where science and ethics meet

Slovensko Zdravniško Društvo
Sekcija za internistično onkologijo

Institute of Oncology Ljubljana
Onkološki inštitut Ljubljana
Sektor za internistično onkologijo

Interactive Training in Applied GCP for Investigators & Site Personnel

GCP compliance in Conducting Clinical Research

21 & 22 November 2014
Institute of Oncology, Ljubljana, Slovenia

www.efgcp.eu * info@efgcp.eu

EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE

Strokovni odbor:

doc. dr. Barbara Jezeršek-Novakovič. dr.med.
prof.dr. Branko Zakotnik, dr.med.
doc. dr. Janja Ocvirk, dr.med.
dr. Simona Borštnar, dr.med.
doc. dr. Boštjan Šeruga, dr.med.
dr. Breda Škrbinc, dr.med.
mag. Erika Matos, dr.med.

Organizacijski odbor:

mag. Erika Matos, dr.med.
doc. dr. Janja Ocvirk, dr.med.
Marko Boc, dr.med.
Lidija Kristan

Urednika zbornika:

mag. Erika Matos, dr.med.
Marko Boc, dr.med.

Organizator in izdajatelj (založnik):

Sektor za internistično onkologijo, Onkološki inštitut Ljubljana
Sekcija za internistično onkologijo
Ljubljana, 2014

Interactive Training in Applied GCP for Investigators & Site Personnel

GCP Compliance in Conducting Clinical Research

21 & 22 November 2014
Institute of Oncology, Ljubljana, Slovenia

INTRODUCTION

Performance of clinical trials according to Good Clinical Practice (GCP) principles has been introduced as a European regulatory requirement by the Clinical Trial Directive 2001/20/EC. Strict adherence to this standard ensures patient protection and reliable data. It is the basis for acceptance of publications and for patients' access to new treatments. This standard has implications for all stakeholders and processes in clinical trials. However, despite overall commitment and best intentions to apply to these requirements, monitoring, audits and inspections regularly find deficiencies of different levels of severity.

In this 1.5-day course, current experience and requirements of GCP-conform set-up and performance of clinical trials will be presented, their practical implications and examples discussed and pragmatic solutions for your daily practice elaborated.

FACULTY

The Institute of Oncology and the European Forum for Good Clinical Practice have assembled an international faculty of national agency and ethics committee representatives and experts in GCP-conform clinical trials performance:

Nicky Dodsworth, Chairman of the EFGCP Education Working Party & Vice President Global Quality Assurance Premier Research, United Kingdom

Ingrid Klingmann, Chairman of EFGCP & Expert in Drug Development Planning and Site Management Support, Pharmaplex bvba, Belgium

Janez Primožič, MD, PhD, Member of the National Medical Ethics Committee, retired paediatrician, former Head of the Department for Child Surgery and Intensive Therapy, University Medical Centre Ljubljana, Slovenia

Maja Schara, Senior Adviser for Clinical Trials, Agency for Medicinal Products and Medical Devices of the Republic of Slovenia (JAZMP)

AGENDA

Day 1: Friday 21st November 2014

09:00-09:45	**Welcome & Introduction - Principles of GCP** *Nicky Dodsworth*
09:45-10:15	**From ICH-GCP Standard to Slovenian clinical trial legislation** *Nicky Dodsworth & Maja Schara*
10:15-10:45	**Ethics committees and ethical review** *Ingrid Klingmann & Janez Primožič*
10:45-11:15	*Coffee Break*
11:15-11:45	**Optimising the Informed Consent process** *Ingrid Klingmann*
11:45-13:00	**Set-up of a clinical trial at the investigator site** *Ingrid Klingmann*
13:00-14:30	*Lunch Break & Satellite lecture (Takeda)*
14:30-15:30	**Principles of document management** *Nicky Dodsworth*
15:30-16:00	**Quality management at a clinical trial site** *Nicky Dodsworth*
16:00-16:30	*Coffee Break*
16:30-17:30	**Reliable safety management at the site** *Ingrid Klingmann*
	Exercise: Assessment of AEs and an SAE
17:30	End of Day 1

Day 2: Saturday 22nd November 2014

08:00-09:00	Skupščina Sekcije za internistično onkologijo
09:00-10:30	**Principles of clinical trial management** *Ingrid Klingmann*
	Exercise: Planning your resources for study execution
10:30-10:50	*Coffee Break*
10:50-12:00	**Critically important aspects in clinical trial management** *Nicky Dodsworth*
12:00-12:30	Final test and joined review of correct answers
12:30	End of Day 2

FACULTY BIOGRAPHIES

Nicky Dodsworth, Premier Research, is currently Vice President, Global Quality Assurance for Premier Research with responsibility for pharmaceutical and medical device studies.
Nicky is an active member of European Forum for Good Clinical Practice (EFGCP), in 2011 she was appointed Chair of the Education Working Party and is a member of the Audit Working Party. Nicky has conducted widespread training for various groups and has presented in 14 different countries. During 2010, she started to run the recently accredited EMWA Workshop on Quality Awareness in CSR Development. She is a Senior Associate Member of the Royal Society of Medicine. In 2009 Nicky became a Chartered Scientist, an award from the Science Council in the UK which is awarded to individuals who are professional scientists practicing and/or advancing science and for whom this is an integral part of their daily work. Nicky has worked closely with the Institute of Clinical Research since 1996, she is currently Co-Chair of the GCP Forum and she also works closely with the Ethics Forum. In July 2011, Nicky became a member of the Research Quality Assurance, West & Wales Organising Group which promotes information exchange at a regional level.
Nicky has written many publications, including addressing risk mitigation in clinical research, quality by design and risk management, risk based approaches, training and education, auditing and inspections, fraud and misconduct, ISO 14155, implementing quality in times of change, improving quality through metrics, standards for Ethics Committees in Europe, Standard Operating Procedures and running trials in Eastern Europe and Russia. Nicky has assisted in preparation of the 4th Edition of Fraud and Misconduct, Royal Society of Medicine Press, by writing the chapter on enhanced audits. She has given over 60 lectures and presentations with various audiences across 13 different countries, many from academia and the NHS on clinical trials, good clinical practice, quality, risk assessment, informed consent, audits and audit findings, fraud and misconduct as well as on Ethics Committees.

Ingrid Klingmann, MD, PhD, FFPM, FBCPM, PHARMAPLEX bvba, European Forum for Good Clinical Practice, Brussels (Belgium). Dr. med. Ingrid Klingmann is specialized in General Medicine, Clinical Pharmacology and Pharmaceutical Medicine.
After having joined pharmaceutical industry as medical advisor, she held senior management positions in different international contract research organisations and was responsible for operational, scientific, regulatory and business aspects of international clinical research projects from Phase I to Phase IV.
Since January 2003 she has her own pharmaceutical development and site management support consulting company. For 4 years she was also CEO of two investigative sites in London, UK, performing clinical trials in acute and chronic pain as well as musculo-skeletal diseases.
Dr. Klingmann is Chairman of the Board of the European Forum for Good Clinical Practice (EFGCP). On behalf of EFGCP she was Work Package Leader of the PatientPartner Project and is currently Coordinator of the IMI project PharmaTrain and she is Work Package Leader of EUPATI, responsible for developing the EUPATI Network, the EUPATI National Platforms and the Ethics Panel.
Dr. Klingmann chairs the clinical research module of the post-graduate Master in Regulatory Affairs course at the University of Bonn, Germany, and co-chairs the Diploma Course in Clinical Trial Practices at the University of Basel, Switzerland.

Janez Primožič, MD, phD, Associate professor of paediatrics was heading Division for pediatric surgery and intensive care of the Department of surgery at the University Medical Center in Ljubljana from 1987 until 2010 when he retired. He completed his training in pediatric intensive care in UK (Great Ormond Street Hospital and Liverpool Childrens' Hospital) and in USA (Oakland Childrens' Hospital, Childrens' Hospital in Detroit, Childrens' Hospital in Albuquerque).
In 1989 he was hired by the Ministry of Public Health in Kuwait to establish pediatric intensive care unit at Al Sabah Hospital and was its first head. His main professional interest was postoperative care of children undergoing heart surgery. In the year 1994 he developed the project of extracorporeal membranous oxygenation (ECMO) and implemented it for children in Slovenia. Due to his work with critically sick children he was soon envolved in resolving ethical problems and dilemmas. In 1994 he became the member of the Slovenian National Committee for Medical Ethics. He published several articles in domestic and international (SCI rated) medical journals.
Regarding professional societies he was the president of the Slovenian Paediatric Society and as delegate founder of the European Society for Pediatric and Neonatal Intensive Care (ESPNIC). He is a member of honour of the Slovenian Society of Intensive Medicine.

Maja Schara

Curriculum vitae	
Full first and surname	Maja Schara
DOB	28.7.1964
Nationality	Slovenian
Professional address	JAZMP-Agency for Medicinal Products and Medical Devices Einspielerjeva 6 1000 Ljubljana, Slovenia tel: + 386 8 2000 500 e-mail: maja.schara@jazmp.si
Current position	since 2009: JAZMP-Senior adviser for clinical trials
Previous position	1997-2009: JAZMP- department for Import of medicinal products and medical devices
	1992-1997: Dental trade d.o.o.-Regulatory Affairs adviser
	1990-1991: Internships: Pharmacy of Ljubljana
Education	1979-1983: Classical Grammar School, Ljubljana
	1983-1990: The Faculty of Pharmacy, University of Ljubljana: MPharm

where science and ethics meet

The European Forum for Good Clinical Practice (EFGCP) is a not-for-profit organisation established by, and for, those with a professional involvement in clinical research. It is dedicated to promoting the interests of patients in clinical research through the development of European ethical and scientific standards. The EFGCP provides a common meeting ground for the many disciplines and organisations affected by GCP.

EFGCP VISION:

A Europe that leads the development of new treatments through research integrity in partnership with patients and researchers.

EFGCP is the leading multi-stakeholder forum in Europe where science & ethics meet to promote Good Clinical Practice in biomedical research.

EFGCP MISSION:

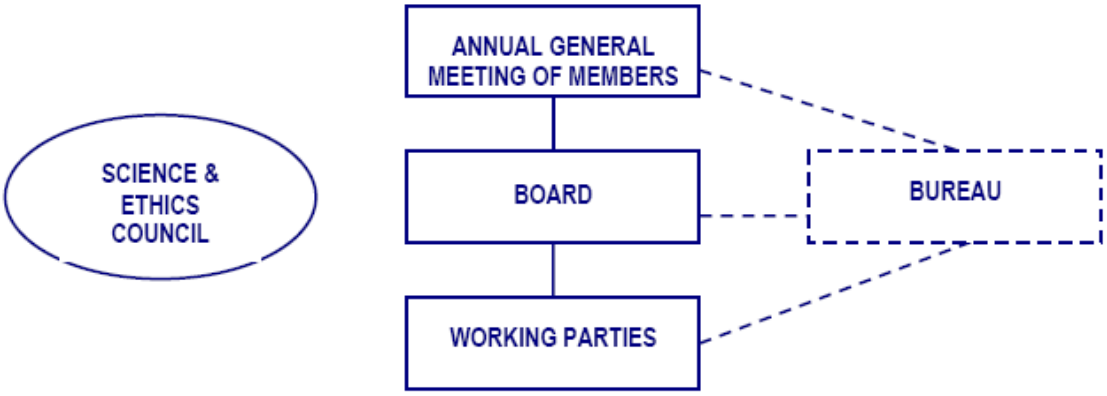
- To promote open discussion on critical issues in biomedical research and health,
- To promote education and awareness leading to the application of ethical and scientific requirements in clinical research.
- To facilitate the transfer of knowledge and skills across disciplines and sectors including training and advice.
- To promote a renewed emphasis on human values in research involving human participants.

The EFGCP is a European organisation with a global vision. This is reflected in the many collaborative partnerships it has developed with European, North American and International Research patient, research, and regulatory organisations.

FUNDING

The basic source of funds for the EFGCP is membership fees. Additional funding for specific EFGCP activities is developed according to the objectives and scope of the activity concerned. In order to maintain its independence and high ethical standards, the EFGCP actively seeks funding across a wide range of funding organisations, including public (i.e. EU funded-projects) and private institutions. All EFGCP financial engagements are guided by the principles of independence in decision-making and transparency.

STRUCTURE



MEMBERSHIP

Membership in the EFGCP is open to professionals and individuals, representing patient groups, ethics committees, academic & industry research enterprises, regulatory officials, and those concerned to develop Good Clinical Practice in Europe.

BOARD

The EFGCP is governed by a Board of Directors. The Board has responsibility for providing leadership, policy-making, and financial decision-making in accordance with the Charter of Incorporation. Board members are elected by the EFGCP General Assembly. The members are elected for a term of 3 years, which is renewable. The Board is responsible to ensure that the EFGCP is managed to continually comply with the ethical and scientific standards required for providing European leadership in Good Clinical Practice.

SCIENCE & ETHICS COUNCIL

The EFGCP Science & Ethics Council is composed of leading European and international experts representing major institutions affecting the regulation and practices of Good Clinical Practice. It pools the efforts of the Board including the Working Parties chairpersons and the previous Advisory Council under one same roof.

Although the executive power of the EFGCP continues to rest with the Board, the Council takes the lead in matters of Science and Ethics. The Working Parties which would like to broaden their activities, issue more position papers and propose topics for conference receive recommendations and approval from the new Council.

The Science & Ethics Council contributes to the development of the EFGCP by

- increasing input into EFGCP planning and projects,
- extending the EFGCP basis of expertise and competence, and
- increasing the awareness and recognition of the contributions to GCP made by the EFGCP.

The Science and Ethics Council sees to optimally reflect the various components of the clinical research community: the patient associations, the sponsors, the CROs, the investigators and their networks, the ethics committees and the authorities. By itself, the new Council with 2 meetings a year will provide a unique opportunity for Forum discussions. The members of the Science & Ethics Council are regularly invited to participate in EFGCP Events either as experts in particular subjects or in advisory capacity for developing the events

WORKING PARTIES

The EFGCP Working Parties serve as the central reference point for **EFGCP** research and the development of European guidances, reports, and publications in the area of Good Clinical Practice. The Working Parties are composed of EFGCP members with expertise and interest in contemporary areas such as the ethics, science, and regulation of clinical research in Europe and globally.

The following six Working Parties are active:

- Ethics Working Party
- Audit Working Party
- Education Working Party
- Children's Medicines Working Party
- Geriatric Medicines Working Party
- Patients' Roadmap to Treatment Working Party (in collaboration with the European Genetic Alliance Network – EGAN)

BUREAU

The EFGCP Secretariat is the organisational arm of the EFGCP responsible for all the operations of the association and its membership services. The EFGCP events are also managed internally.

ACTIVITIES

To fulfill its mission it is necessary for the EFGCP to organise relevant activities. Activities include Conferences, Workshops, Working Parties, Research Projects (FP6/FP7/IMI), Website, Newsletter and other publications.

PUBLICATIONS

EFGCP is dedicated to bringing leading publications on GCP in Europe and abroad. The EFGCP publishes its own newsletter, The EFGCP News, quarterly as well as a number of European guidelines and key reports (Annual update of the EFGCP Report on *The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe*, freely available on the website)

CONFERENCES & WORKSHOPS

Since its creation, EFGCP has been organising a significant number of conferences and workshops which consist in high level forum discussions characterised by interactive debates on a specific topic with the major stakeholders in the selected area. Among the organisations that have participated in projects led by the EFGCP are the European Commission, the European Parliament, EMA, EORTC, ESF, EAP, EPPOSI, EuropaBio, EFPIA, ICH, BARQA, WMA, CIOMS, the Faculty of Pharmaceutical Medicine, etc. Please consult the list of past events for further details.

CONTACT INFORMATION:

EFGCP Secretariat
Square de Meeûs - Rue de l'Industrie 4
B-1000 Brussels
Belgium
Tel +32 2 732 87 83 - Fax +32 2 503 31 08
E-mail: info@efgcp.eu
Website: http://www.efgcp.eu

DAY 1

21 NOVEMBER 2014

Interactive Training in Applied GCP for Investigators & Site Personnel

GCP Compliance in Conducting Clinical Research

21 & 22 November 2014

Ingrid Klingmann, MD, PhD, FFPM, FBCPM
EFGCP, Pharmaplex bvba, Brussels
Nicky Dodsworth, DCRR, CSci, MRQA
EFGCP, Premier Research, UK

PRINCIPLES OF GOOD CLINICAL PRACTICE (GCP)

Nicky Dodsworth
Material developed in collaboration with
Prof. Dr. JanHasker G. Jonkman
University of Groningen, The Netherlands &
Dr. Petra Knupfer
Ethics Committee Baden-Württemberg, Germany

Topics

- ICH GCP
- Development of GCP/ Legal aspects
- Declaration of Helsinki
- 13 Principles of ICH GCP
- Questions: True/False

GCP - GOOD CLINICAL PRACTICE

- **International ethical and scientific quality standard**
  - **for designing, conducting, recording and reporting trials with human subjects.**
- **Compliance with this standard provides public assurance**
  - **that the rights, safety, well-being of participants are protected**
  - **that the safety of society is protected (reliable clinical data for market authorization)**

ICH GCP

- **International Conference on Harmonisation**
  of Technical Requirements for Registration of Pharmaceuticals for Human Use
  (first meeting 1991 in Brussels, Belgium)
- **World standard**
  finalized July 17, 1996
  effective January 17, 1997
  - **Representatives of regulatory agencies and pharmaceutical industries of EU, USA, Japan**
  - **Observers of WHO, Canada, EFTA**

How was ICH GCP developed?

- **1977** USA started with formal GCP rules**, FDA GCP**
- **1989 EU-GCP** Note for Guidance
- **1996 ICH GCP** Guideline:
  to harmonize GCP in order to accept clinical data for market authorisation

ICH E6 GCP is still a cornerstone

GCP is based on:

World Medical Association's "**Declaration of Helsinki**"

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the WMA General Assemblies in

1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong, China), 1996 (Somerset West, South Africa), 2000 (Edinburgh, UK), 2002 (Washington, USA), 2004 (Tokyo, Japan), 2008 (Seoul, South Korea)
2013 (Fortaleza, Brazil)

- Best-known declaration of the World Medical Association
- Recommendations for medical researchers

ICH GCP DIVIDED INTO…

1. Glossary
2. **The Principles of ICH GCP**
3. Institutional Review Board/Independent Ethics Committee (IRB/IEC)
4. Investigator
5. Sponsor
6. Clinical Trial Protocol and Protocol Amendment(s)
7. Investigator's Brochure
8. Essential documents for the conduct of a clinical trial

ICH GCP - 13 PRINCIPLES (1)

COMMON SENSE !

1. Clinical trials should be conducted in accordance with the ethical principles in the Declaration of Helsinki, consistent with GCP and the applicable regulatory requirements.
2. A trial should be initiated and continued only if the anticipated benefits – for individual and society - justify the risks.
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.

ICH GCP - 13 PRINCIPLES (2)

4. Non-clinical and clinical information on the investigational product (IMP) should be adequate to support the proposed trial.
5. Trials should be scientifically sound and described in a clear, detailed protocol.
6. The trial should be conducted in compliance with the protocol that has received prior Independent Ethics Committee approval / favourable opinion.
7. The medical care and medical decisions should always be the responsibility of a qualified physician.
8. Each team member involved in conducting the trial should be qualified by education, training and experience to perform his/her respective tasks.

ICH GCP - 13 PRINCIPLES (3)

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, stored in a way that allows accurate reporting, interpretation, verification.
11. Confidentiality of records should be protected respecting confidentiality rules in accordance with regulatory requirements.
12. IMP should be manufactured, handled and stored in accordance with good manufacturing practice (GMP) and used in accordance with the protocol.
13. Systems, procedures that assure the quality of every aspect of the trial (e.g. SOPs, GLP) should be implemented.

TO WHOM DOES THIS APPLY?

- SPONSOR / SPONSOR INVESTIGATOR (Sections 5, 6, 7, and 8)
- CRO / MONITOR (Sections 5, 6, 7, and 8)
- ➢ INVESTIGATOR (PRINCIPAL, SUB-INVESTIGATOR, SITE STAFF, PHARMACIST) (Sections 4 and 8)
- INSTITUTIONAL REVIEW BOARD (IRB) / ETHICS COMMITTEE (EC)/ COMPETENT AUTHORITY (CA) (Sections 3 and 8)

QUESTIONS: TRUE/FALSE

Skills/Training

The skills of an investigator for the performance of a clinical trial are demonstrated by his CV only.

True or False?

True	False
☐	☑

Skills/Training

Related To The Respective Delegated Task

- Education:
  - ✓ Documented College Degree, Education Certificate
- Training:
  - ✓ Documented Training
- Experience:
  - ✓ Documented History Working With The Particular Trial Subject Population AND With Performing/Conducting The Delegated Task

Declaration of Helsinki

ICH GCP provides assurance, consistent with the Declaration of Helsinki, exclusively for sponsors and investigators.

True or False?

True	False
☐	☑

Declaration of Helsinki

- Prior to the 1947 Nuremberg Code there was no generally accepted code of conduct governing the ethical aspects of human research
- The Declaration developed the ten principles first stated in the Nuremberg Code, and tied them to the Declaration of Geneva (1948), a statement of physician's ethical duties.

Risk-Benefit

The rights, safety, and well-being of the trial subjects are the most important considerations but need not prevail over interests of science and society.

True or False?

True	False
☐	☑

Risk-Benefit

Principle 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.

The advancement of medicine is never the most important factor in research; therefore investigators must never sacrifice the interests and rights of study subjects to ensure completion of a trial.

CONCLUSIONS (1)

- **ICH-GCP is based on the Declaration of Helsinki**
- **There are differences in clinical trial performance in different countries but global harmonisation is supported by the ICH-GCP standard**
- **GCP defines the roles and responsibilities of sponsor, investigator, competent authorities and ethics committees**
- **Trial performance according to GCP principles is protecting the study participants**

CONCLUSIONS (2)

- **GCP contributes to better reproducible and more reliable data (less misconduct and/or fraud) through**
  - **Strict compliance with Study Protocol**
  - **Full documentation of all stages of the study (not documented = not done)**
  - **Implementation of quality management system**
    - SOP's
    - Training
    - In-process quality control
    - Audits by independent Quality Assurance Department
  - **Drug accountability**
  - **Archiving**

FROM ICH-GCP STANDARD TO SLOVENIAN CLINICAL TRIAL LEGISLATION

Nicky Dodsworth
Material developed in collaboration with
Prof. Dr. JanHasker G. Jonkman
University of Groningen, The Netherlands &
Dr. Petra Knupfer
Ethics Committee Baden-Württemberg, Germany

GCP Implementation into Law

- Medicines for Human Use (Clinical Trials) Legislation 2004 (Directive 2001/20/EC)
- EU Directive on Good Clinical Practice (Directive 2005/20/EC)
- National Laws
- Compliance with GCP is now a **legal obligation** in Europe for **all trials with investigational medicinal products**

THE EUROPEAN UNION (1)

- **1965: Council Directive 65/65/EEC required "the submission of a dossier containing the results of tests and clinical trials."**
- **1975: Council Directive 75/318/EEC "laid down uniform rules on the presentation of such dossiers."**

THE EUROPEAN UNION (2)

- **2001: Directive 2001/20/EC of the European Commission relates to "the implementation of good clinical practice (GCP) in the conduct of clinical trials on medicinal products for human use." [The Clinical Trials Directive]**
- **2005: Directive 2005/28/EC of the European Commission "lays down principles and detailed guidelines for good clinical practice (GCP) as regards investigational medicinal products for human use." [The GCP Directive]**

THE EUROPEAN UNION (3)

The legislations released by the European Commission have different "legal weight":

- **"Regulation": text has to be implemented in national legislation as it stands**
- **"Directive": the principles have to be implemented in national legislation but leave the member states flexibility of interpretation and adaptation to national legislation**
- **"Guidance": define in detail execution aspects and requirements generally lined out in the Directives**

THE EUROPEAN UNION (4)

- **EudraLex, Volume 10:**

  http://ec.europa.eu/health/documents/eudralex/ vol-10/

  - **Chapter I: Application and application forms**
  - **Chapter II: Monitoring and pharmacovigilance**
  - **Chapter III: Quality of the IMP**
  - **Chapter IV: Inspections**
  - **Chapter V: Additional information**
  - **Chapter VI: Legislation**

THE EUROPEAN UNION (5)

- **EudraLex, Volume 10:**

  Chapter I: Application and application forms

  - **CT-1: Detailed guidance for authorisation of a clinical trial and substantial amendment**
  - **CT-2: Detailed guidance on the application format and documentation to be submitted to ethics committees**
  - **CT-5: Detailed guidance on the EudraCT Database**

THE EUROPEAN UNION (6)

- **EudraLex, Volume 10:**

  Chapter I: Monitoring and pharmacovigilance

  - **CT-3: Detailed guidance on adverse reaction reporting (SUSARs)**
  - **CT-4: Detailed guidance on the EudraVigilance Database**
  - **Q&A specific to AR reporting**
  - **ICH-E2F: Note for guidance on the development of safety update reports**

  Note: there is NO guidance on monitoring of clinical trials!!

THE EUROPEAN UNION (7)

- **EudraLex, Volume 10:**

  Chapter V: Additional Information

  - **ICH-E6: GCP guideline**
  - **GCP guideline for advanced therapy medicinal products**
  - **Recommendations on the content of the Trial Master File**
  - **Ethical considerations for paediatric clinical trials**
  - **Guideline on information to be made public from EudraCT**

THE EUROPEAN UNION (8)

- **EudraLex, Volume 10:**

  Chapter V: Legislation

  - **Directive 2001/20/EC: Clinical Trials Directive**
  - **Commission Directive 2005/28/EC: GCP Directive**
  - **Commission Directive 2003/94/EC: GMP Directive**

CONCLUSIONS (1)

- **EU Directive 2001/20/EC ("Clinical Trials Directive") and Directive 2005/28/EC ("GCP Directive") had to be implemented in national legislation in 2004**
- **In addition, there is a whole European legal framework including European databases, guidelines, processes and forms that had to be integrated in the national legal frameworks to reliably enable ICH-GCP-conform performance of clinical trials**

CONCLUSIONS (2)

- **GCP contributes to better protection of study participants through**
  - **Evaluation / approval of protocol by Medical Ethics Committee**
  - **Only participation after written consent of subject**
  - **Surveillance of adverse events**
  - **Protection of privacy of participants**

Slovenska zakonodaja na področju kliničnih preskušanj zdravil

november 2014

jazmp

Javna agencija Republike Slovenije
za zdravila in medicinske pripomočke

Maja Schara, mag.farm.

Evropska zakonodaja na področju KP

- **Direktiva 2001/20/EC Evropskega parlamenta in Sveta** z dne 4. aprila 2001 o približevanju zakonov in drugih predpisov držav članic v zvezi z izvajanjem dobre klinične prakse pri kliničnem preskušanju zdravil za ljudi (CT direktiva)
- Harmonizacija & pomanjkljivosti

NOVO!

UREDBA (EU) št. 536/2014 EVROPSKEGA PARLAMENTA IN SVETA z dne 16. aprila 2014

o kliničnem preskušanju zdravil za uporabo v humani medicini in razveljavitvi Direktive 2001/20/ES

- Evropska komisija 17. julija 2012 objavila predlog uredbe
- 27. maja 2014 objava v uradnem listu EU
- začetek uporabe: ne pred 28. majem **2016**.

UREDBA – ni potreben prenos v nacionalno zakonodajo - neposredna uporaba v RS

Slovenska zakonodaja na področju kliničnih preskušanj

=

skladna z evropsko zakonodajo

- **Zakon o zdravilih –ZZdr-2** (Ur. list RS, št. 17/2014)
  III. poglavje: Preskušanje zdravil in sočutna uporaba zdravil
- **Pravilnik o kliničnih preskušanjih zdravil** (Ur. l. RS, št. 54/06)
  implementira direktivo 2001/20/ES

Zakon o zdravilih (ZZdr-2) :

klinično preskušanje (33. - 40. člen)

- klinično preskušanje zdravila
- pogoji za klinično preskušanje zdravila
- začetek kliničnega preskušanja zdravila
- odobritev (gensko zdravljenje, zdravljenje s somatskimi celicami, vključno s ksenogenimi celicamizdravila ki vsebujejo GSO) /priglasitev (vsa ostala zdravila)
- spremembe v kliničnem preskušanju zdravila
- prekinitev kliničnega preskušanja
- neintervencijska klinična preskušanja

Zakon o zdravilih (ZZdr-2)

KP se izvaja v skladu z :

- načeli in smernicami dobre klinične prakse
- načeli etike v humani oziroma veterinarski medicini
- zagotavljanjem varovanja osebnih podatkov.

- Zdravila klinično preskušajo izvajalci zdravstvene oziroma veterinarske dejavnosti, ki razpolagajo s kadri, pooblaščenimi za predpisovanje zdravil, v skladu s predpisi in načeli dobre klinične prakse.

Pravilnik o kliničnih preskušanjih zdravil

področja urejanja in pristojnosti:

- pravice in dolžnosti udeležencev v KP (zaščita občutljivejših skupin prebivalstva, mladoletnih oseb…)
- postopek, obliko in vsebino dokumentacije za odobritev KP
- postopek, obliko in vsebino dokumentacije za priglasitev pomembne spremembe
- postopek, obliko in vsebino dokumentacije za obvestilo o zaključku KP
- postopek obveščanja o resnih neželenih učinkih zdravil v KP
- označevanje zdravil v KP
- shranjevanje dokumentacije
- nadzor

Zaščita preizkušancev se zagotavlja:

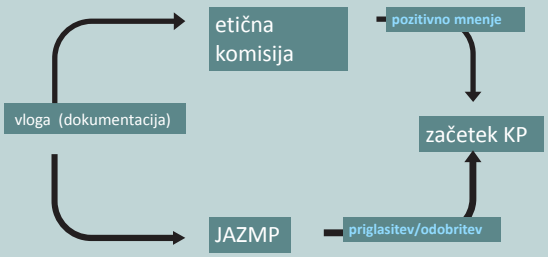
-na podlagi ocene tveganja (razmerje korist/tveganje)
- na podlagi mnenja etične komisije(pozitivno mnenje)
- na podlagi mnenja pristojnih organov (dovoljenje/priglasitev)
-z upoštevanjem pravil o varstvu osebnih podatkov
-s pisnim soglasjem preizkušancev (zaščita občutljivejših skupin prebivalstva, mladoletnih oseb…)
-s spremljanjem resnih neželenih učinkov

Pravilnik o kliničnih preskušanjih zdravil

Udeleženci v sistemu:

- Sponzor -nosilec odgovornosti za začetek, vodenje oz. financiranje
- Raziskovalec
- Preizkušanec

- pristojni organ (JAZMP)
  - izdaja dovoljenja/priglasitev za izvajanje KP
  - nadzorstvo
- etična komisija



Pravilnik o kliničnih preskušanjih zdravil

Vsebina vloge za priglasitev/odobritev KP:

- spremni dopis
- EudraCT številka
- EudraCT obrazec
- protokol
- brošura za raziskovalca
- IMP dokumentacija
- drugi dokumenti/nacionalne zahteve

Pravilnik o kliničnih preskušanjih zdravil

Obveščanje o resnih neželenih učinkih zdravil v KP

- komu poročati (raziskovalec-sponzor-pristojni organ-EC)
- kaj poročati (SUSAR- resni nepričakovani neželeni učinki)
- časovni okvir poročanja (7/15 dni)
- vsebina poročila
- letna varnostna poročila (vsebina, časovnica)

sponzor → ***EudraVigilance – CT modul***

jazmp SLO zakonodaja

Pravilnik o kliničnih preskušanjih zdravil

Ostala poglavja:

- Pomembne spremembe kliničnega preskušanja
- Zaključek kliničnega preskušanja
- Označevanje zdravil
- Shranjevanje dokumentacije
- **Nadzor**

jazmp Nadzor

39. člen Pravilnika o kliničnih preskušanjih zdravil

- Nadzor nad kliničnim preskušanjem zdravila se lahko izvaja pred začetkom, med potekom in po zaključku kliničnega preskušanja zdravila.
- Nadzor nad kliničnim preskušanjem zdravila se lahko izvaja: na mestu preskušanja (klinična ustanova), v laboratorijih, kjer se izvajajo analize za klinično preskušanje zdravila, pri izdelovalcu zdravila in/ali pri sponzorju oz. njegovem pogodbeniku.

Referenca za nadzor na mestu kliničnega preskušanja je ICH GCP smernica.

- pregled glavnega dosjeja študije TMF), pogoji shranjevanja in številnost zdravil, navzkrižno preverjanje podatkov v CRF in zdravstveni dokumentaciji s poudarkom na upoštevanju vključitvenih in izključitvenih kriterijev.
- Zapisnik o inšpekcijskem nadzoru
- Vpis planiranih in izvedenih inšpekcij ter pomanjkljivosti v EudraCT bazo.

jazmp Prekrški in globe

192. člen ZZdr-2 (kazenske določbe), farmacevtski inšpektor izda odločbo, s katero izreče globo za storjeni prekršek

- hujši prekrški - visoke globe …, npr:

➢ z globo od 8.000 do 120.000 eurov se za prekršek kaznuje pravna oseba, če:

– kliničnega preskušanja zdravil ne opravi v skladu s 34. in 35. členom tega zakona,

– ne zavaruje svoje odgovornosti za morebitno škodo, nastalo s preskušanjem zdravila,

–ne priglasi pomembnih sprememb pri kliničnih preskušanjih, ki že potekajo,

– ne pripravi poročila o poteku in rezultatih preskušanja .

jazmp

Št. kliničnih preskušanj v EU/ leto: ~4400
(60% sponzorira farm. ind., 40% nekomercialnih)
Število udeležencev: ~400.000

V SLO letno priglašenih okoli 30 novih kliničnih preskušanj
(80% sponzorira farm. ind., 20% nekomercialnih)

ETHICS COMMITTEES AND ETHICAL REVIEW

Ingrid Klingmann, MD, PhD
EFGCP, Pharmaplex bvba, Brussels

Guiding Principles for ECs

- **Independence** - **in constitution and decision making**
- **Competence** - **in evaluating ethical issues**
- **Interdisciplinarity** - **in composition**
- **Transparency** - **in action**

Development of ECs

- **Spontaneous formation of ECs in hospitals, pharmaceutical companies, external groups**
- **Different development in different countries concerning constitution, requirements, timelines, procedures, outcome, interaction with investigator and sponsor**
- **In more and more countries implementation of ECs in national legislation on different levels - or physicians organisations' internal guidance or requirements**

Development of ECs

Results

- Mostly helpful for investigators
- Difficult for sponsors to cope with differences, changes, unpredictabilities, and partly inexperience of the ECs
- Increasing workload for voluntary EC Members

Development of ECs

Achievements Through Directive 2001/20/EC

- EC systems have been implemented in all national legislations
- ECs get “authority” status because in all EU countries their positive opinion is required before a study can be started
- Single opinion per Member State
- Defined maximum timelines for review

Development of ECs

Achievements Through Directive 2001/20/EC

- Theoretically: Defined list of content of review
- Ongoing involvement of EC during course of the trial
- Clarification of IC procedure for minors and incapacitated subjects

Development of ECs

The Deficiencies

- Directive: not a Regulation
- Establishment and operation of ECs under national responsibility: different national systems remain
- Different systems to reach single opinion: need to contact all involved ECs will remain in most MSs
- Undefined communication lines: applicant according to national provisions

Development of ECs

The Deficiencies

- EU Guidance only on format and accompanying documentation of the application: not on criteria for review
- List of required documentation differs from MS to MS: different application package for each MS in multinational trials
- In some countries the EC reviews the IMPD: potential conflict of confidentiality

The EC Application Process

Principles in the EU

- Favourable opinion required
- One opinion / country, but acceptance of need for local review
- Max. 60 days for review after receipt of complete submission
- Application to EC parallel/sequentially to authority application

The EC Application Process

Principles in the EU

- Applicant submits the required information
- EC gives feed-back whether submission is complete
- Once submission is complete, the clock starts
- One opportunity to request additional information. Clock stops until information is provided

The EC Application Process

Time Frames in the EU

- 60 days after receipt of a complete submission
- 90 days for gene therapy and somatic cell therapy or genetically modified organisms
- 180 days for these products if external consultation is required
- No time limits for xenogenic cell therapy

CONCLUSIONS

- Ethics committees are helpful for investigators and sponsors in ensuring optimal protection of study participants
- The Clinical Trial Directive has set the frame for ethical review in Europe
- Performance of the ethical review is a national responsibility and adheres to the national legislative requirements

KOMISIJA REPUBLIKE SLOVENIJE ZA MEDICINSKO ETIKO (KME)

http://www.kme-nmec.si/

Republic of Slovenia National Medical Ethics Committee (NMEC)

Scope of work presented by the NMEC members:

Assoc. Prof. of paediatrics, Janez Primožič, PhD
Tone Žakelj, professional coordinator of NMEC

I. HISTORY OF MEDICAL ETHICS IN SLOVENIA

- The Committee for medical ethics (CME) was established at the University of Ljubljana Medical Faculty *in the early sixties* of the last century to evaluate ethical acceptability of the proposed medical studies to acquire PhD or MSc degree in medicine at the Medical faculty.

II. HISTORY OF MEDICAL ETHICS IN SLOVENIA

1977

CME was authorized by the Medical Faculty (MF) of the University of Ljubljana to evaluate ethical acceptability of all the medical studies in the Republic of Slovenia.

In the same year, regular teaching of medical ethics was introduced in MF.

JURIDICAL BASIS OF THE NMEC FUNCTIONING IN THE REPUBLIC OF SLOVENIA

- Ministerial Decree on the composition, tasks, competence and mode of working of the NMEC (1995 and amended in 2009).
- CME is obliged to respect the Slovenian & international legally binding documents, national and international guidelines and recommendations being issued by the European Commission for Bioethics of the Council of Europe, and European Commission.
- Statutary notes of the NMEC.

PROPOSER AND APPOINTER OF THE NMEC OF SLOVENIA

The NMEC is an advisory board to the Ministry of Health of the Republic of Slovenia.

APPOINTED BY:

- Minister of Health of the Republic of Slovenia

PROPOSED BY:

- Medical faculties in Ljubljana and Maribor
- Council for Health of the Republic of Slovenia
- Slovenian Medical Chamber
- Slovenian Medical Society

The NMEC members' mandate lasts for 4 years and can be repeated. The members are volunteers.

COMPOSITION OF NMEC BY PROFESSION – 15 members (14 at present)

1	Specialist in forensic medicine and deontology
2	Surgeon, traumatologist
3	Psychiatrist
4	Specialist in internal medicine, angiologist
5	Paediatrician and ethicist
6	Paediatrician, infectologist
7	Paediatrician, intensivist
8	Pulmologist
9	Specialist in family medicine
10	Clinical psychologist
11	Lawyer
12	Theologian
13	Philosopher
14	Lay person – professional coordinator

LEVELS IN THE ORGANIZATION OF THE FORUMS FOR BIOETHICS IN THE WORLD

National Ethics Councils (NEC)

Nuffield Council of Bioethics (UK)
Nationaler Ethikrat (Germany)
Comité Consultatif National d'Ethique (France) …

National committees for biomedical ethics / Research ethics committees (REC)

Regional and hospital committees for biomedical ethics

At present, the NMEC is covering all the functions of the first two listed above.

BASIC DOCUMENTS FOR ETHICAL EVALUATION IN NMEC

- Declaration of Helsinki 2013
- Oviedo Convention 1997 and its protocols
- Slovenian Code of Medical Deontology 1997
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use 2014
- ICH-GCP guidelines
- Slovenian law on medicines, on Patients' rights …

LATEST INTERNATIONAL DOCUMENT

- **Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use**, replacing Directive 2001/20/ES of the European Parliament and the Council.
- Coordination of legislature among the EU member states in the field of good clinical practice regarding pharmaceutical trials in humans.
- Every EU member state has to issue a single final opinion by the central or principal Research Ethics Committee at least in 60 days for the international clinical trials.

WORKLOAD OF THE NMEC

Regular sessions once per month, extraordinary when necessary.

- Per session 40-70 proposals of new studies are presented & discussed; there are additional 70-100 items on the agenda (amendments, reports, comments, etc.). Under "miscellaneous" actual (pressing) ethical problems are dealt with – draft laws, ethical problems (e.g. usage of the human corps/limbs for artistic purposes, circumcision of boys for religious reasons) …
- There is a 3-4% rise in the number of topics on the agenda per year.
- About one percent of the proposals are not approved, for about 20% amendments are demanded.
- Follow-up of the approved works is requested from researchers and ev. problems (e.g. adverse events) have to be reported.

METHODOLOGY OF THE NMEC RESEARCH PROPOSALS EVALUATION (SOP)

- Aim of the study – clear hypothesis.
- Informed consent – composition and clearness.
- Direct or indirect benefit for the patient.
- Inclusion/exclusion criteria.
- Randomization of participants.
- Aim of every procedure in the study.
- Benefits and risks for the participants.
- Discontinuation of the study.
- Extra insurance of participants (in case of damage).

CONTRIBUTION OF NMEC AS AN ADVISORY BOARD TO SLOVENIAN LEGISLATION

I. **LAWS ON:**
- treatment of infertility and the use of methods of fertilization with biomedical assistance
- patients' rights
- mental health

II. **OPINIONS ON:**
- homeopathy and non-academic healing practices
- dealing with human corpses and biological material of human origin
- end-of-life decisions
- eutanasia
- cloning and embryonic stem-cells …

INTERNATIONAL COOPERATION OF THE NMEC

- Participation in regular meetings of the DH-BIO of the Council of Europe.
- Participation in the forums of the National Ethics Councils (NEC).
- In the framework of the *Conférence européenne des comités nationaux d'ethique* (RECs - COMETH).
- On the occasion of the Slovenian presidency of EU in 2008 the NMEC organized the 11th Forum of NEC.
- Renewal of registration within the „Food and drug administration, US Department of Health and Human Services.

FUTURE OF THE NMEC

- Separation of the two duties: National Ethics Council and Research Ethics Committee.
- Professionalization of the administrative services to the NMEC.
- Formation of the Regional/Hospital Ethics Committees.

OPTIMISING THE INFORMED CONSENT PROCESS

Ingrid Klingmann, MD, PhD
EFGCP, Pharmaplex bvba

Content

- **The Informed Consent Process**
- **Information to Clinical Trial Subjects**

Informed Consent Process (1)

- **A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.**
- **Freely given informed consent should be obtained from every subject prior to clinical trial participation**

(ICH-GCP)

Informed Consent Process (2)

- **The IC process consists of**
  - **Patient Information Sheet (PIS)**
  - **Oral explanations provided by the investigator and/or experienced study nurse**
  - **Sufficient time for the participant to make an informed decision about his/her participation**
  - **Signing the Informed Consent Form (IC)**
  - **Copy of PIS and signed IC to participant**
  - **Re-consenting if new information becomes available that could influence the participant's decision to remain in the trial**

Informed Consent Process (3)

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use

ENTR/CT-2, Revision 1, February 2006

Informed Consent Process (4)

- **Give it top priority**
- **Ensure an atmosphere that encourages questions**
- **Go slowly and with easy words together with the subject(s) through the subject information sheet**
- **Have a proper form for the subject to sign**
- **Ensure that patient information is provided by a properly trained person**
- **Ensuring an optimal patient information and consent process is one of the key responsibilities of the investigator**

Informed Consent Process (5)

- Ensure that the subject is re-consented if there is new information relating to the risk-benefit ratio
- In paediatric studies the parents need to be informed and give written “consent”, the child must receive age-adapted information and should give an “assent”, if ever possible in writing. Refusal of a child must be respected
- Keep the proper paperwork

Informed Consent Process (6)

Ethical considerations for clinical trials on medicinal products conducted with the paediatric population

Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC….

ftp://ftp.cordis.europa.eu/pub/fp7/docs/ethical-considerations-paediatrics_en.pdf

Informed Consent Process (7)

- Language used should be as clear, non-technical and easily understandable as possible
- The participant’s understanding of the provided information should be assessed
- ICH-GCP provides a list of topics to be addressed in the Patient Information Sheet

Information to Clinical Trial Subjects (1)

- **What needs to be included in a subject information sheet?**
  - What is the objective of the trial?
  - How long will the trial last?
  - What will I have to do, which tests to undergo, how long to stay in house, and what will be the follow-up procedures in this trial?
  - Is there anything that I am not allowed to do when I'm on the trial?
  - Has the trial been officially approved?
  - Which medication will I get?

Information to Clinical Trial Subjects (2)

- Which side-effects may occur to me?
- What happens if I feel un-well?
- Can I withdraw my consent at any time and under which conditions?
- Who is funding the trial and is there a financial tie between investigator and sponsor?
- Will I be properly compensated and all my travel expenses be met?
- Will I be properly insured against any trial-related damage and what are the conditions?
- Who can I talk to if I have any more questions?

Information to Clinical Trial Subjects (3)

Patients need to be explained and *understand* that

- **they participate in an experiment/alternative treatments**
- **their participation has advantages but also negatives:**
  - they may not get the optimal dose or even receive placebo
  - they may face additional risks
  - the treatment may be too short
  - there may be no follow-on treatment
  - they may never learn which treatment they had
- **the physician has a personal interest in enrolling the patient into the trial**
- **he/she can withdraw the consent at any time**

CONCLUSIONS

- **“Informed consent” is an ongoing PROCESS from advertisement to signature on the consent form until end of the trial**
- **The patient information should be adapted to the subject’s needs, level and capacity of understanding**
- **The informed consent process is the basis for a good compliance of the subject during the trial and is therefore well invested time**

SET-UP OF A CLINICAL TRIAL AT THE INVESTIGATIVE SITE

Ingrid Klingmann, MD, PhD
EFGCP, Pharmaplex bvba, Brussels

Content

- **Today's Responsibilities of a PI**
- **Familiarisation with the Protocol and IB**
- **Adequate Resources**
- **Adequate Facilities**
- **Adequate Medical Care**
- **Adequate Communication**
- **Adequate Administration**
- **Adequate Processes**
- **Delegation of Responsibilities?**

TODAY'S RESPONSIBILITIES OF THE PI

- **Today, the overall responsibility for a clinical trial has been moved away from the PI to the sponsor.**
- **But the PI has the responsibility**
  - **for subject care, information to subjects and safety, including reporting to ECs**
  - **for the reliability of trial performance**
  - **for the quality of the data / results**

DEFINITION OF INVESTIGATOR

- **A doctor or a person following a profession agreed in the MS for investigations because of the scientific background and the experience in patient care it requires.**
- **The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the "Principal Investigator".**

(Directive 2001/20/EC)

FAMILIARISATION WITH PROTOCOL AND IB

- **The PI needs to ensure a comprehensive understanding of**
  - **the current state of the respective area of research**
  - **the IMP**
  - **the protocol**
  - **alternative treatments**
  - **the subject's risks when joining the trial**
  - **GCP requirements**

ADEQUATE RESOURCES

- **The PI needs to ensure reliably available qualified, well-informed and trained resources during preparation, performance and follow-up of the trial**
  - **his own time and physical presence**
  - **investigators and study nurses**
  - **in pharmacy and other required departments**

to perform ALL tasks of the trial within time and budget and the required quality.

ADEQUATE FACILITIES

- **The PI needs to ensure reliably available suitable facilities during preparation, performance and follow-up of the trial**
  - to screen, inform and treat subjects
  - to manage the trial
  - to perform all trial activities incl. data entry
  - to store the trial documentation
  - to store and handle the trial medication
  - to allow for monitoring, audits, inspections

ADEQUATE MEDICAL CARE

- **The PI needs to ensure reliably available medical care during preparation, performance and follow-up of the trial**
  - to diagnose the subjects
  - to decide on subjects' suitability concerning in- and exclusion criteria
  - to make all required medical decisions
  - to ensure complete identification of AEs, their assessment and reporting
  - to provide emergency care

ADEQUATE COMMUNICATION

- **The PI needs to ensure reliably available communication tools and resources during preparation, performance and follow-up of the trial**
  - with the sponsor (incl. monitor and auditor)
  - with the ethics committee
  - with the subject and his family (incl. IC)
  - with the study team
  - with the treating physician

ADEQUATE ADMINISTRATION

- The PI needs to ensure **reliably available administration** throughout the trial
  - signed contract with the sponsor and sub-contractors
  - signed, approved protocol and all other documents required before study start
  - SOPs, job description, CV, training record of all staff members involved in the trial
  - archiving capacities

ADEQUATE PROCESSES

- The PI needs to ensure **reliably available processes** throughout the trial
  - delegation and signature process
  - subject identification, screening and enrolment processes, IMP distribution and accountability process
  - randomisation process
  - CRF completion and query process
  - AE assessment and reporting process
  - training processes (incl. emergency and GCP)

DELEGATION OF RESPONSIBILITIES?

- What can a PI delegate?
  - communication with the sponsor, monitor, auditor, inspector?
  - familiarity with IB and protocol?
  - information to subjects?
  - decision on inclusion and exclusion criteria?
  - administration of study medication?
  - measurements and assessments?
  - data entry and CRF review?
  - AE assessment and SAE reporting?

CONCLUSIONS

- **The set-up of a clinical trial needs to be methodologically planned**
- **Adequate resources and facilities need to be provided**
- **Optimal medical care for the subject must be ensured at all times**
- **Delegation of responsibilities is possible if the processes and communication lines are well defined**

However, the PI is ultimately responsible!!!

PRINCIPLES OF DOCUMENT MANAGEMENT

Nicky Dodsworth
Material developed in collaboration with
Genevieve Decoster
IT & GCP Consulting, Crupet, Belgium

Content

- **Current Requirements**
- **Study Documents**
  - **Original and Amended Versions**
  - **Computerised vs. Paper Documents**
  - **Archiving Study Documents**
- **Audit Findings**
- **Conclusions**

CURRENT REQUIREMENTS (1)

Global

- ICH E6 – CMPM/ICH/135/95 – Note for Guidance on GCP

Europe

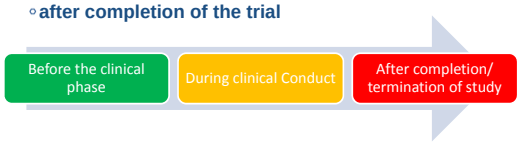
- Volume 10, Chapter V – Recommendation on the Content of the Trial Master File and Archiving – July 2006
- Directive 2005/28/EC, Chapter 4
- Directive 2001/20/EC – Article 15(5) and Article 21(2)
- Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials, 01 August 2010

US

- CFR Title 21, Part 312

CURRENT REQUIREMENTS (2)

- **Essential documents are generated and filed throughout the entire clinical trial process.**
- **Some must be available:**
  - **before the trial starts**
  - **during the conduct of the trial**
  - **after completion of the trial**



ESSENTIAL DOCUMENTS (1)

- **Any or all of the trial documents may be subject to and should be available for:**
  - **On-site monitoring**
  - **Audit by the sponsor**
  - **Inspection by the regulatory authorities (domestic and/or non-domestic inspections)**

ESSENTIAL DOCUMENTS (2)

Essential documents - demonstrate compliance with GCP and applicable regulatory requirements

- **Essential documents are:**
  - **Trial-specific**
  - **Country-specific for regulatory documents; in EU, there are EU documents and domestic documents**
  - **Identical at each investigational site (multi-centre trials)**
  - **Filed and archived at the investigational sites according to local regulations and site procedure**
  - **Unambiguous, signed and dated as appropriate.**

ESSENTIAL DOCUMENTS (3)

'Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.'

Ref: Vol 10 The rules governing medicinal products in the European Union

ARCHIVING REQUIREMENTS

- **In the EU, the investigators must retain the trial documents for at least 5 years after its completion (longer if locally required by competent authorities).**
- **Medical files are retained in accordance with local legislation and hospital practice.**
- **The investigator should take measures to prevent accidental or premature destruction of these documents.**

EU Directive 2005/28 on Principles of GCP effective as of Jan 29, 2006

RECORDS AND REPORTS

- **The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports*.**
- **Data reported on the CRF should be consistent with the source documents or the discrepancies should be explained*. CRF should be completed as soon as the data are available.**
- **The investigator should maintain the trial documents as specified in Essential Documents** and as required by domestic regulatory requirement(s)*.**

ICH-GCP section 4.9 ** ICH-GCP section 8.0

Ref: Annual report of the Good Clinical Practice Inspectors Working Group 2012
Adopted by the GCP IWG on 21 May 2013

Figure 2. Inspections conducted per type of site

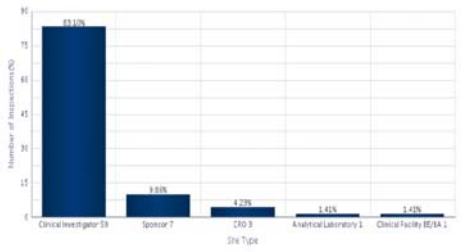


Figure 2 represents the number of inspections conducted in 2012 per type of site. Most inspections were conducted at clinical investigator sites (83%).

Ref: Annual report of the Good Clinical Practice Inspectors Working Group 2012
Adopted by the GCP IWG on 21 May 2013

Number of findings per sub-category of the top 3 main categories (general, investigational site and trial management) graded by critical, major and minor

		# Inspected Deficiencies			# Inspected Deficiencies Total
Deficiency Category Name	Deficiency Sub Category Name	Critical	Major	Minor	
General	Contracts/Agreements	-	9	9	18
	Direct Access to Data	-	1	-	1
	Essential Documents	1	38	93	132
	Facilities and Equipment	-	4	4	8
	Organisation and Personnel	-	7	26	33
	Qualification/Training	-	16	24	40
	Randomization/Blinding/Codes IMP	-	1	1	2
	SOPs	2	33	23	58
	Source Documentation	8	29	45	82
General Total		**11**	**138**	**225**	**374**
Investigational Site	Protocol Compliance (Assessment of Efficacy)	1	7	9	17
	Protocol Compliance (Others)	-	32	27	59

What do we look for at Audit/ Inspection?

- Files are present/available for audit
- Filing up to date, depending on status of study
- Chronology of events/able to recreate study
- Filing in date order
- Follow ICH GCP/ Vol 10
- Review against SOPs/templates
- Free of sticky labels
- File notes/ regular QC
- No tippex!

COMMON AUDIT FINDINGS

COMMON AUDIT FINDINGS - GENERAL

- Absent files/sections/stored 'elsewhere' e.g. EC compliance statement, key correspondence, laboratory certification, CVs for new staff missing, validation of equipment
- Documents are not signed or dated or documents may have pages with different dates/versions (e.g. CRF)
- Poor version control, latest version missing
- Subject identifiable information in files
- Incomplete documents e.g. pages missing, CVs with no evidence of GCP training, current position not listed, key site personnel not listed on site signature log

CORRESPONDENCE

- Ensure 'key' correspondence is filed – make sure important decisions are documented
- Audit trial maintained for issues
- Avoid duplications
- Header of e-mail correct?
- E-mail etiquette!!!

These may not always be findings but they can be very frustrating

RESEARCH STAFF

- Lack of evidence of GCP training amongst Principal Investigator (PI) and research staff involved in the clinical trial
- Inadequate arrangements for cover in absence of the PI
- Delegation logs incomplete. Delegated responsibilities not clear
- Lack of documentary evidence of the PI involvement in clinical trial (e.g. informed consent procedure)

TRAINING RECORDS

- A training form should be maintained at the investigational site
- When a monitor or a PI or any other person provides training on procedures or in the use of equipment, the completion of the training should also be recorded on the form
- A training certificate and training agenda should be provided to the attendee and should be filed

The certificate should bear the training topics, the trainer's name and the duration of the training session

INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

- Missing or unsigned documentation (e.g. shipping records, temperature log, duration of transportation, drug accountability)
- Inadequate provisions for storage of IMPs (i.e. not kept separate from IMPs for other studies, not temperature controlled)
- Emergency codes not available at the site at the start of the study

ELECTRONIC RECORDS AND SOURCE DOCUMENTS

- Monitors had no access to e-records and/or e-source documents
- The computer programmes were not validated
- The computer screens were not user-protected

Both the investigator and the monitor argued that the programmes used were provided by Microsoft (e.g. Microsoft Excel 2007) and were therefore 'valid' programmes!!

CONTRACT MANAGEMENT

- Omissions, errors and discrepancies in contracts
- Responsibilities of collaborating parties not clearly defined (external lab, pharmacy, caterer, courier, etc.)
- Lack of consistency between protocol and contract
- (Many activities performed by hospital personnel, not directly involved in the study)

CONCLUSION

- You can be a very experienced investigator and not fully comply with GCP document requirements
- Before embarking on a clinical trial, make sure that
  - **you have the time, the resources and the facilities**
  - **you and your team are trained on the project and on GCP requirements**
  - **you understand the local legal requirements**

Only proper documentation can protect the subjects, yourself, your team and the sponsor

QUALITY MANAGEMENT AT A CLINICAL TRIAL SITE

Nicky Dodsworth
Material developed in collaboration with
Ingrid Klingmann
Pharmaplex bvba
Wezembeek-Oppem, Belgium

TOPICS

- Definition and elements of a Quality Management System
- Definition of SOP
- How to write an SOP
- Areas to cover by SOPs

According to the Clinical Trials Directive a **sponsor** of a clinical trial must have a quality management system in place. But does an **investigative site** have the same obligation?

YES, because……

- it this is the best way to protect the patient and to ensure patient safety
- it is the best way to ensure ethical and scientific good practice
- it is the best way to ensure reliability of the results
- it is the best way to pass an inspection without problems

What is a Quality Management System (QMS)?

A QMS is……

A set of co-ordinated activities to direct and control an organisation in order to continually improve the effectiveness and efficiency of its performance. (ISO 9000:2000)

ELEMENTS OF A QMS

- Standard Operating Procedures
- Training of personnel
- Appropriate resources of people, time, money
- Appropriate facilities
- Quality assurance
- Quality control

QA VS. QC (1)

- All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented and reported in compliance with GCP and the applicable regulatory requirements.

(ICH GCP Guideline Section 1.46)

QA VS. QC (2)

- The operational techniques and activities undertaken *within the quality assurance system* to verify that the requirements for quality of the trial-related activities have been fulfilled.

(ICH GCP Guideline Section 1.47)

INDEPENDENCE OF QA

- While QC is continuously performed by staff members involved in the “production process”, the person(s) responsible for QA *must* be as independent as possible: separate department reporting directly to top management.

AUDIT VS. INSPECTION

- Systematic, independent examination
- Evaluation to show trial related activities and data were recorded, analysed and accurately reported to protocol, SOPs, GCP and regulatory requirements
- Conducted by a regulatory authority
- Official review of documents, records, facilities deemed to be related to a clinical trial
- Conducted at trial site, sponsor/CRO facilities or any other establishment

GRADING OF INSPECTION/ AUDIT FINDINGS (1)

“Critical” finding:

Definition:

Condition, practices or processes that adversely affect the rights, safety or well-being of subjects and/or quality and integrity of data

Critical observations are considered totally unacceptable

GRADING OF INSPECTION/ AUDIT FINDINGS (2)

"Critical" finding:

- **Possible consequences:**
  - **rejection of data and/or legal action required**
  - **drug "non approvable" by competent authority**
- **Observation classified as "critical" may include:**
  - **pattern of deviations classified as "major"**
  - **bad quality of the data**
  - **absence of source documents**
  - **fraud**

GRADING OF INSPECTION/ AUDIT FINDINGS (3)

"Major" finding:

- **Definition:**
- **Condition, practices or processes that might adversely affect**
  - **the rights, safety or well being of subjects and/or**
  - **quality and integrity of data**

Major observations are serious deficiencies and are direct violations of GCP principles

GRADING OF INSPECTION/ AUDIT FINDINGS (4)

"Major" finding:

- **Possible consequences:**
  - **data may be rejected and/or legal action are required**
- **Observations classified as "major" may include**
  - **pattern of deviations classified as "minor"**

GRADING OF INSPECTION/ AUDIT FINDINGS (5)

“Minor” finding:

- **Possible consequences:**
- **Observation classified as “minor”, indicate the need for**
- **improvement of conditions, practices and processes**
- **Many “minor” observations may indicate:**
  - **bad quality**
  - **Several minor findings may lead to a ‘MAJOR FINDING’ with its consequences**

STANDARD OPERATING PROCEDURES (SOPs)

Exercise:

Please spend three minutes to write down how you prepare a cup of coffee.

Swap your method with your neighbour…

DEFINITION OF SOP

- Detailed, written instructions to achieve **uniformity** of the performance of a specific function.

(ICH GCP Guideline Section 1.55)

HOW TO WRITE AN SOP (1)

- Description of
  - who
  - what
  - when
  - where
  - how

  … of a process
- Must be a true reflection of what is really done – if not: either change the procedure or the SOP!

HOW TO WRITE AN SOP (2)

- An SOP should:
  - ➢be concise
  - ➢be user-friendly and helpful
  - ➢provide step-by-step instructions (in logical order)
  - ➢cover every specific task that is repeated
  - ➢identify responsibilities (avoid sharing!)
  - ➢promote consistency across organisations
  - ➢aid training of staff

HOW TO WRITE AN SOP (3)

- General principles:
  - Consistent within an organisation
  - Completed by related Work Instructions and Forms
  - Reviewed and officially approved
  - Current
  - Reviewed regularly (every 1-2 years) in line with a renewal plan for the SOP system

HOW TO WRITE AN SOP (4)

- General principles:
  - available to all staff / team members
  - maintained centrally
  - distributed in a controlled, documented manner
  - storage of historical SOPs in the archive

HOW TO WRITE AN SOP (5)

- Administrative SOPs:
  - SOP on SOPs
  - Responsibilities and management of the site
  - Patient stipend and reimbursement of expenses
  - Records management
  - General administration
  - Disaster recovery plan

HOW TO WRITE AN SOP (6)

- Clinical SOPs:
  - preparation/review/approval of protocol + amendments
  - data handling
  - interaction with sponsor
  - interaction with ethics committee
  - handling of IMP and study-related medication
  - pharmacovigilance
  - medical emergencies
  - informed consent
  - patient visits
  - study site file

HOW TO WRITE AN SOP (7)

- Recruitment SOPs:
  - Advertisement
  - Patient recruitment
- Quality Assurance SOPs:
  - QA audits
  - Regulatory inspections
- Training SOPs:
  - Staff training

QUESTIONS: TRUE/FALSE

Quality Control

Auditors and Inspectors are only responsible for quality control activities.

True or False?

True	False
☐	☑

Quality Control

ICH GCP 1.47…operational techniques and activities….to verify that the requirements for quality….have been fulfilled.

'Quality is everyone's responsibility'
W. Edwards Deming

RELIABLE SAFETY MANAGEMENT AT THE SITE

Ingrid Klingmann, MD, PhD
Material developed in collaboration with
Genevieve Decoster
IT & GCP Consulting, Crupet, Belgium

THE CONCEPT OF SAFETY

- **No such thing as absolute safety, every life activity is associated with a risk**
- **Need to know the risks & the benefits to evaluate if a course of action or a course of medicine is worth taking!**
- **Risk/benefit profile: Need to understand these for every drug**

"what is acceptable will differ between products & patients"

- **By the time drugs reach the market the risks are usually low, but for an accurate assessment, post-marketing clinical studies are critical as spontaneous reporting is very unreliable**

THALIDOMIDE TRAGEDY

- **Thalidomide, one of the first drugs recognized to cause birth defect in humans (1961).**
- **The thalidomide tragedy led to much stricter testing being required for drugs before their marketing authorization**

PHARMACOVIGILANCE

- **Currently used in the treatment of some malignancies and HIV-infected patients**

DEFINITION: ADVERSE EVENT

Clinical Trials Directive 2001/20/EC:

- **Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;**

DEFINITION: ADVERSE REACTION

Clinical Trials Directive 2001/20/EC:

- **All untoward and unintended responses to an investigational medicinal product related to any dose administered;**

SEVERITY / SERIOUSNESS

- **Severity of adverse events in clinical trials is reported according to ICH E2a guideline as**
  - **Grade 1 = mild**
  - **Grade 2 = moderate**
  - **Grade 3 = severe**
- **This is not the same as SERIOUS which is based on patient outcome, seriousness serves as a guide for defining regulatory reporting obligations**

Adverse Events: Defining *Relatedness*

- **Definitely related:** There is a certainty that the event is related to the investigational product.
- **Probably related:** There is high likelihood that the event is related to the investigational product.
- **Possibly related:** There is a likelihood that the investigational product is the cause of the event, but other causes cannot be ruled out.
- **Unlikely to be related:** It is not likely that the event is related to the investigational product, and other more likely causes are present.
- **Unrelated:** Evidence exists that the event is related to something other than the investigational product

DEFINITION: SERIOUS ADVERSE EVENT

Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- is medically significant






THIS SHOULD BE REPORTED BY THE INVESTIGATOR to THE SPONSOR, IMMEDIATELY

DEFINITION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE DRUG REACTION SUSAR

- **Suspected** (causality at least possible)
- **Unexpected** (not in Investigator Brochure or Summary of Product Characteristics, Package Insert for marketed products)
- **Serious**
- **Adverse**
- **Reaction**

THIS IS EVALUATED AND REPORTED ONLY BY THE SPONSOR

INVESTIGATOR'S RESPONSIBILITIES

Investigators are responsible for

- Training all site staff on the relevance and process of reliable adverse event collection
- Collecting all spontaneously mentioned complaints and related relevant information completely and
- Collecting systematically questioned complaints (AE checklists) and questionnaires according to the requirements of the protocol
- Reporting all adverse events in the source documents and the case report forms

INVESTIGATOR'S RESPONSIBILITIES

Investigators are responsible for

- Reporting laboratory abnormalities identified in the protocol as critical to safety evaluations
- Assessing the adverse events according to the definitions in the protocol
- Reporting serious adverse events (SAEs) within 24 hours to the sponsor
- Notifying ethics committee (health authorities) if requested in the national legislation
- Regularly communicates with site staff and monitor about patients' safety reports and own observations

SPONSOR'S RESPONSIBILITIES

- Sponsors (commercial and non-commercial clinical trials) is responsible for processing:
  - Serious Adverse Events (SAE) as reported by the investigators
  - When an SAE is qualified to become a Suspected Unexpected Serious Adverse Reactions (SUSAR), it should be reported expeditedly to authorities and quarterly to Ethics Committees.
    - 7 days for life-threatening/death
    - 15 days for all others
  - Annual Safety Reports

The assessment of expected/unexpected is the responsibility of the sponsor

SAFETY REQUIREMENTS IN EUROPEAN MEMBER STATES (EU)

- Adverse Reactions (usually only drug-related, in some countries also drug-unrelated)
- Investigational Medicinal Product (IMP), and the comparator (active ingredient or placebo)
- Expedited Reports
- Suspected Unexpected Serious Adverse Reactions (SUSARs)
- Annual Safety Reports ("DSUR")

EU 2001/20/EC , ICH E2A,B,C, D, M adverse reactions
CPMP/ICH/377/95 Expedited reports
CPMP/ICH/287/95 Individual Case

EUDRAVIGILANCE

- EudraVigilance (European Union Drug Regulating Authorities Pharmacovigilance) is the European data processing network and management system for reporting and evaluation of SUSARs during the development of new drugs and following the marketing authorization of medicinal products in the European Economic Area (EEA).
- Database should provide an overview of SUSARs in all clinical trials in the EU

It is the sponsor's responsibilities to report a SUSAR to the national competent authorities (CA), the Ethics Committees and the investigators

MedDRA

- MedDRA terminology standardises AE original terms and must be applied prior to analyse clinical trial results (especially safety data e.g. AEs & SAEs)
- MedDRA terminology applies to all phases of drug development including post-registration studies, but excluding data from animal studies. MedDRA is not a dictionary defining terms
- MedDRA consists of 26 System Organ Classes (SOC) listing more than 60,000 terms. There are 5 hierarchical levels of coding from the lowest level term (LLT) up to the high level term (SOC)
- CTCAE version 4.0 mapping MedDRA version 12.1

MedDRA = Medical Dictionary for Regulatory Activities

OVERALL CONCLUSION (1)

- **Handling drug safety, whether in clinical trial environment or routine medical practice using prescribed medicines, requires a lot of expertise**
- **Drug safety monitoring is a worldwide concern, not just a country obligation**

OVERALL CONCLUSION (2)

Investigators, sponsors, ethics committees, DSMB (Data Safety Monitoring Board) and health authorities should work together to ensure an adequate protection of trial participants.

Systems to report safety whether it's AE, SAE, or SUSAR should be simple, accurate, reliable, and understood by each stakeholder.

ANY QUESTIONS?

EXERCISE

- **Carefully read one of the Case Studies**
- **Identify all adverse events of this patient**
- **Consider their causality with the study medication**
- **Decide whether this is a Serious Adverse Event**
- **Decide the causality of the SAE**

Exercise

Assessment of Adverse Events and Serious Adverse Events

Narrative Patient 1

The patient with randomisation number 08 (enrolment number 12MB94) is a 26 year old female with a height of 1,70 m and a weight of 62 kg. Last menses on December 10, 2009. No special events in the medical history but since the age of 18 the patient suffers from a monthly migraine around the time of her menses. In the oral examination a fully bone-impacted right mandibular third molar was identified as the likely source of pain and inflammation experienced by the patient in the last 6 months.

The patient fulfilled all inclusion and exclusion criteria and the oral surgery was performed according to protocol and without any special problems. The patient was enrolled into the trial on January 08, 2010 as she developed 3h 30 minutes after end of surgery a sufficient level of pain. Dosing occurred at 14:00. At the 300 min pain assessment after dosing the patient reported no more pain.

1 h 10 min after dosing the patient complained about severe dizziness lasting for 30 min, combined with mild vomiting once, lasting 1 min. At 4 h 25 min after dosing the patient complained about moderate sleepiness, lasting for 2 hours, and a mild degree of burning eyes, lasting for 45 min. 7 hours after dosing the patient was released from the site without pain and without any ongoing adverse events.

At the follow-up visit on 15 January 2010 the patient reported that in the morning of 10 January 2010 she woke-up at 6:30 with severe headache and near-to-vomiting, she rushed out of bed, collapsed, lost conscious for at least 5 minutes and when she woke up she could not remember anymore where she was and what happened. Her husband heard a bump, but only reacted after ca. 5 minutes when he realized that his wife had not left bed as intended at that time of the morning. He found her on the floor, bleeding at the back of her head as she obviously hit the edge of the bed table when she tried to get out of bed, lost conscious and fell. Her husband realized that she was disoriented and confused and brought her to the Mulhouse city hospital. After surgical closure of the 4 cm long laceration at the head with 5 stitches the patient was hospitalized on 15 January 2010 at 07:30 for suspicion of a concussion and potential development of subarachnoidal bleeding. As the patient rapidly recovered and all performed diagnostic did not reveal any pathological finding the patient was released 24 hours later with the diagnosis “concussion after orthostatic collapse with cranial wounding” and recommended to stay in bed for another two days.

At the follow-up visit the patient had still the stitches but was otherwise without any pathological finding.

Narrative Patient 2

The patient with randomisation number 25 (enrolment number 32KK98) is a 21 year old male with a height of 1,82 m and a weight of 85 kg. There were no special findings in his medical history and the patient fulfilled all inclusion and exclusion criteria. His dental status showed a fully bone impacted left mandibular third molar that had caused swelling and pain at different occasions.

He underwent standard, un-eventful oral surgery of the left mandibular third molar on 15 January 2010 and was enrolled 4 hours after end of surgery as he developed a sufficient level of pain and was dosed at 13:30. At 14:10 he complained about moderate stomach cramps over 15 min which disappeared spontaneously. The pain assessments revealed that his pain level did not decrease after dosing but increased further and at 15:00 his pain was unbearable and he requested rescue medication. He received 400 mg ibuprofen and at the 120 min pain assessment the patient had no more measurable pain. At 17:00 the patient complained about mild hallucinations in form of light signals with gentle music, lasting for 30 min, moderate dizziness, lasting for 35 min, and moderate tiredness, lasting for 50 minutes. The symptoms disappeared spontaneously. 6.5 hours after dosing the patient had no more adverse events and pain and was released from the site.

The next morning at 7:30 the patient woke-up pain in the left cheek but with 2 times 400 mg ibuprofen within 4 hours the pain was tolerable. The next morning the patient woke up with heavy headache on the side of surgery, realized extended swelling and heat of the left cheek and strong pain in the wound area, combined with a rhythmic bumping. As he could not sustain the pain anymore despite 2 times 400 mg ibuprofen rescue medication the patient decided to go to the ambulance of the dental university hospital in Basel as the clinical research site was closed on that Sunday. There he was immediately hospitalized (11:30) due to an extended abscess in the left cheek with subcutaneous infiltration of the whole left side of the face up to the eye brow which required broad opening of the wound, cleaning, drainaging and systemic antibiotic therapy. As a bacteriogramme was not available treatment was started with high dose amoxicillin and naproxen for 3 days. The abscess diminished under this therapy and after 3 days the patient could be released from the hospital with oral follow-on treatment.

At the follow-on visit on 22 January 2010 the patient was in good general health, had no pain and the wound was healing without any signs of infection.

Narrative Patient 3

The patient with randomisation number 31 (enrolment number 38SK90) is a 29 year old male with a height of 1,76 m and a weight of 74 kg. The physical examination showed no abnormalities and the medical history did not reveal any other disease but pertussis in the age of 4 and rubeola in the age of 6. The patient is in a good physical condition and is a professional mountain biker. His dental status revealed an partially bone-impacted right mandibular third molar that caused inflammation at several occasions.

The patient underwent standard, un-eventful oral surgery on January 27, 2010 and was enrolled into the trial 4h 15 min after surgery, at 13:25 when he developed a sufficient pain level. Medication took place at 13:30. At 14:20 the patient complained about severe headache, lasting for one hour but he did not request an analgesic. The headache disappeared spontaneously. At 16:00 the patient experienced mild dizziness which became severe at 18:00. After performance of all study related activities at 19:30 the dizziness had decreased to a mild intensity again and thus the patient was released from the site.

On January 29, 2010 the PI received an e-mail from a surgeon at the Clinique des 3 Frontières in Saint-Louis who informed the PI that this patient had an accident with his mountain bike after he left the site. He had become severely dizzy again and hit a truck that was parked in a narrow street. He fell badly and had to be hospitalized with a complexly broken right leg, contusions at the right arm and right side of the thorax as well as suspicion of internal injury and bleeding. He had to undergo surgery for his leg and needs to remain hospitalised for another 2 weeks. Fortunately, there were no internal injuries or bleeding detected. The patient will not be able to come to the follow-up visit 7 days after surgery. The stitches in the dental wound will be removed in the hospital.

DAY 2

22 NOVEMBER 2014

PRINCIPLES OF CLINICAL TRIAL MANAGEMENT

Ingrid Klingmann, MD, PhD
EFGCP, Pharmaplex

Content

- 1 -
Human Resource Planning

Human Resource Planning

Proper planning of the site staff requirements for a clinical trial is vital to its success.

Prerequisites:

- Clear understanding of the Project, the Sub-Projects, the Work Packages and Deliverables to be performed
- Experience concerning time required per task
- Realistic estimation of the required / available time frames for the trial with best case and worst case scenarios
- Comprehensive understanding of available own resources and resources to be identified outside

Human Resource Planning

Factors affecting human resource requirements in clinical trial sites:

- Type of tasks to be performed
- Number of tasks within one trial distributed over time
- Number of patients to be screened and enrolled per month
- Duration of the different tasks and total study duration
- Percent of staff availability
- Likelihood of peaks and troughs
- Likelihood of staff turn-over / downtime
- Experience level of staff

Human Resource Planning

How best to calculate the required staff?

1. List the tasks to be performed per patient per visit with the function(s) involved and the expected duration.
2. Map the hours / minutes required for one patient per visit per job category.
3. Calculate whether all trial activities can be performed by one person or whether there is a need to include two persons in parallel to be able to perform the tasks within the required time window.
4. Define whether a person needs to give support / input to somebody else's activity (e.g. supervision / quality control).

Human Resource Planning

How best to calculate the required staff?

5. Decide on the number of patients that can realistically be expected to be enrolled per day. Make also a best case scenario and a worst case scenario.
6. Figure out how many patients one person could handle per day, taking into account a staggering of trial activities, respectively, how much staff you would need to handle this number of enrolled patients of the realistic estimate, the best and the worst case.

Human Resource Planning

Calculation of staff availability:

1 Fulltime Equivalent	**1 FTE**
A year has	365 days
Minus 52 x 2 Weekend days	= 261 days
Minus 12 bank holidays	= 249 days
Minus 30 days vacation	= 219 days
Minus 10 days sick leave / kid's leave / etc.	= 209 days
Minus 9 days training / seminars / conferences	= **200 days**
Divided by 12 months:	**One person will be in the average 17 days / month at work**

Human Resource Planning

Calculation of staff availability:

As the month has in the average 20 working days you need more than 1 FTE to cover a full-time job function.

Experience has shown that it is prude to assume 1.5 FTEs to reliably cover a full-time position and to be able to cope with vacation and sick-leave.

Human Resource Planning

Calculation of staff availability:

Calculation of required manager time has to be calculated with different parameters:

- Type of responsibilities
- Number of responsibilities
- Number of direct reports
- Frequency of travel
- Etc.

Depending on the type of responsibility the main question is: does this have to be a full-time position or is part-time possible?

Human Resource Planning

Ongoing staff planning

It is of vital importance to the success of the trial performance that a detailed staffing plan is worked out, agreed and communicated to all staff on a

- weekly,
- bi-weekly or
- four-weekly basis

to ensure that every function is reliably covered at all times required.

- 2 -
Communication Planning

Communication Planning

Communication is the basis for living and working together, happens therefore constantly

but

Miscommunication or lack of communication happen very frequently

Prepare a Communication Plan

Communication Planning

A Communication Plan is helpful to

- Minimise / avoid misunderstandings
- Motivate internal and external team members
- Clearly outline expectations, tasks and responsibilities of all parties
- Document what was done
- Makes sound business sense

Communication Planning

Define your "Stakeholders":

- Who needs which information
- When they will need it
- How it will be given to them
- By whom

Informational needs and methods of distribution vary widely

Suitable Tools for Communication

- E-Mail
- Telephone
- Regular meetings
- Telephone conferences
- Video conferences
- Periodic update reports
- Newsletters
- Web platforms
- Operations Plan
- Monitoring Manual
- Data Entry Manual
- Trial Assessments Manual
- Training Manual
- Stakeholder Communication Plan

- 3 -
Facility Planning

Facility Planning

„Resource Planning“ also means planning and maintenance of all aspects of the facilities and work environment.

- Space
- Office material
- Clinic material
- Trial medication
- Rescue medication
- Emergency trolley equipment
- All materials for trial-related assessments , e.g. VAS, BP devices, etc.
- Centrifuges
- Fridge
- PCs, Printers, Fax
- Telephone and IT-lines
- Kitchen equipment
- Drinks + food for patients

Facility Planning

When planning space required for a trial the flow of study activities should be mirrored.

- Reception and waiting area
- Quiet room for IC
- Cabinet for physical examination
- Sufficiently large assessment area
- Toilets + showers
- Lab area
- Temperature controlled medication storage room
- Kitchen
- Storage room
- Archive
- Offices for staff
- Office for monitors/auditors

Facility Planning

Ongoing facility planning

- Space should be planned in such a way that it can easily be adapted to the needs of the respective trial
- For all areas there needs to be a reliable procedure in place that supervises the stock of the respective material/utilities and ensures early replacement.

There is nothing more frustrating than having patients ready for inclusion but no study medication inhouse

EXERCISE

- **Carefully read the study synopsis**
- **Define the study activities foreseen for the Screening Visit**
- **Rank the activities according to your department practice and work flow**
- **Decide on the person performing the activity**
- **Decide on the time this activity will take**
- **Calculate how long it will take the patient to stay**

Protocol

Prospective, Randomized, Double-blind, Dose-finding Study to Evaluate the Efficacy and Safety of R-Megaprofen in Comparison to Placebo and Paracetamol

Protocol No: MP 75
EudraCT-No: 2012-234567-88

Sponsor:
Minipharm GmbH & Co
Marienweg 1
D-59385 Pharmadorf
Germany

Coordinating Investigator:
Prof. Dr. Raffael Megastar
Kreiskrankenhaus
Hebelstrasse 32
010423 Kerngesund
Germany

Protocol Version: 1.0
Date: 16 March 2013

Confidential

Summary Information

Title:	A Prospective Randomised, Double-blind, Dose-finding study to Evaluate the Efficacy and Safety of R-Megaprofen in comparison to Placebo and Paracetamol.
Protocol Number:	MP 75
EudraCT Number:	2012-234567-88
Sponsor:	Minipharm GmbH & Co Marienweg 1 D-59385 Pharmadorf Germany
Protocol Author:	Dr. Karl Maier Minipharm GmbH Marienweg 1 D-59385 Pharmadorf Germany
Study Manager/CRO:	Sarah Butler CRO Ltd 35-36 Shenley Pavilions Chalkdell Drive Shenley Wood Milton Keynes MK5 6LB United Kingdom
Medical Director:	Dr. Karl Maier Minipharm GmbH Marienweg 1 D-59385 Pharmadorf Germany
Coordinating Investigator and Principal Investigator Germany:	Prof. Dr. Raffael Megastar Kreiskrankenhaus Hebelstrasse 32 010423 Kerngesund Germany
Principal Investigator UK:	Dr Jeremy Underdog UCL Analgesia Centre 256 Gray's Inn Road London WC1X 8LD

United Kingdom

Bioanalytical Laboratory:	Minipharm GmbH & Co Marienweg 1 D-59385 Pharmadorf Germany
Blood Biochemistry Laboratory:	The Doctor's Laboratory 55 Wimpole Street London W1G 8LQ
Drug Name:	R-Megaprofen
Manufacturer:	Manufac AG Küchenstr.10 D-5001 Köln Germany
Contact Person:	Dr. Karl Maier Minipharm GmbH Marienweg 1 D-59385 Pharmadorf Germany Tel: +49 555 784 39 98 Fax: +49 555 784 39 99 e-mail: karl.maier@minipharm.com

1 Study Synopsis

1.1 Title

A Prospective Randomised, Double-blind, Dose-finding Study to Evaluate the Efficacy and Safety of R-Megaprofen in Comparison to Placebo and Paracetamol.

1.2 Objectives

1.2.1 Primary Objective

To investigate the analgesic efficacy of different doses of R-Megaprofen within 3 hours after drug administration in comparison to placebo and paracetamol in patients with acute moderate to severe pain after impacted or partly impacted lower third molar withdrawal.

1.2.2 Secondary Objectives

To identify the optimal analgesic dose of R-Megaprofen in comparison to placebo and paracetamol.

To identify the non-effect dose of R-Megaprofen.

To investigate the onset of action of the optimal dose of R-Megaprofen in comparison to placebo and paracetamol.

To investigate the duration of action of R-Megaprofen in comparison to placebo and paracetamol.

To investigate the percentage of patients requiring rescue medication under the different treatments.

To investigate the relationship between analgesic efficacy and plasma concentrations of R-Megaprofen and paracetamol.

To investigate the safety of R-Megaprofen.

1.2.3 Study Design

This Phase II study will be two-centre, double-blind, randomised, single-dose and six-arm parallel in design. It will evaluate the analgesic efficacy and safety of R-Megaprofen compared to placebo and evaluate the dose response relationship of different doses of R-Megaprofen following third molar extraction under local anaesthetic.

1.2.4 Study Population

Approximately 430 patients, aged between 18 and 45 years inclusive, will be screened. It is estimated that 10 – 25% of those screened will not satisfy all the

necessary inclusion/exclusion criteria. Approximately 360 patients who satisfy all the inclusion/exclusion criteria will be scheduled for dental surgery. It is estimated that only 85% of patients who undergo surgery will reach the necessary pain level within the designated time period post surgery (six hours). Hence, the first 306 patients that meet the inclusion criteria with respect to pain level after surgery will be randomised to one of six treatment groups;

1.2.5 Study Medication

Group 1 50mg R-Megaprofen
Group 2 100mg R-Megaprofen
Group 3 200mg R-Megaprofen
Group 4 400mg R-Megaprofen
Group 5 1000mg paracetamol
Group 6 placebo

1.2.6 Study Plan

Patients who meet all admission criteria after undergoing screening procedures will undergo surgical removal of one partial or complete bony impacted third mandibular molar. A second ipsilateral maxillary third molar or adjacent supernumary tooth may be removed if warranted by the surgeon, and if its removal requires routine surgical procedures. Following surgery, when post-surgical pain has reached the required intensity, patients will be randomised to receive one of six treatments. Patients must have moderate to severe pain to be randomised, which will be defined by a recording of at least 2 on a Verbal Rating Scale (VRS 0 - 3), and confirmed by recording at least 50mm on a Visual Analog Scale (VAS 100mm). Patients will record their pain level and pain relief at 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300 and 360 minutes after study drug administration. Patients will indicate time to first perceptible pain relief and time to meaningful pain relief via two masked stop watches started at the time of dose intake. All patients will have blood samples drawn for PK assessments (within five minutes of pain relief assessments) pre-dose and no later than the following nominal time post-dose 15, 25, 35, 45, 65, 95, 125, 185 and 245, 305 and 365 minutes. If a blood sample is delayed, the exact time of withdrawal and a comment should be entered in the CRF.

Patients who meet the pain threshold for inclusion into the study (VRS of at least 2, and VAS of at least 50mm) may request rescue medication at any time during the pain assessment period (six hours post-dosing). However, patients will be asked to refrain from using rescue medication until 60 minutes post-dose in order to give the study medication a reasonable opportunity to work. Randomised patients will be considered evaluable when at least the first pain assessment 10 minutes post-dosing is completed. The rescue medication provided will be 400mg Ibuprofen. The time to administration of rescue medication will be recorded in the CRF. Patients will continue to have pain assessments and blood samples taken for PK analysis until six hours post surgery even if they take rescue medication. All patients (including non-dosers) will be required to remain in the clinic for the recovery period and assessment periods.

Patients who do not meet the pain threshold necessary for inclusion into the study within six hours after surgery are considered non-dosers and will remain under supervision in the clinic for up to another six hours. Non-dosers will be administered analgesia as deemed appropriate by the investigator. The time to administration of analgesia and details of the type and dose of medication used will be recorded in the CRF.

Patients who request rescue analgesics prior to meeting the pain threshold necessary for inclusion into the study will remain in the clinic for six hours as well. Patients who request analgesia prior to meeting the inclusion criteria will be considered non-dosers.

1.2.7 Study Duration and Timings

The length of the study for each patient will be three study visits within 38 days: a screening visit, which may take place up to 28 days prior to the oral surgery day, a visit at the oral surgery day and finally a follow up visit which will take place 7 (±3) days after surgery. The study will be completed within 5 months.

2. Objectives

2.1 Primary Objective

To investigate the analgesic efficacy of different doses of R-Megaprofen within 3 hours after drug administration in comparison to placebo and paracetamol in patients with moderate to severe pain after impacted or partly impacted third molar withdrawal.

2.2 Secondary Objectives

To identify the optimal analgesic dose of R-Megaprofen in comparison to placebo and paracetamol.

To identify the non-effect dose of R-Megaprofen.

To investigate the onset of action of the optimal dose of R-Megaprofen in comparison to placebo and paracetamol.

To investigate the duration of action of R-Megaprofen in comparison to placebo and paracetamol.

To investigate the percentage of patients requiring rescue medication under the different treatments.

To investigate the relationship between analgesic efficacy and plasma concentrations of R-Megaprofen and paracetamol.

To investigate the safety of R-Megaprofen.

3. Study Plan

3.1 Study Design

This Phase II study will be a two-centre, double-blind, randomised, single-dose and six-arm parallel in design. It will evaluate the acute analgesic efficacy and safety of R-Megaprofen compared to placebo and paracetamol and evaluate the dose response relationship of different doses of R-Megaprofen following third molar extraction under local anaesthetic.

3.2 Study Population

3.2.1 Source and Number of Patients

Approximately 306 patients who will satisfy all the admission criteria including a VRS of at least 2 and a VAS of at least 50mm following the surgical extraction of at least one impacted or partly impacted lower third molar, will be randomised to one of six treatment groups.

Fifty patients will be randomised to receive 50mg, 100mg, 200mg, 400mg of R-Megaprofen or 1000mg paracetamol or placebo.

3.2.2 Patient Restrictions and Concomitant Medications

Patients may be resident in the unit for up to 12 hours post-surgery on oral surgery day.

Patients will be asked not to eat anything after 5:00 a.m. prior to attending the clinic on the day of surgery.

Before and after surgery, water and apple juice will be permitted ad libitum.

Patients may have soup 90 minutes post-dose, food will be allowed 3 hours post-dose.

Patients who have taken medication of the types and within the timeframes indicated in the exclusion criteria will not be permitted into the study. Additionally, patients will be asked to refrain from drinking alcohol within 12 hours prior to attending the clinic on the oral surgery day.

Patients may need to take medication e.g. oral contraceptives during the study period (from screening until follow up). It is accepted that analgesics will be required and antibiotic treatment may be required following discharge from the clinic. Details of all medications (including chlorhexidine mouthwash) taken between clinic discharge and follow up visit must be reported to the investigator and the details will be recorded on the CRF.

In order to participate in the study, patients must have their surgery completed before 12 noon.

3.3 Clinical Supplies

3.3.1 Study Medications

The study medication is produced by Manufac AG, Cologne. In order to provide several dosages while using one tablet size, each verum tablet will contain the same amount of 50mg R-Megaprofen.

Further drug information on the placebo to match R-Megaprofen and paracetamol is provided in Appendix B.

Patients will be randomised to one of the following six treatments

Group 1 R-Megaprofen 50mg:
Group 2 R-Megaprofen 100mg:
Group 3 R-Megaprofen 200mg
Group 4 R-Megaprofen 400mg
Group 5 paracetamol 1000mg
Group 6 placebo

In order to ensure complete blinding for research personnel and patients the double dummy technique is used: each patient will receive 8 small tablets (containing R-Megaprofen or placebo) and 2 big tablets (containing paracetamol or placebo)

	Group 1: 50 mg R-Megaprofen	Group 2: 100 mg R-Megaprofen	Group 3: 200 mg R-Megaprofen	Group 4: 400 mg R-Megaprofen	Group 5: no active ingredient	Group 6: 1000 mg paracetamol
# of R-Megaprofen 50 mg tablets	1	2	4	8	0	0
# of R-Megaprofen placebo tablets	7	6	4	0	8	8
# of paracetamol 500 mg tablets	0	0	0	0	0	2
# of paracetamol placebo tablets	2	2	2	2	2	0

Rescue medication in the form of ibuprofen 400 mg will be available to patients at any time during the pain assessment period (six hours post dosing). Secondary rescue medication will be administered to patients at the investigator's discretion.

3.3.2 Accountability of Study Supplies

All material supplied is for use only in this clinical study and should not be used for any other purpose.

The investigator or designee will maintain a full record of drug accountability. A Drug Dispensing Log must be kept current and will contain the following information:

- the identification of the patient to whom the drug was dispensed;

- the date(s) and quantity of the drug dispensed to the patient.

The inventory must be available for inspection by the study monitor during the study. At the end of the study, drug supplies will be verified by the monitor. Drug supplies will then be either collected by the study monitor or returned by the investigator or designee to Minipharm GmbH.

3.3.3 Storage of Clinical Supplies

Clinical supplies must be stored in compliance with the label requirements at room temperature between 15°C - 25°C in a secure, locked, dry area away from direct sunlight.

3.4 Study Schedule

The study schedule is summarised in Table 1.

3.4.1 Selection and Screening Phase

Potential patients will contact the site to enquire about the study (in response to advertisements, word of mouth, etc). The medium through which patients became aware of the site and the study will be detailed on the telephone screen report.

A Research Ethics Committee approved telephone screen will be used to obtain information to assess a patient's eligibility into and availability to participate in the study.

Patients who satisfy the eligibility and availability requirements of the telephone screen will be scheduled to attend a pre-screening examination at the study site.

The investigator or designee will discuss the details of the study with suitable patients, who will subsequently be provided with written information about the study and be given adequate time to read and consider the information provided. If the patient wishes to participate in the study, they will be required to give written informed consent before any screening procedures are performed. All patients who provide signed informed consent will be assigned an enrolment number.

Patients undergo panoramic dental x-ray to determine whether the patient has at least one partial or complete bony impacted lower third molar. The oral surgeon performs an oral examination of the patient and decides on the suitability of the patient from a dental point of view.

Patients who fail oral screening will not proceed any further. A single page CRF detailing the outcome of oral screening will be completed also for these patients.

Those patients considered to be eligible following oral screening will proceed to have a medical assessment with the investigator or designee and details will be recorded on the CRF. The medical assessment will include demographics (age, sex, race, height and weight), relevant medical history and relevant allergies, in particular hypersensitivity to paracetamol or ibuprofen (rescue medication), and any agents used for local anaesthesia. A history of oral health and details of any medications currently being taken by the patient will be recorded. Measurement of vital signs (heart rate and blood pressure) will be conducted to confirm that they are within clinically acceptable limits. Blood will be drawn for analysis of biochemistry, urine for urinanalysis.

A urine drug screen will be performed to test for illegal drug use (excluding cannabis). Patients who test positive for illegal drug use maybe re-tested if in the investigator's opinion the result is likely to be false. However, patients who retest positive for illegal drug use will be discontinued from the study.

A urine pregnancy test will be performed on all female patients of child bearing potential at screening, these test must prove negative for a patient to be eligible to participate in the study.

Breath alcohol tests will be performed and must prove negative before a patient can proceed in the study.

Patients will then be scheduled to return to the site within 28 days for oral surgery, and they will be instructed to fast from 5:00 a.m. prior to attending the clinic on the day of surgery.

3.4.2 Baseline Phase

Patients will arrive at the clinic at a pre-appointed time on the morning of oral surgery for the following assessments and procedures prior to surgery:

- Review of haematology and blood biochemistry results from screening visit
- Urine drug screen (excluding cannabis), result must be available prior to dosing
- Alcohol breath test, result must be available prior to dosing
- Urine pregnancy tests (females of child bearing potential only), result must be available prior to dosing
- Vital signs (heart rate and blood pressure)
- Insert indwelling cannula into an appropriate vein in the arm
- Training in stopwatch procedures

- Training in pain assessment scales and clinical definitions of what is meant by perceptible and meaningful pain relief will be provided.

- Oral examination (to confirm oral examination findings from pre-screening examination)

3.4.3 Treatment Phase

After successful completion of all baseline assessments and procedures the patients will undergo oral surgery:

- Local anaesthetic administered

- Oral surgery performed employing standard techniques

- Post surgical pain assessments will be performed when patients complain of pain

- Randomisation to treatment group, if moderate to severe pain (recorded as a 2 for moderate and 3 for severe on the VRS, and at least 50 mm on the VAS) is experienced.

- Pre-dose blood sample taken

- Administration of study medication according to the randomisation schedule

- Two stopwatches started, to be stopped at 'perceptible' and at 'meaningful' pain relief

- Pain assessment using the 4 point VRS and 100mm VAS as well as pain relief assessments using the 5-point (VRS) categorical scale will be made at 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300 and 360 minutes post-dose prompted by the clinic staff

- Blood samples will be drawn for PK analysis via an indwelling cannula in the crook of the arm, near the wrist or the back of the hand within five minutes of completing their pain assessments made at 15, 25, 35, 45, 65, 95, 125, 185, 245, 305 and 365 minutes post-dose. There is no associated PK sample for the 50 minute pain assessments. After each blood sample is taken the iv cannula should be flushed with 3 ml isotonic sodium chloride solution

- The blood samples have to be centrifuged for 5 minutes within 3 minutes after blood withdrawal. After centrifuging plasma has to be drawn and stored in tubes labelled with the same patient number and the blood withdrawal time point. These samples need to be stored at – 70°C until analysis. The plasma levels of R-Megaprofen will be determined using a validated HPLC method in the Minipharm GmbH laboratory. R-Megaprofen will be determined in a first batch of 72 patients. This will result in approximately 12 measurements per

time point and medication group. Knowing about the inter-subject variability of R-Megaprofen plasma levels and the relatively weak co-relation of NSAIDs plasma level and levels of pain relief (reference) the first batch shall be used to test if a relationship exists. As patients will not gain important medical information by learning the results of their PK analysis it is acceptable for the sponsor to decide if and how many more PK samples should be analysed. The exact number of samples analysed will be documented in the final report. The analysis of further patient plasma levels may be undertaken after closure of the study database and thus be viewed as being a non-integral part of the study. Relevant results of an extended analysis will be distributed to all parties having received the study report.

As very late time-points are missing the half life of the drug cannot be determined from this PK analysis.
Patients may request rescue medication at any time following the administration of study drug. However they will be asked to abstain until 60 minutes after administration of study drug, if possible. The exact time of administration will be recorded on the CRF. All randomised patients will continue with pain assessments and blood sampling to 6 hours even if they take the rescue medication.

If pain of at least moderate intensity is not experienced within six hours following surgery, randomisation will not take place, and study medication will not be dispensed. The patient will be considered a non-doser, and the investigator will ensure that proper and appropriate care is administered.

Discharge from the clinic and schedule to return in seven (±3) days for follow-up procedures.

3.4.4 Follow up

Patients will return to the clinic seven (±3) days after surgery and will undergo the following procedures:

- Urine pregnancy test (females of child bearing potential only)
- Vital signs (heart rate and blood pressure)
- Follow up oral examination
- Blood and urine collection for safety laboratory parameters
- Physical examination

The investigator or designee will question the patient regarding any adverse events experienced since their oral surgery. Any findings will be recorded in the CRF.

4. Study Procedures and Assessments

4.1 Dental Procedures

4.1.1 Pre- Screen Oral Examination

An oral examination will take place at the screening examination to establish whether a patient has at least one partial or complete bony impacted lower third molar. This will consist of a visual inspection of teeth, gums/tissue for signs of oedema, erythema or infection.

4.1.2 Panoramic Dental X-ray

Panoramic dental X-rays will be taken at the oral screening examination to confirm the appropriate bony impacted mandibular third molar is present.

Possible levels of impaction are:

1. Fully erupted or partially covered by soft tissue = erupted.
2. Submerged, covered only by soft tissue = soft tissue.
3. Partial bony impaction = partially imbedded in bone.
4. Full bony impaction = fully imbedded and covered by alveolar bone.

4.1.3 Standardised Local Anaesthesia

Patients will be asked to rinse for 1 minute with chlorhexidine 0.1% solution. A mixture of prilocaine 3% and felypressin 0.54 µg/ml will be used for local anaesthesia. In the lower jaw an inferior alveolar nerve block as well as a lingual nerve block (local anaesthesia) will be performed as well as local buccal infiltration to the operation side. The usual dose is between 3.6 and 5.4 ml (the maximum dose allowed is 10 ml). In case an ipsilateral third molar is to be removed in the upper jaw, local anaesthesia at the tuberosity palatine foramen and buccal palatal infiltration in this area will be performed. The usual dosage for this is between 1.8 and 3.6 ml (the maximum dose allowed is 6 ml).

The doses of local anaesthesia used for lower and upper third molar removal will be recorded separately for each of these in the CRF. Any deviation from anaesthesia protocol will be thoroughly documented in the CRF.

4.1.4 Third Molar Extraction Surgery

Third molar extractions surgery will be performed under local anaesthesia by a suitably qualified dental surgeon. The surgical procedure will consist of an incision from the anterior border of the mandibular ramus continued as a marginal incision as necessary. Thereafter, the buccal mucoperiosteal flap is elevated and bone is removed using a bur irrigated with sterile physiological saline solution. If necessary, splitting of the tooth will be performed. Finally, the wound is cleaned, irrigated and closed with 3-0 sutures. Patients may have additional teeth removed if warranted by the dental surgeon. Oral surgery must be completed by noon.

The details of any local anaesthetic or other medications including chlorhexidine mouthwash used during surgery will be detailed on the concomitant medications page of the CRF.

4.1.5 Follow up Oral Examination

At the follow up visit an oral examination will be performed which will consist of:

1. absorption of sutures (if not absorbed, they will be removed) and healing at surgical site

2. signs / symptoms of infection

3. discomfort

4.2 Pain Assessments

4.2.1 Pain Assessment Plan

All pain assessments will be conducted by the patient. Pain assessments taken up to and including six hours will be recorded in the CRFs.

Soon after oral surgery, the patients will recover from the local anaesthesia. This will be prior to administration of study medication and will be known as the recovery period. During the recovery period, patients will record the level of post-surgical pain on a 4 (0, 1, 2, 3) point VRS. When the patient indicates the level of pain to be 2 or above on the VRS, this is considered to equate to pain of moderate/severe intensity. To confirm the appropriate level of pain intensity for entry into the study, patients will also record the level of post-surgical pain intensity on a VAS. When the patient indicates a level of at least 50 mm on the VAS, this is considered to equate to pain of at least moderate intensity.

Patients will not be informed of the pain intensity levels which they need to achieve in order to be randomised. Patients will be instructed to alert site staff when they perceive any change in their level of pain. Staff will instruct patients to complete the pain intensity assessments. If the patient indicates the level of pain to be 2 or above on the VRS then site staff will measure the VAS pain intensity assessment. If the VAS does not reflect at least moderate (50 mm) pain, patients will be advised that they do not qualify to be randomised into the study and to remain in the recovery area. They will be asked to alert site staff again when they perceive any change in their level of pain. When a patient reports a change in pain to study staff they will be asked to complete the VRS and VAS scales again until such time as they meet the inclusion criteria. Patients who do not experience moderate to severe pain within 6 hours will not be randomised.

Patients who experience moderate to severe pain as indicated by a score of 2 or more on a VRS and confirmed by VAS score of at least 50 mm on a 100 mm scale within 6 hours will be randomised to one of the six treatment groups. The

qualifying VRS and VAS pain intensity scores for entry into the study will be recorded on the case report form as the baseline level of pain. The patient may then be randomised according to the randomisation schedule and baseline pain level and study medication will be administered. Patients will receive 2 masked stop watches and will be instructed to stop the first stop watch when they first notice perceptible pain relief, and to stop the second stop watch when meaningful pain relief is noticed. Patients will subsequently complete evaluations of pain intensity and pain relief at 10, 20, 30, 40 50, 60, 90, 120, 180, 240, 300 and 360 minutes post-dose. A running digital timer and the patient's source document will prompt the site staff to alert the patient to conduct pain assessments at these intervals.

All VAS and VRS assessments completed during the recovery period, before the baseline assessment of pain reaches moderate/severe in intensity will be available to monitor source documents.

4.2.2 Pain Assessment Instruments

Pain intensity will be evaluated using a 4-point categorical scale (VRS) and a 100 mm VAS.

4.2.2.1 Verbal Rating Score (VRS)

0 = No pain or none
1 = Mild
2= Moderate
3 = Severe

Where No pain or none, Mild, Moderate and Severe are defined to the patient as:

No pain or none	=	that is that you are having absolutely no pain at the surgical site.
Mild	=	is pain you can't ignore, but not something you would normally treat.
Moderate	=	is pain that interferes with your concentration. You would have difficulty reading or watching TV. You would definitely feel that you need to treat the pain.
Severe	=	is pain that not only interferes with your concentration but also causes you to change what you are doing in some way. You would definitely feel that you need to treat the pain.

This assessment will be elicited on the CRF by the statement, **"My pain at this time is".**

4.2.2.2 Visual Analogue Score (VAS)

Patients will indicate their pain intensity on a pre-drawn 100 mm scale by drawing a line, approximately perpendicular to the scale and that bisects the scale. One end of the scale will be marked “No pain”, and the opposite end will be marked “Worst possible pain”. The VAS used in the recovery period and in the pain assessment period will be the same.

Site staff must ensure the patient completes this assessment properly i.e. that the vertical line drawn by the patient crosses the scale. The VAS score (mm) will be measured by the site staff. The measurement must be taken from the left side of the scale (“No pain”) to the right side of the scale (“Worst possible Pain”).

4.2.2.3 Pain Relief Verbal Rating Score

Patients will rate the amount of pain relief from starting pain using a 5-point categorical scale as either:

- No relief or exacerbation = 0
- A little relief = 1
- Some relief = 2
- A lot of relief = 3
- Complete relief = 4

Defined as:

- No relief: means the same amount of pain you started with or worse.
- A little relief: means the pain is less than half gone
- Some relief: means the pain is about half gone
- A lot of relief: means the pain is more than half gone
- Complete relief: means there is no pain

The statement **“My relief from starting pain is”** will be used for this assessment on the CRF’s.

4.2.2.4 Stopwatch Method/Time to Pain Relief

After patients have been administered study medication, the site staff will simultaneously conduct the following stopwatch procedure:

1. Start both masked stop watches and instruct the patient to stop the first stopwatch upon feeling the first perceptible pain relief. The site staff will give the patient specific directions regarding this i.e. **“I want you to stop this watch, marked ‘Perceptible’, when you first feel <u>any pain relief whatsoever</u>. This doesn’t mean when you feel completely better, although you might, but when you first feel <u>any difference in the pain</u> you have now.”**

2. Instruct the patient to stop the second stopwatch upon feeling meaningful pain relief. The site staff will give the patient specific directions regarding this i.e. **“I**

want you to stop this watch, marked 'Meaningful', when the pain relief is meaningful to you."

3. A digital timer will be started and will be placed with the CRF. The CRF will reflect the time of dose and all subsequent scheduled pain assessment and PK blood draw time points.

4.3 Pharmacokinetics

4.3.1 Blood Samples for Pharmacokinetic Analyses

Blood samples (5ml) will be drawn from an indwelling cannula situated in a suitable vein into lithium heparinised tubes The cannula will be flushed after sampling with approximately 2 ml saline. Blood samples will be drawn pre-dose (within 15 minutes of dosing) and no later than the following nominal times post dose 15, 25, 35, 45, 65, 95, 125, 185, 245, 305 and 365 minutes.

The target sample times will be recorded on the CRF's. The nominal times (the times the blood samples will be taken relative to the actual dosing time) should be entered on the CRF prior to dosing. The actual sample times (sample times actually taken) should be recorded alongside the nominal times on the CRF and should be entered at the time of or soon as possible after sampling. All times must be recorded in the 24 hour format.

Where a cannula is used, and where a blockage occurs during the study it may be necessary to obtain subsequent samples by venepuncture. This must be recorded with an explanation on the CRF.

Blood samples will be centrifuged at 3000rpm/ 4˚C for 15 minutes. Approximately 2ml plasma will be separated from each sample, split into two equal aliquots and each placed into 3.6ml polypropylene screw top tube labelled with the study number, subject number, and time point of the blood sample and will be frozen at -20˚C within 1 hour of sampling.

Approximately 70/130 ml of blood will be collected from each subject throughout the study (including 10ml for screening assessments and discards).

4.4 Safety Variables

4.4.1 Vital Signs (heart rate and blood pressure measurements)

Systolic and diastolic blood pressure as well as heart rate at rest after 5 minutes in sitting position will be measured during the screening-visit, at baseline immediately before study medication administration and during the follow up-visit. The blood pressure will be measured using non-invasive equipment.

The following normal ranges for blood pressure and heart rate are provided as a guide only.

- Blood Pressure:
- Systolic 90 -150 mm Hg
- Diastolic 60 – 90 mm Hg

- Heart rate: 50 – 100 beats per minute

The investigator can interpret individual findings based on the patient's age, physical state and level of fitness. Patients with readings marginally outside the normal range may be included in the study if in the investigator's opinion these are not clinically significant.

4.4.2 Urine Drug Screen

Urine samples will be collected at screening and baseline and tested for benzodiazepines, opiates, amphetamines and barbiturates. The results of these tests must be available prior to dosing. Patients with positive results will be re-tested (at the discretion of the investigator) or withdrawn. One re-test only will be allowed per patient.

4.4.3 Laboratory Parameters

Blood and urine samples will be obtained during the screening visit and during the follow-up visit for determination of laboratory parameters. The following parameters will be measured:

Haematology
B-ESR
B-haemoglobin
B-platelets
B-white blood cells

Clinical chemistry
S-ALAT
S-albumin
S-alkaline phosphatase
S-ASAT
S-bilirubin total
S-calcium
S-creatinine
S-CRP
S-glucose
S-GT
S-potassium
S-sodium
S-urea

Urine (measurement by dip-stick)
Blood
Glucose
Leucocytes
Protein

4.4.4 Urine Pregnancy Test

Female patients of child bearing potential will provide urine samples at screening, baseline and follow up for pregnancy testing.

4.4.5 Alcohol Breath Test

Patients will undertake a breath alcohol assessment by blowing into an alcometer at baseline.

4.5 Adverse Events

All adverse events (adverse experiences / adverse drug experiences) encountered during the clinical study, whether spontaneously reported by the patient at any time during the study or elicited by the investigator in a standard manner at the study visits, will be reported in the CRF.

The investigator or designee must ask the patient the following question during each visit including any follow-visits: **“Have you felt unwell, experienced any symptoms or taken any medication (since your last visit) (today) (since your last dose) (since your last session)”.**

All adverse events encountered during the clinical study will be reported on the CRF.

Study Schedule

Procedure	Study Period																
					Pain Assessment Period												
	Screening Visit	Baseline	Oral Surgery	Recovery Period	10 mins post dose	20 mins post dose	30 mins post dose	40 mins post dose	50 mins post dose	60 mins post dose	90 mins post dose	120 mins post dose	180 mins post dose	240 mins post dose	300 mins post dose	360 mins post dose	Follow Up 7 (+/-3) days
Inclusion/exclusion criteria	X			X*													
Demographics and medical history	X																
Current / concomitant medications	X	X							X								X
Vital signs (heart rate and blood pressure)	X	X															X
Blood biochemistry (ALT, AST) & Haematology	X																
Urine drug screen	X	X															
Pregnancy test (if applicable)	X	X															X
Dental X-rays	X																
Oral examination	X	X															X
Patient training using stopwatches & assessment scales	X	X															
Alcohol breath test		X															
Tooth extraction(s)			X														
Pain intensity assessment on VRS				X*													
Pain intensity assessment on VAS				X*													
Pain relief assessment on VRS					X	X	X	X	X	X	X	X	X	X	X	X	
Randomisation / dispense study medication				X*													
PK samples taken within 5 min completion of pain assessments				X*	X	X	X	X		X	X	X	X	X	X	X	
Adverse events																	X
Medical sign off																	X

*****Patients will be randomised following qualifying post-surgical pain assessments of moderate to severe intensity. Pain Intensity assessment on VRS must be 2 or 3 indicating moderate to severe pain, and Pain intensity assessment on VAS must be at least 50 mm confirming moderate pain.

α Blood biochemistry results reviewed.

γ PK sample taken 15 minutes prior to dosing

CRITICALLY IMPORTANT ASPECTS IN CLINICAL TRIAL MANAGEMENT

Nicky Dodsworth
Material developed in collaboration with
Ingrid Klingmann
Pharmaplex bvba
Wezembeek-Oppem, Belgium

Topics

- **Feasibility**
- **Trial Organisation and Management**
- **PRACTICAL**
- **Protocol Violations**
- **Dosing Compliance**
- **Drug Handling and Accountability**
- **Staff Turnover**
- **Fraud & Misconduct**

FEASIBILITY (1)

- **The Principal Investigator (PI) is the sponsor's partner in planning the most time-critical element of a clinical trial: the patient recruitment period**
- **It is the PI's responsibility to provide realistic and reliable information on the number of subjects he can contribute to ensure the GCP and to confirm availability of adequate resources throughout the trial with all involved stakeholders**

FEASIBILITY (2)

- Crucial
  - number of suitable subjects available
  - number of suitable subjects willing to participate in the trial
  - resources available to manage the involvement of this number of subjects

DIFFICULTIES OF FEASIBILITY IN PRACTICE (1)

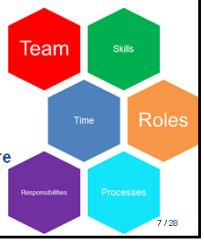
- Time point of feasibility request in the preparation phase of a protocol: PI should have the possibility to impact the protocol details
- Serial letter to many sites requesting information with limited chance of ultimately getting involved
- Limited or no resources to generate data instead of "wild guesses" of recruitment numbers
- Questions impossible to answer correctly (e.g. "Which percentage of your suitable subjects would be prepared to participate in this trial?")

DIFFICULTIES OF FEASIBILITY IN PRACTICE (2)

- Proposed solutions:
  - Appoint a dedicated team member to generate/collect information on your key population, their typical in- and exclusion parameters, and history of former trial experience
  - When a new IT system gets implemented in the hospital, ensure that searching for diagnosis, in- and exclusion criteria is possible
  - Clarify generally - potentially also with the EC - the confidentiality issues involved in reviewing subject files from other departments / hospitals

TRIAL ORGANISATION AND MANAGEMENT (1)

- **Today a clinical trial is a "PROJECT" and – like in any other organisation – needs properly planned and implemented processes, resources, facilities, budget and defined responsibilities:**
  - **define the team**
  - **ensure team members have appropriate skills (incl. GCP!!!), experience and time**
  - **assign roles and responsibilities**
  - **agree on and implement processes and procedures for all study activities – ensure SOPs, work instructions, forms, logs, lists are in place**



TRIAL ORGANISATION AND MANAGEMENT (2)

- **ensure awareness, commitment, resources and budget for involved other functions/departments**
- **ensure all contractual agreements with sponsor, hospital, sub-contractors, etc. are signed, in place**
- **ensure medical liability insurance covers clinical trials**
- **ensure adequate facilities for all study activities and patient visits**
- **ensure that investigator fee and subject compensation / reimbursement process is established**

TRIAL ORGANISATION AND MANAGEMENT (3)

- **ensure all technical elements like eCRF, IVRS, central lab/ECG/scan reading, etc. are in place**
- **ensure that randomisation, blinding and un-blinding procedures are in place and understood**
- **ensure appropriate IMP storage, handling, accountability process**
- **ensure appropriate sample handling, storage, shipment (special attention and conditions for biological samples!!!)**
- **ensure that source documents are defined, accessible, and properly stored**

TRIAL ORGANISATION AND MANAGEMENT (4)

- ensure that **AE assessment and reporting** procedures are in place and understood
- ensure **training** of all staff members in all trial-related activities, tasks and technologies
- agree on **communication** process amongst all stakeholders including the sponsor

Last but not least:

- **ensure** that the ethical review of the project has not only been performed by the EC but that ***every staff member*** **applies ethical considerations in their interaction with subjects in a trial**

PROTOCOL VIOLATIONS (1)

- **Typical areas of protocol violations:**
  - wrong diagnosis
  - in- and exclusion criteria ignored
  - forbidden pre- or concomitant medication
  - expired IMP administered, titration mistakes
  - informed consent process not correct and/or conducted in time
  - mandatory assessments not performed or not at the right time
  - visit windows not respected
  - diary completion not timely, with errors and gaps

PROTOCOL VIOLATIONS (2)

- **How much flexibility is there concerning in- and exclusion criteria? e.g.:**
  - age
  - health status
  - pre-medication
  - laboratory values

NONE !!!

Sponsor and investigators need to agree UP FRONT in the protocol on how flexible criteria can be

PROTOCOL VIOLATIONS (3)

- **How much flexibility is there concerning visit windows?**
  - **agree UP FRONT with sponsor in the protocol on number and time points of visits, on breadth of the windows in relation to time point and relevance of the visit**
  - **avoid violations as much as possible but**
  - **subject needs come first!**
  - **document unavoidable violations with reasons, sign and date them!**

DOSING COMPLIANCE

- **Dilemma:**
  - **most critical for judgment on PK, efficacy and safety of the IMP – but most difficult to ensure (if IMP is not administered by study staff)**
- **Possible solutions:**
  - **compliance measurement tool provided by sponsor**
  - **compliance reminder tool provided by sponsor**
  - **information of subject about relevance of compliance**
  - **follow-up by study staff**

DRUG HANDLING AND ACCOUNTABILITY (1)

- **Definition of IMP:**
  Active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but:
  - used / assembled (formulated or packaged) in a way different from the authorised form, or
  - when used for an unauthorised indication, or
  - when used to gain further information about the authorised form

DRUG HANDLING AND ACCOUNTABILITY (2)

- **Definition of non-IMP:**
  - **rescue medication**
  - **challenge agents (in most EU member States)**
  - **concomitant medication**
  - **baseline therapy**

DRUG HANDLING AND ACCOUNTABILITY (3)

- **Good Manufacturing Practice (GMP):**
  - **is an established quality standard for IMP production and control**
  - **is regulated by Directives 2003/94/EC, Directive 2004/27/EC, Directive 2001/20/EC and Annex 13 of the Notice to Applicants "Rules Governing Medicinal Products in the EU", Volume 4**
  - **requires specially authorised facilities**
  - **requires a "Qualified Person"**

(Annex 16 of the "Rules Governing Medicinal Products in the EU", Volume 4)

DRUG HANDLING AND ACCOUNTABILITY (4)

"Manufacturing" versus "Dispensing"

Manufacturing processes:

- **packaging**
- **labeling**
- **serial dilution**

→ must be performed by GMP-certified pharmacy

Dispensing:

- **reconstitution**
- **additional label information, e.g. subject initials, date of preparation, expiry date**

→

can be performed by site staff

DRUG HANDLING AND ACCOUNTABILITY (5)

- **IMP storage**
  - site must have the required storing facilities (e.g. temperature controlled)
  - site must have system to monitor and document the storage conditions
  - access to IMP storage must be controlled and documented
  - expiry dates have to be closely monitored
  - re-labeling requires SOP

DRUG HANDLING AND ACCOUNTABILITY (6)

"Accountability" versus "Reconciliation"

Accountability:

The collection of information and documentation that is associated with the disposition of IMP related to the site, i.e. the quantity received from the sponsor, dispensed and returned versus protocol requirements and subjects usage

Reconciliation:

Correlation between records from the sponsor and from the site

STAFF TURNOVER

- **not only possible but highly likely**
- **has to be foreseen from the beginning**
- **reliable processes need to be in place for**
  - staff search
  - training
  - hand-over
  - documentation compilation (CV, signature log, training record, etc.)
  - communication of change to sponsor and other team members

PRACTICAL

FRAUD/ MISCONDUCT (1)

- Fabrication
  the act of intentionally falsifying research results, e.g. "Fudging", "massaging", or outright manufacture of experimental data.
- Falsification
  the act of producing something that lacks authenticity with the intent to commit fraud or deception, e.g. changing inclusion/exclusion criteria so a patient can enter a study

Definitions: Wikipedia

FRAUD/ MISCONDUCT (2)

- Plagiarism

the use or close imitation of the language and thoughts of another author and the representation of them as one's own original work.

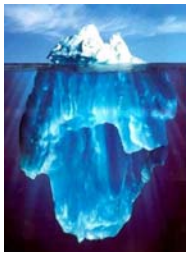
- Theft

the illegal taking of another person's property without that person's freely-given consent.

Definitions: Wikipedia

FRAUD/ MISCONDUCT (3)

- Sloppiness
- Carelessness
- Lack of understanding
- Lack of training



FRAUD/ MISCONDUCT (4) – Warning Signs

- Accessibility of Investigator and his staff
- Faster recruitment/fewer withdrawals
- Differences from other sites
- Odd working days/hours
- Quality of 'essential' documents – documents missing, cannot be found, may 'find' them later, separate notes made, only one pen used through out, very clean notes (no coffee marks!), identical data for different subjects
- Return of IMP in immaculate condition, IMP irregularities
- No medical licence
- No PI expertise
- High volume of work/other studies at site

FRAUD/ MISCONDUCT (5) – Warning Signs

- Discovery of issues – how have these come to light?
- Signatures
- AE/SAE under reporting
- IP/device accountability
- Unusual lab results
- Evidence that the randomisation code has been broken
- Bad feedback from previous studies
- CRF completion too good?
- Clean diary cards
- Unlikely trends – all visits same time apart
- Motives

CONCLUSION

Today, the basis for a successful clinical trial is not only

“Good Science” and “Good Ethical Standards” anymore but it requires an equal level of

“Good Project Management Standards” and “Good Regulatory Practice”

In other words:

all elements of

GOOD CLINICAL PRACTICE

ANNEXES

1/ World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects

2/ ICH E6 – Guideline for Good Clinical Practice – European Medicines Agency

3/ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

4/ News and updates on pharmaceuticals - EudraLex - Volume 10 Clinical trials guidelines | Public health, European Commission

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. 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). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. 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 subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

European Medicines Agency

July 2002
CPMP/ICH/135/95

ICH Topic E 6 (R1)
Guideline for Good Clinical Practice

Step 5

NOTE FOR GUIDANCE ON GOOD CLINICAL PRACTICE
(CPMP/ICH/135/95)

TRANSMISSION TO CPMP	July 1996
FINAL APPROVAL BY CPMP	July 1996
DATE FOR COMING INTO OPERATION	January 1997
POST STEP ERRATA (linguistic minor corrections)	July 2002

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 85 75 Fax (44-20) 75 23 70 40
E-mail: mail@emea.eu.int http://www.emea.eu.int

TABLE OF CONTENT

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. 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 may have an impact on the safety and well-being of human subjects.

1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 Amendment (to the protocol)

See Protocol Amendment.

1.4 Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 Approval (in relation to Institutional Review Boards)

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded,

analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 Audit Certificate
A declaration of confirmation by the auditor that an audit has taken place.

1.8 Audit Report
A written evaluation by the sponsor's auditor of the results of the audit.

1.9 Audit Trail
Documentation that allows reconstruction of the course of events.

1.10Blinding/Masking
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11Case Report Form (CRF)
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12Clinical Trial/Study
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13Clinical Trial/Study Report
A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14Comparator (Product)
An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15Compliance (in relation to trials)
Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16Confidentiality
Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17Contract
A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18Coordinating Committee
A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19Coordinating Investigator
An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20Contract Research Organization (CRO)
A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21Direct Access
Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsorís proprietary information.

1.22Documentation
All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23Essential Documents
Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24Good Clinical Practice (GCP)
A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)
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.

1.26Impartial Witness
A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subjectís legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27Independent Ethics Committee (IEC)
An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28Informed Consent
A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29Inspection
The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organizationís (CROís) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30Institution (medical)
Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31Institutional Review Board (IRB)
An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32Interim Clinical Trial/Study Report
A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33Investigational Product
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34Investigator
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 and may be called the principal investigator. See also Subinvestigator.

1.35Investigator / Institution
An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36Investigator's Brochure
A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigatorís Brochure).

1.37Legally Acceptable Representative
An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38Monitoring
The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39Monitoring Report
A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsorís SOPs.

1.40Multicentre Trial
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41Nonclinical Study
Biomedical studies not performed on human subjects.

1.42Opinion (in relation to Independent Ethics Committee)
The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43Original Medical Record
See Source Documents.

1.44Protocol
A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45Protocol Amendment
A written description of a change(s) to or formal clarification of a protocol.

1.46Quality Assurance (QA)
All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47Quality Control (QC)
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48Randomization
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49Regulatory Authorities
Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)
Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51Source Data

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

1.52Source Documents

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54Sponsor-Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57Subject/Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59Trial Site

The location(s) where trial-related activities are actually conducted.

1.60Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package

insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61 Vulnerable Subjects

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 patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 Well-being (of the trial subjects)

The physical and mental integrity of the subjects participating in a clinical trial.

2. 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).

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.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 Responsibilities

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:
trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigatorís current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.
The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval / negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

3.1.3 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.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subjectís legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subjectís legally acceptable representative is not possible (see 4.8.15), the IRB/IEC 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).

3.1.8 The IRB/IEC 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.

3.1.9 The IRB/IEC 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.

3.2 Composition, Functions and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

a) At least five members.
b) At least one member whose primary area of interest is in a nonscientific area.
c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.
A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:
- a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).
- b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).
- c) All adverse drug reactions (ADRs) that are both serious and unexpected.
- d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:
- a) Its trial-related decisions/opinions.
- b) The reasons for its decisions/opinions.
- c) Procedures for appeal of its decisions/opinions.

3.4 Records

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).
The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 Investigator's Qualifications and Agreements

4.1.1 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).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institutionís written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the

investigator/institution should supply a copy of the updated Investigatorís Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 Compliance with Protocol

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

a) to the IRB/IEC for review and approval/favourable opinion,
b) to the sponsor for agreement and, if required,
c) to the regulatory authority(ies).

4.6 Investigational Product(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institutionís duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Subjects

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subjectís consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subjectís legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subjectís willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or

not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subjectís participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subjectís legally acceptable representative, and after the subject or the subjectís legally acceptable representative has orally consented to the subjectís participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subjectís legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the trial involves research.
b) The purpose of the trial.
c) The trial treatment(s) and the probability for random assignment to each treatment.
d) The trial procedures to be followed, including all invasive procedures.
e) The subject's responsibilities.
f) Those aspects of the trial that are experimental.
g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
j) The compensation and/or treatment available to the subject in the event of trial-related injury.
k) The anticipated prorated payment, if any, to the subject for participating in the trial.
l) The anticipated expenses, if any, to the subject for participating in the trial.
m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subjectís identity will remain confidential.

p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
s) The expected duration of the subject's participation in the trial.
t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subjectís participation in the trial, the subject or the subjectís legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subjectís legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subjectís understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:
a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
b) The foreseeable risks to the subjects are low.
c) The negative impact on the subjectís well-being is minimized and low.
d) The trial is not prohibited by law.
e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subjectís legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10Progress Reports

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the

subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trialís outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

5.1 Quality Assurance and Quality Control

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 Contract Research Organization (CRO)

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 Trial Design

5.4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5 Trial Management, Data Handling, and Record Keeping

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a) Ensure and document that the electronic data processing system(s) conforms to the sponsorís established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).
b) Maintains SOPs for using these systems.
c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
d) Maintain a security system that prevents unauthorized access to the data.
e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
f) Maintain adequate backup of the data.
g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 Investigator Selection

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);
(b) to comply with procedures for data recording/reporting;
(c) to permit monitoring, auditing and inspection (see 4.1.4) and
(d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 Allocation of Responsibilities

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 Compensation to Subjects and Investigators

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 Confirmation of Review by IRB/IEC

5.11.1 The sponsor should obtain from the investigator/institution:

a) The name and address of the investigator's/institutionís IRB/IEC.
b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.
c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12 Information on Investigational Product(s)

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13 Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies

of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 Supplying and Handling Investigational Product(s)

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:

a) Ensure timely delivery of investigational product(s) to the investigator(s).
b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).
c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:

a) Take steps to ensure that the investigational product(s) are stable over the period of use.
b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 Record Access

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16Safety Information

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17Adverse Drug Reaction Reporting

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18Monitoring

5.18.1 Purpose

The purposes of trial monitoring are to verify that:

a) The rights and well-being of human subjects are protected.
b) The reported trial data are accurate, complete, and verifiable from source documents.
c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors

a) Monitors should be appointed by the sponsor.
b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitorís qualifications should be documented.
c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsorís SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 Extent and Nature of Monitoring

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigatorsí training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsorís requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a) Acting as the main line of communication between the sponsor and the investigator.
b) Verifying that the investigator has adequate qualifications and resources (see 4.1, 4.2, 5.6) and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
c) Verifying, for the investigational product(s):
    i) That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
    ii) That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
    iii) That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
    iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
    v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.
e) Verifying that written informed consent was obtained before each subject's participation in the trial.
f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.
h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
i) Verifying that the investigator is enroling only eligible subjects.
j) Reporting the subject recruitment rate.
k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
m) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
    i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
    ii) Any dose and/or therapy modifications are well documented for each of the trial subjects.
    iii) Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
    iv) Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
    v) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.
o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).
p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).
q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

5.18.5 Monitoring Procedures

The monitor(s) should follow the sponsorís established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 Monitoring Report

a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.
b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.
c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.
d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsorís designated representative.

5.19Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 Purpose

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 Selection and Qualification of Auditors

a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.
b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditorís qualifications should be documented.

5.19.3 Auditing Procedures

a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.
b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).
c) The observations and findings of the auditor(s) should be documented.

d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.
e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20Noncompliance

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institutionís participation in the trial. When an investigator's/institutionís participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23Multicentre Trials

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigatorís Brochure.

6.1 General Information

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:
- a) Randomization.
- b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
- a) When and how to withdraw subjects from the trial/ investigational product treatment.
- b) The type and timing of the data to be collected for withdrawn subjects.
- c) Whether and how subjects are to be replaced.
- d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 Quality Control and Quality Assurance

6.12 Ethics

Description of ethical considerations relating to the trial.

6.13Data Handling and Record Keeping

6.14Financing and Insurance
Financing and insurance if not addressed in a separate agreement.

6.15Publication Policy
Publication policy, if not addressed in a separate agreement.

6.16Supplements
(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. INVESTIGATORíS BROCHURE

7.1 Introduction
The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.
This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.
Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 General Considerations

The IB should include:

7.2.1 Title Page

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 Confidentiality Statement

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 Contents of the Investigatorís Brochure

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 Table of Contents

An example of the Table of Contents is given in Appendix 2

7.3.2 Summary

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 Introduction

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 Physical, Chemical, and Pharmaceutical Properties and Formulation

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 Nonclinical Studies

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- CarcinogenicitySpecial studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities.

Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

a) Pharmacokinetics and Product Metabolism in Humans
   - A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
   - Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
   - Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
   - Population subgroups (e.g., gender, age, and impaired organ function).
   - Interactions (e.g., product-product interactions and effects of food).
   - Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

b) Safety and Efficacy
   A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.
   The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

c) Marketing Experience
   The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 Summary of Data and Guidance for the Investigator

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse

drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 APPENDIX 1:

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:
Research Number:
Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:
Release Date:

Replaces Previous Edition Number:
Date:

7.5 APPENDIX 2:

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

NB: References on 1. Publications
2. Reports
These references should be found at the end of each chapter
Appendices (if any)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 Introduction

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority (ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institutionís site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsorís auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Located in Files of Sponsor
8.2.1	**INVESTIGATORÍS BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	**INFORMATION GIVEN TO TRIAL SUBJECT**		X	X
	- INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent		
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	**INSURANCE STATEMENT** (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,** e.g.:	To document agreements	X	X
	- investigator/institution and sponsor		X	X
	- investigator/institution and CRO			(where required) X
	- sponsor and CRO		X	X
	- investigator/institution and authority(ies) (where required)			

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Located in Files of Sponsor
8.2.7	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X
8.2.8	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)
8.2.10	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	X	X

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Located in Files of Sponsor
8.2.12	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s) , and support reliability of results	X (where required)	X
8.2.13	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	**INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigatorís Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X
8.2.15	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.19	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	**TRIAL INITIATION MONITORING REPORT**	To document that trial procedures were reviewed with the investigator and the investigatorís trial staff (may be combined with 8.2.19)	X	X

8.3 During the Clinical Conduct of the Trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.1	**INVESTIGATORÍS BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

8.3.3	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:**
	- protocol amendment(s)
	- revision(s) of:
	  - informed consent form
	  - any other written information to be provided to the subject
	  - advertisement for subject recruitment (if used)
	- any other documents given approval/favourable opinion
	- continuing review of trial (where required)
		To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.4	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)**	(see 8.2.10)	X	X
8.3.6	**UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(see 8.2.15.)	X	X
8.3.9	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 8.2.16)		X
8.3.10	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the monitor		X
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X

- notes of telephone calls

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.12	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Sponsor
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigatorís staff confirms the observations recorded	X (copy)	X (original)
8.3.15	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2	X (where required)	X
8.3.18	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X

8.3.19	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	**SUBJECT ENROLMENT LOG**	To document chronological enrolment of subjects by trial number	X	
8.3.23	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	**SIGNATURE SHEET**	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

	Title of Document	Purpose	Located in Files of Investigator/ Institution	Located in Files of Sponsor
8.4.1	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	**AUDIT CERTIFICATE** (if available)	To document that audit was performed		X
8.4.5	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial	X	
8.4.8	**CLINICAL STUDY REPORT**	To document results and interpretation of trial	X (if applicable)	X

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission [1],

Having regard to the opinion of the Economic and Social Committee [2],

Acting in accordance with the procedure laid down in Article 251 of the Treaty [3],

Whereas:

(1) Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [4] requires that applications for authorisation to place a medicinal product on the market should be accompanied by a dossier containing particulars and documents relating to the results of tests and clinical trials carried out on the product. Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, pharmaco-toxicological and clinical standards and protocols in respect of the testing of medicinal products [5] lays down uniform rules on the compilation of dossiers including their presentation.

(2) The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the 1996 version of the Helsinki Declaration. The clinical trial subject's protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and Member States' competent authorities, and rules on the protection of personal data.

(3) Persons who are incapable of giving legal consent to clinical trials should be given special protection. It is incumbent on the Member States to lay down rules to this effect. Such persons may not be included in clinical trials if the same results can be obtained using persons capable of giving consent. Normally these persons should be included in clinical trials only when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient, thereby outweighing the risks. However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological and psychological differences from adults, which make age- and development- related research important for their benefit. Medicinal products, including vaccines, for children need to be tested scientifically before widespread use. This can only be achieved by ensuring that medicinal products which are likely to be of significant clinical value for children are fully studied. The clinical trials required for this purpose should be carried out under conditions affording the best possible protection for the subjects. Criteria for the protection of children in clinical trials therefore need to be laid down.

(4) In the case of other persons incapable of giving their consent, such as persons with dementia, psychiatric patients, etc., inclusion in clinical trials in such cases should be on an even more restrictive basis. Medicinal products for trial may be administered to all such individuals only when there are grounds for assuming that the direct benefit to the patient outweighs the risks. Moreover, in such cases the written consent of the patient's legal representative, given in cooperation with the treating doctor, is necessary before participation in any such clinical trial.

(5) The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.

(6) In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. The harmonisation of technical requirements for the development

[1] OJ C 306, 8.10.1997, p. 9 and OJ C 161, 8.6.1999, p. 5.
[2] OJ C 95, 30.3.1998, p. 1.
[3] Opinion of the European Parliament of 17 November 1998 (OJ C 379, 7. 12. 1998, p. 27). Council Common Position of 20 July 2000 (OJ C 300, 20.10.2000, p. 32) and Decision of the European Parliament of 12 December 2000. Council Decision of 26 February 2001.
[4] OJ 22, 9.2.1965, p. 1/65. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).
[5] OJ L 147, 9.6.1975, p. 1. Directive as last amended by Commission Directive 1999/83/EC (OJ L 243, 15.9.1999, p. 9).

of medicinal products should therefore be pursued through the appropriate fora, in particular the International Conference on Harmonisation.

(7) For medicinal products falling within the scope of Part A of the Annex to Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products [1], which include products intended for gene therapy or cell therapy, prior scientific evaluation by the European Agency for the Evaluation of Medicinal Products (hereinafter referred to as the 'Agency'), assisted by the Committee for Proprietary Medicinal Products, is mandatory before the Commission grants marketing authorisation. In the course of this evaluation, the said Committee may request full details of the results of the clinical trials on which the application for marketing authorisation is based and, consequently, on the manner in which these trials were conducted and the same Committee may go so far as to require the applicant for such authorisation to conduct further clinical trials. Provision must therefore be made to allow the Agency to have full information on the conduct of any clinical trial for such medicinal products.

(8) A single opinion for each Member State concerned reduces delay in the commencement of a trial without jeopardising the well-being of the people participating in the trial or excluding the possibility of rejecting it in specific sites.

(9) Information on the content, commencement and termination of a clinical trial should be available to the Member States where the trial takes place and all the other Member States should have access to the same information. A European database bringing together this information should therefore be set up, with due regard for the rules of confidentiality.

(10) Clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and several trial sites, often in different Member States. Member States' current practices diverge considerably on the rules on commencement and conduct of the clinical trials and the requirements for carrying them out vary widely. This therefore results in delays and complications detrimental to effective conduct of such trials in the Community. It is therefore necessary to simplify and harmonise the administrative provisions governing such trials by establishing a clear, transparent procedure and creating conditions conducive to effective coordination of such clinical trials in the Community by the authorities concerned.

(11) As a rule, authorisation should be implicit, i.e. if there has been a vote in favour by the Ethics Committee and the competent authority has not objected within a given period, it should be possible to begin the clinical trials. In exceptional cases raising especially complex problems, explicit written authorisation should, however, be required.

(12) The principles of good manufacturing practice should be applied to investigational medicinal products.

(13) Special provisions should be laid down for the labelling of these products.

(14) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceuticals industry may be of great benefit to the patients concerned. The Directive should therefore take account of the special position of trials whose planning does not require particular manufacturing or packaging processes, if these trials are carried out with medicinal products with a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directives 75/319/EEC and 91/356/EEC, and on patients with the same characteristics as those covered by the indication specified in this marketing authorisation. Labelling of the investigational medicinal products intended for trials of this nature should be subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational products and in Directive 91/356/EEC.

(15) The verification of compliance with the standards of good clinical practice and the need to subject data, information and documents to inspection in order to confirm that they have been properly generated, recorded and reported are essential in order to justify the involvement of human subjects in clinical trials.

(16) The person participating in a trial must consent to the scrutiny of personal information during inspection by competent authorities and properly authorised persons, provided that such personal information is treated as strictly confidential and is not made publicly available.

(17) This Directive is to apply without prejudice to Directive 95/46/EEC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data [2].

(18) It is also necessary to make provision for the monitoring of adverse reactions occurring in clinical trials using Community surveillance (pharmacovigilance) procedures in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk.

[1] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7)

[2] OJ L 281, 23.11.1995, p. 31.

(19) The measures necessary for the implementation of this Directive should be adopted in accordance with Council Decision 1999/468/EC of 28 June 1999 laying down the procedures for the exercise of implementing powers conferred on the Commission [1],

HAVE ADOPTED THIS DIRECTIVE:

Article 1

Scope

1. This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products as defined in Article 1 of Directive 65/65/EEC, in particular relating to the implementation of good clinical practice. This Directive does not apply to non-interventional trials.

2. Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

3. The principles of good clinical practice and detailed guidelines in line with those principles shall be adopted and, if necessary, revised to take account of technical and scientific progress in accordance with the procedure referred to in Article 21(2).

These detailed guidelines shall be published by the Commission.

4. All clinical trials, including bioavailability and bioequivalence studies, shall be designed, conducted and reported in accordance with the principles of good clinical practice.

Article 2

Definitions

For the purposes of this Directive the following definitions shall apply:

(a) 'clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in either one site or multiple sites, whether in one or more than one Member State;

(b) 'multi-centre clinical trial': a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries;

(c) 'non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data;

(d) 'investigational medicinal product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form;

(e) 'sponsor': an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial;

(f) 'investigator': a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator;

(g) 'investigator's brochure': a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects;

(h) 'protocol': a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

(i) 'subject': an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control;

[1] OJ L 184, 17.7.1999, p. 23.

(j) 'informed consent': decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

(k) 'ethics committee': an independent body in a Member State, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent;

(l) 'inspection': the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect;

(m) 'adverse event': any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment;

(n) 'adverse reaction': all untoward and unintended responses to an investigational medicinal product related to any dose administered;

(o) 'serious adverse event or serious adverse reaction': any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

(p) 'unexpected adverse reaction': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

Article 3

Protection of clinical trial subjects

1. This Directive shall apply without prejudice to the national provisions on the protection of clinical trial subjects if they are more comprehensive than the provisions of this Directive and consistent with the procedures and time-scales specified therein. Member States shall, insofar as they have not already done so, adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent.

2. A clinical trial may be undertaken only if, in particular:

(a) the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored;

(b) the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time;

(c) the rights of the subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with Directive 95/46/EC are safeguarded;

(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial; if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation;

(e) the subject may without any resulting detriment withdraw from the clinical trial at any time by revoking his informed consent;

(f) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor.

3. The medical care given to, and medical decisions made on behalf of, subjects shall be the responsibility of an appropriately qualified doctor or, where appropriate, of a qualified dentist.

4. The subject shall be provided with a contact point where he may obtain further information.

Article 4

Clinical trials on minors

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

Article 5

Clinical trials on incapacitated adults not able to give informed legal consent

In the case of other persons incapable of giving informed legal consent, all relevant requirements listed for persons capable of giving such consent shall apply. In addition to these requirements, inclusion in clinical trials of incapacitated adults who have not given or not refused informed consent before the onset of their incapacity shall be allowed only if:

(a) the informed consent of the legal representative has been obtained; consent must represent the subject's presumed will and may be revoked at any time, without detriment to the subject;

(b) the person not able to give informed legal consent has received information according to his/her capacity of understanding regarding the trial, the risks and the benefits;

(c) the explicit wish of a subject who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods and relates directly to a life-threatening or debilitating clinical condition from which the incapacitated adult concerned suffers;

(f) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress shall be specially defined and constantly monitored;

(g) the Ethics Committee, with expertise in the relevant disease and the patient population concerned or after taking advice in clinical, ethical and psychosocial questions in the field of the relevant disease and patient population concerned, has endorsed the protocol;

(h) the interests of the patient always prevail over those of science and society; and

(i) there are grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all.

Article 6

Ethics Committee

1. For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.

2. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue requested.

3. In preparing its opinion, the Ethics Committee shall consider, in particular:

(a) the relevance of the clinical trial and the trial design;

(b) whether the evaluation of the anticipated benefits and risks as required under Article 3(2)(a) is satisfactory and whether the conclusions are justified;

(c) the protocol;

(d) the suitability of the investigator and supporting staff;

(e) the investigator's brochure;

(f) the quality of the facilities;

(g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in Article 3;

(h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

(i) any insurance or indemnity to cover the liability of the investigator and sponsor;

(j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;

(k) the arrangements for the recruitment of subjects.

4. Notwithstanding the provisions of this Article, a Member State may decide that the competent authority it has designated for the purpose of Article 9 shall be responsible for the consideration of, and the giving of an opinion on, the matters referred to in paragraph 3(h), (i) and (j) of this Article.

When a Member State avails itself of this provision, it shall notify the Commission, the other Member States and the Agency.

5. The Ethics Committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned.

6. Within the period of examination of the application for an opinion, the Ethics Committee may send a single request for information supplementary to that already supplied by the applicant. The period laid down in paragraph 5 shall be suspended until receipt of the supplementary information.

7. No extension to the 60-day period referred to in paragraph 5 shall be permissible except in the case of trials involving medicinal products for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms. In this case, an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy, there shall be no time limit to the authorisation period.

Article 7

Single opinion

For multi-centre clinical trials limited to the territory of a single Member State, Member States shall establish a procedure providing, notwithstanding the number of Ethics Committees, for the adoption of a single opinion for that Member State.

In the case of multi-centre clinical trials carried out in more than one Member State simultaneously, a single opinion shall be given for each Member State concerned by the clinical trial.

Article 8

Detailed guidance

The Commission, in consultation with Member States and interested parties, shall draw up and publish detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data.

Article 9

Commencement of a clinical trial

1. Member States shall take the measures necessary to ensure that the procedure described in this Article is followed for commencement of a clinical trial.

The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion and inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance. The procedures to reach these decisions can be run in parallel or not, depending on the sponsor.

2. Before commencing any clinical trial, the sponsor shall be required to submit a valid request for authorisation to the competent authority of the Member State in which the sponsor plans to conduct the clinical trial.

3. If the competent authority of the Member State notifies the sponsor of grounds for non-acceptance, the sponsor may, on one occasion only, amend the content of the request referred to in paragraph 2 in order to take due account of the grounds given. If the sponsor fails to amend the request accordingly, the request shall be considered rejected and the clinical trial may not commence.

4. Consideration of a valid request for authorisation by the competent authority as stated in paragraph 2 shall be carried out as rapidly as possible and may not exceed 60 days. The Member States may lay down a shorter period than 60 days within their area of responsibility if that is in compliance with current practice. The competent authority can nevertheless notify the sponsor before the end of this period that it has no grounds for non-acceptance.

No further extensions to the period referred to in the first subparagraph shall be permissible except in the case of trials involving the medicinal products listed in paragraph 6, for which an extension of a maximum of 30 days shall be permitted. For these products, this 90-day period may be extended by a further 90 days in the event of consultation of a group or a committee in accordance with the regulations and procedures of the Member States concerned. In the case of xenogenic cell therapy there shall be no time limit to the authorisation period.

5. Without prejudice to paragraph 6, written authorisation may be required before the commencement of clinical trials for such trials on medicinal products which do not have a marketing authorisation within the meaning of Directive 65/65/EEC and are referred to in Part A of the Annex to Regulation (EEC) No 2309/93, and other medicinal products with special characteristics, such as medicinal products the active ingredient or active ingredients of which is or are a biological product or biological products of human or animal origin, or contains biological components of human or animal origin, or the manufacturing of which requires such components.

6. Written authorisation shall be required before commencing clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms. No gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity.

7. This authorisation shall be issued without prejudice to the application of Council Directives 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms [1] and 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms [2].

8. In consultation with Member States, the Commission shall draw up and publish detailed guidance on:

(a) the format and contents of the request referred to in paragraph 2 as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure;

(b) the presentation and content of the proposed amendment referred to in point (a) of Article 10 on substantial amendments made to the protocol;

(c) the declaration of the end of the clinical trial.

Article 10

Conduct of a clinical trial

Amendments may be made to the conduct of a clinical trial following the procedure described hereinafter:

(a) after the commencement of the clinical trial, the sponsor may make amendments to the protocol. If those amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the sponsor shall notify the competent authorities of the Member State or Member States concerned of the reasons for, and content of, these amendments and shall inform the ethics committee or committees concerned in accordance with Articles 6 and 9.

On the basis of the details referred to in Article 6(3) and in accordance with Article 7, the Ethics Committee shall give an opinion within a maximum of 35 days of the date of receipt of the proposed amendment in good and due form. If this opinion is unfavourable, the sponsor may not implement the amendment to the protocol.

If the opinion of the Ethics Committee is favourable and the competent authorities of the Member States have raised no grounds for non-acceptance of the abovementioned substantial amendments, the sponsor shall proceed to conduct the clinical trial following the amended protocol. Should this not be the case, the sponsor shall either take account of the grounds for non-acceptance and adapt the proposed amendment to the protocol accordingly or withdraw the proposed amendment;

(b) without prejudice to point (a), in the light of the circumstances, notably the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product where that new event is likely to affect the safety of the subjects, the sponsor and the investigator shall take appropriate urgent safety measures to protect the subjects against any immediate hazard. The sponsor shall forthwith inform the competent authorities of those new events and the measures taken and shall ensure that the Ethics Committee is notified at the same time;

(c) within 90 days of the end of a clinical trial the sponsor shall notify the competent authorities of the Member State or Member States concerned and the Ethics Committee that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

Article 11

Exchange of information

1. Member States in whose territory the clinical trial takes place shall enter in a European database, accessible only to the competent authorities of the Member States, the Agency and the Commission:

(a) extracts from the request for authorisation referred to in Article 9(2);

(b) any amendments made to the request, as provided for in Article 9(3);

[1] OJ L 117, 8.5.1990, p. 1. Directive as last amended by Directive 98/81/EC (OJ L 330, 5.12.1998, p. 13).
[2] OJ L 117, 8.5.1990, p. 15. Directive as last amended by Commission Directive 97/35/EC (OJ L 169, 27.6.1997, p. 72).

(c) any amendments made to the protocol, as provided for in point a of Article 10;

(d) the favourable opinion of the Ethics Committee;

(e) the declaration of the end of the clinical trial; and

(f) a reference to the inspections carried out on conformity with good clinical practice.

2. At the substantiated request of any Member State, the Agency or the Commission, the competent authority to which the request for authorisation was submitted shall supply all further information concerning the clinical trial in question other than the data already in the European database.

3. In consultation with the Member States, the Commission shall draw up and publish detailed guidance on the relevant data to be included in this European database, which it operates with the assistance of the Agency, as well as the methods for electronic communication of the data. The detailed guidance thus drawn up shall ensure that the confidentiality of the data is strictly observed.

Article 12

Suspension of the trial or infringements

1. Where a Member State has objective grounds for considering that the conditions in the request for authorisation referred to in Article 9(2) are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof.

Before the Member State reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week.

In this case, the competent authority concerned shall forthwith inform the other competent authorities, the Ethics Committee concerned, the Agency and the Commission of its decision to suspend or prohibit the trial and of the reasons for the decision.

2. Where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform him thereof, indicating the course of action which he must take to remedy this state of affairs. The competent authority concerned shall forthwith inform the Ethics Committee, the other competent authorities and the Commission of this course of action.

Article 13

Manufacture and import of investigational medicinal products

1. Member States shall take all appropriate measures to ensure that the manufacture or importation of investigational medicinal products is subject to the holding of authorisation. In order to obtain the authorisation, the applicant and, subsequently, the holder of the authorisation, shall meet at least the requirements defined in accordance with the procedure referred to in Article 21(2).

2. Member States shall take all appropriate measures to ensure that the holder of the authorisation referred to in paragraph 1 has permanently and continuously at his disposal the services of at least one qualified person who, in accordance with the conditions laid down in Article 23 of the second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products [1], is responsible in particular for carrying out the duties specified in paragraph 3 of this Article.

3. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 21 of Directive 75/319/EEC, without prejudice to his relationship with the manufacturer or importer, is responsible, in the context of the procedures referred to in Article 25 of the said Directive, for ensuring:

(a) in the case of investigational medicinal products manufactured in the Member State concerned, that each batch of medicinal products has been manufactured and checked in compliance with the requirements of Commission Directive 91/356/EEC of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use [2], the product specification file and the information notified pursuant to Article 9(2) of this Directive;

(b) in the case of investigational medicinal products manufactured in a third country, that each production batch has been manufactured and checked in accordance with standards of good manufacturing practice at least equivalent to those laid down in Commission Directive 91/356/EEC, in accordance with the product specification file, and that each production batch has been checked in accordance with the information notified pursuant to Article 9(2) of this Directive;

(c) in the case of an investigational medicinal product which is a comparator product from a third country, and which has a marketing authorisation, where the documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of good manufacturing practice referred to above cannot be obtained, that each production batch has undergone all relevant analyses, tests or checks necessary to confirm its quality in accordance with the information notified pursuant to Article 9(2) of this Directive.

Detailed guidance on the elements to be taken into account when evaluating products with the object of releasing batches within the Community shall be drawn up pursuant to the good manufacturing practice guidelines, and in particular Annex 13 to the said guidelines. Such guidelines will be adopted in accordance with the procedure referred to in Article 21(2) of this Directive and published in accordance with Article 19a of Directive 75/319/EEC.

[1] OJ L 147, 9.6.1975, p. 13. Directive as last amended by Council Directive 93/39/EC (OJ L 214, 24.8.1993, p. 22).
[2] OJ L 193, 17.7.1991, p. 30.

Insofar as the provisions laid down in (a), (b) or (c) are complied with, investigational medicinal products shall not have to undergo any further checks if they are imported into another Member State together with batch release certification signed by the qualified person.

4. In all cases, the qualified person must certify in a register or equivalent document that each production batch satisfies the provisions of this Article. The said register or equivalent document shall be kept up to date as operations are carried out and shall remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member States concerned. This period shall in any event be not less than five years.

5. Any person engaging in activities as the qualified person referred to in Article 21 of Directive 75/319/EEC as regards investigational medicinal products at the time when this Directive is applied in the Member State where that person is, but without complying with the conditions laid down in Articles 23 and 24 of that Directive, shall be authorised to continue those activities in the Member State concerned.

Article 14

Labelling

The particulars to appear in at least the official language(s) of the Member State on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging, shall be published by the Commission in the good manufacturing practice guidelines on investigational medicinal products adopted in accordance with Article 19a of Directive 75/319/EEC.

In addition, these guidelines shall lay down adapted provisions relating to labelling for investigational medicinal products intended for clinical trials with the following characteristics:

— the planning of the trial does not require particular manufacturing or packaging processes;

— the trial is conducted with medicinal products with, in the Member States concerned by the study, a marketing authorisation within the meaning of Directive 65/65/EEC, manufactured or imported in accordance with the provisions of Directive 75/319/EEC;

— the patients participating in the trial have the same characteristics as those covered by the indication specified in the abovementioned authorisation.

Article 15

Verification of compliance of investigational medicinal products with good clinical and manufacturing practice

1. To verify compliance with the provisions on good clinical and manufacturing practice, Member States shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analyses in the clinical trial and/or the sponsor's premises.

The inspections shall be conducted by the competent authority of the Member State concerned, which shall inform the Agency; they shall be carried out on behalf of the Community and the results shall be recognised by all the other Member States. These inspections shall be coordinated by the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93. A Member State may request assistance from another Member State in this matter.

2. Following inspection, an inspection report shall be prepared. It must be made available to the sponsor while safeguarding confidential aspects. It may be made available to the other Member States, to the Ethics Committee and to the Agency, at their reasoned request.

3. At the request of the Agency, within the framework of its powers as provided for in Regulation (EEC) No 2309/93, or of one of the Member States concerned, and following consultation with the Member States concerned, the Commission may request a new inspection should verification of compliance with this Directive reveal differences between Member States.

4. Subject to any arrangements which may have been concluded between the Community and third countries, the Commission, upon receipt of a reasoned request from a Member State or on its own initiative, or a Member State may propose that the trial site and/or the sponsor's premises and/or the manufacturer established in a third country undergo an inspection. The inspection shall be carried out by duly qualified Community inspectors.

5. The detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial, archiving, qualifications of inspectors and inspection procedures to verify compliance of the clinical trial in question with this Directive shall be adopted and revised in accordance with the procedure referred to in Article 21(2).

Article 16

Notification of adverse events

1. The investigator shall report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the sponsor according to the reporting requirements and within the time periods specified in the protocol.

3. For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

4. The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the Member States in whose territory the clinical trial is being conducted, if they so request.

Article 17

Notification of serious adverse reactions

1. (a) The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the Member States concerned, and to the Ethics Committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

(b) All other suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

(c) Each Member State shall ensure that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are recorded.

(d) The sponsor shall also inform all investigators.

2. Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety.

3. (a) Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in a European database to which, in accordance with Article 11(1), only the competent authorities of the Member States, the Agency and the Commission shall have access.

(b) The Agency shall make the information notified by the sponsor available to the competent authorities of the Member States.

Article 18

Guidance concerning reports

The Commission, in consultation with the Agency, Member States and interested parties, shall draw up and publish detailed guidance on the collection, verification and presentation of adverse event/reaction reports, together with decoding procedures for unexpected serious adverse reactions.

Article 19

General provisions

This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community.

Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available free of charge by the sponsor.

The Member States shall inform the Commission of such conditions.

Article 20

Adaptation to scientific and technical progress

This Directive shall be adapted to take account of scientific and technical progress in accordance with the procedure referred to in Article 21(2).

Article 21

Committee procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, set up by Article 2b of Directive 75/318/EEC (hereinafter referred to as the Committee).

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period referred to in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. The Committee shall adopt its rules of procedure.

Article 22

Application

1. Member States shall adopt and publish before 1 May 2003 the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith inform the Commission thereof.

They shall apply these provisions at the latest with effect from 1 May 2004.

When Member States adopt these provisions, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by Member States.

2. Member States shall communicate to the Commission the text of the provisions of national law which they adopt in the field governed by this Directive.

Article 23

Entry into force

This Directive shall enter into force on the day of its publication in the Official Journal of the European Communities.

Article 24

Addressees

This Directive is addressed to the Member States.

Done at Luxembourg, 4 April 2001.

For the European Parliament	*For the Council*
The President	*The President*
N. FONTAINE	B. ROSENGREN

European Commission
Public Health

News and updates on pharmaceuticals

EudraLex - Volume 10 Clinical trials guidelines

Volume 10 of the publications "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

General information (July 2006)

Chapter I: Application and Application Form

- Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial (revision 3 of March 2010)
    - Annex 1 revised Pdf version Word version (revision 4 of November 2009) - EudraCT Version 8.0 uses the Revision 4 dated November 2009 of the Clinical Trials Application Form. For more information please refer to the EudraCT website
    - Substantial Amendment Notification Form : PDF version - Word version (revision 3 of June 2010)
    - Declaration of the End of Trial Form : PDF version - Word version (revision 3 of June 2010)
- Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (revision 1 of February 2006)
- Detailed guidance on the European clinical trials database (EUDRACT Database) (revision of April 2004)

Chapter II: Safety Reporting

- Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3') (June 2011)
- ICH guideline E2F - Note for guidance on development safety update reports (September 2010)

Chapter III: Quality of the Investigational Medicinal Product

- Template for the qualified person's declaration equivalence to EU GMP for Investigational Medicinal Products manufactured in third countries (may 2013)
- Good manufacturing practices for manufacture of investigational medicinal products (February 2010)

  Community basic format for manufacturing authorisation / Community basic format for manufacturers / importers
- Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials
- Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (May 2012)
- Guidance on Investigational Medicinal Products (IMPs) and 'non investigational medicinal products' (NIMPs) (rev. 1, March 2011)

Chapter IV: Inspections

- Guidance for the preparation of GCP inspections (June 2008)
- Recommendation on inspection procedures for the verification of good clinical practice compliance (July 2006)
- Guidance for the conduct of GCP inspections (June 2008)
- Annex I to Guidance for the conduct of GCP inspections - investigator site (June 2008)
- Annex II to Guidance for the conduct of GCP inspection - clinical laboratories (June 2008)
- Annex III to Guidance for the conduct of GCP inspections - computer systems (June 2008)
- Annex IV to Guidance for the conduct of GCP inspections - Sponsor and CRO (June 2008)
- Annex V to Guidance for the conduct of GCP inspections - Phase I Units (November 2008)
- Annex VI to Guidance for the conduct of GCP inspections - Record keeping and archiving of documents (March 2010)
- Annex VII to Guidance for the conduct of GCP inspections - Bioanalytical part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials (November 2008)
- Guidance for coordination of GCP inspections and co-operation between GCP inspectors, the reference and concerned Member States and CMD(h) , in the context of the evaluation of the GCP compliance of marketing authorization applications for mutual recognition and decentralized procedures (June 2009)
- Guidance for exchange of GCP Inspection Reports according to Article 15(2) of Directive 2001/20/EC (revision 1 - May 2009)
- Guidance for the communication on GCP inspections and findings (June 2008)
- Procedure for standardisation of GCP inspection entries in EudraCT (November 2008)
- Guidance for the preparation of Good Clinical Practice inspection reports (June 2008)
- Recommendations on the qualifications of inspectors verifying compliance in clinical trials with the provisions of Good Clinical Practice (July 2006)

Chapter V: Additional Information

- Guidelines on good clinical practice (ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95) (1996)
- Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (December 2009)
- Recommendation on the content of the trial master file and archiving (July 2006)
- "Questions & Answers" Document - Version 11.0 (May 2013)
- Ethical considerations for clinical trials on medicinal products conducted with the paediatric population (2008)
- Guideline 2008/C168/02 on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products (July 2008)
- List of fields contained in the 'EudraCT' clinical trials database to be made public, in accordance with Article 57(2) of Regulation (EC) No 726/2004 and its implementing guideline 2008/C168/02 (February 2009)
- Guideline 2009/C28/01 on the information concerning paediatric clinical trials to be entered into the EU Database on Clinical Trials (EudraCT) and on the information to be made public by the European Medicines Agency (EMEA), in accordance with Article 41 of Regulation (EC) No 1901/2006 (February 2009)
- List of fields to be made public from EudraCT for Paediatric Clinical Trials in accordance with Article 41 of Regulation (EC) No 1901/2006 and its implementing guideline 2009/C28/01 (February 2009)
- Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (October 2012)
- Technical guidance on the format of the data fields of result-related information on clinical trials submitted in accordance with Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 (January 2013)
- EudraCT - List of additional fields contained in EudraCT (reasons for negative opinions of the Ethics Committee) (November 2010)

Chapter VI: Legislation

- Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products

for human use.

- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (Official Journal L 262, 14/10/2003 p. 22 - 26).

- Eudralex on CD

Last update: 10/05/2013 | Top
loading

FOR ANY INFORMATION

European Forum for Good Clinical Practice (EFGCP)

EFGCP Secretariat
Square de Meeûs – Rue de l'Industrie 4
BE-1000 Brussels, Belgium
Tel: +32.2.732 87 83
Fax: +32.2.503 31 08
E-mail: secretariat@efgcp.eu
Website: www.efgcp.eu

SAVE THE DATE!

Mitigating Risks in the Lifecycle of Medical Devices: Options and Challenges in Building Clinical Evidence

4 December 2014
The Hotel, Brussels, Belgium

Organised by the newly formed
Joint Medical Technology Working Party of

EFGCP
where science and ethics meet

MedTech Europe
from diagnosis to cure

The upcoming European Regulation on Medical Devices will change the landscape for the development of medical devices. This multi-stakeholder workshop will offer the floor for an exchange of views and opinions on topics of particular complexity and input to the relevant decision-makers.

Setting effective ethical and quality clinical standards for medical technology studies is critical to ensuring that patients have access to safe and effective treatment. For the first time, patient representatives, healthcare providers, ethicists, competent authorities, industry and policymakers will be able to present and discuss their needs and expectations, the options and opportunities for mitigating risks in the development and full life cycle of medical devices and the best ways of building clinical evidence.

Objectives:

- Understand the differences between clinical trials with medicines and medical devices
- Identify suitability of concepts and lessons learned in medicines development for clinical development of medical devices
- Discuss how best to ensure the required ethical and quality standards in medical device trials

For any information please contact
the EFGCP team at
conferences@efgcp.eu
Tel: +32 2 732 87 83 or visit www.efgcp.eu

EFGCP Annual Conference 2015

How do we improve health without betraying confidentiality within current and upcoming EU Regulations?

27 & 28 January 2015 – Brussels, Belgium

PROGRAMME COMMITTEE

Insa Bruns, Central Office of the KKS-Network, Germany - **Anna Chioti**, CRP-Santé, Luxembourg - **Hugh Davies**, Health Research Authority, UK - **Lode Dewulf**, UCB Pharma Belgium - **Nicky Dodsworth**, Premier Research, UK - **Robert Frost**, GSK, UK - **Yves Geysels**, Quintiles, Belgium - **Shahid Hanif**, ABPI, UK - **Sarah Hills**, Euradia, UK - **Laurence Hugonot-Diener**, Broca Hospital/ MedForma, France - **Heinrich Klech**, Medical University Vienna, Austria - **Ingrid Klingmann**, Pharmaplex, Belgium - **Olga Kubar,** Pasteur Institute/EFGCP, Russia - **Rick Lilley,** UCB Pharma, Belgium - **Marianne Maman**, Novartis Pharma AG, Switzerland - **Anastassia Negrouk,** EORTC, Belgium - **Achenyo Ochuma**, ABPI, UK - **Heather Sampson**, Toronto East General Hospital / University of Toronto, Toronto, Canada - **Mark Taylor,** Confidentiality Advisory Group, UK - **Beth Thompson**, Wellcome Trust, UK

ABOUT EFGCP

For twenty one years the European Forum for Good Clinical Practice has acted as a forum to bring patients, researchers, sponsors, competent authorities and ethics committees together and debate current topics. It is one of the most fora for multi stakeholder debate. In the 2015 Annual Conference we will debate the tensions between confidentiality and transparency in health research.

It will provide an opportunity to hear up to date information from experts involved, listen to differing viewpoints, particularly those of patients and patient groups whose voice must be central in this debate. It will also present opportunity to consider current solutions.

To follow the development of the programme visit our website: **www.efgcp.eu**

What is the price of maintaining confidentiality for patients in health research?

OVERVIEW

Progress in our understanding of the factors underpinning good health is leading us towards developing better treatments. Much of this advance is founded on the use of personal data, such as our health records. Without access to this data, medical progress would be seriously impeded and proposed restrictive access to clinical information poses a serious, immediate threat to research. There is a real danger we will sleepwalk into a position where we undermine health research designed to provide health care benefit.

This has been recognised within the discussions around the new EU Clinical Trial Regulations but it could be irreparably damaged by proposed Data Protection Regulations. While protection of privacy must be a central tenet of any legislation, some amendments will make vital research unworkable. The use of personal health data in research would become impossible in practice. This poses a significant risk to our health. Our conference will seek to strike a balance in answering the key questions.

OBJECTIVES

- A description and report on data protection arrangements in research across the EU through the EFGCP Research Ethics Committee survey
- Debate on and development of a draft statement on secondary use of data in research
- EFGCP report and recommendations that will be provided to those involved in the legislative process.

WHO WILL ATTEND

- European and National regulatory authority representatives
- Health authority representatives
- Pharma, CRO and industry professionals
- Ethics Committees
- Patient organisations
- Clinical Research professionals

And many others

For any query please contact the EFGCP Secretariat
Tel: +32 2 732 87 83
Email: conferences@efgcp.eu

EFGCP
where science and ethics meet

EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE

Individual Membership Form

Welcome to EFGCP! Joining EFGCP provides you with an opportunity to promote ethics and science in European research through the single European organisation devoted to Good Clinical Practice and medicinal product development.

WHO JOINS EFGCP?

Membership in EFGCP is open to professionals and individuals representing patient groups, ethics committees, academic & industry research enterprises, regulatory officials, and those concerned to develop the ethics and science of Good Clinical Practice in Europe and globally.

BENEFITS OF JOINING EFGCP

EFGCP provides a unique meeting place for decision-making in the fields of ethics and science in Good Clinical Practice. Your participation in this forum will contribute to the advancement of research in an environment that puts the patient's interest first.

As an EFGCP member, you will benefit from:

- An access to the leading European and international discussions on ethics and science in clinical research.
- An opportunity to contribute to the development of Good Clinical Practice in Europe and globally.
- A direct access to the foremost developments in European regulatory and ethical discussions on GCP and the development of medicinal products.
- Access to EFGCP Working Parties engaging current ethics and GCP issues in health research (Ethics, Audit, Education, Children's Medicines, EGAN-EFGCP Patients' Roadmap to Treatment and Geriatric Medicines) (subject to the chairs' approval).
- A way to build excellence in clinical research within your institution through dialogue with others.
- Personal login to the members' area of the EFGCP Website with unlocked access to information and members' general directory.
- Regular updates through e-mails, conferences, workshops and publications (The biannual 'EFGCP News', meeting reports and guidelines).
- Reduced registration fees for all EFGCP events.

INDIVIDUAL MEMBERSHIP REGISTRATION FEE

The annual EFGCP membership registration fee is set according to the members' status. Membership is valid one full year independently of the calendar year.

EFGCP Membership Automatic Renewal: Your membership will renew automatically unless you notify us otherwise. This means that at the beginning of the membership year, we will charge you automatically for the next membership period to guarantee uninterrupted access to benefits. A reminder email giving you the opportunity to update payment or contact information, or cancel your auto-renewal membership will be sent at least one month prior to your annual membership renewal date.

Please fax, e-mail or mail this form to:

EFGCP Secretariat, Rue de l'Industrie 4 - 1000 Brussels, Belgium
Tel +32 (0)2 732 87 83; Fax +32 (0)2 503 31 08; E-mail: membership@efgcp.eu
www.efgcp.eu

EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE

Individual Membership Form

Registration Details

☐ Mr. ☐ Ms. ☐ Dr. ☐ Prof.

Family Name: ..... First Name: .....

Position: ..... Department: .....

Organisation/Company: .....

Address: .....

Zip Code: ..... City: ..... Country: .....

Phone: ..... Fax: .....

Email: .....

Member's Profile and Membership Fee

☐	Academic Organisation	€70	☐	Insurance Company	€140
☐	Association	€70	☐	Medical Journalist	€70
☐	Biotech Industry	€140	☐	Medical Society	€70
☐	Care Giver	€70	☐	National Regulatory Authority/Agency	€70
☐	Consultant	€140	☐	Non-Governmental Organisation	€70
☐	CRO Industry	€140	☐	Nurse	€70
☐	Device Manufacturer	€140	☐	Nutrition Company	€140
☐	Ethics Committee	€70	☐	Other	Contact us
☐	EU Project Consortium Member (non commercial / commercial)	€70/€140	☐	Patient Organisation/Advocate	€70
☐	European Regulatory Authority/Agency	€70	☐	Pharmaceutical Industry	€140
☐	Hospital Pharmacist/Lab Staff	€70	☐	Retired Member	€30
☐	HTA commercial stakeholder (non commercial / commercial)	€70/€140	☐	Student*	€30

All fees are excluding VAT to be added according to your or your organisation VAT status:

21% VAT	*VAT Registered and not VAT Registered Members from Belgium* *Not VAT registered Members from EU and Rest of the World*
0% VAT	*VAT Registered Members from EU and Rest of the World*

*** Please provide a certificate issued by your university that states your full-time student status when returning this membership form.**

Please fax, e-mail or mail this form to:

EFGCP Secretariat, Rue de l'Industrie 4 - 1000 Brussels, Belgium
Tel +32 (0)2 732 87 83; Fax +32 (0)2 503 31 08; E-mail: membership@efgcp.eu
www.efgcp.eu

EUROPEAN FORUM FOR GOOD CLINICAL PRACTICE

Individual Membership Form

Billing Information (To be completed for VAT-registered members)

Organisation/Company: .....

VAT #: .....

Contact Person: .....

Position: ..... Department: .....

Address: .....

Zip code: ..... City: ..... Country: .....

Phone: ..... Fax: .....

Email: ..... Purchase Order # or other reference: .....

Way of Payment

☐ **BANK TRANSFER** All charges to be borne by principal, to the order of the EFGCP.

Account Holder:	EFGCP Events	**Bank Name:**	ING, Brussels, Belgium	**BIC/Swift**	BBRUBEBB
Account #:	310-1960818-49	**IBAN:**	BE97 3101 9608 1849	**Communication**	Invoice # Member's name

☐ **CREDIT CARD:** ☐ VISA ☐ American Express ☐ Mastercard

Cardholder: ..... **Amount:** ……*+VAT if applicable*

Card #: ..... **Expiry date:** ..... **Security Code (CVC):** .....

Date: ..... **Signature:** .....

A proforma invoice will be provided along with the membership confirmation. The formal invoice will be sent once payment is received.

Please fax, e-mail or mail this form to:

EFGCP Secretariat, Rue de l'Industrie 4 - 1000 Brussels, Belgium

Tel +32 (0)2 732 87 83; Fax +32 (0)2 503 31 08; E-mail: membership@efgcp.eu

www.efgcp.eu