients – sometimes as high as 30%. Dr. Wang calls the investigator of this trial, Dr. Su Liu, and informs him: *“The EC will not be able to review your EC application at this point in time. The EC asks for an independent committee to monitor the trial and for you to provide the committee with safety reporting.”* Dr. Liu fully understands the concerns and is well aware that some of the participants will die during the course of the trial. Dr. Liu clearly states he will contact the sponsor and subsequently draws up a new protocol for the EC to review. After some discussion, the investigator and sponsor decide to establish a data safety and monitoring committee (DSMC) for this trial – comprising an intensive care clinician independent of the trial conduct, a biostatistician and the director of the clinical trials center at the institution. Each of the three committee members is to be given essential participant safety information during the course of the trial – via email from the trial monitor. The monitoring committee chair can call for a committee meeting at any time. There will be an un-blinded interim safety analysis after 12 participants have been treated, where the committee will inform the sponsor and the EC of its interim analysis interpretations and subsequent recommendations. Dr. Liu submits his revised EC application based on this new strategy.

Comments to Data Safety Monitoring - Scenario 1

Dr. Wang, the EC chair, rapidly studies the revised EC application from Dr. Liu. He specifically reviews the added section on the DSMC and finds the protocol solid, even outstanding, thinking: *“In fact, I will ask for such a monitoring procedure for other studies, especially single-centre trials that include participants with severe diseases. It is very difficult for us at the EC level to know exactly what happens at the trial-site level, but independent data and safety monitoring will provide some sort of assurance for the EC and the participants. Well done. I hope the test article is proven efficient since we still lack effective treatment for sepsis patients.”* Dr. Wang leaves his office for the staff canteen, sees Dr. Liu at a corner dining table with some colleagues, and waves at him, gesturing a thumbs up.

Note: An EC should ensure there is a monitoring plan for clinical trials through regular reports and continuing review reports. However, the DSMC offers a better choice of monitoring since it is responsible for overlooking a particular trial and its operational procedures are trial-specific. But establishment of a DSMC should be selective, reserved only for certain types of high-risk multi-centre trials or when design decisions are to be made during the course of a trial.

Participant Recruitment Procedures – Scenarios

The following pages include scenarios about participant recruitment procedures for trial participants. Will the EC approve the recruitment procedures? Write your comments, and view ours.

Participant Recruitment Procedures - Scenario 1

"I don't see any problems with finding the patients you need," says Dr. Karen Kim. *"In fact, I can think of a few cases that immediately come to mind. I look forward to working with you on this study."* As soon as she puts down the telephone, Dr. Kim starts to have second thoughts. While not concluding that finding suitable cases for the trial will be particularly difficult, she decides that it is perhaps best to draw up some sort of advertisement, to supplement the pool of existing patients already on her lists. Dr. Kim sits for a while, thinking. If only she can provide the required number of participants for the trial, she is certain that the sponsor will allow her to publish a paper on the results once the trial is complete, particularly as this is a new and promising drug for the treatment of influenza. Dr. Kim goes in search of her research assistant. With her assistant's help, Dr. Kim prepares and submits the following advertisement to her EC, along with all other relevant EC application documents:

DO YOU HAVE INFLUENZA?

If your answer is **"YES"** you may be considered an eligible participant for entry into a clinical trial of a promising new drug for the treatment of influenza. By participating in the trial, you will receive the following benefits:

- Free medication.
- Free medical examinations by a qualified physician.
- Reimbursement of travel costs to and from the hospital.

For further information contact: Dr. Kim - telephone 2020 2345

Participant Recruitment Procedures - Scenario 2

Professor Hirsch Barash looks up from the pile of documents he is reading and says to the trial monitor sitting opposite him: *"I think we might have problems finding suitable patients for this trial. We'll need to prepare some sort of recruitment ad and have it placed in the local newspaper to encourage people to participate. But it's no problem. I'll just ask my research nurse to write something up."* *"That's excellent,"* says Joyce, the monitor, as she also gets up from her chair. But before leaving, she remembers that she needs to remind Professor Barash: *"Don't forget to submit your advertisement to your EC for their approval; otherwise we can't use it,"* she says. *"No problem,"* replies Professor Barash in a loud voice as he opens the door to his office and motions her to leave. *"Goodbye!"* The following advertisement is duly scripted and submitted to the EC together with the EC application documents.

ATOPIC DERMATITIS RESEARCH PARTICIPANTS

We are seeking participants who are willing to participate in a clinical trial involving the use of a new medicine for the treatment of atopic dermatitis. To be eligible for entry into the trial, you should be between 8 and 60 years old and otherwise healthy but with a confirmed diagnosis of atopic dermatitis. While participating in the trial, you will receive the following benefits:

- Free medical examinations and laboratory investigations.
- An allowance of \$50 per day for taking part in the trial, which lasts 2 days.
- Free refreshments.
- Free medical consultations from a qualified medical practitioner.

For further information about the trial, please call Professor Barash at 2345 6789.

Participant Recruitment Procedures - Scenario 3

Dr. Tommy Norman, an eminent hepatologist is currently the investigator for an international trial of a new drug to treat patients with chronic hepatitis B. To date, he has managed to recruit only six patients for a trial in which he agreed to recruit 20. Dr. Norman is very keen to recruit all 20 participants, because this was the target number he had agreed to recruit for the sponsor, a large multinational pharmaceutical company. In addition, he knows if he recruits all 20 participants, this will help ensure that he will be asked to be the principal investigator of another trial by the same company. Dr. Norman decides that the best way to find suitable participants is to advertise for them and therefore designs and prints an advertisement that could be made into posters, to be placed around various parts of the hospital where he works. Dr. Norman compiles the following advertisement and sends it off to the EC as an amendment at his hospital for approval:

DR. T. Norman IS SEEKING PATIENTS WITH CHRONIC HEPATITIS B

If you have chronic hepatitis and are aged 18 years or over, you may be considered an eligible participant for entry into a clinical trial lasting for 18 months of a drug for the treatment of chronic hepatitis B. By participating in the trial, you will receive the following benefits:

- Free medical examinations by Dr. Tommy Norman.
- Reimbursement of travel costs to and from the hospital.
- Your doctor will be informed that you are taking part in this clinical trial.

This advertisement has been approved by the clinical research ethics committee at The General Hospital at West East.

For further information, please contact Dr. Tommy Norman, The General Hospital, West East - Telephone: 2876 0000.

Comments to Participant Recruitment Procedures - Scenario 1

After some thought, Dr. Kim does not imagine she will be able to recruit enough patients from her clinic for an influenza trial of a new promising test article. However, she is really interested in this trial since it has the potential to be a good candidate for subsequent publication. Dr. Kim is a serious *collector* of academic publications as she is very focused on her academic career. Dr. Kim writes an advertisement for a local newspaper and forwards it to the EC at her hospital. A few days later, the chair of the EC informs Dr. Kim by email that she is not allowed to use a phrase like “*a promising new drug*” in an advertisement for trial participant recruitment. Wording such as “*promising*” or “*new*” is not permitted, since it is a test article. It is not known if the drug will be “*promising*,” and it is not “*new*” until it has been approved by the regulatory authority. The EC chair also writes that he has no further comments about the contents of the advertisement and that he will be happy to expedite the review after Dr. Kim submits an appropriate advertisement.

Note: This advertisement tries to gain the attention of potential participants by using unsuitable and inaccurate phrasing such as - “*a promising new drug.*”

Comments to Participant Recruitment Procedures - Scenario 2

Professor Barash is seeking participants willing to participate in a clinical trial involving the use of a new medicine for the treatment of atopic dermatitis. He decides to post a participant recruitment advisement in a local newspaper. But before this, the advertisement must be submitted to the institution’s EC for review and approval. An expedited review is undertaken by an EC member delegated by the EC chair. The reviewer finds the advertisement too “*commercial*” in nature by repeating the word “*free*” three times and also indicating the exact allowance amount. The written reply from the EC suggests that the four bullet points should be reduced to two: “*Free medical examinations and laboratory investigations*” and “*An allowance will be provided for taking part in the study.*” The letter also spells out the inappropriateness of using the phrase “*a new medicine,*” and suggests wording along the lines of “*a medicine under clinical testing.*” The delegated EC member requests a revised version of the advertisement for her review and acceptance.

Note: This advertisement is an example of undue emphasis on reimbursement and free medical care services.

Comments to Participant Recruitment Procedures - Scenario 3

Dr. Norman has clear recruitment problems with a sponsored chronic hepatitis B clinical trial. He needs to find more patients since he is eager to continue collaborating with this international pharmaceutical company, which is the leader in hepatitis B and C drug development. The recruitment problem is that Dr. Norman has three other competing sponsored trials, and also that the chief of service in the liver disease clinic is the global principal investigator in a large investigator-initiated chronic hepatitis B trial. Dr. Norman must find potential trial participants elsewhere and he anticipates that putting up poster advertisements around his hospital will help accelerate the recruitment process. He formulates a short, distinct message

and asks his PhD student candidate to forward the text to the EC. In just a few days, the EC informs him the advertisement has been subject to an expedited EC review and is approved.

Note: This advertisement is clear and informative and does not include any promises or exaggerations.

Qualification of Investigator – Scenarios

The following scenarios address the qualification of an investigator. Does the investigator in each case qualify for the trial? Write your comments, and view ours.

Qualification of Investigator - Scenario 1

Dr. Yu Lung Wong is a certified traditional medicine practitioner in Clear Water Bay in Hong Kong. His clinic is very popular among the local residential population, so popular that he has not been able to take a break for a single day during the past year. His nickname among the locals is in fact “*Seven to Eleven.*” Despite this heavy workload, he has agreed to be the investigator of an herbal extract oncology trial sponsored by a local herbal medicine company, Golden Trust. He will recruit the cancer patients through his own clinic. Dr. Wong has finally completed the EC application and will now send it to the EC of a local medical teaching institution where he is a temporary lecturer.

Qualification of Investigator - Scenario 2

Mr. Christopher Lindbergh is the chief pharmacist at a university-affiliated hospital, and he is fascinated with vaccines and their development. He has previously been involved in several vaccine trials but only as the co-investigator. During the past year, he has written a trial protocol himself, aiming to study the effect of an oral flu vaccine in combination with an injectable flu vaccine. One is produced by a US company and the other by a UK company, and both companies have decided to provide their vaccines free of charge. Mr. Lindbergh has also been fortunate to get enough financial support from the local airline company, Spirit Space. Two pediatricians in his hospital are willing to act as co-investigators. Mr. Lindbergh is of course very pleased when he drops his EC application into the application mailbox at the local EC office, thinking: “*I will become the principal investigator. YES!*”

Investigator Qualification - Scenario 3

Dr. Susanna Black is the head of the department of nursing at an Australian medical school. She is a nurse by training and she acquired her PhD degree five years ago in the UK. Dr. Black has been able to secure a research grant from the Health Promotion Research Fund for an interventional *quit smoking* randomised clinical trial. The trial will have two groups of current smokers; one group will be followed without intervention, and the other will be given educational information by means of lectures, videos and brochures. Dr. Black enters her office and finds a brown envelope on her desk. She opens it. Dr. Black is very surprised when she reads: “*The ethics committee has after much consideration not approved your application as it stands.*”

Comments to Qualification of Investigator - Scenario 1

Dr. Wong is not a formally trained physician in a modern medical school, but he received a university degree in traditional Chinese medicine (TCM) and obtained a license to practice as a traditional practitioner. The EC review of the herbal extract oncology trial provokes disagreement among the committee members. Some members argue that Dr. Wong is in fact qualified by training, and has documented experiences; therefore, he should be allowed to act as the investigator of the trial. Other members strongly feel

that a physician trained in *Western medicine* must be included in the trial, at least as a co-investigator, in order to provide proper care to the cancer patients of the trial. The mandatory practice of this particular EC is to ask the investigator to join the EC meeting for a short presentation, thus allowing the EC members to raise questions. Dr. Wong tells the EC members that he was not able to identify any oncologist willing to be a co-investigator, after asking around at several hospitals. After Dr. Wong leaves the meeting, the EC members can not reach a consensus. The EC chair decides to refer the case to the faculty's research committee, so a policy statement can be developed on the proper qualifications of an investigator. The research committee is still working on this delicate matter.

Note: In some countries, complementary and alternative medicines are seen as a proper and important part of health care delivery. However, a certified complementary medicine practitioner might not be qualified as a clinical trial investigator when chronically ill patients are studied because standard treatment usually involves a combination of Western and traditional medicines.

Comments to Qualification of Investigator - Scenario 2

"Hello, Mr. Lindbergh? My name is Eva Karlquist, the secretary of the EC. The EC chair, Professor Per Ekholm, has asked me to call and inform you that we have encountered some problems with your EC application and that we need to postpone the EC review planned for this afternoon. You can call Professor Ekholm tomorrow at 121212 for further clarifications." *"Hello, Professor Ekholm. This is Mr. Lindbergh, the principal investigator of a flu vaccine trial. I was asked to call you in relation to this trial."* *"Yes, the problem we have with this trial is that the principle investigator is not a qualified medical doctor, and we have some safety concerns since the participants are infants and the vaccine may induce severe adverse events in the worst-case scenario. I myself have raised this concern. I do not object that you remain as the principal investigator, but I will insist that one of two medically qualified co-investigators is named as the leader of the clinical team during the entire course of the trial."* *"Oh. Of course, Professor Ekholm. I will certainly arrange this and re-submit my EC application this afternoon."* Mr. Lindbergh is very pleased when he drops his revised EC application into the application mailbox at the local EC office, thinking: *"I will become the principal investigator. YES, YES, YES!"*

Note: Some countries do not allow non-physicians to take up the role of principal investigator of a clinical trial.

Comments to Qualification of Investigator - Scenario 3

Dr. Black's EC application was rejected on the grounds that some of the EC members thought it was unethical to follow smokers without providing any sort of information about the risk of smoking. With some modifications to the design, the EC approves the revised EC application. The EC members did not dispute the qualification of Dr. Black as the sole investigator since it is an anti-smoking health promotion interventional trial.

Conflict of Interest - Scenarios

The following pages include scenarios about conflicts of interest. Can you identify any conflict of interest that may influence the trial outcome? How can the influence of conflict of interest be managed? Write your comments, and view ours.

Conflict of Interest - Scenario 1

Professor Bjorn Hanson is an eminent researcher and head of the department of surgery in a large university teaching hospital. He is also a member of a research team consisting of four other clinicians, and he holds a patent for a new diagnostic procedure for detecting breast cancer. Other members of the research team include Dr. Smith, who is second in command to Professor Hanson; Dr. Chan, who is Deputy to Dr. Smith, and Dr. Brown, a new doctor, who joined the department a few months ago. Professor Hanson has asked Dr. Smith if he would be the principal investigator of a trial for the new diagnostic procedure to detect the treatment effect on breast cancer in a large number of female participants. Dr. Smith is very happy that Professor Hanson has invited him to conduct the trial and feels that Dr. Chan and Dr. Brown could gain more experience if they also helped him as co-investigators of the trial. Dr. Smith therefore submits an application to the hospital's EC.

Conflict of Interest - Scenario 2

Three years ago, Dr. James King won a modest amount of money as a result of placing a winning bet in a horse race, and he used the money to purchase some shares in the pharmaceutical company PCure. Recently, Dr. King was approached by PCure and was asked if he would be the global principal investigator for a trial the company wished to conduct, in which he would be responsible for recruiting approximately 30% of the total number of participants. Naturally, Dr. King is extremely pleased, because this is the first large clinical trial involving the academic institution where he works. After accepting the offer, he submits an application to his EC and also completes a conflict of interest form in which he states that three years ago he had invested US\$100,000 in shares in the pharmaceutical company currently sponsoring the trial.

Conflict of Interest - Scenario 3

Dr. Raymond Ronaldo is a consultant physician at a large district hospital and also a member of the development board of a large multinational pharmaceutical company. Although Dr. Ronaldo receives no financial benefits for his duties on the board, he was awarded a US\$150,000 research grant from the company several years back. Dr. Ronaldo has now been approached by the medical director of the same pharmaceutical company where he is a development board member to be the principal investigator for a multi-centre, randomised, double-blind trial of a new angiotensin-converting enzyme inhibitor drug. Dr. Ronaldo submits an application to the EC at the university along with an investigator's conflict of interest form.

Conflict of Interest - Scenario 4

After Dr. Goran Bend devoted 10 years to developing a scoliosis device, he will finally be able to use it in patients. The device is novel because its initial curvature will become more or less straight over a period of a few months once implanted in patients. The project has sufficient financial support from a government research fund, and the patent of the device is jointly owned by Dr. Bend and his university. The first trial will be conducted on five adolescent patients with scoliosis, and the primary objective is to observe safety. Dr. Bend will be the principal investigator, and he has completed the protocol himself. *"This is a day to remember,"* thinks Dr. Bend when he asks his secretary to send the application to his EC along with an investigator's conflict of interest form.

Comments to Conflict of Interest - Scenario 1

Professor Hanson holds a patent of a diagnostic procedure that is to be tested by junior medical staff in his department. The EC members identified a remote possibility that the trial results or data will be affected or biased because the patent ownership belongs to Professor Hanson. One EC member elaborated: *"The junior staff members are in fact highly dependent on Professor Hanson since, as department head, he makes major decisions in relation to their work, promotion and salary. The junior doctors may thus be tempted not to report any problems with the diagnostic procedure. There is a potential risk that the trial data will be altered to reflect better results. I suggest that the EC should either ensure that the evaluation of the diagnostic procedure is made in a blinded manner or suggest that it be conducted in another department, perhaps in another hospital."*

Note: Conflict of interest does not necessarily mean that a trial report is misleading, but it may lead to a conclusion that it is not regarded as reliable.

Comments to Conflict of Interest - Scenario 2

Dr. James King is not just a lucky man on the race course, off the course he is also a much sought-after clinical trial investigator. Dr. King invested the US\$ 100,000-winnings from the number 7 brown horse on which he placed his bet into PCure, an up-and-coming pharmaceutical company. Now, three years later, he has been offered the chance to serve as the global principal investigator for a PCure trial. The EC chair asked the EC members: *"Is there a possibility of the risk of Dr. James altering the data so that the drug trial is a success and that eventually, his stock shares will increase in value? In my view, this is highly unlikely. The value of the shares is not likely to increase due to the positive results from one single trial. Maybe the value will increase when the test article receives approval for distribution and marketing, based on the results of many other trials of which Dr. King has had no possibility to exert influence."*

Note: One international company developed a drug that became the leader in sales for several years. The initial results of the clinical trials were published in 1985-86, but it was not until several years later and after many additional trials that the drug received market approval in the US and the shares of the company increased in value.

Comments to Conflict of Interest Scenario 3

Dr. Raymond Ronaldo may have a conflict of interest since is a member of the development board of a large pharmaceutical company from which he some years ago received quite a sizeable research grant of US\$150,000. Now, this scenario is not unusual and may not be regarded as a conflict of interest issue as long as Dr. Ronaldo properly discloses this relationship, for instance, at presentations at scientific conferences or when he submits manuscripts for publication in scientific journals. However, in the present scenario, Dr. Ronaldo will also act as the principal investigator for a new drug owned by the same company, and the EC has to decide if there are questionable conflict-of-interest circumstances that should be avoided. The EC decides to interview Dr. Ronaldo to find out more details about whether he is expecting additional financial support from the company and what his role will be as the principal investigator, i.e., if there is a possibility of risk that the data will be altered or manipulated.

Note: The current trend is that such information should be publicly available. Some countries have made this a legal requirement.

Comments to Conflict of Interest - Scenario 4

Dr. Bend has worked for a decade to develop a scoliosis medical device owned by himself and his university. By acting as the principal investigator for the first clinical trial of five patients, Dr. Bend can unquestionably come into a difficult conflict-of-interest situation. Dr. Bend has a strong financial interest in the device, and any negative trial results may thus be ignored and not reported. The EC decides not to allow him to be the principal investigator, rather suggesting a “*neutral*” orthopedic surgeon instead.

Note: The way to mitigate apparent conflicts of interest is to avoid them entirely when possible.

Clinical Trial Insurance and Indemnity – Scenarios

The following pages include scenarios about clinical trial insurance and indemnity. Is insurance/indemnity required to cover treatment-related adverse events or side-effects? Write your comments, and view ours.

Clinical Trial Insurance and Indemnity - Scenario 1

A highly concentrated extract of the essential components of raw ginseng has been developed and refined by a local biotechnology company. The company is convinced it is beneficial for the elderly, as it is known from anecdotal evidence that the extract has the effect of *improving a person's well-being*. Because this is the first time such a highly concentrated form of ginseng will be used in humans, the sponsors have decided that they should test a moderate dose of the extract in a small pilot trial of geriatric participants. The director of the biotechnology company asks the marketing department to find a suitable investigator willing to help them conduct the trial. The company contacts Dr. Salemi Ansari, a physician working at a local hospital who has an interest in performing clinical trials on alternative therapies. Dr. Ansari proposes that the biotechnology company conduct a 3-month pilot trial on 20 healthy geriatric volunteer participants from the local community. Dr. Ansari agrees to help write a protocol for the trial, after which he submits an application to his hospital EC to perform the trial.

Clinical Trial Insurance - Scenario 2

Professor Mori Koyama is an orthopaedic specialist at a well-known university hospital. The professor and his colleagues in the department of orthopaedic surgery have recently developed new biogenic injectable bone cement. The new cement, when injected into a cavity of a collapsed spinal vertebra, hardens and supports the vertebra and prevents it from collapsing further. It also prevents or reduces the amount of pain experienced by patients with such a condition. Only one other similar cement is currently available. However, it is less biogenic than the cement developed by Professor Koyama, and it also takes much longer to harden. Professor Koyama has performed a number of pre-clinical trials of the new cement in animals, with good results, and now wishes to try the cement in human patients. He therefore prepares all the necessary documents, such as a trial protocol and informed consent documentation, and submits the application to his hospital's EC.

Clinical Trial Insurance and Indemnity - Scenario 3

Dr. Bing Huang is a consulting physician in the department of medicine. The marketing department of an international pharmaceutical company recently asked him if he would be the principal investigator of a trial to assess patients' preference and sensory comparison of three different corticosteroids that are already registered in the country. The trial medication will be administered nasally to patients with perennial seasonal allergic rhinitis. Dr. Huang reviews the trial protocol and notes that the inclusion criteria involve males and non-pregnant, non-lactating females, of at least 18 years of age with a two-year history of allergic rhinitis (perennial or seasonal). Each patient enrolled in the trial will receive the test article in a

random fashion as a single dose, followed by a 15-minute testing period before another test article is administered. The trial medication will be tested separately with two other comparative medications. Afterwards, a participant preference questionnaire will be administered to each participant, as criteria for evaluation. Dr. Huang considers the trial to be straightforward and therefore, with the necessary relevant documents, submits an application to his hospital EC.

Clinical Trial Insurance and Indemnity - Scenario 4

Professor Karen Gutter is a senior surgeon at a private academic hospital and an expert on liver transplant surgery. She has been able to develop several novel surgical procedures, especially among healthy liver donors. As a result, the surgical complication rate among donors has dropped by over 70%. Professor Gutter now aims to further improve the transplant procedures by using a new, small surgical instrument that might reduce blood loss during surgery. This pilot trial will include five liver transplant donors, and Professor Gutter will serve as the lead surgeon and principal investigator. The EC application has been completed, and Professor Gutter is convinced it will be approved at the next EC meeting in two weeks' time.

Comments to Clinical Trial Insurance - Scenario 1

In this scenario, the industry sponsor plans to test a new concentrated ginseng extract in 20 geriatric participants. Ginseng extract has been used for decades – even centuries – as a traditional treatment, especially in the elderly or in patient groups with diminished quality of life. One could thus argue that ginseng is a documented safe herbal extract, since its safety profile has been proven through extensive usage. Documented side-effects of ginseng include nervousness, excitability, decreased ability to concentrate, decreased blood sugar levels, an estrogen-like effect, and, in a few reported cases, asthma attacks and increased level of blood pressure. However, the ginseng test article to be studied is not the same as traditionally used ginseng extract, since it has been refined and is highly concentrated. The side-effect profile of this new ginseng extract has not yet been defined in humans, and the risk can thus be seen as more than minimal. In fact, the EC requires the sponsor to supply both the indemnity agreement and a copy of the valid insurance policy for the clinical trial.

Note: The EC also requests access to pre-clinical safety data and details about the manufacturing of the test article. The EC regards the risk as too high for geriatric participants and asks for an initial trial on young, healthy participants.

Comments to Clinical Trial Insurance and Indemnity - Scenario 2

Professor Koyama and his colleagues have developed a new biogenic injectable bone cement that is expected to prevent/reduce the amount of pain experienced by patients with collapsed spinal vertebra. The EC application delineates a trial of the cement in participants. The EC members determine that the pre-clinical data and the technical description of the bone cement device appropriately address any major safety concerns in testing the device for the first time in humans. However, the proposed clinical trial involves more than minimal risk. Since it is investigator-initiated and the university has to take up any potential indemnity claims, the EC requests a

copy of a valid clinical trial insurance policy in line with the current institutional policies in this issue.

Note: The cost of medical device clinical trial insurance is usually higher than the cost for drug trials. Medical devices are commonly exempted from an institutional master clinical trial insurance policy.

Comments to Clinical Trial Insurance and Indemnity - Scenario 3

Dr. Huang has submitted an EC application for a trial of three different corticosteroids that are already registered in the country. Just to make it clear, each of the three corticosteroids is labeled for use in patients with rhinitis, but not in combination with each other. The EC discusses the protocol and determines that the trial involves more than minimum risk because of the combination therapy. The main reason the EC asks the sponsor to take on the indemnity and clinical trial insurance responsibility is that the normal institutional health plan policies do not cover routine care if it is needed as a result of participating in the trial.

Note: Indemnity issues related to clinical trials have different implications in countries with efficient, low-cost public health care, compared to countries without a similar health care system.

Comments to Clinical Trial Insurance and Indemnity - Scenario 4

Professor Gutter is an expert in liver transplant surgery. She has proposed a new surgical liver transplant procedure for donors that may reduce blood loss during surgery. The pilot trial will include five liver transplant donors. This trial comes with high risk, since it will test a new surgical procedure in normal participants during a partial liver transplant operation. The surgery itself is risky and the new surgical procedure has not yet been proven to be beneficial and safe. Some institutions would say that an insurance policy must be in place for similar investigator-initiated surgical procedure trials, while other institutions might not. Local governmental and institutional regulations will drive the EC decision here, but any indemnity issues should ideally be covered by the institution.

Note: When there is no indemnification guarantee and policy insurance in place, the potential participants should be informed in the written informed consent form about the consequences of this. *“This institution has not provision to offer financial compensation or absorb the costs of medical treatment if you are injured as a result of participating in this study.”*

Essential Clinical Trial Documents – Scenarios

This page includes scenarios about essential clinical trial documents. What positions should be taken by the EC? Write your comments, and view ours.

Essential Trial Documents - Scenario 1

Dr. Sarko Kwabean is a junior physician at the most prestigious university hospital in the capital. He has been approached by a large pharmaceutical company to be an investigator in a multinational osteoporosis clinical trial. Dr. Kwabean has accepted the offer, and on the upcoming Friday, he will fly to Johannesburg, South Africa, for an investigators' meeting. It is his first time to visit South Africa, and he is very proud. There will be 23 people at the meeting: five staff from the sponsor, one from a central laboratory services provider, one GCP educator, eleven investigators and five research nurses. The meeting stretches over two full days and most of the discussions pertain to the trial protocol, diagnostic criteria, GCP and the other essential trial documents. The sponsor, an American company, requests each investigator to sign a conflict-of-interest form because this is a requirement of the US Food and Drug Administration. Dr. Kwabean puts up his hand and asks, *"Why should we sign a conflict-of-interest form? We are not US citizens, and we are conducting the trial outside the US."* One of the more senior investigators interrupts abruptly by saying, *"This is your first trial, I assume? You see, a conflict of interest form is seen as an essential trial document, since we must ensure that we have no conflicts that may distort the data that we will collect during the course of the trial. In fact, our institutional EC requires a signed conflict-of-interest form in order to initiate the EC application review process."* Dr. Kwabean signs the conflict-of-interest form and asks for a copy to bring home so he can submit it to his own EC. Even though he has already submitted the EC application, he will also submit the conflict-of-interest form.

Comments to Essential Trial Documents - Scenario 1

The Faculty of Medicine Board has its monthly meeting the next day, after Dr. Kwabean has returned from Johannesburg, and this is the first board meeting he has attended. Dr. Charles Msrah comes up to Dr. Kwabean just before the board meeting and congratulates him for being invited as an investigator on the multinational osteoporosis trial, saying: *"As you know, I have been appointed as the new EC chair. The first project that I have studied is your EC trial application. Everything seems to be in order with the application, but why have you included a signed US FDA conflict of interest form? That is not a requirement by our regulatory authority or by our institution. I assume that this is just a simple mistake from your side. If you like, I can return the signed form tomorrow."* Dr. Kwabean looks surprised and says: *"Oh, thank you."* But he quietly ponders: Does this mean that there are different requirements in different countries? Strange.

Note: Some clinical trial documents are seen as essential in some countries, but not so in others.

Clinical Trial Registration – Scenarios

The following pages include scenarios about trial registration. What positions should be taken by the EC? Write your comments, and view ours.

Clinical Trial Registration - Scenario 1

Professor Bernard Registrar is planning a multi-centre, investigator-initiated diabetes trial with investigators at 17 sites in eight countries over three continents. The agreements and budgets have been completed for every site. The current priority is to complete the EC application form for each site – 17 different application forms to be completed in total, each taking four full working days for one of his staff. Professor Registrar reflects: *“That’s sixty-eight full working days! Why can’t all ECs use the same EC application form? We need more standardisation.”* One of his staff enters the office, indicating to him that one of the EC application forms specifically refers to clinical trial registration. This EC requires entering of the trial in the local trials registry prior to an EC review so it can assess and approve the information registered. The rationale behind this request is that *“potential study participants may use the trials registry for identification of potential trials open for participation.”* Professor Registrar closes his eyes and groans: *“That’s it.”*

Clinical Trial Registration - Scenario 2

Dr. Steven Swan is the acting EC chair for the week. He is in his university’s hospital office reading through the applications for the upcoming EC review meeting. He feels satisfied since this is the first time he has been asked to be the EC chair. Svennis Ericsson, the EC secretary, transfers a call to Dr. Swan. *“Hello, my name is Dr. Paula Editora from the Journal of Scientific Insight. We have received a manuscript from Dr. Lisa Sting at your university. Her manuscript is of great interest to us, and we have decided to proceed by sending it to three external reviewers. Dr. Sting has posted her trial on your local trials registry and she has provided the details of the approved EC application. Everything seems to be just fine, but we would like to confirm that the EC application ID number and approval date as disclosed on the trials registry are consistent with your EC’s records. Dr. Swan, can you please call me back at 123459 once you have checked the details? Thank you for your assistance.”*

Comments to Clinical Trial Registration - Scenario 1

Professor Registrar is distressed because one of the ECs in his multinational clinical trial demands that the trial be enlisted with the local registry prior to an EC review, so it can assess and approve the information registered. He has never ever heard of such a request, so he decides to call the local EC chair, Dr. Anne Straight, for a discussion and explains the odd EC requirement. Dr. Straight replies: *“Well, I can’t provide a straight-forward answer since I have never heard of such a requirement before. In fact, I have never even thought about it. Our written procedures state that any text in the advertisements for participant recruitment should be reviewed and accepted by the EC. So is a trials registry an advertisement? I assume this is up to the individual EC to determine. However, we know that potential trial participants are searching*

more often through public registries for potential trials. The question you have raised is, in fact, very much an ethical one since the text provided online is virtually always in English and not translated into a local language, say, in Spanish. Sorry, but I cannot give you a direct reply. Hopefully, I will be able to provide some feedback once I return from a research ethics meeting in Barcelona by the end of next week. Well, at least I can tell you this: You have to comply with the requirements of the EC you refer to. Professor Registrar, let me get back to you next week."

Note: This scenario addresses a potentially new, ethical matter related to clinical trial registration. Does the trial registry information posted serve as a regulatory or publication policy requirement alone, or does it also serve as a trial recruitment advertisement?

Comments to Clinical Trial Registration - Scenario 2

Dr. Swan, the acting EC chair, has been approached by Dr. Paula Editora from the *Journal of Scientific Insight*. Dr. Editora wishes to confirm an EC application ID number and approval date disclosed on a registry for consistency with the EC's records. The reason for this is that the journal is reviewing a manuscript based on the results of this trial. Dr. Swan calls the EC secretary, Svennis, and asks him for assistance in the matter. Dr. Swan speculates: *"What should I do if it appears that the trial has not obtained approval from our EC or that the date or EC application ID number is incorrect? In that case, I must wait until the appointed EC chair returns next week."* Svennis phones again to confirm the details of the registered trial are consistent with the EC's records. Within minutes, Dr. Editora receives a phone call from Dr. Swan.

Note: Trial registration information can be utilised to confirm important details about a clinical trial as illustrated in this scenario. But the scenario also raises concerns. Is the identity of the person requesting the information reliable? What kind of information can an EC disclose to a third party without breaching its obligation of confidentiality to the investigator?

Dissemination of Trial Results – Scenarios

This page includes a scenario about dissemination of trial results. What positions should be taken by the EC? Write your comments, and view ours.

Dissemination of Trial Results - Scenario 1

Dr. Hans Beck jumps into the green public minibus that will take him to his job at the regional geriatric hospital. He nods at a person he vaguely recognises sitting in the front row but has difficulty remembering her name. He sits down and starts reading the recent medical association newspaper. Oh, there is an advertisement for a geriatric consultant post at the Land Hospital. I must apply, he thinks. He feels a tap on his shoulder and looks up into the indigo coloured eyes of the lady he saw at the front of the bus. *“Hello, Dr. Beck. Terrible weather we are having, and it is predicted to continue even up to the weekend. We have met before. My name is Gretel Graf, the hospital’s EC’s secretary. I would just like to remind you that you have an outstanding final report for the Alzheimer’s clinical trial that you completed over a year ago. I have sent you three reminders. Is it possible to have the report soon, please? You see, Dr. Beck, we are expecting an internal audit of the EC in the next month, and it would not be so good if the audit identifies the outstanding report.”* Dr. Beck is a bit surprised and upset that the lady had approached him in the bus when so many people can hear the conversation. He answers seriously: *“The trial was not successful, so there is nothing to be reported, and I really have much more important matters to take care of than writing reports that have no value whatsoever for anyone.”* The bus stops at the hospital and Dr. Beck quickly jumps out onto the rainy and windy sidewalk.

Comments to Dissemination of Trial Results - Scenario 1

Dr. Beck enters his office and the phone is already ringing. It is the EC chair, and he is not at all happy. *“Please, be so kind as to give us the final report of your Alzheimer’s trial by 6 pm today at the latest. Do I really need to inform you that the hospital has strict rules for dissemination of trial results? The results must be reported to the EC 6 months after the completion of the trial at latest, using a specific EC form as listed on the EC’s intranet. There are three reasons for this requirement, and they are not dependent on whether the trial was successful. Our institution strongly feels that the participants should have the right to know the trial outcome, the local community should know about the type of research conducted in its hospital, and the international research community should be notified about the outcome of positive as well as negative trials. Your report will be published on our clinical trials registry website. You have been informed about our internal policy, and you have also signed a contract stating that you will comply with it. Please be reminded, six pm.”*

Note: Some institutions have strict rules for dissemination of trial results, while others have more relaxed rules. This EC in fact decides to evaluate the outstanding report for non-compliance of the investigator.

Local Laws and Institutional Guidelines – Scenarios

This page includes a scenario about local laws and institutional guidelines. What positions should be taken by the EC? Write your comments, and view ours.

Local Laws and Institutional Guidelines - Scenario 1

Professor Bernadette Bardot has worked as a dermatologist in a university hospital in New Zealand for eight years after leaving her home town of Nice, France. She smiles as she thinks: If you don't make a decision, nothing will happen. I like this country, but I will return home one day for sure. Professor Bardot has developed a product that may prevent the spreading of skin cancer, i.e., melanoma. The product is to be injected subcutaneously around the area where melanoma is thought to have spread, just before the tumour resection surgery is performed. The test article has worked extremely well in both rats and rabbits. Melanoma is very common in France compared with many other countries, so Dr. Bardot sees an opportunity to collaborate with her previous hospital in France. She calls her old mentor Professor Jack Lamarck in Nice to see if he knows of any dermatologists in his hospital who might be interested in taking part in the melanoma trial she is planning. Professor Lamarck listens for a minute before replying: *"Well, it's nice to hear from you after so many years. How is life Down Under?"* Professor Bardot responds: *"Good, almost too good, thank you. I'm currently planning a melanoma clinical trial and want to find an investigator in France, preferably in Nice, to collaborate with. Do you have any potential candidates in mind?"* There is a moment of silence before Professor Lamarck sighs and says: *"Oh, Bernadette, you have been away from Europe for many years. You have probably not heard about the 2004 European Directive on clinical trials. Today, investigator-initiated trials conducted in Europe must follow the same strict regulations as industry-sponsored trials for applications, monitoring, GCP training, clinical trial insurance, adverse event reporting, etc. It has become tricky to conduct trials, especially for funding reasons. I just want you to know about the local requirements in France and in the European Union, but I can anyhow get you in contact with the local EC chair for a consultation."*

Comments to Local Laws and Institutional Guidelines - Scenario 1

Professor Bardot has been absent from France for eight years and has not heard about the new clinical trial regulations implemented in Europe - EU Directive 2001/20 - in 2004. She has the opportunity to discuss the regulations and requirements with the EC chair at a hospital in Nice. After listening to the chair, Professor Bardot decides to proceed with the trial as planned, since she is able to secure a grant for the trial from a private donor. She is confident that she will be able to conduct the trial in France and is currently working on the EC application, together with her new collaborator in Nice.

Note: Each jurisdiction has its own governing laws and guidelines that must be followed when applying for trial conduct to the regulatory authority and/or the local EC.

Proportionate EC Review: Expedited/Full - Scenarios

The following pages include scenarios about expedited or full EC review. Is an expedited review enough or should a full review be conducted? Write your comments, and view ours.

Proportionate EC Review: Expedited/Full - Scenario 1

Mondays are always busy for Dr. Sam Carter, and he has a lot of patients to see in the clinic today. To make matters worse, he knows the session is going to be long and hard, particularly as the air conditioning is not working properly. Without further thought of what lies ahead for the rest of the day, Dr. Carter starts to go through the stack of documents that his secretary has just placed on his office desk. As he reads each document in turn, his attention is suddenly drawn to a large batch of papers sent by a pharmaceutical company for which he is currently conducting a clinical trial. The papers contain two reports, both of which appear to relate to the trial for which he was the investigator. As he slowly reads them, he becomes aware they contain information about some adverse events that had occurred in some patients enrolled in the trial – the same trial for which he is currently recruiting patients. The first concerned a female patient who took the trial medication and died as a result of a car accident in which she was the driver. Dr. Carter slowly wipes his brow and continues reading the second report, which refers to two further patients enrolled in the trial: a male aged 41 who had committed suicide, and a female aged 27 with long-standing type II diabetes mellitus, who also died suddenly. The reports go on to say that all had been enrolled in a trial conducted under the same protocol, except it was conducted at a European investigative site. As he continues to read, Dr. Carter suddenly breathes a short sigh of relief when he reads a statement from the pharmaceutical company's medical director, saying the investigator at the European site concluded there was no relationship between the deaths and the trial medication. Dr. Carter quickly glances at his watch, and as he walks out of his office, he calls out to his secretary: *"Please prepare the reports for submitting to the EC for me to sign off."* With that, he briskly walks away to his clinic.

Proportionate EC Review: Expedited/Full - Scenario 2

Dr. Steven Groth, an investigator for a two-year multi-centre, open-label trial of a new test article for the treatment of chronic hepatitis B, is asked to recruit ten patients for the trial. It would require each patient to visit his hospital clinic a total of 20 times in the first year. Dr. Groth has submitted the initial application to conduct the trial to the EC of the hospital at which he works, and approval was given to him to conduct it. Six months after recruiting the first patient, Dr. Groth receives a telephone call from the medical director of the sponsor, telling him the sponsor would like to amend the trial protocol. The medical director explains that the amendment is minor in that it involves increasing the number of visits to his hospital clinic from 20 to 26. Dr. Groth submits the amended protocol to his EC.

Proportionate EC Review: Expedited/Full - Scenario 3

Dr. Lars Strong, a cardiothoracic surgeon, has recently returned from the United States after attending a symposium about the new ways of treating patients with atherosclerotic plaque of the carotid arteries. While there, Dr. Strong met up with Dr. Bush, a good friend he first met when they were at medical school together. Dr. Bush told Dr. Strong he was currently working on an exciting research project at Academia University, involving a new surgical procedure for the treatment of atherosclerotic plaque, and was looking for more investigators willing to collaborate with him in the trial. Dr. Strong felt privileged that Dr. Bush had considered him suitable to help with his research and agreed to collaborate. Before he left the symposia, Dr. Bush mentioned to Dr. Strong that he already submitted the trial protocol to his own EC at Academia University, and he went on to say they had approved his trial without any major problems. Dr. Strong should simply notify the local EC about this fact, and they would “*rubber stamp*” or approve his EC application, because it had already been approved by Academia University.

Comments to Proportionate EC Review: Expedited/Full - Scenario 1

This scenario elaborates on serious adverse events reporting of clinical trials. Dr. Sam Carter was involved in an international industry-sponsored clinical trial, and any serious adverse events that happen at any trial sites must be reported to each participating investigator. In this case, the report came from the sponsoring company - which is the common way of distributing information - and included two serious adverse events: two death cases. However, the medical director of the sponsor stated that the investigator at the European site involved in the two events did not regard the two deaths as related to the trial medication. Therefore, there was apparently no reason to conclude that trial participants recruited and managed by Dr. Carter were at a higher risk because of the new knowledge of the two deaths. Dr. Carter takes the correct action, i.e., to submit the reports on the two deaths to the local EC to ensure an independent review and to obtain opinion of the events. The chair of the EC decides to conduct an expedited review.

Note: Serious adverse event reports to the EC are numerous for large-scale multinational trials, sometimes totaling 10,000 reports a year for 100 industry-sponsored trials. The EC chair in this scenario reviews all incoming adverse events reports, but will only see that a full EC review is made for treatment related and not for unrelated adverse events.

Comments to Proportionate EC Review: Expedited/Full - Scenario 2

Dr. Groth has been informed by the sponsor of a drug trial that it has decided to amend the trial protocol. The amendment means that each trial participant has to visit the hospital 26 times, not 20 times as the original protocol spelled out. Any protocol amendment must be reviewed by the local EC; and the change can be adopted only after the EC provides written approval for the change. This is why Dr. Groth submitted the amended protocol to his EC. The EC chair thinks the increased number of trial visits might increase the level of risk for the trial participants, owing to the increased number of clinical procedures, so he decides that a full EC review

should apply. Some participants may also feel the increased number of visits would make it impossible to continue trial participation. A revised informed consent form has to be approved by the EC and subsequently signed by each of the trial participants.

Note: This is a very common scenario, i.e., protocol amendments. A full EC review is required if the change may increase the risk of harm for the participants. Informed consent forms often require amendments and must be signed by each trial participant, before amendments can go ahead.

Comments to Proportionate EC Review: Expedited/Full - Scenario 3

Dr. Strong is invited by an old friend to participate in an investigator-initiated surgical procedure clinical trial. His friend mentions that the protocol has been approved by the EC at Academia University. Dr. Strong is led to believe that his own EC will “*rubber stamp*” or expedite the approval of his EC application since it has already been approved by his friend’s university. However, the chair of the local EC does not agree that an expedited review should apply, since there is no formal agreement in place between Academia University and his own institution on mutual acceptance of approved EC applications. The medical practice, investigator’s experience, patient population and other factors may differ significantly between the two institutions. A full review of the protocol is thus seen as appropriate to ensure the trial is also ethically sound in the second institution.

Note: This is not a very common type of EC application scenario. However, it is important to stress that the local EC should undertake a full review on human interventional studies and accept the decisions of other ECs only when there is a formal written arrangement to do so. Examples are a centralised EC that serves several institutions or a mutual recognition of the EC decisions made at two individual institutions.

Continuing Review – Scenarios

This page includes one scenario about continuing review. What actions are required by the EC? Write your comments, and view ours.

Continuing Review - Scenario 1

Two years ago, Dr. Stella Simpson initiated a single-centre, randomised, blinded lung cancer trial to study the effect of the combination of two recently registered anti-cancer drugs. She has worked day and night on this trial. To her satisfaction, she has been able to recruit 76 patients into the trial out of the anticipated 120 with an additional 18 months to go. After her morning round in the ward, Dr. Simpson eats a quick breakfast in the hospital cafeteria and starts reading one of the scientific oncology journals she subscribes to. Dr. Simpson suddenly starts to cough, and while her face turns white. The clinical trial in the article she is reading is seemingly identical to her ongoing trial. However, the investigators have been able to prove the combination therapy to be slightly more effective than the standard treatment, with 55% of patients responding to the combination therapy. Dr. Simpson notes that the first author listed in the publication is one of her previous residential ward doctors who left two years ago for a large national cancer centre in Europe. *“What can I do?”* she wonders. *“And I have to complete my annual EC trial continuing review progress report today. Will the EC stop my current trial if I inform them about the results of the European trial?”*

Comments to Continuing Review - Scenario 1

Dr. Simpson has experienced the worst day of her life. One of her previous internship doctors has copied her trial protocol and published the results in a renowned international cancer journal. Dr. Simpson reflects and then reminds herself that the stolen protocol is, in fact, not the final one; she amended genomics and proteomics methodologies into the protocol after that *“bandit”* left for Europe. Dr. Simpson writes in her EC continuing review report: *“To my great satisfaction, I have identified a recent publication based on an almost identical study design as ours. That trial showed some benefit of the combination therapy over the standard treatment, with 55% of the patients being responders. This means that my patients most likely benefit from being participants in our trial. Moreover, our trial is unique compared to the published trial since we have access to important biomarkers, thus allowing us to identify the characteristics of responders/non-responders.”* The EC chair writes in his reply letter that the trial must continue since it is clearly beneficial for the participating patients and that the protocol has an even higher scientific value than first anticipated. The chair also reflects on the excellent patient recruitment rate.

Note: Emerging knowledge about a test medication can provoke a re-assessment of the value of a clinical trial. Newly published results of other similar trials can have both positive and negative effects. The EC continuing review report is one of the regular points for re-assessment.

Acceptability of Trial – Scenarios

The following pages include scenarios focused on the acceptability of clinical trials – e.g., trial design and the scientific value. Are there problems in the trial design of each scenario? Write your comments, and view ours.

Acceptability of Trial - Scenario 1

Dr. Susana Soares is a consultant physician specialising in endocrinology in a busy district hospital, and has been working in this post for over 5 years. Recently, Dr. Soares was invited to be an investigator for a major pharmaceutical company and asked to conduct a phase III trial of a new anti-diabetic agent in patients with type-2 (non-insulin dependent) diabetes. She asks the sponsor of the trial to send her the trial protocol and the investigator's brochure for the drugs so she may review the trial before making a decision. The next day, the trial documents arrive. From the protocol, Dr. Soares notes that the trial is a phase III, randomised, double-blind trial, comparing a newly registered oral anti-diabetic agent with another currently available treatment on the market. Furthermore, she notes that it is a multicentre, global trial, recruiting 100 patients in total, of which she will be required to recruit 10. More important, she notes that patients who are enrolled into the trial must first undergo a 2-week washout period that consists of a regimen of diet and exercise, after which, they will be randomised to the trial medication or the control medication. Dr. Soares thinks the trial is pretty straightforward and contacts the sponsor again to confirm that she will conduct the trial. At the same time, she asks the sponsor to send her the rest of the trial-related documents, such as the informed consent documentation. After receiving all the required documents, Dr. Soares submits her application to the EC of the hospital where she works.

Acceptability of Trial - Scenario 2

Dr. Jose Hernández, a consultant physician, works at a large district hospital. He receives a visit from Silvia Calusi, a large international pharmaceutical company representative, after having discussed a trial with her a few days previously on the telephone. As Silvia arrives at Dr. Hernández's office, she greets him: *"Hello. I have the study protocol and documents for the pneumonia study that I want to discuss. Would you mind signing the confidentiality agreement before we go ahead and discuss the study further?"* She hands Dr. Hernández a pen. Dr. Hernández quickly signs the form, after which Silvia briefly reviews the trial protocol with him. Dr. Hernández notes that the trial is a randomised controlled trial, comparing a conventional antibiotic for the treatment of pneumonia with the new treatment. Before the participants are randomised, there would be a short run-in period where the participants would be given no medication for the first two days, so that microbiological tests can be performed in order to establish the diagnosis. After this, each participant would be randomised to either the conventional medication or the new trial medication. After going through the rest of the protocol with Dr. Hernández, Silvia asks him to read the investigator's brochure and other documents and then to contact her to confirm his intention to be an investigator. Dr. Hernández subsequently

reads the protocol and other documents, notifies Silvia and then decides to submit an application to the EC at his hospital.

Acceptability of Trial - Scenario 3

ACME currently manufactures and markets a drug approved by the regulatory authorities in the US for the treatment of benign prostatic hypertrophy. Although the drug is very safe, an interesting but common, not harmful side-effect of the drug is that it stimulates the growth of hair. The pharmaceutical company of the drug has now reached the stage in the development process where it would like to conduct a multicentre, phase IIIb, open-label trial of a test article for the new indication. ACME contacts Dr. Daniela Massironi, a consultant dermatologist at a university hospital, to see if she would be the investigator for the trial. Dr. Massironi reviews the trial protocol and examines information about its observed side-effects and toxicity, as well as the information from additional studies conducted for the new indication. Dr. Massironi agrees to be an investigator for the sponsor and subsequently submits an application to the EC at the hospital where she works.

Acceptability of Trial - Scenario 4

A pharmaceutical company in Japan markets an approved drug for the treatment of hypertension. The drug is currently available for use by doctors in Japan, but at a dose that is half the therapeutic level that is normally prescribed in other countries. To date, there have been no serious adverse events reported relating to the use of the hypertension drug. The pharmaceutical company now wishes to market the same drug, also for the treatment of hypertension, in accordance with international practices, but at double the currently approved dose in Japan. Because the regulatory authorities in Japan prohibit the conduct of clinical trials of the drug at twice the therapeutic dosage, the pharmaceutical company would like to arrange for the trial to be conducted in another country where such studies are permitted. The company has approached a clinician at a university medical institution in South Africa who is willing to be the investigator of a multicentre, international trial that will examine the efficacy and safety of the higher dose antihypertensive drug in a population of 300 patients. Dr. Victor Stone is the investigator with whom they have decided to collaborate, and after reviewing the trial protocol along with the other trial documents, Dr. Stone decides to submit an application to the EC.

Comments to Acceptability of Trial - Scenario 1

This scenario addresses a diabetes phase III drug trial with Dr. Susana Soares, a consultant physician specialising in endocrinology as the investigator. During the EC review meeting, all members expresses concern that patients enrolled into the trial must first undergo a 2-week “*washout period*” that consists of a regimen of diet and exercise, without any diabetic drug treatment. The EC members request an in-depth clarification from the investigators of how the washout period might affect the patients and their diabetes status.

Note: Whenever there is a “*washout period*” in a clinical trial design, EC members should be alert and consider the associated risks of not providing any treatment to the participants. Certain disease trials that require

continuing medication – such as severe asthma – should not use a “washout period” design.

Comments to Acceptability of Trial - Scenario 2

Dr. Jose Hernández is to embark on an industry-sponsored pneumonia clinical trial, and an application has reached the local EC. The trial is a randomised controlled trial, comparing a conventional antibiotic for the treatment of pneumonia with a new treatment. During the EC review meeting, one member notes that there would be a “run-in period” for the first two days before the participant is randomised to one of two treatment arms. The same EC member pointed out that local standard medical practice is to initiate pneumonia drug treatment at the time of diagnosis and that it would be seen as unethical to wait for two days in initiating the treatment. The protocol was for this reason not accepted by the EC.

Note: A “run-in period” is a period before a clinical trial is commenced when no treatment is given. It commonly serves to screen ineligible or non-compliant participants. Standard pneumonia treatment practice varies from one health care institution to another, so the trial design could have been acceptable in other settings.

Comments to Acceptability of Trial - Scenario 3

A drug effective in the treatment of benign prostatic hypertrophy has been shown to have an interesting side-effect. It seemingly stimulates the growth of hair. Dr. Daniela Massironi, a consultant dermatologist, has agreed to be an investigator for a phase IIIb, open label trial of the drug for the new indication, and has submitted an application to the institutional EC. The EC review mostly focused on the open label design and it was promptly decided that a better trial design should be adopted, such as a randomised, blinded trial. The EC thus asks for a revised protocol.

Note: An open-label trial is a type of clinical trial in which both the researchers and participants know which treatment is being administered. An open-label trial may be unavoidable under some circumstances, but in most cases, a blinded design can be adopted, as in this scenario and especially in a phase III confirmatory trial.

Comments to Acceptability of Trial - Scenario 4

Dr. Victor Stone, a South African cardiologist, is willing to take on a hypertension treatment trial sponsored by a Japanese company, and the EC application is under review. The issue brought to light during the EC review meeting is that the drug has been approved for usage in Japan but is labeled for a lower dosage than the dosage to be used in the trial. The EC members express concerns about the safety profile of the drug, since previous experiences in usage were from a lower dose. The EC members still believe the predicible risk is low, since similar compounds are available on the local market with a comparably high dosage. The EC decides that the first three patients of the trial should be treated in a hospital setting and that safety reports for the three participants should be provided to the EC before the full protocol is approved.

Note: An adaptive design to collect safety data on a few patients can reduce much of the safety concern expressed by EC members.

Trial Amendments - Scenarios

This page includes a scenario about trial amendments. What action is required by the EC? Write your comments, and view ours.

Trial Amendments - Scenario 1

Dr. Ben Bolt is the investigator for a phase IV multicentre, randomised, double-blind, placebo control trial of a new beta2 agonist for the treatment of asthma and chronic bronchitis. A requirement of the trial is that a 24-hour contact name and telephone number of a clinical research coordinator be provided to all participants who are enrolled in the trial by means of the participant information sheet. The contact information is provided to the participants for the purpose of giving them a means to reach someone in case they experience any problems in relation to the trial medication or for consulting someone about specific medical problems in an emergency. Halfway through the trial, while still recruiting participants, Dr. Bolt decides that the name of the person whom the patients should contact in the event of an emergency has to be changed. This will mean that the informed consent form will also have to be amended. Dr. Bolt thinks it would be wise to contact the trial monitor employed by the pharmaceutical company sponsoring the trial for this task. The monitor makes all the necessary changes to the informed consent form for Dr. Bolt and informs him that she will send him a copy of the amended documents for submission to his EC for review. The next day the amended documents arrive on Dr. Bolt's desk, and he prepares to submit them to his EC with a cover letter.

Comments to Trial Amendments - Scenario 1

Dr. Bolt makes minor changes among his research team members, meaning that the contact person for the patients included in a clinical trial needs to be altered. The participant informed consent form also needs to be updated. The trial monitor makes those changes and recommends they should be reviewed and approved by the EC. For this reason, the amendment is submitted to the EC. The EC chair approves the changes in the informed consent form and asks the EC secretary to place it into the specific trial file.

Note: Some trial changes may not be subject to an EC review, but minor changes that alter the content of the informed consent form should always be reported to the EC, so that the EC can review and approve the changed form.

Adverse Event Reporting – Scenarios

The following scenarios concern adverse events reporting. What action will be taken by the EC? Write your comments, and view ours.

Adverse Event Reporting - Scenario 1

Professor Estrada Solano, a cardiothoracic surgeon at a busy hospital, is currently conducting an investigator-initiated clinical trial involving a newly developed heart pacemaker device. During the trial, Professor Solano conducted surgical operations on 10 patients over a 6-week period in which he implanted the new pacemaker device. Two weeks after completing all 10 pacemaker insertions, two patients experienced serious adverse events. One required admission to the intensive care unit to treat life-threatening haemodynamic problems, and the other developed a life-threatening pulmonary embolism, which was successfully treated. Both adverse events were graded as severe and undesirable, and with an unrelated attribution. The remaining eight patients who underwent surgery to receive the implanted pacemaker recovered uneventfully from their operation, and their condition continues to be successfully managed. Professor Solano reports the two serious adverse events within 24 hours to the EC at the hospital where he works.

Adverse Event Reporting - Scenario 2

Dr. Pyatat Pourpongporn is a consulting surgeon in the department of surgery at a large hospital. He is involved in the practice of a new surgical procedure for the treatment of patients with liver cancer. Dr. Pourpongporn has performed the new surgical procedure on more than 100 patients over a period of five years. However, 15 patients have died of post-surgical complications. Within 24 hours after each of the deaths, Dr. Pourpongporn duly reported them to his EC as serious adverse events. According to information previously supplied to the EC by Dr. Pourpongporn, when he first submitted an application to the EC for review, the supporting literature stated that the usual post-operative mortality rate for patients with the type of liver disease that he is treating is 5% within 3 months.

Comments to Adverse Event Reporting - Scenario 1

Professor Solano has reported two adverse events from the same trial to the local EC; both adverse events were graded as severe and undesirable, but with an unrelated attribution. The EC chair reviewed the two adverse events in an expedited manner, even though they were serious in nature. The two adverse event reports clearly spell out that there was no relationship between the adverse events and the pacemaker device trial. In fact, the two patients had already experienced similar serious events prior to the initiation of the trial.

Note: Some ECs do not require reporting of the two serious adverse events exemplified here, since they are not defined as being related to the trial, while other ECs request that all serious adverse events be reported.

Comments to Adverse Event Reporting - Scenario 2

Dr. Pourpongporn has seen 15 death cases in 100 liver cancer patients following the new surgical procedure. The 15 deaths have continuously been reported to the EC, and the most recent death was reported last week. The EC chair reviewed this newly reported death and found out the investigator thought the death was most likely related to the surgery, rather than to the disease itself. The patient suffered from extensive post-operative abdominal bleeding because of a long-lasting and difficult surgery. The chair reviewed the other 14 deaths reported to the EC for this trial and found they all happened several months after surgery, owing to tumour recurrence. Since the last reported adverse event was related to the surgery, the chair decides to bring up the case at an upcoming full EC review meeting. He also thinks the review of this scenario would be educational for new/novice EC members.

Note: Extensive surgical procedures always come with high risks, so the risk-benefit balance is very much present. One should thus consider that 5% of the liver cancer patients who undergo established surgery will normally die within 3 months. The observed frequency of death of the liver cancer patients is expected and thus not a concern for the EC.

Unanticipated Problems – Scenarios

This page includes a scenario about anticipated problems. What action is required by the EC? Write your comments, and view ours.

Unanticipated Problems - Scenario 1

Dr. Charles River receives an emergency phone call from the clinical manager at his outpatient clinic: *“Dr. River, one of your patients has fallen ill, and she is now in a coma. Can you please come to the clinic at once, or should we transfer the patient to the ICU immediately?”* *“What is the name of the patient? Katrina Carlsberg? Oh, she is involved in an asthma treatment clinical trial, and she was dosed 30 minutes ago. Transfer her at once to the ICU. I will hurry over right away.”* Dr. River writes a report to the EC the next morning describing the unexpected serious adverse event. Fortunately, the patient has almost fully recovered, but is still under observation in the ICU. It appears that the trial research assistant had given the patient a dosage of the test article that is five times higher than the stated dosage in the protocol. That is, the assistant forgot to dilute the test article.

Unanticipated Problems - Scenario 2

Dr. Maxim Smirnoff is a consultant physician in general medicine working in a busy hospital. He has been invited to be an investigator for a trial by an international pharmaceutical company whose research unit is based in the US state of Connecticut. It is a multi-centre, double-blind, placebo-controlled and randomised trial involving a drug to treat hypertension. Recently, the pharmaceutical company sent Dr. Smirnoff some reports of incidents, where three patients enrolled in the trial at a site in Canada fainted without warning and suffered severe concussions to their heads as a result of suddenly falling down. The pharmaceutical company’s medical director decided to notify Dr. Smirnoff as a matter of urgency because the investigator in Canada reported that the serious adverse events were possibly related to the trial drug.

Unanticipated Problems - Scenario 3

Dr. Louisa Coma is walking to her usual outpatient psychiatric clinic shift on a Friday afternoon. She will first meet two participants in a depression treatment clinical trial, and thereafter she will see four ordinary patients. She walks up to Clara Stift, the outpatient clinic manager, to let her know she has arrived to take up her duties. Clara turns her head to the left as she always does when there is a *“problem.”* She says, *“Dr. Coma, there is a problem. One of the trial participants is not fit to come today. She is lying in the ICU unit at Grant Hospital. The chief of service at that unit wants you to call him at 84 84 84 84.”* *“This is Dr. Coma. How is my patient, and why is she in your ICU unit?”* *“Well, Dr. Coma, the patient is not well. She jumped off a bridge and into the river in downtown last night, obviously trying to take her own life. She is in fairly stable condition, but she needs to be closely monitored. She had a note in her pocket stating that she was in a depression clinical trial, and your contact number was also included. Do you know what kind of treatment she is receiving, or is the treatment blinded?”* *“I don’t know what treatment she has been given, but I will call the sponsor of the trial and let you know as soon as possible. I will drive over to your hospital once I have completed my outpatient clinic shift in about two hours.”* Dr. Coma calls the sponsor at once and finds

out that the participant is on treatment with the test article in combination with standard care treatment. The participant is taken out from the trial at once. The adverse event is defined as *unexpected* and life-threatening and thus *serious*, and *possibly* related to the test article. Consequently, the event is reported to the local EC.

Comments to Unanticipated Problems - Scenario 1

This scenario describes a situation whereby a research assistant gives a trial participant a much higher dose of a test article than stated in the protocol. This kind of non-compliance happens now and again, just as in normal clinical care, sometimes causing damage and long-term health consequences, including death. The EC did not see the adverse event as linked to the test article. However, the EC regarded the incident as very serious, since it was caused by a protocol violation and caused unnecessary harm to the participant. The sponsor was of course cleared of all responsibilities and the university had insurance coverage in place for the non-compliance and the extra cost of the hospital care that was needed. The EC decided to set up a committee to review the incident and see how similar problems could be prevented. There were two major questions: Why did this happen? Why was the investigator not present in the outpatient clinic?

Note: The EC should investigate the reason for the lack of oversight of the investigator and also evaluate non-compliance of the research assistant. Normal medical care is subject to complaints due to misconduct, and there is often a mechanism in place to handle such anticipated problems. In the same way, the EC or a separate committee should be prepared to handle anticipated problems that may take place within clinical research projects.

Comments to Unanticipated Problems - Scenario 2

Dr. Smirnoff has just been informed about three serious test product-related serious events at another site in a trial that he is currently involved in as an Investigator. The three hypertension patients fainted without warning and suffered severe concussions to their heads as a result of suddenly falling down. Dr. Smirnoff also knows that many anti-hypertension drugs come with risks; many drugs have been related to rare but serious adverse events. Dr. Smirnoff critically considers stopping his participation in this trial and decides to contact the medical director of the sponsoring company for detailed clarification. He reports the three AEs to his local EC and elaborates on his concerns in his AE report. The EC decides to postpone the full EC review of the three AEs until Dr. Smirnoff is able to discuss the situation with the sponsor. However, the EC chair has already decided to suggest at the next EC meeting to establish a local data safety and monitoring committee for this trial, should it continue.

Note: ECs struggle with the continuous stream of adverse event reports, especially from multinational trials with a large sample size.

Comments to Unanticipated Problems - Scenario 3

A patient who is suffering from depression is taking part in a depression treatment clinical trial has tried to take her life by jumping into a river. She is currently in the ICU ward and is likely to recover from the incident. The EC

chair decides to bring up the adverse event report for a full EC review at the next scheduled EC meeting. The chair also asks Dr. Coma to contact the sponsor for more information about any possible relationship between the test article treatment and the incident. Dr. Coma is also invited to be present during the upcoming EC meeting, so that the EC review can be done efficiently.

Note: An unexpected serious adverse event like the one described here should always be taken seriously. The EC should try to collect as much information as possible to ensure that the EC can make a correct interpretation and to reach the best possible decision.

Suspension or Termination of a Trial – Scenarios

This page includes a scenario about suspension or termination of a trial. What action is required by the EC? Write your comments, and view ours.

Suspension or Termination of a Trial - Scenario 1

Dr. Carmen Lopez is not only well known for her language skills, being able to speak six different languages fluently, but she is also the most popular oncologist in the country. Virtually all pharmaceutical companies wish to have her work as their investigator, since she has a large patient pool at the university cancer clinic, as well as at her private clinic in the centre of the capital. Dr. Lopez is involved in many ongoing clinical trials and one is a phase II trial of a test article for leukemia. She has been able to recruit 34 patients into this trial and several are getting better, while others are getting worse, and some have even died during the course of the trial. Dr. Lopez has a strong feeling that the test article is very efficient, although she cannot state this for sure, since she is blinded for the type of treatment given to each patient. Whenever she examines participants who are getting worse, she feels unhappy and dissatisfied with her institution. *“If the test article is in fact so effective, we must stop the trial so that all participants are given the new effective test drug,”* she reasons. Dr. Lopez decides to call the office of the EC chair, Professor Roberto Carlos. His secretary explains that he is on conference leave, but *“he responds to emails day and night.”* Professor Carlos is in Myanmar for a conference, but he still replies by email within 10 minutes. *“Mingalaba in Burmese. Translate that if you can. This time I got you. You should contact the sponsor and clarify your gut feeling and then ask for an interim un-blinded data analysis. If they refuse, the EC will arrange a meeting once I’m back in town, so that we can make a formal request for the analysis.”*

Comments to Suspension or Termination of a Trial - Scenario 1

Dr. Lopez has a strong feeling that the oncology test article is highly efficient and wishes to stop the trial so that all participants can have access to the test article. She feels that it is unethical to continue the trial, since the new drug can save lives. The EC chair, Professor Carlos, has advised her to contact the sponsor for an interim unblinded statistical analysis. The sponsor, a German company, responds quickly to the request and pools the data of 78 participants. It is confirmed that the new drug is very efficient, and after contact with the regulatory authority, the trial is terminated. A new protocol is developed so that all participants are provided the new treatment, and the trial is now open labeled without having a control group.

Note: This is close to a real-life scenario. There can be good reasons to terminate a trial following an unblinded interim statistical analysis. It is, however, important to maintain the treatment code blinded until a decision has been made. It may not always be the case that a test article is associated with increased risk of adverse events or, as in this scenario, with increased benefits. The sponsor must always be involved in the decision, and regulatory authorities must be consulted so that all parties reach a consensus prior to the suspension or termination of a trial.

Complaints - Scenarios

The following page includes a scenario about complaints from a trial participant. What action is required by the EC? Write your comments, and view ours.

Complaints - Scenario 1

Dr. Bernadette Schumann is the principal investigator of a trial that compares the safety and efficacy of a newly developed nasal continuous positive airway pressure (CPAP) compressor for the treatment of patients with obstructive sleep apnea. The sponsor has asked Dr. Schumann to recruit six participants with diagnosed obstructive sleep apnea for the trial. After an evaluation, each patient will be supplied with a new CPAP compressor on a temporary loan basis for the duration of the trial. The participants will then be assessed for any improvements in their snoring symptoms and improvements in quality of life. Mr. Gerard Brücker, who was not enrolled in the trial, has been a patient of Dr. Schumann's for several years and also has obstructive sleep apnea. When first diagnosed, he was told by Dr. Schumann that he would have to purchase his own nasal CPAP compressor to treat the symptoms, as the hospital did not supply them to patients free of charge. Mr. Brücker subsequently discovers that Dr. Schumann has supplied a friend he first met at the clinic with a new machine for the treatment of his sleep apnea problems and becomes very annoyed. Mr. Brücker writes a letter of complaint to the hospital chief executive and to the local newspaper, complaining that Dr. Schumann was showing favouritism to some patients by supplying them with a CPAP compressor for free. The chief executive at the hospital passes a copy of the letter to Dr. Schumann, who in turn reports the matter to her EC in her continuing progress report.

Comments to Complaints - Scenario 1

Dr. Schumann has received a complaint from a patient, Mr. Brücker, for showing favouritism to a trial participant by supplying equipment free of charge, while the complainant, Mr. Brücker, who is a regular patient, had to pay for the same device. Dr. Schumann reports the incident in the continuing progress EC report. The EC chair ignores the reported event during the expedited review process, since it has nothing to do with research ethics. However, the EC chair still believes it is appropriate to include such less important events in the continuing progress report since it has been circulated in the media and there may be further “noise” in the future.

Note: Institutions should develop a procedure to handle complaints from trial participants by including the name and contact details of a participant advocate, independent of the trial site, in the written informed consent form.

Appeals - Scenarios

This page includes a scenario about appeals. What actions are required by the EC? Write your comments, and view ours.

Appeals - Scenario 1

Dr. Svetlana Zhivago was very upset, or rather furious, when she walked home from the university through the central park. She just got the news that her EC application was rejected on the grounds that her trial had too few subjects and was not scientifically sound. Dr. Zhivago and her colleagues produced a recombinant DNA growth hormone in their university laboratory. A phase I trial in healthy volunteers showed the hormone to be safe. The research team now hopes to test the hormone in a group of 20 short children for one year; 10 will be given the active growth hormone treatment, and 10 will be part of the placebo group. Based on many previously published trials, it is well documented that growth hormone will on average increase growth in short children by at least 4.0 cm over one year of treatment, compared with untreated short children. The biostatistician at the university performed a sample size calculation based on this assumption and it turned out that as few as five participants per study group would be sufficient. The research team decided to recruit 10 participants per group nevertheless, just to be on the safe side, in case the dropout rate was high. Before Dr. Zhivago enters her flat, she knocks on the door of her neighbour, Mr. Nikitin, who is the legal advisor of her university. Mr. Nikitin opens the door. Ten minutes later, Dr. Zhivago goes home with a large smile. Mr. Nikitin had informed her that the university has an appeals committee to hear appeals or objections against EC applications. The committee, which also handles fraud and misconduct cases, meets once every two months and the next meeting is scheduled tomorrow. As the chair of the committee, Mr. Nikitin invited Dr. Zhivago to come to his office at 11am tomorrow to explain the case to the committee members.

Comments to Appeals - Scenario 1

Mr. Nikitin sits down in front of his home computer and logs in to the university library. It is very easy to find information about growth hormone treatment trials in short children – maybe 50 or more publications. The information that Dr. Zhivago had provided is seemingly correct. Mr. Nikitin looks forward to the meeting tomorrow, since this will be the first case for his EC appeals committee.

Note: An EC must have written procedures in place so that any unfavourable decisions can be appealed and handled in an appropriate manner. However, the institutional EC must in the end approve or not deny any EC applications.

Non-compliance – Scenarios

This page includes a scenario about non-compliance of an investigator. What actions are required by the EC? Write your comments, and view ours.

Non-compliance - Scenario 1

Dr. Ingemar Johansson is an academic orthopedic surgeon specialising in hip replacement surgery. He has been in the US for the past six months visiting a highly reputable academic hospital in Florida. During his absence, a young colleague – Dr. Alex Fix – promised to take over the role as the investigator for a multinational investigator-initiated hip replacement clinical trial. Dr. Johansson has now returned to work and discovered some problems with the ongoing hip replacement trial. Dr. Fix has not only violated the trial protocol; he has also involved participants that should not be included in the trial. Two trial participants that Dr. Fix has included and operated on were too high risk for the trial – one had asthma, the other leukemia. The two patients have not experienced any serious adverse events. However, Dr. Johansson must report the discovery to the international trial steering committee since it is a requirement addressed in the trial agreement. Furthermore, Dr. Johansson has to include the two protocol violations in the upcoming continuing progress report to the local EC as required by his hospital, and he submits the report.

Comments to Non-compliance - Scenario 1

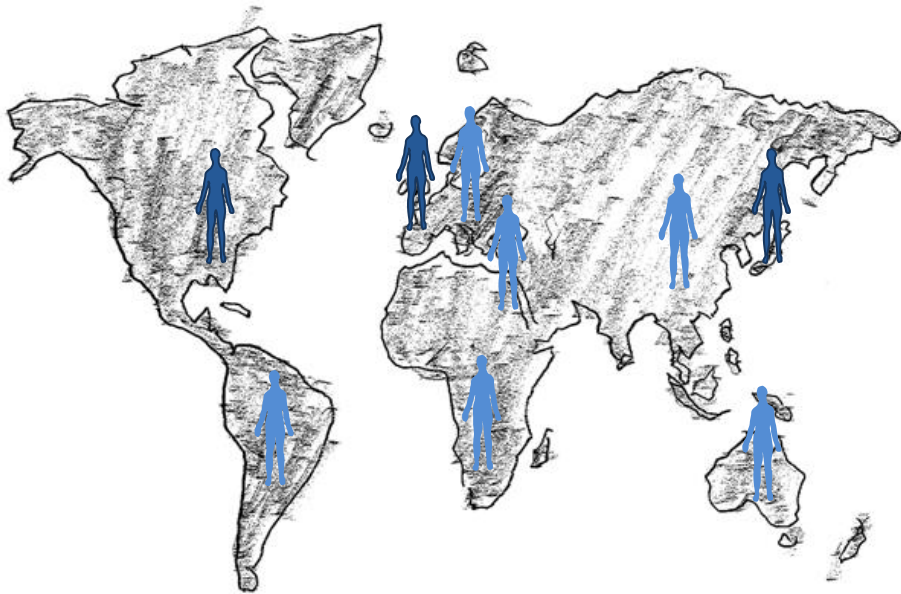
Dr. Johansson is not happy after discovering that Dr. Fix has made a mess of one of his trials when he was on sabbatical leave. Dr. Fix has included and operated on two ineligible patients. Dr. Johansson wrote about the two protocol violations in the continuing progress report to the local EC. The university recently established a disciplinary board for research fraud and misconduct and the EC chair has decided to hand over the annual progress report to this board. The two patients in question are well and have not experienced any trial-related adverse events. The EC chair decides to bring up the case at the upcoming EC meeting so that he can suggest allowing Dr. Johansson to continue with the trial. The EC chair will also bring up the two protocol violations caused by Dr. Fix as they represent non-compliance, and the EC must take action.

Note: Continued EC review of human research projects is important since some studies may face problems that are otherwise not identified. In turn, the risk-benefit balance can be affected.

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