INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE

E6(R2)

Current *Step 4* version

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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.

ADDENDUM

Since the development of the ICH GCP Guideline, the scale, complexity, and cost of clinical trials have increased. Evolutions in technology and risk management processes offer new opportunities to increase efficiency and focus on relevant activities. When the original ICH E6(R1) text was prepared, clinical trials were performed in a largely paper-based process. Advances in use of electronic data recording and reporting facilitate implementation of other approaches. For example, centralized monitoring can now offer a greater advantage, to a broader range of trials than is suggested in the original text. Therefore, this guideline has been amended to encourage implementation of improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human subject protection and reliability of trial results. Standards regarding electronic records and essential documents intended to increase clinical trial quality and efficiency have also been updated.

This guideline should be read in conjunction with other ICH guidelines relevant to the conduct of clinical trials (e.g., E2A (clinical safety data management), E3 (clinical study reporting), E7 (geriatric populations), E8 (general considerations for clinical trials), E9 (statistical principles), and E11 (pediatric populations)).

This ICH GCP Guideline Integrated Addendum provides a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions. In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

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.

1.10 Blinding/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).

1.11 Case 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.

1.12 Clinical 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.

1.13 Clinical 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).

1.14 Comparator (Product)

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

1.15 Compliance (in relation to trials)

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 Confidentiality

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

1.17 Contract

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.

1.18 Coordinating Committee

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

1.19 Coordinating Investigator

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

1.20 Contract 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.

1.21 Direct 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 sponsor's proprietary information.

1.22 Documentation

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.

1.23 Essential 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).

1.24 Good 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.

1.25 Independent 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.

1.26 Impartial 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 subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 Independent 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.

1.28 Informed 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.

1.29 Inspection

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 organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 Institution (medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 Institutional 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.

1.32 Interim Clinical Trial/Study Report

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 Investigational 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.

1.34 Investigator

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.

1.35 Investigator/Institution

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

1.36 Investigator'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. Investigator's Brochure).

1.37 Legally 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.

1.38 Monitoring

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).

1.39 Monitoring Report

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 Multicentre 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.

1.41 Nonclinical Study

Biomedical studies not performed on human subjects.

1.42 Opinion (in relation to Independent Ethics Committee)

The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 Original Medical Record

See Source Documents.

1.44 Protocol

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.

1.45 Protocol Amendment

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

1.46 Quality 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).

1.47 Quality 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.

1.48 Randomization

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.

1.49 Regulatory 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.

1.50 Serious 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).

1.51 Source Data

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

1.52 Source 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).

1.53 Sponsor

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

1.54 Sponsor-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.

1.55 Standard Operating Procedures (SOPs)

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

1.56 Subinvestigator

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.

1.57 Subject/Trial Subject

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

1.58 Subject 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.

1.59 Trial Site

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

1.60 Unexpected 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.

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1.63 Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

1.64 Monitoring Plan

A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.

1.65 Validation of Computerized Systems

A process of establishing and documenting that the specified requirements of a computerized system can be consistently fulfilled from design until decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

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.

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This principle applies to all records referenced in this guideline, irrespective of the type of media used.

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.

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Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.

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 investigator's 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 subject's 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 subject's 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.

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4.2.5 The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

4.2.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

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/institution’s 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 Investigator’s 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/institution's 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 subject's 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 subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's 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 subject's 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 subject's legally acceptable

representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's 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 subject's 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 subject's 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 subject's participation in the trial, the subject or the subject's 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 subject's 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 subject's 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 subject's 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 subject's 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

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4.9.0 The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., *via* an audit trail).

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.

4.10 Progress 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.

4.11 Safety 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 trial’s outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

ADDENDUM

5.0 Quality Management

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results. Quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making.

The methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor should ensure that all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents should be clear, concise, and consistent.

The quality management system should use a risk-based approach as described below.

5.0.1 Critical Process and Data Identification

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.0.2 Risk Identification

The sponsor should identify risks to critical trial processes and data. Risks should be considered at both the system level (e.g., standard operating procedures, computerized systems, personnel) and clinical trial level (e.g., trial design, data collection, informed consent process).

5.0.3 Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk controls by considering:

(a) The likelihood of errors occurring.
(b) The extent to which such errors would be detectable.
(c) The impact of such errors on human subject protection and reliability of trial results.

5.0.4 Risk Control

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk. Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial

results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

5.0.5 Risk Communication

The sponsor should document quality management activities. The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution.

5.0.6 Risk Review

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

5.0.7 Risk Reporting

The sponsor should describe the quality management approach implemented in the trial and summarize important deviations from the predefined quality tolerance limits and remedial actions taken in the clinical study report (ICH E3, Section 9.6 Data Quality Assurance).

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.

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The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

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 sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

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The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

(b) Maintains SOPs for using these systems.

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The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionality testing, data collection and handling, system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized systems should be clear, and the users should be provided with training in their use.

(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).

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(h) Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

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.

5.10 Notification/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/institution's 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.

5.16 Safety 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.

5.17 Adverse 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).

5.18 Monitoring

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 monitor's 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 sponsor's 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 investigators' 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.

ADDENDUM

The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring. The sponsor should document the rationale for the chosen monitoring strategy (e.g., in the monitoring plan).

On-site monitoring is performed at the sites at which the clinical trial is being conducted. Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons (e.g., data managers, biostatisticians).

Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

(a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

(b) examine data trends such as the range, consistency, and variability of data within and across sites.

(c) evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.

(d) analyze site characteristics and performance metrics.

(e) select sites and/or processes for targeted on-site monitoring.

5.18.4 Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's 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 sponsor’s 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 sponsor's designated representative.

ADDENDUM

(e) Reports of on-site and/or centralized monitoring should be provided to the sponsor (including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan. Reporting of centralized monitoring activities should be regular and may be independent from site visits.

ADDENDUM

5.18.7 Monitoring Plan

The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial. The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use. The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures.

5.19 Audit

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 auditor's 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.

5.20 Noncompliance

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.

ADDENDUM

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

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/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 Premature 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).

5.22 Clinical 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.)

5.23 Multicentre 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 Investigator's 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.

6.13 Data Handling and Record Keeping

6.14 Financing and Insurance

Financing and insurance if not addressed in a separate agreement.

6.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

6.16 Supplements

(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. INVESTIGATOR'S 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 Investigator's 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
- Carcinogenicity
- Special 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/institution's 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 sponsor's auditor and inspection by the regulatory authority(ies).

ADDENDUM

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

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	**Sponsor**
8.2.1	**INVESTIGATOR'S 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** **- INFORMED CONSENT FORM** (including all applicable translations)	To document the informed consent	X	X
	- 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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
	- 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.: - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required)	To document agreements	 X X X	 X X (where required) X X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
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	**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 Investigator's 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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
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)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.2.18	**MASTER RANDOMISATION LIST**	To document method for randomisation of trial population		X (third party if applicable)
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 investigator's 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	**INVESTIGATOR'S 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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**

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

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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
8.3.11	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
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	
8.3.14	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorised member of the investigator's 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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
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 and 4.11.2	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	

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
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	**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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	**Sponsor**
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

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING E2A

Current *Step 4* version

dated 27 October 1994

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E2A
Document History

First Codification	History	Date	New Codification **November 2005**
E2A	Approval by the Steering Committee under *Step 2* and release for public consultation.	24 June 1993	E2A

Current *Step 4* version

E2A	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	27 October 1994	E2A

CLINICAL SAFETY DATA MANAGEMENT:
DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

ICH Harmonised Tripartite Guideline

Having reached Step 4 of the ICH Process at the ICH Steering Committee meeting on 27 October 1994, this guideline is recommended for adoption to the three regulatory parties to ICH

I. INTRODUCTION

It is important to harmonise the way to gather and, if necessary, to take action on important clinical safety information arising during clinical development. Thus, agreed definitions and terminology, as well as procedures, will ensure uniform Good Clinical Practice standards in this area. The initiatives already undertaken for marketed medicines through the CIOMS-1 and CIOMS-2 Working Groups on expedited (alert) reports and periodic safety update reporting, respectively, are important precedents and models. However, there are special circumstances involving medicinal products under development, especially in the early stages and before any marketing experience is available. Conversely, it must be recognised that a medicinal product will be under various stages of development and/or marketing in different countries, and safety data from marketing experience will ordinarily be of interest to regulators in countries where the medicinal product is still under investigational-only (Phase 1, 2, or 3) status. For this reason, it is both practical and well-advised to regard pre-marketing and post-marketing clinical safety reporting concepts and practices as interdependent, while recognising that responsibility for clinical safety within regulatory bodies and companies may reside with different departments, depending on the status of the product (investigational vs. marketed).

There are two issues within the broad subject of clinical safety data management that are appropriate for harmonisation at this time:

(1) the development of standard definitions and terminology for key aspects of clinical safety reporting, and

(2) the appropriate mechanism for handling expedited (rapid) reporting, in the investigational (i.e., pre-approval) phase.

The provisions of this guideline should be used in conjunction with other ICH Good Clinical Practice guidelines.

II. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

A. Basic Terms

Definitions for the terms adverse event (or experience), adverse reaction, and unexpected adverse reaction have previously been agreed to by consensus of the more than 30 Collaborating Centres of the WHO International Drug Monitoring Centre (Uppsala, Sweden). [Edwards, I.R., et al, Harmonisation in Pharmacovigilance. *Drug Safety* 10(2): 93-102, 1994.] Although those definitions can pertain to situations involving clinical investigations, some minor modifications are necessary, especially to accommodate the pre-approval, development environment.

The following definitions, with input from the WHO Collaborative Centre, have been agreed:

1. Adverse Event (or Adverse Experience)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

2. 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 products" 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 well-accepted definition of an adverse drug reaction in the post-marketing setting is found in WHO Technical Report 498 [1972] and reads as follows:

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 disease or for modification of physiological function.

The old term "side effect" has been used in various ways in the past, usually to describe negative (unfavourable) effects, but also positive (favourable) effects. It is recommended that this term no longer be used and particularly should not be regarded as synonymous with adverse event or adverse reaction.

3. Unexpected 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 medicinal product). (See section III.C.)

B. Serious Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring, consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to the significant, unexpected information they provide, justify expedited reporting.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

> The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all:

> *A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:*
>
> * *results in death,*
>
> * *is life-threatening,*
>
> *NOTE:* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
>
> * *requires inpatient hospitalisation or prolongation of existing hospitalisation,*
>
> * *results in persistent or significant disability/incapacity, or*
>
> * *is a congenital anomaly/birth defect.*

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

C. Expectedness of an Adverse Drug Reaction

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented, and a guideline is needed on how to define an event as "unexpected" or "expected" (expected/unexpected from the perspective of

previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

As stated in the definition (II.A.3.), an "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

1. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as the source document in that country. (See section III.F. and ICH Guideline for the Investigator's Brochure.)

2. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

III. STANDARDS FOR EXPEDITED REPORTING

A. What Should be Reported?

1. Single Cases of Serious, Unexpected ADRs

All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. It also applies to cases not reported directly to a sponsor or manufacturer (for example, those found in regulatory authority-generated ADR registries or in publications). The source of a report (investigation, spontaneous, other) should always be specified.

Expedited reporting of reactions which are serious but expected will ordinarily be inappropriate. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subject to *expedited* reporting.

Information obtained by a sponsor or manufacturer on serious, unexpected reports from any source should be submitted on an expedited basis to appropriate regulatory authorities if the minimum criteria for expedited reporting can be met. See section III.B.

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs. For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality.

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship," "suspected causality," or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

2. Other Observations

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgement should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:

a. For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.

b. A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.

c. A major safety finding from a newly completed animal study (such as carcinogenicity).

B. Reporting Time Frames

1. Fatal or Life-Threatening Unexpected ADRs

Certain ADRs may be sufficiently alarming so as to require very rapid notification to regulators in countries where the medicinal product or indication, formulation, or population for the medicinal product are still not approved for marketing, because such reports may lead to consideration of suspension of, or other limitations to, a clinical investigations program. Fatal or life-threatening, unexpected ADRs occurring in *clinical investigations* qualify for very rapid reporting. Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

2. All Other Serious, Unexpected ADRs

Serious, unexpected reactions (ADRs) that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

3. Minimum criteria for reporting

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met: an identifiable patient; a suspect medicinal product; an identifiable reporting source; and an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Follow-up information should be actively sought and submitted as it becomes available.

C. How to Report

The CIOMS-I form has been a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain basic information/data elements, when available, be included with any expedited report, whether in a tabular or narrative presentation. The listing in Attachment 1 addresses those data elements regarded as desirable; if all are not available at the time of expedited reporting, efforts should be made to obtain them. (See section III.B.)

All reports must be sent to those regulators or other official parties requiring them (as appropriate for the local situation) in countries where the drug is under development.

D. Managing Blinded Therapy Cases

When the sponsor and investigator are blinded to individual patient treatment (as in a double-blind study), the occurrence of a serious event requires a decision on whether to open (break) the code for the specific patient. If the investigator breaks the blind, then it is assumed the sponsor will also know the assigned treatment for that patient. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.

There are several disadvantages to maintaining the blind under the circumstances described which outweigh the advantages. By retaining the blind, placebo and comparator (usually a marketed product) cases are filed unnecessarily. When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory data bases are revised. If the event is serious, new, and possibly related to the medicinal product, then if the Investigator's Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading. Moreover, breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data.

However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it

may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.

E. Miscellaneous Issues

1. Reactions Associated with Active Comparator or Placebo Treatment

It is the sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies. Sponsors must report such events to either the manufacturer of the active control or to appropriate regulatory agencies. Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, for expedited reporting.

2. Products with More than one Presentation or Use

To avoid ambiguities and uncertainties, an ADR that qualifies for expedited reporting with one presentation of a product (e.g., a dosage form, formulation, delivery system) or product use (e.g., for an indication or population), should be reported or referenced to regulatory filings across other product presentations and uses.

It is not uncommon that more than one dosage form, formulation, or delivery system (oral, IM, IV, topical, etc.) of the pharmacologically active compound(s) is under study or marketed; for these different presentations there may be some marked differences in the clinical safety profile. The same may apply for a given product used in different indications or populations (single dose vs. chronic administration, for example). Thus, "expectedness" may be product or product-use specific, and separate Investigator's Brochures may be used accordingly. However, such documents are expected to cover ADR information that applies to all affected product presentations and uses. When relevant, separate discussions of pertinent product-specific or use-specific safety information will also be included.

It is recommended that any adverse drug reactions that qualify for expedited reporting observed with one product dosage form or use be cross referenced to regulatory records for all other dosage forms and uses for that product. This may result in a certain amount of overreporting or unnecessary reporting in obvious situations (for example, a report of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed). However, underreporting is completely avoided.

3. Post-study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

F. INFORMING INVESTIGATORS AND ETHICS COMMITTEES/ INSTITUTIONAL REVIEW BOARDS OF NEW SAFETY INFORMATION

International standards regarding such communication are discussed within the ICH GCP Guidelines, including the addendum on "Guideline for the Investigator's Brochure." In general, the sponsor of a study should amend the Investigator's Brochure as needed, and in accord with any local regulatory requirements, so as to keep the description of safety information updated.

Attachment 1

KEY DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

The following list of items has its foundation in several established precedents, including those of CIOMS-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

1. Patient Details

Initials

Other relevant identifier (clinical investigation number, for example)

Gender

Age and/or date of birth

Weight

Height

2. Suspected Medicinal Product(s)

Brand name as reported

International Non-Proprietary Name (INN)

Batch number

Indication(s) for which suspect medicinal product was prescribed or tested

Dosage form and strength

Daily dose and regimen (specify units - e.g., mg, ml, mg/kg)

Route of administration

Starting date and time of day

Stopping date and time, or duration of treatment

3. Other Treatment(s)

For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.

Start date (and time) of onset of reaction

Stop date (and time) or duration of reaction

Dechallenge and rechallenge information

Setting (e.g., hospital, out-patient clinic, home, nursing home)

Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

5. Details on Reporter of Event (Suspected ADR)

Name

Address

Telephone number

Profession (speciality)

6. Administrative and Sponsor/Company Details

Source of report: was it spontaneous, from a clinical investigation (provide details), from the literature (provide copy), other?

Date event report was first received by sponsor/manufacturer

Country in which event occurred

Type of report filed to authorities: initial or follow-up (first, second, etc.)

Name and address of sponsor/manufacturer/company

Name, address, telephone number, and FAX number of contact person in reporting company or institution

Identifying regulatory code or number for marketing authorisation dossier or clinical investigation process for the suspected product (for example IND or CTX number, NDA number)

Sponsor/manufacturer's identification number for the case (this number must be the same for the initial and follow-up reports on the same case).

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

E8(R1)

Final version

Adopted on 6 October 2021

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

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ICH HARMONISED GUIDELINE

GENERAL CONSIDERATIONS FOR CLINICAL STUDIES

E8(R1)

ICH Consensus Guideline

TABLE OF CONTENTS

1. OBJECTIVES OF THIS DOCUMENT

Clinical studies of medicinal products are conducted to provide information that can ultimately improve access to safe and effective products with meaningful impact on patients, while protecting those participating in the studies. This document provides guidance on the clinical development lifecycle, including designing quality into clinical studies, considering the broad range of clinical study designs and data sources used.

The ICH document "General Considerations for Clinical Studies" is intended to:

1. Describe internationally accepted principles and practices in the design and conduct of clinical studies that will ensure the protection of study participants and facilitate acceptance of data and results by regulatory authorities
2. Provide guidance on the consideration of quality in the design and conduct of clinical studies across the product lifecycle, including the identification, during study planning, of factors that are critical to the quality of the study, and the management of risks to those factors during study conduct
3. Provide an overview of the types of clinical studies performed during the product lifecycle, and describe study design elements that support the identification of quality factors critical to ensuring the protection of study participants, the integrity of the data, the reliability of results, and the ability of the studies to meet their objectives
4. Provide a guide to the ICH efficacy documents to facilitate user's access

General principles are described in Section 2 of this document, followed by a discussion of designing quality into clinical studies in Section 3. A broad overview of drug development planning and the information provided by different types of studies needed to progress development through the lifecycle of the product is given in Section 4. In Section 5, important elements of clinical study design are described that reflect the variety of designs used in drug development as well as the range of data sources available. Section 6 addresses study conduct, ensuring the safety of study participants, and study reporting. Some considerations for identifying factors that are critical to the quality of a study are provided in Section 7.

The ICH Efficacy guidelines are an integrated set of guidance covering the planning, design, conduct, safety, analysis, and reporting of clinical studies. ICH E8 provides an overall introduction to clinical development, designing quality into clinical studies and focusing on those factors critical to the quality of the studies. The guidelines should be considered and used in an integrated, holistic way rather than focusing on only one guideline or subsection.

For the purposes of this document, a clinical study is meant to refer to a study of one or more medicinal products in humans, conducted at any point in a product’s lifecycle, both prior to and following marketing authorisation. The focus is on clinical studies to support regulatory decisions, recognizing these studies may also inform health policy decisions, clinical practice guidelines, or other actions. The term "drug" should be considered synonymous with therapeutic, preventative, or diagnostic medicinal products. The term “drug approval” refers to obtaining marketing authorisation for the drug.

2. GENERAL PRINCIPLES

2.1 Protection of Clinical Study Participants

Important principles of ethical conduct of clinical studies and the protection of participants, including special populations, have their origins in the Declaration of Helsinki and should be observed in the conduct of all human clinical investigations. These principles are stated in other ICH guidelines, in particular, ICH E6-Good Clinical Practice.

As further described in the E6 guideline, the investigator and sponsor have responsibilities for the protection of study participants together with the Institutional Review Board/Independent Ethics Committee.

The confidentiality of information that could identify participants should be protected in accordance with the applicable regulatory and legal requirement(s).

Before initiating a clinical study, sufficient information should be available to ensure that the drug is acceptably safe for the planned study in humans. Emerging non-clinical, clinical, and pharmaceutical quality data should be reviewed and evaluated, as they become available, by qualified experts to assess the potential implications for the safety of study participants. Ongoing and future studies should be appropriately adjusted as needed, to take new knowledge into consideration and to protect study participants. Throughout drug development, care should be taken to ensure all study procedures and assessments are necessary from a scientific viewpoint and do not place undue burden on study participants.

2.2 Scientific Approach in Clinical Study Design, Planning, Conduct, Analysis, and Reporting

The essence of clinical research is to ask important questions and answer them with appropriate studies. The primary objectives of any study should reflect the research questions and be clear and explicitly stated. Clinical studies should be designed, planned, conducted, analysed, and reported according to sound scientific principles to achieve their objectives.

Quality of a clinical study is considered in this document as fitness for purpose. The purpose of a clinical study is to generate reliable information to answer the research questions and support decision making while protecting study participants. The quality of the information generated should therefore be sufficient to support good decision making.

Quality by design in clinical research sets out to ensure that the quality of a study is driven proactively by designing quality into the study protocol and processes. This involves the use of a prospective, multidisciplinary approach to promote the quality of protocol and process design in a manner proportionate to the risks involved, and clear communication of how this will be achieved.

Across the product lifecycle, different types of studies will be conducted with different objectives and designs and may involve different data sources. For purposes of this guideline, development planning is considered to cover the entire product lifecycle (Section 4). The Annex provides a broad categorisation of study type by objective within the different stages of drug development. Studies should be rigorously designed to address the study objectives with

careful attention to the design elements, such as the choice of study population and response variables and the use of methods to minimize biases in the findings (Section 5).

The cardinal logic behind serially conducted studies is that the results of prior studies should inform the plan of later studies. Emerging data will frequently prompt a modification of the development strategy. For example, results of a confirmatory study may suggest a need for additional human pharmacology studies.

The availability of multi-regional data as a result of the increased globalisation of drug development programmes, facilitated by the harmonisation of ICH Guidelines, minimises the need to conduct individual studies in different regions. The results of a study are often used in regulatory submissions in multiple regions, and the design should also consider the relevance of the study results for regions other than the one(s) in which the study is conducted. Further guidance is provided by ICH E5 Ethnic Factors, ICH E6, and ICH E17 Multi-Regional Clinical Trials.

Early engagement with regulatory authorities to understand local/regional requirements and expectations is encouraged and will facilitate the ability to design quality into the study.

2.3 Patient Input into Drug Development

Consulting with patients and/or patient organisations during drug development can help to ensure that patients' perspectives are captured. The views of patients (or of their caregivers/parents) can be valuable throughout all phases of drug development. Involving patients early in the design of a study is likely to increase trust in the study, facilitate recruitment, and promote adherence. Patients also provide their perspective of living with a condition, which may contribute to the determination, for example, of endpoints that are meaningful to patients, selection of the appropriate population and duration of the study, and use of acceptable comparators. This ultimately supports the development of drugs that are better tailored to patients' needs.

3. DESIGNING QUALITY INTO CLINICAL STUDIES

The quality by design approach to clinical research (Section 3.1) involves focusing on critical to quality factors to ensure the protection of the rights, safety, and wellbeing of study participants, the generation of reliable and meaningful results, and the management of risks to those factors using a risk-proportionate approach (Section 3.2). The approach is supported by the establishment of an appropriate framework for the identification and review of critical to quality factors (Section 3.3) at the time of design and planning of the study, and throughout its conduct, analysis, and reporting.

3.1 Quality by Design of Clinical Studies

Quality is a primary consideration in the design, planning, conduct, analysis, and reporting of clinical studies and a necessary component of clinical development programmes. The likelihood that a clinical study will answer the research questions while preventing important errors can be dramatically improved through prospective attention to the design of all components of the study protocol, procedures, associated operational plans and training. Activities such as document and data review and monitoring, where conducted retrospectively, are an important part of a quality assurance process; but, even when combined with audits, they are not sufficient to ensure quality of a clinical study.

Good planning and implementation of a clinical study also derive from attention to the design elements of clinical studies as described in Section 5, such as:

- the need for clear pre-defined study objectives that address the primary scientific question(s);
- selection of appropriate participants that have the disease, condition, or molecular/genetic profile that is being studied;
- use of approaches to minimise bias, such as randomisation, blinding or masking, and/or control of confounding;
- endpoints that are well-defined, measurable, clinically meaningful, and relevant to patients.

Operational criteria are also important, such as ensuring a clear understanding of the feasibility of the study, selection of suitable investigator sites, quality of specialised analytical and testing facilities and procedures, and processes that ensure data integrity.

3.2 Critical to Quality Factors

A basic set of factors relevant to ensuring study quality should be identified for each study. Emphasis should be given to those factors that stand out as critical to study quality. These critical to quality factors are attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results. These quality factors are considered to be critical because, if their integrity were to be undermined by errors of design or conduct, the reliability or ethics of decision-making based on the results of the study would also be undermined. Critical to quality factors should also be considered holistically, so that dependencies among them can be identified. Section 7 of this document provides considerations that can help identify critical to quality factors for a study.

The design of a clinical study should reflect the state of knowledge and experience with the drug; the condition to be treated, diagnosed or prevented; the underlying biological mechanism (of both the condition and the treatment); and the population for which the drug is intended. As research progresses, knowledge increases and uncertainties about the pharmacology, safety and efficacy of a drug decrease. Knowledge of the drug at any point in development will continually inform the identification of critical to quality factors and control processes used to manage them.

The sponsor and other parties designing quality into a clinical study should identify the critical to quality factors. Having identified those factors, it is important to determine the risks that threaten their integrity and decide whether they can be accepted or should be mitigated, based on their probability, detectability and impact. Where it is decided that risks should be mitigated, the necessary control processes should be put in place and communicated, and the necessary actions taken to mitigate the risks. The term risk is used here in the context of general risk management methodology applicable to all factors of a study.

Proactive communication of the critical to quality factors and risk mitigation activities will support understanding of priorities and resource allocation by the sponsor and investigator sites. Proactive support (e.g., training to site staff, relevant to their role, and description of critical to quality factors and potential mitigation measures in the protocol) will enhance correct

implementation of study protocol, procedures, and associated operational plans and process design.

Perfection in every aspect of an activity is rarely achievable or can only be achieved by use of resources that are out of proportion to the benefit obtained. The quality factors should be prioritised to identify those that are critical to the study, at the time of the study design, and study procedures should be proportionate to the risks inherent in the study and the importance of the information collected. The critical to quality factors should be clear and should not be cluttered with minor issues (e.g., due to extensive secondary objectives or processes/data collection not linked to the proper protection of the study participants and/or primary study objectives).

3.3 Approach to Identifying the Critical to Quality Factors

A key aspect of a quality approach to study design is to ask whether the objectives being addressed by the study are clearly articulated; whether the study is designed to meet the research question it sets out to address; whether these questions are meaningful to patients; and whether the study hypotheses are specific and scientifically valid. The approach to the identification of the critical to quality factors should consider whether those objectives can be met, well and most efficiently, by the chosen design and data sources. Patient consultation early in the study design process can contribute to this approach and ultimately help to identify the critical to quality factors. Study designs should be operationally feasible and avoid unnecessary complexity. Protocols and case report forms/data collection methods should enable the study to be conducted as designed and avoid unnecessary data collection.

Identification of critical to quality factors will be enhanced by approaches that include the following elements:

3.3.1 Establishing a Culture that Supports Open Dialogue

Creating a culture that values and rewards critical thinking and open, proactive dialogue about what is critical to quality for a particular study or development programme, going beyond sole reliance on tools and checklists, is encouraged. Open dialogue can facilitate the development of innovative methods for ensuring quality.

Inflexible, “one size fits all” approaches should be discouraged. Standardised operating procedures are necessary and beneficial for conducting good quality clinical studies, but study specific strategies and actions are also needed to effectively and efficiently support quality in a study.

Evidence used to inform the study design should be gathered and reviewed, before and during the study, in a transparent manner, while acknowledging gaps in data and conflicting data, where present and known, and anticipating the possible emergence of such gaps or conflicts.

3.3.2 Focusing on Activities Essential to the Study

Efforts should be focused on activities that are essential to the reliability and meaningfulness of study outcomes for patients and public health, and the safe, ethical conduct of the study for participants. Consideration should be given to eliminating nonessential activities and data collection from the study to increase quality by simplifying conduct, improving study

efficiency, and targeting resources to critical areas. Resources should be deployed to identify and prevent or control errors that matter.

3.3.3 Engaging Stakeholders in Study Design

Clinical study design is best informed by input from a broad range of stakeholders, including patients and healthcare providers. It should be open to challenge by subject matter experts and stakeholders from outside, as well as within, the sponsor organisation.

The process of building quality into the study may be informed by participation of those directly involved in successful completion of the study such as clinical investigators, study coordinators and other site staff, and patients/patient organisations. Clinical investigators and potential study participants have valuable insights into the feasibility of enrolling participants who meet proposed eligibility criteria, whether scheduled study visits and procedures may be overly burdensome and lead to early dropouts, and the general relevance of study endpoints and study settings to the targeted patient population. They may also provide insight into the value of a treatment in the context of ethical issues, culture, region, demographics, and other characteristics of subgroups within a targeted patient population.

Early engagement with regulatory authorities is encouraged, particularly when a study has novel elements considered critical to quality (e.g., defining patient populations, procedures, or endpoints).

3.3.4 Reviewing Critical to Quality Factors

Accumulated experience and knowledge, together with periodic review of critical to quality factors should be used to determine whether adjustments to risk control mechanisms are needed, because new or unanticipated issues may arise once the study has begun.

Studies with adaptive features and/or interim decision points need specific attention during proactive planning and ongoing review of critical to quality factors, and risk management (ICH E9 Statistical Principles for Clinical Trials).

3.3.5 Critical to Quality Factors in Operational Practice

The foundation of a successful study is a protocol that is both scientifically sound and operationally feasible. A feasibility assessment involves consideration of study design and implementation elements that could impact the successful completion of clinical development from an operational perspective.

Feasibility considerations also include but are not limited to regional differences in medical practice and patient populations, the availability of qualified investigators/site personnel with experience in conducting a clinical study (ICH E6), availability of equipment and facilities required to successfully conduct the study, availability of the targeted patient population, and ability to enrol a sufficient number of participants to meet the study objectives. The retention and follow up of study participants are also key critical to quality factors. Consideration of these and other critical to quality factors relating to study feasibility can inform study design and enhance quality implementation.

4. DRUG DEVELOPMENT PLANNING

This section provides general principles to consider in drug development planning. Drug development planning adheres to the principles of scientific research and good study design that ensure the reliability and interpretability of results. Efficient drug development includes appropriately planned interactions with regulatory authorities throughout development to ensure alignment with requirements for product quality and to support approval in the condition or disease, including possible post-approval studies to address remaining questions. Throughout this process there is critical attention to the protection of the rights, safety and wellbeing of study participants.

Drug development planning builds on knowledge acquired throughout the investigational process to reduce levels of uncertainty as the process moves from target identification through non-clinical and clinical evaluation. Such planning encompasses quality of medicinal product, including chemistry, manufacturing and controls (CMC), and non-clinical and clinical studies (pre and post-approval). Modelling and simulation may inform drug development throughout the process. Planning may also include regional considerations for product introduction into the market, such as health technology assessments.

It is important to ensure that the experiences, perspectives, needs, and priorities of relevant stakeholders relating to the development and evaluation of the drug throughout its lifecycle are captured and meaningfully incorporated into drug development planning.

Clinical development may also feature requirements for co-development of validated biomarkers, diagnostic testing, or devices that facilitate the safe and effective use of a drug.

The types of studies that may contribute to drug development are described in subsections 4.2 and 4.3 and summarised in the Annex.

4.1 Quality of Investigational Medicinal Product

Ensuring adequate quality and characterisation of physicochemical properties of investigational medicinal product is an important element in planning a drug development programme and is addressed in ICH and regional quality guidelines. More extensive characterisation may be required for complex or biological products. Formulations should be well characterised in the drug development plan, including information on bioavailability, wherever feasible, and should be appropriate for the stage of drug development and the targeted patient population. Age-appropriate formulation development may be a consideration when clinical studies are planned in paediatric populations (ICH E11- E11A Clinical Trials in Pediatric Population).

Evaluation of the quality of a drug may extend to devices required for its administration or a companion diagnostic to identify the targeted population.

Changes in a product during development should be supported by comparability data to ensure the ability to interpret study results across the development programme. This includes establishing links between formulations through bioequivalence studies or other means.

4.2 Non-Clinical Studies

Guidance on non-clinical safety studies is provided in ICH M3 Nonclinical Safety Studies, ICH Safety (S) Guidelines and related Q&A documents, as well as in regional guidance. The non-clinical assessment usually includes toxicology, carcinogenicity, immunogenicity, pharmacology, pharmacokinetics, and other evaluations to support clinical studies (and may encompass evidence generated in *in vivo* and *in vitro* models, and by modelling and simulation). The scope of non-clinical studies, and their timing with respect to clinical studies, depend on a variety of factors that inform further development, such as the drug's chemical or molecular properties; pharmacological basis of principal effects (mechanism of action); route(s) of administration; absorption, distribution, metabolism, and excretion (ADME); physiological effects on organ systems; dose/concentration-response relationships; metabolites; and duration of action and use. Use of the drug in special populations (e.g., pregnant or breast-feeding women, children) may require additional non-clinical assessments. Guidance for non-clinical safety studies to support human clinical studies in special populations should be reviewed (see, e.g., ICH S5 Reproductive Toxicology, S11 Nonclinical Paediatric Safety, and M3).

Assessment of the preclinical characteristics, including physiological and toxicological effects of the drug, serve to inform clinical study design and planned use in humans. Before proceeding to studies in humans there should be sufficient non-clinical information to support initial human doses and duration of exposure.

4.3 Clinical Studies

Clinical drug development, defined as studying the drug in humans, is conducted in a sequence that builds on knowledge accumulated from non-clinical and previous clinical studies. The structure of the drug development programme will be shaped by many considerations and comprised of studies with different objectives, different designs, and different dependencies. The Annex provides an illustrative list of example studies and their objectives. Although clinical drug development is often described as consisting of four temporal phases (phases 1-4), it is important to appreciate that the phase concept is a description and not a requirement, and that the phases of drug development may overlap or be combined.

To develop new drugs efficiently, it is essential to identify their characteristics in the early stages of development and to plan an appropriate development programme based on this profile. Initial clinical studies may be more limited in size and duration to provide an early evaluation of short-term safety and tolerability as well as proof of concept of efficacy. These studies may provide pharmacodynamic, pharmacokinetic, and other information needed to choose a suitable dosage range and/or administration schedule to inform further clinical studies. As more information is known about the drug, clinical studies may expand in size and duration, may include more diverse study populations, and may include more secondary endpoints in addition to the primary measures of efficacy. Throughout development, new data may suggest the need for additional studies.

The use of biomarkers has the potential to facilitate the availability of safer and more effective drugs, to guide dose selection, and to enhance a drug's benefit-risk profile (see ICH E16 Qualification of Genomic Biomarkers) and may be considered throughout drug development. Clinical studies may evaluate the use of biomarkers to better target patients more likely to

benefit and less likely to experience adverse reactions, or as intermediate endpoints that could predict clinical response.

The following subsections describe the types of studies that typically span clinical development from the first studies in humans through late development and post-approval.

4.3.1 Human Pharmacology

The protection of study participants should always be the first priority when designing early clinical studies, especially for the initial administration of an investigational product to humans (usually referred to as phase 1). These studies may be conducted in healthy volunteer participants or in a selected population of patients who have the condition or the disease, depending on drug properties and the objectives of the development programme.

These studies typically address one or a combination of the following aspects:

4.3.1.1 Estimation of Initial Safety and Tolerability

The initial and subsequent administration of a drug to humans is usually intended to determine the tolerability of the dose range expected to be evaluated in later clinical studies and to determine the nature of adverse reactions that can be expected. These studies typically include both single and multiple dose administration.

4.3.1.2 Pharmacokinetics

Characterisation of a drug's absorption, distribution, metabolism, and excretion continues throughout the development programme, but the preliminary characterisation is an essential early goal. Pharmacokinetic studies are particularly important to assess the clearance of the drug and to anticipate possible accumulation of parent drug or metabolites, interactions with metabolic enzymes and transporters, and potential drug-drug interactions. Some pharmacokinetic studies are commonly conducted in later phases to answer more specialised questions. For orally administered drugs, the study of food effects on bioavailability is important to inform the dosing instructions in relation to food. Obtaining pharmacokinetic information in sub-populations with potentially different metabolism or excretion, such as patients with renal or hepatic impairment, geriatric patients, children, and ethnic subgroups should be considered (ICH E4 Dose-Response Studies, E7 Clinical Trials in Geriatric Population, E11, and E5, respectively).

4.3.1.3 Pharmacodynamics & Early Measurement of Drug Activity

Depending on the drug and the endpoint of interest, pharmacodynamic studies and studies relating drug levels to response (PK/PD studies) may be conducted in healthy volunteer participants or in patients with the condition or disease. If there is an appropriate measure, pharmacodynamic data can provide early estimates of activity and efficacy and may guide the dosage and dose regimen in later studies.

4.3.2 Exploratory and Confirmatory Safety and Efficacy Studies

After initial clinical studies provide sufficient information on safety, clinical pharmacology and dose, exploratory and confirmatory studies (usually referred to as phases 2 and 3, respectively) are conducted to further evaluate both the safety and efficacy of the drug. Depending on the nature of the drug and the patient population, this objective may be combined in a single or

small number of studies. Exploratory and confirmatory studies may use a variety of study designs depending on the objective of the study.

Exploratory studies are designed to investigate safety and efficacy in a selected population of patients for whom the drug is intended. Additionally, these studies aim to refine the effective dose(s) and regimen, refine the definition of the targeted population, provide a more robust safety profile for the drug, and include evaluation of potential study endpoints for subsequent studies. Exploratory studies may provide information on the identification and determination of factors that affect the treatment effect and, possibly combined with modelling and simulation, serve to support the design of later confirmatory studies.

Confirmatory studies are designed to confirm the preliminary evidence accumulated in earlier clinical studies that a drug is safe and effective for use for the intended indication and recipient population. These studies are often intended to provide an adequate basis for marketing approval, and to support adequate instructions for use of the drug and official product information. They aim to evaluate the drug in participants with or at risk of the condition or disease who represent those who will receive the drug once approved. This may include investigating subgroups of patients with frequently occurring or potentially relevant co-morbidities (e.g., cardiovascular disease, diabetes, hepatic and renal impairment) to characterise the safe and effective use of the drug in patients with these conditions.

Confirmatory studies may evaluate the efficacy and safety of more than one dose or the use of the drug in different stages of disease or in combination with one or more other drugs. If the intent is to administer a drug for a long period of time, then studies involving extended exposure to the drug should be conducted (ICH E1 Clinical Safety for Drugs used in Long-Term Treatment). Irrespective of the intended duration of administration, the duration of effect of the drug will also inform the duration of follow-up.

Study endpoints selected for confirmatory studies should be clinically relevant and reflect disease burden or be of adequate surrogacy for predicting disease burden or sequelae.

4.3.3 Special Populations

Some groups in the general population require additional investigation during drug development because they have unique risk/benefit considerations, or because they can be anticipated to need modification of the dose or schedule of a drug. ICH E5 and E17 provide a framework for evaluating the impact of ethnic factors on a drug's effect. Particular attention should be paid to the ethical considerations related to informed consent in vulnerable populations (ICH E6 and E11). Studies in special populations may be conducted during any phase of development to understand the drug effects in these populations. Some considerations of special populations are the following:

4.3.3.1 Investigations in pregnant women

Investigation of drugs that may be used in pregnancy is important. Where pregnant women volunteer to be enrolled in a clinical study, or a participant becomes pregnant while participating in a clinical study, follow-up evaluation of the pregnancy and its outcome and the reporting of outcomes are necessary.

4.3.3.2 Investigations in lactating women

Excretion of the drug or its metabolites into human milk should be examined where applicable and feasible. When nursing mothers are enrolled in clinical studies their babies are usually also monitored for the effects of the drug.

4.3.3.3 Investigations in children

ICH E11 provides an outline of critical issues in paediatric drug development and approaches to the safe, efficient, and ethical study of drugs in paediatric populations.

4.3.3.4 Investigations in geriatric populations

ICH E7 provides an outline of critical issues in developing drugs for use in geriatric populations and approaches to their safe, efficient, and ethical study.

4.3.4 Post-Approval Studies

After the approval of a drug, additional studies may be conducted to further understand the safety and efficacy of the drug in its approved indication (usually referred to as phase 4). These are studies that were not considered necessary for approval but are often important for optimising the drug's use. They may be of any type but should have valid scientific objectives. Post-approval studies may be conducted to address a regulatory requirement.

Post-approval studies may be performed to provide additional information on the efficacy, safety, and use of the drug in populations more diverse than included in the studies conducted prior to marketing authorisation. Studies with long-term follow-up or with comparisons to other treatment options or standards of care may provide important information on safety and efficacy. Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies and studies designed to support use under the approved indication (e.g., mortality/morbidity studies, epidemiological studies). These studies may explore use of the drug in the real-world setting of clinical practice and may also inform health economics and health technology assessments.

4.4 Additional Development

After initial approval, drug development may continue with studies of new or modified indications in new patient populations, new dosage regimens, or new routes of administration. If a new dose, formulation, or combination is studied, additional non-clinical and/or human pharmacology studies may be indicated. Data from previous studies or from clinical experience with the approved drug may inform these programmes.

5. DESIGN ELEMENTS AND DATA SOURCES FOR CLINICAL STUDIES

Study objectives impact the choice of study design and data sources, which in turn impact the strength of a study to support regulatory decisions and clinical practice. As discussed in Section 4, there are a wide variety of study objectives in drug development. Similarly, there is a wide range of study designs and data sources to address these objectives. Sections 5.1 through 5.6 discuss key elements that may be used to define the study design, and Section 5.7 discusses the various data sources that may be used for the study.

Clear objectives will help to specify the study design, and conversely, the process of specifying the design may help to further clarify the objectives. At the design stage, the objectives may

need to be modified if substantial practical considerations and limitations or other risks to critical to quality factors are identified. The study objectives are further refined through specification of estimands. Estimands, discussed in ICH E9(R1) Addendum: Statistical Principles for Clinical Trials, provide a precise description of the treatment effects reflecting the clinical questions posed by the study objectives. The estimand summarises at a population level what the outcomes would be in the same patients under the different treatment conditions being compared.

An important distinction between studies is whether the allocation of individuals to the study drug(s) is controlled by the study procedures or allocation to the drug is not controlled but exposure to the drug(s) is observed in the study. In this document, the former case is referred to as an interventional study and the latter case is referred to as an observational study.

Interventional studies, and in particular randomised studies, play a central role in drug development, as they can better control biases. The designs of randomised studies range from simple parallel group designs to more complex variants. For example, adaptive design studies allow prospectively planned modifications to the study, such as changes in the population studied or changes in doses of the drug studied over the course of the study, based on accumulating data. Master protocol studies allow for the investigation of multiple drugs or multiple conditions under a shared framework. Platform studies allow for multiple drugs to be investigated in a continuous manner, with different drugs entering the study at different times and leaving the study based on pre-specified decision rules.

Studies without randomisation (whether interventional or observational) can play a role as well in certain settings when randomisation is not feasible. Observational studies are often conducted post-approval but can be of utility as complementary sources of evidence during development and across the life cycle of a drug.

Along with the breadth of study designs, there are multiple sources of data that studies may employ. Traditionally, studies have used study-specific data collection processes. Data such as that obtained from electronic medical records or digital health technologies may be leveraged to increase the efficiency of studies or generalisability of study results.

This section presents important elements that define the design of a clinical study including population, treatment, control group, response variable, methods to reduce bias, statistical analysis, and data sources. It is intended to assist in identifying the critical to quality factors necessary to achieve the study objectives, while also enabling flexibility in study design and promoting efficiency in study conduct. Although the focus is on interventional studies, the discussion is intended to apply to both interventional and observational studies. The elements outlined here are expected to be relevant to study types and data sources that are used in clinical studies now and that may be developed in the future.

5.1 Study Population

The population to be studied should be chosen to support the study objectives and is defined through the inclusion and exclusion criteria for the study. The degree to which a study succeeds in enrolling the desired population will impact the ability of the study to meet its objectives.

The study population may be narrowly defined to reduce the risk to study participants or to maximise the sensitivity of the study for detecting a certain effect. Conversely, it may be broadly defined to more closely represent the diverse populations for which the drug is intended. In general, studies conducted early in a development programme, when little is known about the safety of the drug, are more homogeneous in study population definitions. Studies conducted in the later phases of drug development or post-approval are often more heterogeneous in study population definitions. Such studies should involve participants who are representative of the diverse populations which will receive the intervention in clinical practice. Available knowledge about participant characteristics that may predict disease outcomes or effects of the intervention can be used to further define the study population.

The number of participants (sample size) in a study should be large enough to provide a reliable answer to the questions addressed (see ICH E9). This number is usually determined by the primary objective of the study. If the sample size is determined on some other basis, then this should be made clear and justified. For example, a sample size determined to address safety questions or meet important secondary objectives may need larger numbers of participants than needed for addressing the primary efficacy question (see ICH E1). If study objectives include obtaining information on certain subgroups, then efforts should be made to ensure adequate representation of these subgroups.

5.2 Treatment Description

The treatment(s), including controls, under study should be described explicitly and specifically. These might be individual treatments (including different doses or regimens), combinations of treatments, or no treatments, and can include specification of background treatments. The definition of treatments should align with the objectives of the study (ICH E9(R1)). For example, if the objective of the study is to understand the effect of the treatment in clinical practice, the study may specify that the background treatment, if any, is up to the discretion of the participants and healthcare providers. If the objectives are to understand the effect of the drug when added to a specific background treatment, the background treatment should be defined explicitly and specifically for all groups including controls.

5.3 Choice of Control Group

The major purpose of a control group is to separate the effect of the treatment(s) from the effects of other factors such as natural course of the disease, other medical care received, or observer or patient expectations (E10 Choice of Control Group in Clinical Trials). The treatment effect of interest may be the effect relative to not receiving the drug or the effect relative to receiving other therapies. Comparisons may be made with placebo, no treatment, standard of care, other treatments, or different doses of the drug under investigation.

The source of control group data may be internal or external to the study. The intent of using an internal control group is to help ensure that the only differences between treatment groups are due to the treatment they receive and not due to differences in the selection of participants, the timing and measurement of study outcomes, or other differences. A special case of an internal control group is when each participant serves as their own internal control by receiving the drug and control at different points of time. With use of an external control group, individuals are selected from an external source, and the individuals may have been treated at an earlier time (historical control group) or during the same time but in another setting than participants in the study.

Important limitations of the use of external controls are discussed in ICH E10. Particular care is needed to minimise the likelihood of erroneous inference. The use of an external control requires that the disease course is well known and predictable. External control individuals may differ from study participants with respect to demographic and background characteristics (e.g., medical history, concurrent diseases). In addition, external control individuals may differ from participants in the study with respect to concurrent care and the measurement of study outcomes and other data elements. Because the use of internal controls generally mitigates the potential for bias better than external controls, particularly in conjunction with randomisation, the suitability of the use and choice of external control should be carefully considered and justified. Section 5.5 discusses the sources of bias which can arise in observational studies and is relevant to the use of external controls.

Participant level data may not be available for some choices of external control groups. Summary measures may be available to form the basis of comparisons with treated participants to estimate drug effects and test hypotheses about those effects. There is, however, less ability to control for differences in characteristics between study individuals in the external control group and study participants in the internal treatment groups in making these comparisons or examining the quality and completeness of individual data elements. Additionally, there may not be the ability to examine subgroups or modify the response variable to be consistent with the response variable used in the study.

5.4 Response Variables

A response variable is an attribute of interest that may be affected by the drug. The response variable may relate to pharmacokinetics, pharmacodynamics, efficacy, or safety of the drug, or to the use of the drug including, for example, in adherence to risk minimisation measures post-approval. Study endpoints are the response variables that are chosen to assess drug effects.

The primary endpoint should be capable of providing clinically relevant and convincing evidence related to the primary objective of the study (ICH E9). Secondary endpoints are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives. Exploratory endpoints are used to further explain or to support study findings or to explore new hypotheses for later research. The choice of endpoints should be meaningful for the intended population and may also take into account the views of patients. The definition of each study endpoint should be specific and include how and at what time points in a participant's treatment course of the drug and follow-up it is ascertained.

Knowledge of the drug, along with the clinical context and purpose of a given study affect what response variables should be collected. For example, a proof-of-concept study of relatively short duration may employ a pharmacodynamic outcome rather than the outcome of primary interest (ICH E9). A larger study of longer duration could then be used to confirm a clinically meaningful effect on the outcome of primary interest. In other cases, such as a study where the safety profile of the drug is well characterised, the extent of safety data collection may be tailored to the objectives of the study.

5.5 Methods to Reduce Bias

The study design should address potential sources of bias that can undermine the reliability of results. Although different types of studies are subject to different sources of bias, this section

addresses some common sources. ICH E9 discusses principles for controlling and reducing bias mainly in the context of interventional studies.

In studies with internal control groups**,** randomisation is used to ensure comparability of treatment groups, thereby minimising the possibility of bias in treatment assignment.

Randomisation at the start of the study addresses differences between the groups at the time of randomisation but does not prevent bias due to differences arising during the study. Events after randomisation (particularly intercurrent events (ICH E9(R1)) may affect the validity and interpretation of comparisons between treatment groups. Examples include treatment discontinuation or use of rescue medications. There may also be differences in the follow-up patterns between the groups due to participants in one group discontinuing the study at different rates, because of, for example, adverse events or perceived lack of efficacy. Careful consideration of the potential for intercurrent events to occur during the study and their impact will help with the identification of critical to quality factors, such as reducing study discontinuation, continuing data collection following treatment discontinuation, and retrieving data after study discontinuation, if appropriate. It is important when defining the treatment effect (estimand) to account for the occurrence of intercurrent events.

Concealing the treatment assignments (blinding) limits the occurrence of conscious or unconscious bias in the conduct and interpretation of a clinical study that may affect the course of treatment, monitoring, endpoint ascertainment, and participants' responses. In a single-blind study the investigator is aware of the treatment, but the participant is not. When the investigators who are involved in the treatment or clinical evaluation of the participants are also unaware of the treatment assignments, the study is referred to as double-blind. In an open-label study, the consequences of the lack of blinding may be reduced through the use of pre-specified decision rules for aspects of study conduct, such as recruitment, treatment assignment, participant management, safety reporting, and response variable ascertainment. Blinding for staff at the study sites or sponsor should be implemented where feasible.

Knowledge of interim results (whether individual or treatment group level) has the potential to introduce bias or influence the conduct of the study and interpretation of study results. Specific considerations related to information flow and confidentiality are therefore necessary.

Observational studies introduce unique challenges to the assessment and control of bias. These include ensuring that the individuals have the condition under study and ensuring comparability between treatment groups, in prognostic factors associated with the choice of therapies, in the ascertainment of response variables, and in post-baseline concomitant patient care. These challenges may also exist with the use of external controls in an interventional study. Methods exist that may mitigate some of these challenges and should be considered during the design phase.

5.6 Statistical Analysis

The statistical analysis of a study encompasses important elements necessary to achieving the study objectives. The specification and documentation of the statistical analysis are important for ensuring the integrity of the study findings. The principal features of the statistical analysis should be planned during the design of the study and should be clearly specified in a protocol written before the study begins (ICH E9). Full details of the planned statistical analysis should be specified and documented before knowledge of the study results that may reveal the drug

effects, which may be accomplished using a separate statistical analysis plan. The protocol should define the estimand(s) following the framework established in ICH E9(R1).

Statistical analyses of primary and secondary endpoints that address key study objectives with respect to both efficacy and safety should be described in the protocol, including any interim analyses and/or planned design adaptations. Other statistical aspects of the study that should be described in the protocol include the analytical methods for any planned estimation and tests of hypotheses about the drug effect and a justification of the sample size.

The statistical analysis should include pre-specified sensitivity analyses for assessing the impact of the assumptions made for the primary and important secondary analyses on the results of the study (E9(R1)). For example, if the analysis relies on a particular assumption about the reasons for missing data, sensitivity analyses should be planned to assess the impact of that assumption on the study results. In the case of observational studies, sensitivity analyses might, for example, consider additional potential confounders.

For double-blind studies, the statistical analysis should be finalised before treatment assignments are revealed. Therefore, if a study includes one or more interim analyses, the planned statistical analysis should not be changed after an interim analysis that involves unblinding. For open-label and single-blind studies, details pertaining to the primary and important secondary analyses would ideally be finalised before the first participant is randomised or allocated to study intervention.

Pre-specification of the analysis approach is particularly important for studies that make use of existing data sources rather than primary data collection (Section 5.7), not only for the statistical analysis planned for the study but also for any feasibility analysis to assess the applicability of the existing data. For example, for a single-arm interventional study with an external control, the specifics of the external control should be defined prior to the conduct of the interventional aspect of the study. Pre-specification of the analysis should be in place so that any review of the existing data sources prior to the design of the study does not threaten the study integrity.

The statistical analysis should be carried out in accordance with the prospectively defined analysis plan, and all deviations from the plan should be indicated in the study report (E3 Clinical Study Reports).

5.7 Study Data

Study data comprise all information generated, collected, or used in the context of the study ranging from existing source data to study-specific assessments. The study data should contain the necessary information to conduct the statistical analysis specified in the protocol and statistical analysis plan, as well as to monitor for participant safety, protocol adherence, and data integrity.

Study data can be broadly classified into two types: (1) data generated specifically for the present study (primary data collection) and (2) data obtained from sources external to the present study (secondary data use). Data generated for the study may be collected via case report forms, laboratory measurements, electronic patient reported outcomes, or mobile health tools. Examples of external sources of data include historical clinical studies, national death

databases, disease and drug registries, claims data, and medical and administrative records from routine medical practice. A study may make use of both types of data.

For all data sources, procedures to ensure the protection of personal data of the individuals being studied should be implemented. The study protocol, and if applicable the informed consent, should explicitly address the protection of personal data. Regulations related to protection of individuals' data need to be followed. When considering data from external sources, it is important to ascertain whether the regulatory authorities accept the use of such data for purposes other than the original intent.

Study data should be of sufficient quality to address the objectives of the study and, in interventional studies, to monitor participant safety. Data quality attributes include consistency (uniformity of ascertainment over time), accuracy (correctness of collection, transmission, and processing), and completeness (lack of missing information). These aspects should be proactively considered during study planning by identifying the factors, critical to the quality of the study, associated with data sourcing, collection, and processing.

The use of standards for data recording and coding (or recoding) is important to support data reliability, facilitate correct analysis and interpretation of results, and promote data sharing. Internationally accepted data standards exist for many sources of study data and should be used where applicable.

With primary data collection, the methods and standards established for use at the point of capture and the subsequent processing provide an opportunity to prospectively ensure the quality of the data.

With secondary data use, the relevance of the available data should be considered and clearly described in the study protocol. For example, when using existing electronic health record data to ascertain the study endpoint rather than through primary data collection, information in the health record about outcomes may need to be converted to the study endpoint.

In some cases, secondary data use may not be sufficient for all aspects of the study and may need to be supplemented by primary data collection. The quality of data collected for a different purpose should be evaluated when re-used in the context of the present study. Careful quality control processes may have been applied during their acquisition; where used, those processes were not necessarily designed with the objectives of the present study in mind.

There are several additional considerations with secondary data use. For example, methods to conceal the treatment should be considered when selecting and prior to analysing data from external sources. As another example, absence of affirmative information on a condition or event does not necessarily mean the condition or event is not present. There may also be a delay between the occurrence of events and their appearance in existing data sources. To the extent possible, uncertainties and potential sources of bias should be addressed at the study design stage, during data analysis, and in the interpretation of the study results.

6. CONDUCT, SAFETY MONITORING, AND REPORTING

6.1 Study Conduct

The principles and approaches set out in this guideline, including those of quality by design, should inform the approach taken to the conduct and reporting of clinical studies. Risk proportionate mitigation measures should be employed to ensure the integrity of the critical to quality factors.

6.1.1 Protocol Adherence

Adherence to the study protocol and other relevant documents is essential, and many aspects of adherence should be considered among the study's critical to quality factors. Successful application of the quality by design principles may minimise the need for modifications to the protocol and make adherence throughout the study more likely. If modification of the protocol becomes necessary, a clear description of the rationale for the modification should be provided in a protocol amendment, and the impact of the modification on study conduct should be carefully considered.

6.1.2 Training

Individuals involved in study conduct should receive training commensurate with their role in the study and this training should occur prior to their becoming involved in the study. Updated training or retraining may be needed to address issues related to critical to quality factors observed during the course of the study, and/or implement protocol modifications.

6.1.3 Data Management

The manner and timelines in which study data are collected and managed are critical contributors to overall study data quality. Operational checks, centralised data monitoring, and statistical surveillance can identify important data quality issues for corrective action. Data management procedures should account for the diversity of data sources in use for clinical studies (Section 5.7). For interventional clinical studies, further guidance on data management is available in ICH E6.

6.1.4 Access to Interim Data

Inappropriate access to data during the conduct of the study may compromise study integrity (Sections 5.5 and 5.6 and ICH E9). In studies with planned interim analyses, special attention should be given to which individuals have access to the data and results. Even in studies without planned interim analyses, special attention should be paid to any ongoing monitoring of unblinded data to avoid inappropriate access.

6.2 Participant Safety during Study Conduct

Important standards of ethical conduct and the protection of participants in clinical studies are described in Section 2.1. This section describes safety related considerations during the conduct of the study.

6.2.1 Safety Monitoring

The goals of safety monitoring are to protect study participants and to characterise the safety profile of the drug. Procedures and systems for the identification, monitoring, and reporting of safety concerns during the study should be clearly specified. The approach should reflect the

type and objectives of the study, the risks to the study participants and what is known about the drug and the study population. Guidance is available on reporting of safety data to appropriate authorities and on the content and timing of safety reports (ICH E2A-E2F Pharmacovigilance, and, for interventional clinical trials in particular, ICH E6).

6.2.2 Withdrawal Criteria

Clear criteria for stopping treatment or study procedures for a study participant while remaining in the study are necessary to ensure the protection of the participants but should also minimise loss of critical data.

6.2.3 Data Monitoring Committee

An important component of safety monitoring in many clinical studies is the use of an independent data monitoring committee. This group monitors accumulating data while the study is being conducted to make recommendations on whether to continue, modify, or terminate a study.

During programme planning, the need for an independent data monitoring committee to monitor safety data across studies in a development programme should also be assessed. If a data monitoring committee is needed for either an individual study or across the development programme, procedures governing its operation and, in particular the review of unblinded data in an interventional trial, while preserving study integrity (ICH E9) should be established prior to study start.

6.3 Study Reporting

Clinical studies and their results should be adequately reported using formats appropriate for the type of study (interventional or observational studies) and information being reported. ICH E3 focuses particularly on the report format for interventional clinical trials, but the basic principles may be applied to other types of clinical studies (ICH E3 Q&A). The design of the study report should be part of the quality by design process. The report should describe the critical to quality factors in the study. The reporting of study results should be comprehensive, accurate, and timely.

Consideration should be given to providing a factual summary of the overall study results to study participants in an objective, balanced and nonpromotional manner, including relevant safety information and any limitations of the study. In addition, consideration could be given to providing individual participants with information about their study specific results (e.g., their treatment arm, test results). The information should be conveyed by someone involved in the health management of the participant (e.g., the clinical investigator). Participants should be informed about the information they will receive and when they will receive it at the time of providing informed consent.

The transparency of clinical research in drug development includes the registration of clinical studies, before they start, on publicly accessible and recognised databases, and the public posting of clinical study results. Adopting such practices for observational studies also promotes transparency. Making objective and unbiased information publicly available can benefit public health in general, as well as the indicated patient populations, through enhancing clinical research, reducing unnecessary clinical studies, and informing decisions in clinical practice.

7. CONSIDERATIONS IN IDENTIFYING CRITICAL TO QUALITY FACTORS

The identification of critical to quality factors should be supported by proactive, cross-functional discussions and decision making at the time of study planning, as described in Section 3. Different factors will stand out as critical for different types of studies, following the concepts introduced in Sections 4 through 6.

In designing a study, the following aspects should be considered, where applicable, to support the identification of critical to quality factors:

- Engagement of all relevant stakeholders, including patients, is considered during study planning and design.
- The prerequisite non-clinical studies, and where applicable, clinical studies, are complete and adequate to support the study being designed.
- The study objectives address relevant scientific questions appropriate for a given study's role in the development programme, taking into account the accumulated knowledge about the product.
- The clinical study design supports a meaningful comparison of the effects of the drug when compared to the chosen control group.
- Adequate measures are used to protect participants' rights, safety, and welfare (informed consent process, Institutional Review Board/Ethics Committee review, investigator and clinical study site training, pseudonymisation).
- Information provided to the study participants should be clear and understandable.
- Competencies and training required for the study by sponsor and investigator staff, relevant to their role, should be identified.
- The feasibility of the study should be assessed to ensure the study is operationally viable.
- The number of participants included, the duration of the study, and the frequency of study visits are sufficient to support the study objective.
- The eligibility criteria should be reflective of the study objectives and be well documented in the clinical study protocol.
- The protocol specifies the collection of data needed to meet the study objectives, understand the benefit/risk of the drug, and monitor participant safety.
- The choice of response variables and the methods to assess them are well-defined and support evaluation of the effects of the drug.
- Clinical study procedures include adequate measures to minimise bias (e.g., randomisation, blinding).
- The statistical analysis plan is pre-specified and defines the analysis methods appropriate for the endpoints and the populations of interest.
- Systems and processes are in place that support the study conduct to ensure the integrity of critical study data.
- The extent and nature of study monitoring are tailored to the specific study design and objectives and the need to ensure participants' safety.
- The need for and appropriate role of a data monitoring committee is assessed.
- The reporting of the study results is planned, comprehensive, accurate, timely, and publicly accessible.

These considerations are not exhaustive and may not apply to all studies. Other aspects may need to be considered to identify the critical to quality factors for each individual study.

ANNEX: TYPES OF CLINICAL STUDIES

Drug development is ideally a logical, stepwise process in which information from early studies is used to support and plan later studies. The actual sequence of studies conducted in a particular drug development programme, however, may reflect different dependencies and overlapping study types. Studies may also involve adaptive designs (which may bridge or combine different study types as listed below) or designs that are intended to investigate multiple drugs or multiple indications or both (e.g., studies conducted under a master protocol). In the table below, types of clinical studies are categorised by objectives. Illustrative examples, not intended to be exhaustive or exclusive, are provided. Study objectives appearing under one type may also occur under another.

Type of Study	*Objective(s) of Study*	*Study Examples*
Human Pharmacology	• Assess tolerance and safety • Define/describe clinical PK[1] and PD[2] • Explore drug metabolism and drug interactions • Evaluate activity, assess immunogenicity • Assess renal/hepatic tolerance • Assess cardiac toxicity	• BA[3]/BE[4] studies under fasted/fed conditions • Dose-tolerance studies • Single and multiple-rising dose PK and/or PD studies • Drug-drug interaction studies • QTc prolongation study • Human factor studies for drug delivery devices
Exploratory	• Explore use for the intended indication • Estimate dose/dosing regimen for subsequent studies • Explore dose-response/exposure-response relationship • Provide basis for confirmatory study design (e.g., targeted population, clinical endpoints, patient reported outcome measures, factors affecting treatment effects)	• Randomised controlled clinical trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures • Dose finding studies • Biomarker exploration studies • Studies to validate patient reported outcomes • Adaptive designs that may combine exploratory and confirmatory objectives
Confirmatory	• Demonstrate/confirm efficacy • Establish safety profile in larger, more representative patient populations • Provide an adequate basis for assessing the benefit/risk relationship to support licensing	• Randomised controlled clinical trials to establish efficacy in larger, more representative patient populations • Dose-response studies • Clinical safety studies • Studies of mortality/morbidity outcomes • Studies in special populations

	• Establish dose-response/exposure-response relationship • Establish safety profile and confirm efficacy in specific populations (e.g., paediatrics, elderly)	• Studies that seek to demonstrate efficacy for multiple drugs in a single protocol
Post-Approval	• Extend understanding of benefit/risk relationship in general or special populations and/or environments • Identify less common adverse reactions • Refine dosing recommendations	• Comparative effectiveness studies • Long-term follow-up studies • Studies of mortality/morbidity or other additional endpoints • Large, simple randomised trials • Pharmacoeconomic studies • Pharmacoepidemiology studies • Observational studies of the use of the drug in clinical practice • Disease or drug registries

[1]PK -Pharmacokinetic

[2]PD - Pharmacodynamic

[3]BA studies - Bioavailability

[4] BE studies - Bioequivalence

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version

dated 5 February 1998

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E9
Document History

First Codification	History	Date	New Codification **November 2005**
E9	Approval by the Steering Committee under *Step 2* and release for public consultation.	16 January 1997	E9

Current *Step 4* version

E9	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	5 February 1998	E9

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 5 February 1998, this guideline is recommended for adoption to the three regulatory parties to ICH

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STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

I. INTRODUCTION

1.1 Background and Purpose

The efficacy and safety of medicinal products should be demonstrated by clinical trials which follow the guidance in 'Good Clinical Practice: Consolidated Guideline' (ICH E6) adopted by the ICH, 1 May 1996. The role of statistics in clinical trial design and analysis is acknowledged as essential in that ICH guideline. The proliferation of statistical research in the area of clinical trials coupled with the critical role of clinical research in the drug approval process and health care in general necessitate a succinct document on statistical issues related to clinical trials. This guidance is written primarily to attempt to harmonise the principles of statistical methodology applied to clinical trials for marketing applications submitted in Europe, Japan and the United States.

As a starting point, this guideline utilised the CPMP (Committee for Proprietary Medicinal Products) Note for Guidance entitled 'Biostatistical Methodology in Clinical Trials in Applications for Marketing Authorisations for Medicinal Products' (December, 1994). It was also influenced by 'Guidelines on the Statistical Analysis of Clinical Studies' (March, 1992) from the Japanese Ministry of Health and Welfare and the U.S. Food and Drug Administration document entitled 'Guideline for the Format and Content of the Clinical and Statistical Sections of a New Drug Application' (July, 1988). Some topics related to statistical principles and methodology are also embedded within other ICH guidelines, particularly those listed below. The specific guidance that contains related text will be identified in various sections of this document.

E1A:	The Extent of Population Exposure to Assess Clinical Safety
E2A:	Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
E2B:	Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports
E2C:	Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs
E3:	Structure and Content of Clinical Study Reports
E4:	Dose-Response Information to Support Drug Registration
E5:	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6:	Good Clinical Practice: Consolidated Guideline
E7:	Studies in Support of Special Populations: Geriatrics
E8:	General Considerations for Clinical Trials
E10:	Choice of Control Group in Clinical Trials
M1:	Standardisation of Medical Terminology for Regulatory Purposes
M3:	Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.

This guidance is intended to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product in the context of its overall clinical development. The document will also assist scientific experts charged with preparing application summaries or assessing evidence of efficacy and safety, principally from clinical trials in later phases of development.

1.2 Scope and Direction

The focus of this guidance is on statistical principles. It does not address the use of specific statistical procedures or methods. Specific procedural steps to ensure that principles are implemented properly are the responsibility of the sponsor. Integration of data across clinical trials is discussed, but is not a primary focus of this guidance. Selected principles and procedures related to data management or clinical trial monitoring activities are covered in other ICH guidelines and are not addressed here.

This guidance should be of interest to individuals from a broad range of scientific disciplines. However, it is assumed that the actual responsibility for all statistical work associated with clinical trials will lie with an appropriately qualified and experienced statistician, as indicated in ICH E6. The role and responsibility of the trial statistician (see Glossary), in collaboration with other clinical trial professionals, is to ensure that statistical principles are applied appropriately in clinical trials supporting drug development. Thus, the trial statistician should have a combination of education/training and experience sufficient to implement the principles articulated in this guidance.

For each clinical trial contributing to a marketing application, all important details of its design and conduct and the principal features of its proposed statistical analysis should be clearly specified in a protocol written before the trial begins. The extent to which the procedures in the protocol are followed and the primary analysis is planned a priori will contribute to the degree of confidence in the final results and conclusions of the trial. The protocol and subsequent amendments should be approved by the responsible personnel, including the trial statistician. The trial statistician should ensure that the protocol and any amendments cover all relevant statistical issues clearly and accurately, using technical terminology as appropriate.

The principles outlined in this guidance are primarily relevant to clinical trials conducted in the later phases of development, many of which are confirmatory trials of efficacy. In addition to efficacy, confirmatory trials may have as their primary variable a safety variable (e.g. an adverse event, a clinical laboratory variable or an electrocardiographic measure), a pharmacodynamic or a pharmacokinetic variable (as in a confirmatory bioequivalence trial). Furthermore, some confirmatory findings may be derived from data integrated across trials, and selected principles in this guidance are applicable in this situation. Finally, although the early phases of drug development consist mainly of clinical trials that are exploratory in nature, statistical principles are also relevant to these clinical trials. Hence, the substance of this document should be applied as far as possible to all phases of clinical development.

Many of the principles delineated in this guidance deal with minimising bias (see Glossary) and maximising precision. As used in this guidance, the term 'bias' describes the systematic tendency of any factors associated with the design, conduct, analysis and interpretation of the results of clinical trials to make the estimate of a treatment effect (see Glossary) deviate from its true value. It is important to identify potential sources of bias as completely as possible so that attempts to limit such bias may be made. The presence of bias may seriously compromise the ability to draw valid conclusions from clinical trials.

Some sources of bias arise from the design of the trial, for example an assignment of treatments such that subjects at lower risk are systematically assigned to one treatment. Other sources of bias arise during the conduct and analysis of a clinical trial. For example, protocol violations and exclusion of subjects from analysis based upon knowledge of subject outcomes are possible sources of bias that may affect the accurate assessment of the treatment effect. Because bias can occur in subtle or unknown ways and its effect is not measurable directly, it is important to evaluate the robustness of the results and primary conclusions of the trial. Robustness is a concept that refers to the sensitivity of the overall conclusions to various limitations of the data, assumptions, and analytic approaches to data analysis. Robustness implies that the treatment effect and primary conclusions of the trial are not substantially affected when analyses are carried out based on alternative assumptions or analytic approaches. The interpretation of statistical measures of uncertainty of the treatment effect and treatment comparisons should involve consideration of the potential contribution of bias to the p-value, confidence interval, or inference.

Because the predominant approaches to the design and analysis of clinical trials have been based on frequentist statistical methods, the guidance largely refers to the use of frequentist methods (see Glossary) when discussing hypothesis testing and/or confidence intervals. This should not be taken to imply that other approaches are not appropriate: the use of Bayesian (see Glossary) and other approaches may be considered when the reasons for their use are clear and when the resulting conclusions are sufficiently robust.

II. CONSIDERATIONS FOR OVERALL CLINICAL DEVELOPMENT

2.1 Trial Context

2.1.1 Development Plan

The broad aim of the process of clinical development of a new drug is to find out whether there is a dose range and schedule at which the drug can be shown to be simultaneously safe and effective, to the extent that the risk-benefit relationship is acceptable. The particular subjects who may benefit from the drug, and the specific indications for its use, also need to be defined.

Satisfying these broad aims usually requires an ordered programme of clinical trials, each with its own specific objectives (see ICH E8). This should be specified in a clinical plan, or a series of plans, with appropriate decision points and flexibility to allow modification as knowledge accumulates. A marketing application should clearly describe the main content of such plans, and the contribution made by each trial. Interpretation and assessment of the evidence from the total programme of trials involves synthesis of the evidence from the individual trials (see Section 7.2). This is facilitated by ensuring that common standards are adopted for a number of features of the trials such as dictionaries of medical terms, definition and timing of the main measurements, handling of protocol deviations and so on. A statistical summary, overview or meta-analysis (see Glossary) may be informative when medical questions are addressed in more than one trial. Where possible this should be envisaged in the plan so that the relevant trials are clearly identified and any necessary common features of their designs are specified in advance. Other major statistical issues (if any) that are expected to affect a number of trials in a common plan should be addressed in that plan.

2.1.2 Confirmatory Trial

A confirmatory trial is an adequately controlled trial in which the hypotheses are stated in advance and evaluated. As a rule, confirmatory trials are necessary to provide firm evidence of efficacy or safety. In such trials the key hypothesis of interest follows directly from the trial's primary objective, is always pre-defined, and is the hypothesis that is subsequently tested when the trial is complete. In a confirmatory trial it is equally important to estimate with due precision the size of the effects attributable to the treatment of interest and to relate these effects to their clinical significance.

Confirmatory trials are intended to provide firm evidence in support of claims and hence adherence to protocols and standard operating procedures is particularly important; unavoidable changes should be explained and documented, and their effect examined. A justification of the design of each such trial, and of other important statistical aspects such as the principal features of the planned analysis, should be set out in the protocol. Each trial should address only a limited number of questions.

Firm evidence in support of claims requires that the results of the confirmatory trials demonstrate that the investigational product under test has clinical benefits. The confirmatory trials should therefore be sufficient to answer each key clinical question relevant to the efficacy or safety claim clearly and definitively. In addition, it is important that the basis for generalisation (see Glossary) to the intended patient population is understood and explained; this may also influence the number and type (e.g. specialist or general practitioner) of centres and/or trials needed. The results of the confirmatory trial(s) should be robust. In some circumstances the weight of evidence from a single confirmatory trial may be sufficient.

2.1.3 Exploratory Trial

The rationale and design of confirmatory trials nearly always rests on earlier clinical work carried out in a series of exploratory studies. Like all clinical trials, these exploratory studies should have clear and precise objectives. However, in contrast to confirmatory trials, their objectives may not always lead to simple tests of pre-defined hypotheses. In addition, exploratory trials may sometimes require a more flexible approach to design so that changes can be made in response to accumulating results. Their analysis may entail data exploration; tests of hypothesis may be carried out, but the choice of hypothesis may be data dependent. Such trials cannot be the basis of the formal proof of efficacy, although they may contribute to the total body of relevant evidence.

Any individual trial may have both confirmatory and exploratory aspects. For example, in most confirmatory trials the data are also subjected to exploratory analyses which serve as a basis for explaining or supporting their findings and for suggesting further hypotheses for later research. The protocol should make a clear distinction between the aspects of a trial which will be used for confirmatory proof and the aspects which will provide data for exploratory analysis.

2.2 Scope of Trials

2.2.1 Population

In the earlier phases of drug development the choice of subjects for a clinical trial may be heavily influenced by the wish to maximise the chance of observing specific clinical effects of interest, and hence they may come from a very narrow subgroup of the total patient population for which the drug may eventually be indicated. However by the time the confirmatory trials are undertaken, the subjects in the trials should more closely mirror the target population. Hence, in these trials it is generally helpful to

relax the inclusion and exclusion criteria as much as possible within the target population, while maintaining sufficient homogeneity to permit precise estimation of treatment effects. No individual clinical trial can be expected to be totally representative of future users, because of the possible influences of geographical location, the time when it is conducted, the medical practices of the particular investigator(s) and clinics, and so on. However the influence of such factors should be reduced wherever possible, and subsequently discussed during the interpretation of the trial results.

2.2.2 Primary and Secondary Variables

The primary variable ('target' variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. There should generally be only one primary variable. This will usually be an efficacy variable, because the primary objective of most confirmatory trials is to provide strong scientific evidence regarding efficacy. Safety/tolerability may sometimes be the primary variable, and will always be an important consideration. Measurements relating to quality of life and health economics are further potential primary variables. The selection of the primary variable should reflect the accepted norms and standards in the relevant field of research. The use of a reliable and validated variable with which experience has been gained either in earlier studies or in published literature is recommended. There should be sufficient evidence that the primary variable can provide a valid and reliable measure of some clinically relevant and important treatment benefit in the patient population described by the inclusion and exclusion criteria. The primary variable should generally be the one used when estimating the sample size (see section 3.5).

In many cases, the approach to assessing subject outcome may not be straightforward and should be carefully defined. For example, it is inadequate to specify mortality as a primary variable without further clarification; mortality may be assessed by comparing proportions alive at fixed points in time, or by comparing overall distributions of survival times over a specified interval. Another common example is a recurring event; the measure of treatment effect may again be a simple dichotomous variable (any occurrence during a specified interval), time to first occurrence, rate of occurrence (events per time units of observation), etc. The assessment of functional status over time in studying treatment for chronic disease presents other challenges in selection of the primary variable. There are many possible approaches, such as comparisons of the assessments done at the beginning and end of the interval of observation, comparisons of slopes calculated from all assessments throughout the interval, comparisons of the proportions of subjects exceeding or declining beyond a specified threshold, or comparisons based on methods for repeated measures data. To avoid multiplicity concerns arising from post hoc definitions, it is critical to specify in the protocol the precise definition of the primary variable as it will be used in the statistical analysis. In addition, the clinical relevance of the specific primary variable selected and the validity of the associated measurement procedures will generally need to be addressed and justified in the protocol.

The primary variable should be specified in the protocol, along with the rationale for its selection. Redefinition of the primary variable after unblinding will almost always be unacceptable, since the biases this introduces are difficult to assess. When the clinical effect defined by the primary objective is to be measured in more than one way, the protocol should identify one of the measurements as the primary variable on the basis of clinical relevance, importance, objectivity, and/or other relevant characteristics, whenever such selection is feasible.

Secondary variables are either supportive measurements related to the primary objective or measurements of effects related to the secondary objectives. Their pre-definition in the protocol is also important, as well as an explanation of their relative importance and roles in interpretation of trial results. The number of secondary variables should be limited and should be related to the limited number of questions to be answered in the trial.

2.2.3 Composite Variables

If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or 'composite' variable, using a pre-defined algorithm. Indeed, the primary variable sometimes arises as a combination of multiple clinical measurements (e.g. the rating scales used in arthritis, psychiatric disorders and elsewhere). This approach addresses the multiplicity problem without requiring adjustment to the type I error. The method of combining the multiple measurements should be specified in the protocol, and an interpretation of the resulting scale should be provided in terms of the size of a clinically relevant benefit. When a composite variable is used as a primary variable, the components of this variable may sometimes be analysed separately, where clinically meaningful and validated. When a rating scale is used as a primary variable, it is especially important to address such factors as content validity (see Glossary), inter- and intra-rater reliability (see Glossary) and responsiveness for detecting changes in the severity of disease.

2.2.4 Global Assessment Variables

In some cases, 'global assessment' variables (see Glossary) are developed to measure the overall safety, overall efficacy, and/or overall usefulness of a treatment. This type of variable integrates objective variables and the investigator's overall impression about the state or change in the state of the subject, and is usually a scale of ordered categorical ratings. Global assessments of overall efficacy are well established in some therapeutic areas, such as neurology and psychiatry.

Global assessment variables generally have a subjective component. When a global assessment variable is used as a primary or secondary variable, fuller details of the scale should be included in the protocol with respect to:

1) the relevance of the scale to the primary objective of the trial;

2) the basis for the validity and reliability of the scale;

3) how to utilise the data collected on an individual subject to assign him/her to a unique category of the scale;

4) how to assign subjects with missing data to a unique category of the scale, or otherwise evaluate them.

If objective variables are considered by the investigator when making a global assessment, then those objective variables should be considered as additional primary, or at least important secondary, variables.

Global assessment of usefulness integrates components of both benefit and risk and reflects the decision making process of the treating physician, who must weigh benefit and risk in making product use decisions. A problem with global usefulness variables is that their use could in some cases lead to the result of two products being declared equivalent despite having very different profiles of beneficial and adverse effects. For example, judging the global usefulness of a treatment as equivalent or superior to an

alternative may mask the fact that it has little or no efficacy but fewer adverse effects. Therefore it is not advisable to use a global usefulness variable as a primary variable. If global usefulness is specified as primary, it is important to consider specific efficacy and safety outcomes separately as additional primary variables.

2.2.5 Multiple Primary Variables

It may sometimes be desirable to use more than one primary variable, each of which (or a subset of which) could be sufficient to cover the range of effects of the therapies. The planned manner of interpretation of this type of evidence should be carefully spelled out. It should be clear whether an impact on any of the variables, some minimum number of them, or all of them, would be considered necessary to achieve the trial objectives. The primary hypothesis or hypotheses and parameters of interest (e.g. mean, percentage, distribution) should be clearly stated with respect to the primary variables identified, and the approach to statistical inference described. The effect on the type I error should be explained because of the potential for multiplicity problems (see Section 5.6); the method of controlling type I error should be given in the protocol. The extent of intercorrelation among the proposed primary variables may be considered in evaluating the impact on type I error. If the purpose of the trial is to demonstrate effects on all of the designated primary variables, then there is no need for adjustment of the type I error, but the impact on type II error and sample size should be carefully considered.

2.2.6 Surrogate Variables

When direct assessment of the clinical benefit to the subject through observing actual clinical efficacy is not practical, indirect criteria (surrogate variables - see Glossary) may be considered. Commonly accepted surrogate variables are used in a number of indications where they are believed to be reliable predictors of clinical benefit. There are two principal concerns with the introduction of any proposed surrogate variable. First, it may not be a true predictor of the clinical outcome of interest. For example it may measure treatment activity associated with one specific pharmacological mechanism, but may not provide full information on the range of actions and ultimate effects of the treatment, whether positive or negative. There have been many instances where treatments showing a highly positive effect on a proposed surrogate have ultimately been shown to be detrimental to the subjects' clinical outcome; conversely, there are cases of treatments conferring clinical benefit without measurable impact on proposed surrogates. Secondly, proposed surrogate variables may not yield a quantitative measure of clinical benefit that can be weighed directly against adverse effects. Statistical criteria for validating surrogate variables have been proposed but the experience with their use is relatively limited. In practice, the strength of the evidence for surrogacy depends upon (i) the biological plausibility of the relationship, (ii) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome and (iii) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome. Relationships between clinical and surrogate variables for one product do not necessarily apply to a product with a different mode of action for treating the same disease.

2.2.7 Categorised Variables

Dichotomisation or other categorisation of continuous or ordinal variables may sometimes be desirable. Criteria of 'success' and 'response' are common examples of dichotomies which require precise specification in terms of, for example, a minimum percentage improvement (relative to baseline) in a continuous variable, or a ranking categorised as at or above some threshold level (e.g., 'good') on an ordinal rating scale.

The reduction of diastolic blood pressure below 90mmHg is a common dichotomisation. Categorisations are most useful when they have clear clinical relevance. The criteria for categorisation should be pre-defined and specified in the protocol, as knowledge of trial results could easily bias the choice of such criteria. Because categorisation normally implies a loss of information, a consequence will be a loss of power in the analysis; this should be accounted for in the sample size calculation.

2.3 Design Techniques to Avoid Bias

The most important design techniques for avoiding bias in clinical trials are blinding and randomisation, and these should be normal features of most controlled clinical trials intended to be included in a marketing application. Most such trials follow a double-blind approach in which treatments are pre-packed in accordance with a suitable randomisation schedule, and supplied to the trial centre(s) labelled only with the subject number and the treatment period so that no one involved in the conduct of the trial is aware of the specific treatment allocated to any particular subject, not even as a code letter. This approach will be assumed in Section 2.3.1 and most of Section 2.3.2, exceptions being considered at the end.

Bias can also be reduced at the design stage by specifying procedures in the protocol aimed at minimising any anticipated irregularities in trial conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems, and also to handle the problems that do occur in the analysis of data.

2.3.1 Blinding

Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed.

A double-blind trial is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. This includes anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol. This level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded. If any of the sponsor staff who are not involved in the treatment or clinical evaluation of the subjects are required to be unblinded to the treatment code (e.g. bioanalytical scientists, auditors, those involved in serious adverse event reporting), the sponsor should have adequate standard operating procedures to guard against inappropriate dissemination of treatment codes. In a single-blind trial the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa. In an open-label trial the identity of treatment is known to all. The double-blind trial is the optimal approach. This requires that the treatments to be applied during the trial cannot be distinguished (appearance, taste, etc.) either before or during administration, and that the blind is maintained appropriately during the whole trial.

Difficulties in achieving the double-blind ideal can arise: the treatments may be of a completely different nature, for example, surgery and drug therapy; two drugs may have different formulations and, although they could be made indistinguishable by the use of capsules, changing the formulation might also change the pharmacokinetic

and/or pharmacodynamic properties and hence require that bioequivalence of the formulations be established; the daily pattern of administration of two treatments may differ. One way of achieving double-blind conditions under these circumstances is to use a 'double-dummy' (see Glossary) technique. This technique may sometimes force an administration scheme that is sufficiently unusual to influence adversely the motivation and compliance of the subjects. Ethical difficulties may also interfere with its use when, for example, it entails dummy operative procedures. Nevertheless, extensive efforts should be made to overcome these difficulties.

The double-blind nature of some clinical trials may be partially compromised by apparent treatment induced effects. In such cases, blinding may be improved by blinding investigators and relevant sponsor staff to certain test results (e.g. selected clinical laboratory measures). Similar approaches (see below) to minimising bias in open-label trials should be considered in trials where unique or specific treatment effects may lead to unblinding individual patients.

If a double-blind trial is not feasible, then the single-blind option should be considered. In some cases only an open-label trial is practically or ethically possible. Single-blind and open-label trials provide additional flexibility, but it is particularly important that the investigator's knowledge of the next treatment should not influence the decision to enter the subject; this decision should precede knowledge of the randomised treatment. For these trials, consideration should be given to the use of a centralised randomisation method, such as telephone randomisation, to administer the assignment of randomised treatment. In addition, clinical assessments should be made by medical staff who are not involved in treating the subjects and who remain blind to treatment. In single-blind or open-label trials every effort should be made to minimise the various known sources of bias and primary variables should be as objective as possible. The reasons for the degree of blinding adopted should be explained in the protocol, together with steps taken to minimise bias by other means. For example, the sponsor should have adequate standard operating procedures to ensure that access to the treatment code is appropriately restricted during the process of cleaning the database prior to its release for analysis.

Breaking the blind (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the subject's physician for the subject's care. Any intentional or unintentional breaking of the blind should be reported and explained at the end of the trial, irrespective of the reason for its occurrence. The procedure and timing for revealing the treatment assignments should be documented.

In this document, the blind review (see Glossary) of data refers to the checking of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind.

2.3.2 Randomisation

Randomisation introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. During subsequent analysis of the trial data, it provides a sound statistical basis for the quantitative evaluation of the evidence relating to treatment effects. It also tends to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar. In combination with blinding, randomisation helps to avoid possible bias in the selection and allocation of subjects arising from the predictability of treatment assignments.

The randomisation schedule of a clinical trial documents the random allocation of treatments to subjects. In the simplest situation it is a sequential list of treatments (or treatment sequences in a crossover trial) or corresponding codes by subject

number. The logistics of some trials, such as those with a screening phase, may make matters more complicated, but the unique pre-planned assignment of treatment, or treatment sequence, to subject should be clear. Different trial designs will require different procedures for generating randomisation schedules. The randomisation schedule should be reproducible (if the need arises).

Although unrestricted randomisation is an acceptable approach, some advantages can generally be gained by randomising subjects in blocks. This helps to increase the comparability of the treatment groups, particularly when subject characteristics may change over time, as a result, for example, of changes in recruitment policy. It also provides a better guarantee that the treatment groups will be of nearly equal size. In crossover trials it provides the means of obtaining balanced designs with their greater efficiency and easier interpretation. Care should be taken to choose block lengths that are sufficiently short to limit possible imbalance, but that are long enough to avoid predictability towards the end of the sequence in a block. Investigators and other relevant staff should generally be blind to the block length; the use of two or more block lengths, randomly selected for each block, can achieve the same purpose. (Theoretically, in a double-blind trial predictability does not matter, but the pharmacological effects of drugs may provide the opportunity for intelligent guesswork.)

In multicentre trials (see Glossary) the randomisation procedures should be organised centrally. It is advisable to have a separate random scheme for each centre, i.e. to stratify by centre or to allocate several whole blocks to each centre. More generally, stratification by important prognostic factors measured at baseline (e.g. severity of disease, age, sex, etc.) may sometimes be valuable in order to promote balanced allocation within strata; this has greater potential benefit in small trials. The use of more than two or three stratification factors is rarely necessary, is less successful at achieving balance and is logistically troublesome. The use of a dynamic allocation procedure (see below) may help to achieve balance across a number of stratification factors simultaneously provided the rest of the trial procedures can be adjusted to accommodate an approach of this type. Factors on which randomisation has been stratified should be accounted for later in the analysis.

The next subject to be randomised into a trial should always receive the treatment corresponding to the next free number in the appropriate randomisation schedule (in the respective stratum, if randomisation is stratified). The appropriate number and associated treatment for the next subject should only be allocated when entry of that subject to the randomised part of the trial has been confirmed. Details of the randomisation that facilitate predictability (e.g. block length) should not be contained in the trial protocol. The randomisation schedule itself should be filed securely by the sponsor or an independent party in a manner that ensures that blindness is properly maintained throughout the trial. Access to the randomisation schedule during the trial should take into account the possibility that, in an emergency, the blind may have to be broken for any subject. The procedure to be followed, the necessary documentation, and the subsequent treatment and assessment of the subject should all be described in the protocol.

Dynamic allocation is an alternative procedure in which the allocation of treatment to a subject is influenced by the current balance of allocated treatments and, in a stratified trial, by the stratum to which the subject belongs and the balance within that stratum. Deterministic dynamic allocation procedures should be avoided and an appropriate element of randomisation should be incorporated for each treatment allocation. Every effort should be made to retain the double-blind status of the trial. For example, knowledge of the treatment code may be restricted to a central trial office from where the dynamic allocation is controlled, generally through telephone

contact. This in turn permits additional checks of eligibility criteria and establishes entry into the trial, features that can be valuable in certain types of multicentre trial. The usual system of pre-packing and labelling drug supplies for double-blind trials can then be followed, but the order of their use is no longer sequential. It is desirable to use appropriate computer algorithms to keep personnel at the central trial office blind to the treatment code. The complexity of the logistics and potential impact on the analysis should be carefully evaluated when considering dynamic allocation.

III. TRIAL DESIGN CONSIDERATIONS

3.1 Design Configuration

3.1.1 Parallel Group Design

The most common clinical trial design for confirmatory trials is the parallel group design in which subjects are randomised to one of two or more arms, each arm being allocated a different treatment. These treatments will include the investigational product at one or more doses, and one or more control treatments, such as placebo and/or an active comparator. The assumptions underlying this design are less complex than for most other designs. However, as with other designs, there may be additional features of the trial that complicate the analysis and interpretation (e.g. covariates, repeated measurements over time, interactions between design factors, protocol violations, dropouts (see Glossary) and withdrawals).

3.1.2 Crossover Design

In the crossover design, each subject is randomised to a sequence of two or more treatments, and hence acts as his own control for treatment comparisons. This simple manoeuvre is attractive primarily because it reduces the number of subjects and usually the number of assessments needed to achieve a specific power, sometimes to a marked extent. In the simplest 2×2 crossover design each subject receives each of two treatments in randomised order in two successive treatment periods, often separated by a washout period. The most common extension of this entails comparing n(>2) treatments in n periods, each subject receiving all n treatments. Numerous variations exist, such as designs in which each subject receives a subset of n(>2) treatments, or ones in which treatments are repeated within a subject.

Crossover designs have a number of problems that can invalidate their results. The chief difficulty concerns carryover, that is, the residual influence of treatments in subsequent treatment periods. In an additive model the effect of unequal carryover will be to bias direct treatment comparisons. In the 2×2 design the carryover effect cannot be statistically distinguished from the interaction between treatment and period and the test for either of these effects lacks power because the corresponding contrast is 'between subject'. This problem is less acute in higher order designs, but cannot be entirely dismissed.

When the crossover design is used it is therefore important to avoid carryover. This is best done by selective and careful use of the design on the basis of adequate knowledge of both the disease area and the new medication. The disease under study should be chronic and stable. The relevant effects of the medication should develop fully within the treatment period. The washout periods should be sufficiently long for complete reversibility of drug effect. The fact that these conditions are likely to be met should be established in advance of the trial by means of prior information and data.

There are additional problems that need careful attention in crossover trials. The most notable of these are the complications of analysis and interpretation arising from the loss of subjects. Also, the potential for carryover leads to difficulties in assigning adverse events which occur in later treatment periods to the appropriate

treatment. These, and other issues, are described in ICH E4. The crossover design should generally be restricted to situations where losses of subjects from the trial are expected to be small.

A common, and generally satisfactory, use of the 2×2 crossover design is to demonstrate the bioequivalence of two formulations of the same medication. In this particular application in healthy volunteers, carryover effects on the relevant pharmacokinetic variable are most unlikely to occur if the wash-out time between the two periods is sufficiently long. However it is still important to check this assumption during analysis on the basis of the data obtained, for example by demonstrating that no drug is detectable at the start of each period.

3.1.3 Factorial Designs

In a factorial design two or more treatments are evaluated simultaneously through the use of varying combinations of the treatments. The simplest example is the 2×2 factorial design in which subjects are randomly allocated to one of the four possible combinations of two treatments, A and B say. These are: A alone; B alone; both A and B; neither A nor B. In many cases this design is used for the specific purpose of examining the interaction of A and B. The statistical test of interaction may lack power to detect an interaction if the sample size was calculated based on the test for main effects. This consideration is important when this design is used for examining the joint effects of A and B, in particular, if the treatments are likely to be used together.

Another important use of the factorial design is to establish the dose-response characteristics of the simultaneous use of treatments C and D, especially when the efficacy of each monotherapy has been established at some dose in prior trials. A number, m, of doses of C is selected, usually including a zero dose (placebo), and a similar number, n, of doses of D. The full design then consists of m×n treatment groups, each receiving a different combination of doses of C and D. The resulting estimate of the response surface may then be used to help to identify an appropriate combination of doses of C and D for clinical use (see ICH E4).

In some cases, the 2×2 design may be used to make efficient use of clinical trial subjects by evaluating the efficacy of the two treatments with the same number of subjects as would be required to evaluate the efficacy of either one alone. This strategy has proved to be particularly valuable for very large mortality trials. The efficiency and validity of this approach depends upon the absence of interaction between treatments A and B so that the effects of A and B on the primary efficacy variables follow an additive model, and hence the effect of A is virtually identical whether or not it is additional to the effect of B. As for the crossover trial, evidence that this condition is likely to be met should be established in advance of the trial by means of prior information and data.

3.2 Multicentre Trials

Multicentre trials are carried out for two main reasons. Firstly, a multicentre trial is an accepted way of evaluating a new medication more efficiently; under some circumstances, it may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable time-frame. Multicentre trials of this nature may, in principle, be carried out at any stage of clinical development. They may have several centres with a large number of subjects per centre or, in the case of a rare disease, they may have a large number of centres with very few subjects per centre.

Secondly, a trial may be designed as a multicentre (and multi-investigator) trial primarily to provide a better basis for the subsequent generalisation of its findings.

This arises from the possibility of recruiting the subjects from a wider population and of administering the medication in a broader range of clinical settings, thus presenting an experimental situation that is more typical of future use. In this case the involvement of a number of investigators also gives the potential for a wider range of clinical judgement concerning the value of the medication. Such a trial would be a confirmatory trial in the later phases of drug development and would be likely to involve a large number of investigators and centres. It might sometimes be conducted in a number of different countries in order to facilitate generalisability (see Glossary) even further.

If a multicentre trial is to be meaningfully interpreted and extrapolated, then the manner in which the protocol is implemented should be clear and similar at all centres. Furthermore the usual sample size and power calculations depend upon the assumption that the differences between the compared treatments in the centres are unbiased estimates of the same quantity. It is important to design the common protocol and to conduct the trial with this background in mind. Procedures should be standardised as completely as possible. Variation of evaluation criteria and schemes can be reduced by investigator meetings, by the training of personnel in advance of the trial and by careful monitoring during the trial. Good design should generally aim to achieve the same distribution of subjects to treatments within each centre and good management should maintain this design objective. Trials that avoid excessive variation in the numbers of subjects per centre and trials that avoid a few very small centres have advantages if it is later found necessary to take into account the heterogeneity of the treatment effect from centre to centre, because they reduce the differences between different weighted estimates of the treatment effect. (This point does not apply to trials in which all centres are very small and in which centre does not feature in the analysis.) Failure to take these precautions, combined with doubts about the homogeneity of the results may, in severe cases, reduce the value of a multicentre trial to such a degree that it cannot be regarded as giving convincing evidence for the sponsor's claims.

In the simplest multicentre trial, each investigator will be responsible for the subjects recruited at one hospital, so that 'centre' is identified uniquely by either investigator or hospital. In many trials, however, the situation is more complex. One investigator may recruit subjects from several hospitals; one investigator may represent a team of clinicians (subinvestigators) who all recruit subjects from their own clinics at one hospital or at several associated hospitals. Whenever there is room for doubt about the definition of centre in a statistical model, the statistical section of the protocol (see Section 5.1) should clearly define the term (e.g. by investigator, location or region) in the context of the particular trial. In most instances centres can be satisfactorily defined through the investigators and ICH E6 provides relevant guidance in this respect. In cases of doubt the aim should be to define centres so as to achieve homogeneity in the important factors affecting the measurements of the primary variables and the influence of the treatments. Any rules for combining centres in the analysis should be justified and specified prospectively in the protocol where possible, but in any case decisions concerning this approach should always be taken blind to treatment, for example at the time of the blind review.

The statistical model to be adopted for the estimation and testing of treatment effects should be described in the protocol. The main treatment effect may be investigated first using a model which allows for centre differences, but does not include a term for treatment-by-centre interaction. If the treatment effect is homogeneous across centres, the routine inclusion of interaction terms in the model reduces the efficiency of the test for the main effects. In the presence of true heterogeneity of treatment effects, the interpretation of the main treatment effect is controversial.

In some trials, for example some large mortality trials with very few subjects per centre, there may be no reason to expect the centres to have any influence on the primary or secondary variables because they are unlikely to represent influences of clinical importance. In other trials it may be recognised from the start that the limited numbers of subjects per centre will make it impracticable to include the centre effects in the statistical model. In these cases it is not appropriate to include a term for centre in the model, and it is not necessary to stratify the randomisation by centre in this situation.

If positive treatment effects are found in a trial with appreciable numbers of subjects per centre, there should generally be an exploration of the heterogeneity of treatment effects across centres, as this may affect the generalisability of the conclusions. Marked heterogeneity may be identified by graphical display of the results of individual centres or by analytical methods, such as a significance test of the treatment-by-centre interaction. When using such a statistical significance test, it is important to recognise that this generally has low power in a trial designed to detect the main effect of treatment.

If heterogeneity of treatment effects is found, this should be interpreted with care and vigorous attempts should be made to find an explanation in terms of other features of trial management or subject characteristics. Such an explanation will usually suggest appropriate further analysis and interpretation. In the absence of an explanation, heterogeneity of treatment effect as evidenced, for example, by marked quantitative interactions (see Glossary) implies that alternative estimates of the treatment effect may be required, giving different weights to the centres, in order to substantiate the robustness of the estimates of treatment effect. It is even more important to understand the basis of any heterogeneity characterised by marked qualitative interactions (see Glossary), and failure to find an explanation may necessitate further clinical trials before the treatment effect can be reliably predicted.

Up to this point the discussion of multicentre trials has been based on the use of fixed effect models. Mixed models may also be used to explore the heterogeneity of the treatment effect. These models consider centre and treatment-by-centre effects to be random, and are especially relevant when the number of sites is large.

3.3 Type of Comparison

3.3.1 Trials to Show Superiority

Scientifically, efficacy is most convincingly established by demonstrating superiority to placebo in a placebo-controlled trial, by showing superiority to an active control treatment or by demonstrating a dose-response relationship. This type of trial is referred to as a 'superiority' trial (see Glossary). Generally in this guidance superiority trials are assumed, unless it is explicitly stated otherwise.

For serious illnesses, when a therapeutic treatment which has been shown to be efficacious by superiority trial(s) exists, a placebo-controlled trial may be considered unethical. In that case the scientifically sound use of an active treatment as a control should be considered. The appropriateness of placebo control vs. active control should be considered on a trial by trial basis.

3.3.2 Trials to Show Equivalence or Non-inferiority

In some cases, an investigational product is compared to a reference treatment without the objective of showing superiority. This type of trial is divided into two major categories according to its objective; one is an 'equivalence' trial (see Glossary) and the other is a 'non-inferiority' trial (see Glossary).

Bioequivalence trials fall into the former category. In some situations, clinical equivalence trials are also undertaken for other regulatory reasons such as demonstrating the clinical equivalence of a generic product to the marketed product when the compound is not absorbed and therefore not present in the blood stream.

Many active control trials are designed to show that the efficacy of an investigational product is no worse than that of the active comparator, and hence fall into the latter category. Another possibility is a trial in which multiple doses of the investigational drug are compared with the recommended dose or multiple doses of the standard drug. The purpose of this design is simultaneously to show a dose-response relationship for the investigational product and to compare the investigational product with the active control.

Active control equivalence or non-inferiority trials may also incorporate a placebo, thus pursuing multiple goals in one trial; for example, they may establish superiority to placebo and hence validate the trial design and simultaneously evaluate the degree of similarity of efficacy and safety to the active comparator. There are well known difficulties associated with the use of the active control equivalence (or non-inferiority) trials that do not incorporate a placebo or do not use multiple doses of the new drug. These relate to the implicit lack of any measure of internal validity (in contrast to superiority trials), thus making external validation necessary. The equivalence (or non-inferiority) trial is not conservative in nature, so that many flaws in the design or conduct of the trial will tend to bias the results towards a conclusion of equivalence. For these reasons, the design features of such trials should receive special attention and their conduct needs special care. For example, it is especially important to minimise the incidence of violations of the entry criteria, non-compliance, withdrawals, losses to follow-up, missing data and other deviations from the protocol, and also to minimise their impact on the subsequent analyses.

Active comparators should be chosen with care. An example of a suitable active comparator would be a widely used therapy whose efficacy in the relevant indication has been clearly established and quantified in well designed and well documented superiority trial(s) and which can be reliably expected to exhibit similar efficacy in the contemplated active control trial. To this end, the new trial should have the same important design features (primary variables, the dose of the active comparator, eligibility criteria, etc.) as the previously conducted superiority trials in which the active comparator clearly demonstrated clinically relevant efficacy, taking into account advances in medical or statistical practice relevant to the new trial.

It is vital that the protocol of a trial designed to demonstrate equivalence or non-inferiority contain a clear statement that this is its explicit intention. An equivalence margin should be specified in the protocol; this margin is the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator. For the active control equivalence trial, both the upper and the lower equivalence margins are needed, while only the lower margin is needed for the active control non-inferiority trial. The choice of equivalence margins should be justified clinically.

Statistical analysis is generally based on the use of confidence intervals (see Section 5.5). For equivalence trials, two-sided confidence intervals should be used. Equivalence is inferred when the entire confidence interval falls within the equivalence margins. Operationally, this is equivalent to the method of using two simultaneous one-sided tests to test the (composite) null hypothesis that the treatment difference is outside the equivalence margins versus the (composite) alternative hypothesis that the treatment difference is within the margins. Because the two null hypotheses are disjoint, the type I error is appropriately controlled. For

non-inferiority trials a one-sided interval should be used. The confidence interval approach has a one-sided hypothesis test counterpart for testing the null hypothesis that the treatment difference (investigational product minus control) is equal to the lower equivalence margin versus the alternative that the treatment difference is greater than the lower equivalence margin. The choice of type I error should be a consideration separate from the use of a one-sided or two-sided procedure. Sample size calculations should be based on these methods (see Section 3.5).

Concluding equivalence or non-inferiority based on observing a non-significant test result of the null hypothesis that there is no difference between the investigational product and the active comparator is inappropriate.

There are also special issues in the choice of analysis sets. Subjects who withdraw or dropout of the treatment group or the comparator group will tend to have a lack of response, and hence the results of using the full analysis set (see Glossary) may be biased toward demonstrating equivalence (see Section 5.2.3).

3.3.3 Trials to Show Dose-response Relationship

How response is related to the dose of a new investigational product is a question to which answers may be obtained in all phases of development, and by a variety of approaches (see ICH E4). Dose-response trials may serve a number of objectives, amongst which the following are of particular importance: the confirmation of efficacy; the investigation of the shape and location of the dose-response curve; the estimation of an appropriate starting dose; the identification of optimal strategies for individual dose adjustments; the determination of a maximal dose beyond which additional benefit would be unlikely to occur. These objectives should be addressed using the data collected at a number of doses under investigation, including a placebo (zero dose) wherever appropriate. For this purpose the application of procedures to estimate the relationship between dose and response, including the construction of confidence intervals and the use of graphical methods, is as important as the use of statistical tests. The hypothesis tests that are used may need to be tailored to the natural ordering of doses or to particular questions regarding the shape of the dose-response curve (e.g. monotonicity). The details of the planned statistical procedures should be given in the protocol.

3.4 Group Sequential Designs

Group sequential designs are used to facilitate the conduct of interim analysis (see section 4.5 and Glossary). While group sequential designs are not the only acceptable types of designs permitting interim analysis, they are the most commonly applied because it is more practicable to assess grouped subject outcomes at periodic intervals during the trial than on a continuous basis as data from each subject become available. The statistical methods should be fully specified in advance of the availability of information on treatment outcomes and subject treatment assignments (i.e. blind breaking, see Section 4.5). An Independent Data Monitoring Committee (see Glossary) may be used to review or to conduct the interim analysis of data arising from a group sequential design (see Section 4.6). While the design has been most widely and successfully used in large, long-term trials of mortality or major non-fatal endpoints, its use is growing in other circumstances. In particular, it is recognised that safety must be monitored in all trials and therefore the need for formal procedures to cover early stopping for safety reasons should always be considered.

3.5 Sample Size

The number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the

primary objective of the trial. If the sample size is determined on some other basis, then this should be made clear and justified. For example, a trial sized on the basis of safety questions or requirements or important secondary objectives may need larger numbers of subjects than a trial sized on the basis of the primary efficacy question (see, for example, ICH E1a).

Using the usual method for determining the appropriate sample size, the following items should be specified: a primary variable, the test statistic, the null hypothesis, the alternative ('working') hypothesis at the chosen dose(s) (embodying consideration of the treatment difference to be detected or rejected at the dose and in the subject population selected), the probability of erroneously rejecting the null hypothesis (the type I error), and the probability of erroneously failing to reject the null hypothesis (the type II error), as well as the approach to dealing with treatment withdrawals and protocol violations. In some instances, the event rate is of primary interest for evaluating power, and assumptions should be made to extrapolate from the required number of events to the eventual sample size for the trial.

The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected). The basis of these estimates should also be given. It is important to investigate the sensitivity of the sample size estimate to a variety of deviations from these assumptions and this may be facilitated by providing a range of sample sizes appropriate for a reasonable range of deviations from assumptions. In confirmatory trials, assumptions should normally be based on published data or on the results of earlier trials. The treatment difference to be detected may be based on a judgement concerning the minimal effect which has clinical relevance in the management of patients or on a judgement concerning the anticipated effect of the new treatment, where this is larger. Conventionally the probability of type I error is set at 5% or less or as dictated by any adjustments made necessary for multiplicity considerations; the precise choice may be influenced by the prior plausibility of the hypothesis under test and the desired impact of the results. The probability of type II error is conventionally set at 10% to 20%; it is in the sponsor's interest to keep this figure as low as feasible especially in the case of trials that are difficult or impossible to repeat. Alternative values to the conventional levels of type I and type II error may be acceptable or even preferable in some cases.

Sample size calculations should refer to the number of subjects required for the primary analysis. If this is the 'full analysis set', estimates of the effect size may need to be reduced compared to the per protocol set (see Glossary). This is to allow for the dilution of the treatment effect arising from the inclusion of data from patients who have withdrawn from treatment or whose compliance is poor. The assumptions about variability may also need to be revised.

The sample size of an equivalence trial or a non-inferiority trial (see Section 3.3.2) should normally be based on the objective of obtaining a confidence interval for the treatment difference that shows that the treatments differ at most by a clinically acceptable difference. When the power of an equivalence trial is assessed at a true difference of zero, then the sample size necessary to achieve this power is underestimated if the true difference is not zero. When the power of a non-inferiority trial is assessed at a zero difference, then the sample size needed to achieve that power will be underestimated if the effect of the investigational product is less than that of the active control. The choice of a 'clinically acceptable' difference needs justification with respect to its meaning for future patients, and may be smaller than the 'clinically relevant' difference referred to above in the context of superiority trials designed to establish that a difference exists.

The exact sample size in a group sequential trial cannot be fixed in advance because it depends upon the play of chance in combination with the chosen stopping guideline and the true treatment difference. The design of the stopping guideline should take into account the consequent distribution of the sample size, usually embodied in the expected and maximum sample sizes.

When event rates are lower than anticipated or variability is larger than expected, methods for sample size re-estimation are available without unblinding data or making treatment comparisons (see Section 4.4).

3.6 Data Capture and Processing

The collection of data and transfer of data from the investigator to the sponsor can take place through a variety of media, including paper case record forms, remote site monitoring systems, medical computer systems and electronic transfer. Whatever data capture instrument is used, the form and content of the information collected should be in full accordance with the protocol and should be established in advance of the conduct of the clinical trial. It should focus on the data necessary to implement the planned analysis, including the context information (such as timing assessments relative to dosing) necessary to confirm protocol compliance or identify important protocol deviations. 'Missing values' should be distinguishable from the 'value zero' or 'characteristic absent'.

The process of data capture through to database finalisation should be carried out in accordance with GCP (see ICH E6, Section 5). Specifically, timely and reliable processes for recording data and rectifying errors and omissions are necessary to ensure delivery of a quality database and the achievement of the trial objectives through the implementation of the planned analysis.

IV. TRIAL CONDUCT CONSIDERATIONS

4.1 Trial Monitoring and Interim Analysis

Careful conduct of a clinical trial according to the protocol has a major impact on the credibility of the results (see ICH E6). Careful monitoring can ensure that difficulties are noticed early and their occurrence or recurrence minimised.

There are two distinct types of monitoring that generally characterise confirmatory clinical trials sponsored by the pharmaceutical industry. One type of monitoring concerns the oversight of the quality of the trial, while the other type involves breaking the blind to make treatment comparisons (i.e. interim analysis). Both types of trial monitoring, in addition to entailing different staff responsibilities, involve access to different types of trial data and information, and thus different principles apply for the control of potential statistical and operational bias.

For the purpose of overseeing the quality of the trial the checks involved in trial monitoring may include whether the protocol is being followed, the acceptability of data being accrued, the success of planned accrual targets, the appropriateness of the design assumptions, success in keeping patients in the trials, etc. (see Sections 4.2 to 4.4). This type of monitoring does not require access to information on comparative treatment effects, nor unblinding of data and therefore has no impact on type I error. The monitoring of a trial for this purpose is the responsibility of the sponsor (see ICH E6) and can be carried out by the sponsor or an independent group selected by the sponsor. The period for this type of monitoring usually starts with the selection of the trial sites and ends with the collection and cleaning of the last subject's data.

The other type of trial monitoring (interim analysis) involves the accruing of comparative treatment results. Interim analysis requires unblinded (i.e. key

breaking) access to treatment group assignment (actual treatment assignment or identification of group assignment) and comparative treatment group summary information. This necessitates that the protocol (or appropriate amendments prior to a first analysis) contains statistical plans for the interim analysis to prevent certain types of bias. This is discussed in Sections 4.5 & 4.6.

4.2 Changes in Inclusion and Exclusion Criteria

Inclusion and exclusion criteria should remain constant, as specified in the protocol, throughout the period of subject recruitment. Changes may occasionally be appropriate, for example, in long term trials, where growing medical knowledge either from outside the trial or from interim analyses may suggest a change of entry criteria. Changes may also result from the discovery by monitoring staff that regular violations of the entry criteria are occurring, or that seriously low recruitment rates are due to over-restrictive criteria. Changes should be made without breaking the blind and should always be described by a protocol amendment which should cover any statistical consequences, such as sample size adjustments arising from different event rates, or modifications to the planned analysis, such as stratifying the analysis according to modified inclusion/exclusion criteria.

4.3 Accrual Rates

In trials with a long time-scale for the accrual of subjects, the rate of accrual should be monitored and, if it falls appreciably below the projected level, the reasons should be identified and remedial actions taken in order to protect the power of the trial and alleviate concerns about selective entry and other aspects of quality. In a multicentre trial these considerations apply to the individual centres.

4.4 Sample Size Adjustment

In long term trials there will usually be an opportunity to check the assumptions which underlay the original design and sample size calculations. This may be particularly important if the trial specifications have been made on preliminary and/or uncertain information. An interim check conducted on the blinded data may reveal that overall response variances, event rates or survival experience are not as anticipated. A revised sample size may then be calculated using suitably modified assumptions, and should be justified and documented in a protocol amendment and in the clinical study report. The steps taken to preserve blindness and the consequences, if any, for the type I error and the width of confidence intervals should be explained. The potential need for re-estimation of the sample size should be envisaged in the protocol whenever possible (see Section 3.5).

4.5 Interim Analysis and Early Stopping

An interim analysis is any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to formal completion of a trial. Because the number, methods and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol. Special circumstances may dictate the need for an interim analysis that was not defined at the start of a trial. In these cases, a protocol amendment describing the interim analysis should be completed prior to unblinded access to treatment comparison data. When an interim analysis is planned with the intention of deciding whether or not to terminate a trial, this is usually accomplished by the use of a group sequential design which employs statistical monitoring schemes as guidelines (see Section 3.4). The goal of such an interim analysis is to stop the trial early if the superiority of the treatment under study is clearly established, if the demonstration of

a relevant treatment difference has become unlikely or if unacceptable adverse effects are apparent. Generally, boundaries for monitoring efficacy require more evidence to terminate a trial early (i.e. they are more conservative) than boundaries for monitoring safety. When the trial design and monitoring objective involve multiple endpoints then this aspect of multiplicity may also need to be taken into account.

The protocol should describe the schedule of interim analyses, or at least the considerations which will govern its generation, for example if flexible alpha spending function approaches are to be employed; further details may be given in a protocol amendment before the time of the first interim analysis. The stopping guidelines and their properties should be clearly described in the protocol or amendments. The potential effects of early stopping on the analysis of other important variables should also be considered. This material should be written or approved by the Data Monitoring Committee (see Section 4.6), when the trial has one. Deviations from the planned procedure always bear the potential of invalidating the trial results. If it becomes necessary to make changes to the trial, any consequent changes to the statistical procedures should be specified in an amendment to the protocol at the earliest opportunity, especially discussing the impact on any analysis and inferences that such changes may cause. The procedures selected should always ensure that the overall probability of type I error is controlled.

The execution of an interim analysis should be a completely confidential process because unblinded data and results are potentially involved. All staff involved in the conduct of the trial should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons. This principle may be applied to all investigator staff and to staff employed by the sponsor except for those who are directly involved in the execution of the interim analysis. Investigators should only be informed about the decision to continue or to discontinue the trial, or to implement modifications to trial procedures.

Most clinical trials intended to support the efficacy and safety of an investigational product should proceed to full completion of planned sample size accrual; trials should be stopped early only for ethical reasons or if the power is no longer acceptable. However, it is recognised that drug development plans involve the need for sponsor access to comparative treatment data for a variety of reasons, such as planning other trials. It is also recognised that only a subset of trials will involve the study of serious life-threatening outcomes or mortality which may need sequential monitoring of accruing comparative treatment effects for ethical reasons. In either of these situations, plans for interim statistical analysis should be in place in the protocol or in protocol amendments prior to the unblinded access to comparative treatment data in order to deal with the potential statistical and operational bias that may be introduced.

For many clinical trials of investigational products, especially those that have major public health significance, the responsibility for monitoring comparisons of efficacy and/or safety outcomes should be assigned to an external independent group, often called an Independent Data Monitoring Committee (IDMC), a Data and Safety Monitoring Board or a Data Monitoring Committee whose responsibilities should be clearly described.

When a sponsor assumes the role of monitoring efficacy or safety comparisons and therefore has access to unblinded comparative information, particular care should be taken to protect the integrity of the trial and to manage and limit appropriately the sharing of information. The sponsor should assure and document that the internal monitoring committee has complied with written standard operating procedures and

that minutes of decision making meetings including records of interim results are maintained.

Any interim analysis that is not planned appropriately (with or without the consequences of stopping the trial early) may flaw the results of a trial and possibly weaken confidence in the conclusions drawn. Therefore, such analyses should be avoided. If unplanned interim analysis is conducted, the clinical study report should explain why it was necessary, the degree to which blindness had to be broken, provide an assessment of the potential magnitude of bias introduced, and the impact on the interpretation of the results.

4.6 Role of Independent Data Monitoring Committee (IDMC) (see Sections 1.25 and 5.52 of ICH E6)

An IDMC may be established by the sponsor to assess at intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial. The IDMC should have written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the IDMC is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The IDMC is a separate entity from an Institutional Review Board (IRB) or an Independent Ethics Committee (IEC), and its composition should include clinical trial scientists knowledgeable in the appropriate disciplines including statistics.

When there are sponsor representatives on the IDMC, their role should be clearly defined in the operating procedures of the committee (for example, covering whether or not they can vote on key issues). Since these sponsor staff would have access to unblinded information, the procedures should also address the control of dissemination of interim trial results within the sponsor organisation.

V. DATA ANALYSIS CONSIDERATIONS

5.1 Prespecification of the Analysis

When designing a clinical trial the principal features of the eventual statistical analysis of the data should be described in the statistical section of the protocol. This section should include all the principal features of the proposed confirmatory analysis of the primary variable(s) and the way in which anticipated analysis problems will be handled. In case of exploratory trials this section could describe more general principles and directions.

The statistical analysis plan (see Glossary) may be written as a separate document to be completed after finalising the protocol. In this document, a more technical and detailed elaboration of the principal features stated in the protocol may be included (see section 7.1). The plan may include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. The plan should be reviewed and possibly updated as a result of the blind review of the data (see 7.1 for definition) and should be finalised before breaking the blind. Formal records should be kept of when the statistical analysis plan was finalised as well as when the blind was subsequently broken.

If the blind review suggests changes to the principal features stated in the protocol, these should be documented in a protocol amendment. Otherwise, it will suffice to update the statistical analysis plan with the considerations suggested from the blind review. Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

In the statistical section of the clinical study report the statistical methodology should be clearly described including when in the clinical trial process methodology decisions were made (see ICH E3).

5.2 Analysis Sets

The set of subjects whose data are to be included in the main analyses should be defined in the statistical section of the protocol. In addition, documentation for all subjects for whom trial procedures (e.g. run-in period) were initiated may be useful. The content of this subject documentation depends on detailed features of the particular trial, but at least demographic and baseline data on disease status should be collected whenever possible.

If all subjects randomised into a clinical trial satisfied all entry criteria, followed all trial procedures perfectly with no losses to follow-up, and provided complete data records, then the set of subjects to be included in the analysis would be self-evident. The design and conduct of a trial should aim to approach this ideal as closely as possible, but, in practice, it is doubtful if it can ever be fully achieved. Hence, the statistical section of the protocol should address anticipated problems prospectively in terms of how these affect the subjects and data to be analysed. The protocol should also specify procedures aimed at minimising any anticipated irregularities in study conduct that might impair a satisfactory analysis, including various types of protocol violations, withdrawals and missing values. The protocol should consider ways both to reduce the frequency of such problems, and also to handle the problems that do occur in the analysis of data. Possible amendments to the way in which the analysis will deal with protocol violations should be identified during the blind review. It is desirable to identify any important protocol violation with respect to the time when it occurred, its cause and influence on the trial result. The frequency and type of protocol violations, missing values, and other problems should be documented in the clinical study report and their potential influence on the trial results should be described (see ICH E3).

Decisions concerning the analysis set should be guided by the following principles : 1) to minimise bias, and 2) to avoid inflation of type I error.

5.2.1 Full Analysis Set

The intention-to-treat (see Glossary) principle implies that the primary analysis should include all randomised subjects. Compliance with this principle would necessitate complete follow-up of all randomised subjects for study outcomes. In practice this ideal may be difficult to achieve, for reasons to be described. In this document the term 'full analysis set' is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomised subjects. Preservation of the initial randomisation in analysis is important in preventing bias and in providing a secure foundation for statistical tests. In many clinical trials the use of the full analysis set provides a conservative strategy. Under many circumstances it may also provide estimates of treatment effects which are more likely to mirror those observed in subsequent practice.

There are a limited number of circumstances that might lead to excluding randomised subjects from the full analysis set including the failure to satisfy major entry criteria (eligibility violations), the failure to take at least one dose of trial medication and the lack of any data post randomisation. Such exclusions should always be justified. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

(i) the entry criterion was measured prior to randomisation;

(ii) the detection of the relevant eligibility violations can be made completely objectively;

(iii) all subjects receive equal scrutiny for eligibility violations; (This may be difficult to ensure in an open-label study, or even in a double-blind study if the data are unblinded prior to this scrutiny, emphasising the importance of the blind review.)

(iv) all detected violations of the particular entry criterion are excluded.

In some situations, it may be reasonable to eliminate from the set of all randomised subjects any subject who took no trial medication. The intention-to-treat principle would be preserved despite the exclusion of these patients provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment. In other situations it may be necessary to eliminate from the set of all randomised subjects any subject without data post randomisation. No analysis is complete unless the potential biases arising from these specific exclusions, or any others, are addressed.

When the full analysis set of subjects is used, violations of the protocol that occur after randomisation may have an impact on the data and conclusions, particularly if their occurrence is related to treatment assignment. In most respects it is appropriate to include the data from such subjects in the analysis, consistent with the intention-to-treat principle. Special problems arise in connection with subjects withdrawn from treatment after receiving one or more doses who provide no data after this point, and subjects otherwise lost to follow-up, because failure to include these subjects in the full analysis set may seriously undermine the approach. Measurements of primary variables made at the time of the loss to follow-up of a subject for any reason, or subsequently collected in accordance with the intended schedule of assessments in the protocol, are valuable in this context; subsequent collection is especially important in studies where the primary variable is mortality or serious morbidity. The intention to collect data in this way should be described in the protocol. Imputation techniques, ranging from the carrying forward of the last observation to the use of complex mathematical models, may also be used in an attempt to compensate for missing data. Other methods employed to ensure the availability of measurements of primary variables for every subject in the full analysis set may require some assumptions about the subjects' outcomes or a simpler choice of outcome (e.g. success / failure). The use of any of these strategies should be described and justified in the statistical section of the protocol and the assumptions underlying any mathematical models employed should be clearly explained. It is also important to demonstrate the robustness of the corresponding results of analysis especially when the strategy in question could itself lead to biased estimates of treatment effects.

Because of the unpredictability of some problems, it may sometimes be preferable to defer detailed consideration of the manner of dealing with irregularities until the blind review of the data at the end of the trial, and, if so, this should be stated in the protocol.

5.2.2 Per Protocol Set

The 'per protocol' set of subjects, sometimes described as the 'valid cases', the 'efficacy' sample or the 'evaluable subjects' sample, defines a subset of the subjects in the full analysis set who are more compliant with the protocol and is characterised by criteria such as the following:

(i) the completion of a certain pre-specified minimal exposure to the treatment regimen;

(ii) the availability of measurements of the primary variable(s);

(iii) the absence of any major protocol violations including the violation of entry criteria.

The precise reasons for excluding subjects from the per protocol set should be fully defined and documented before breaking the blind in a manner appropriate to the circumstances of the specific trial.

The use of the per protocol set may maximise the opportunity for a new treatment to show additional efficacy in the analysis, and most closely reflects the scientific model underlying the protocol. However, the corresponding test of the hypothesis and estimate of the treatment effect may or may not be conservative depending on the trial; the bias, which may be severe, arises from the fact that adherence to the study protocol may be related to treatment and outcome.

The problems that lead to the exclusion of subjects to create the per protocol set, and other protocol violations, should be fully identified and summarised. Relevant protocol violations may include errors in treatment assignment, the use of excluded medication, poor compliance, loss to follow-up and missing data. It is good practice to assess the pattern of such problems among the treatment groups with respect to frequency and time to occurrence.

5.2.3 Roles of the Different Analysis Sets

In general, it is advantageous to demonstrate a lack of sensitivity of the principal trial results to alternative choices of the set of subjects analysed. In confirmatory trials it is usually appropriate to plan to conduct both an analysis of the full analysis set and a per protocol analysis, so that any differences between them can be the subject of explicit discussion and interpretation. In some cases, it may be desirable to plan further exploration of the sensitivity of conclusions to the choice of the set of subjects analysed. When the full analysis set and the per protocol set lead to essentially the same conclusions, confidence in the trial results is increased, bearing in mind, however, that the need to exclude a substantial proportion of subjects from the per protocol analysis throws some doubt on the overall validity of the trial.

The full analysis set and the per protocol set play different roles in superiority trials (which seek to show the investigational product to be superior), and in equivalence or non-inferiority trials (which seek to show the investigational product to be comparable, see section 3.3.2). In superiority trials the full analysis set is used in the primary analysis (apart from exceptional circumstances) because it tends to avoid over-optimistic estimates of efficacy resulting from a per protocol analysis, since the non-compliers included in the full analysis set will generally diminish the estimated treatment effect. However, in an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully.

5.3 Missing Values and Outliers

Missing values represent a potential source of bias in a clinical trial. Hence, every effort should be undertaken to fulfil all the requirements of the protocol concerning the collection and management of data. In reality, however, there will almost always be some missing data. A trial may be regarded as valid, nonetheless, provided the methods of dealing with missing values are sensible, and particularly if those methods are pre-defined in the protocol. Definition of methods may be refined by updating this aspect in the statistical analysis plan during the blind review. Unfortunately, no universally applicable methods of handling missing values can be recommended. An investigation should be made concerning the sensitivity of the

results of analysis to the method of handling missing values, especially if the number of missing values is substantial.

A similar approach should be adopted to exploring the influence of outliers, the statistical definition of which is, to some extent, arbitrary. Clear identification of a particular value as an outlier is most convincing when justified medically as well as statistically, and the medical context will then often define the appropriate action. Any outlier procedure set out in the protocol or the statistical analysis plan should be such as not to favour any treatment group a priori. Once again, this aspect of the analysis can be usefully updated during blind review. If no procedure for dealing with outliers was foreseen in the trial protocol, one analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect should be performed and differences between their results discussed.

5.4 Data Transformation

The decision to transform key variables prior to analysis is best made during the design of the trial on the basis of similar data from earlier clinical trials. Transformations (e.g. square root, logarithm) should be specified in the protocol and a rationale provided, especially for the primary variable(s). The general principles guiding the use of transformations to ensure that the assumptions underlying the statistical methods are met are to be found in standard texts; conventions for particular variables have been developed in a number of specific clinical areas. The decision on whether and how to transform a variable should be influenced by the preference for a scale which facilitates clinical interpretation.

Similar considerations apply to other derived variables, such as the use of change from baseline, percentage change from baseline, the 'area under the curve' of repeated measures, or the ratio of two different variables. Subsequent clinical interpretation should be carefully considered, and the derivation should be justified in the protocol. Closely related points are made in Section 2.2.2.

5.5 Estimation, Confidence Intervals and Hypothesis Testing

The statistical section of the protocol should specify the hypotheses that are to be tested and/or the treatment effects which are to be estimated in order to satisfy the primary objectives of the trial. The statistical methods to be used to accomplish these tasks should be described for the primary (and preferably the secondary) variables, and the underlying statistical model should be made clear. Estimates of treatment effects should be accompanied by confidence intervals, whenever possible, and the way in which these will be calculated should be identified. A description should be given of any intentions to use baseline data to improve precision or to adjust estimates for potential baseline differences, for example by means of analysis of covariance.

It is important to clarify whether one- or two-sided tests of statistical significance will be used, and in particular to justify prospectively the use of one-sided tests. If hypothesis tests are not considered appropriate, then the alternative process for arriving at statistical conclusions should be given. The issue of one-sided or two-sided approaches to inference is controversial and a diversity of views can be found in the statistical literature. The approach of setting type I errors for one-sided tests at half the conventional type I error used in two-sided tests is preferable in regulatory settings. This promotes consistency with the two-sided confidence intervals that are generally appropriate for estimating the possible size of the difference between two treatments.

The particular statistical model chosen should reflect the current state of medical and statistical knowledge about the variables to be analysed as well as the statistical

design of the trial. All effects to be fitted in the analysis (for example in analysis of variance models) should be fully specified, and the manner, if any, in which this set of effects might be modified in response to preliminary results should be explained. The same considerations apply to the set of covariates fitted in an analysis of covariance. (See also Section 5.7.). In the choice of statistical methods due attention should be paid to the statistical distribution of both primary and secondary variables. When making this choice (for example between parametric and non-parametric methods) it is important to bear in mind the need to provide statistical estimates of the size of treatment effects together with confidence intervals (in addition to significance tests).

The primary analysis of the primary variable should be clearly distinguished from supporting analyses of the primary or secondary variables. Within the statistical section of the protocol or the statistical analysis plan there should also be an outline of the way in which data other than the primary and secondary variables will be summarised and reported. This should include a reference to any approaches adopted for the purpose of achieving consistency of analysis across a range of trials, for example for safety data.

Modelling approaches that incorporate information on known pharmacological parameters, the extent of protocol compliance for individual subjects or other biologically based data may provide valuable insights into actual or potential efficacy, especially with regard to estimation of treatment effects. The assumptions underlying such models should always be clearly identified, and the limitations of any conclusions should be carefully described.

5.6 Adjustment of Significance and Confidence Levels

When multiplicity is present, the usual frequentist approach to the analysis of clinical trial data may necessitate an adjustment to the type I error. Multiplicity may arise, for example, from multiple primary variables (see Section 2.2.2), multiple comparisons of treatments, repeated evaluation over time and/or interim analyses (see Section 4.5). Methods to avoid or reduce multiplicity are sometimes preferable when available, such as the identification of the key primary variable (multiple variables), the choice of a critical treatment contrast (multiple comparisons), the use of a summary measure such as 'area under the curve' (repeated measures). In confirmatory analyses, any aspects of multiplicity which remain after steps of this kind have been taken should be identified in the protocol; adjustment should always be considered and the details of any adjustment procedure or an explanation of why adjustment is not thought to be necessary should be set out in the analysis plan.

5.7 Subgroups, Interactions and Covariates

The primary variable(s) is often systematically related to other influences apart from treatment. For example, there may be relationships to covariates such as age and sex, or there may be differences between specific subgroups of subjects such as those treated at the different centres of a multicentre trial. In some instances an adjustment for the influence of covariates or for subgroup effects is an integral part of the planned analysis and hence should be set out in the protocol. Pre-trial deliberations should identify those covariates and factors expected to have an important influence on the primary variable(s), and should consider how to account for these in the analysis in order to improve precision and to compensate for any lack of balance between treatment groups. If one or more factors are used to stratify the design, it is appropriate to account for those factors in the analysis. When the potential value of an adjustment is in doubt, it is often advisable to nominate the unadjusted analysis as the one for primary attention, the adjusted analysis being supportive. Special attention should be paid to centre effects and to the role of

baseline measurements of the primary variable. It is not advisable to adjust the main analyses for covariates measured after randomisation because they may be affected by the treatments.

The treatment effect itself may also vary with subgroup or covariate - for example, the effect may decrease with age or may be larger in a particular diagnostic category of subjects. In some cases such interactions are anticipated or are of particular prior interest (e.g. geriatrics), and hence a subgroup analysis, or a statistical model including interactions, is part of the planned confirmatory analysis. In most cases, however, subgroup or interaction analyses are exploratory and should be clearly identified as such; they should explore the uniformity of any treatment effects found overall. In general, such analyses should proceed first through the addition of interaction terms to the statistical model in question, complemented by additional exploratory analysis within relevant subgroups of subjects, or within strata defined by the covariates. When exploratory, these analyses should be interpreted cautiously; any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses are unlikely to be accepted.

5.8 Integrity of Data and Computer Software Validity

The credibility of the numerical results of the analysis depends on the quality and validity of the methods and software (both internally and externally written) used both for data management (data entry, storage, verification, correction and retrieval) and also for processing the data statistically. Data management activities should therefore be based on thorough and effective standard operating procedures. The computer software used for data management and statistical analysis should be reliable, and documentation of appropriate software testing procedures should be available.

VI. EVALUATION OF SAFETY AND TOLERABILITY

6.1 Scope of Evaluation

In all clinical trials evaluation of safety and tolerability (see Glossary) constitutes an important element. In early phases this evaluation is mostly of an exploratory nature, and is only sensitive to frank expressions of toxicity, whereas in later phases the establishment of the safety and tolerability profile of a drug can be characterised more fully in larger samples of subjects. Later phase controlled trials represent an important means of exploring in an unbiased manner any new potential adverse effects, even if such trials generally lack power in this respect.

Certain trials may be designed with the purpose of making specific claims about superiority or equivalence with regard to safety and tolerability compared to another drug or to another dose of the investigational drug. Such specific claims should be supported by relevant evidence from confirmatory trials, similar to that necessary for corresponding efficacy claims.

6.2 Choice of Variables and Data Collection

In any clinical trial the methods and measurements chosen to evaluate the safety and tolerability of a drug will depend on a number of factors, including knowledge of the adverse effects of closely related drugs, information from non-clinical and earlier clinical trials and possible consequences of the pharmacodynamic/pharmacokinetic properties of the particular drug, the mode of administration, the type of subjects to be studied, and the duration of the trial. Laboratory tests concerning clinical chemistry and haematology, vital signs, and clinical adverse events (diseases, signs and symptoms) usually form the main body of the safety and tolerability data. The

occurrence of serious adverse events and treatment discontinuations due to adverse events are particularly important to register (see ICH E2A and ICH E3).

Furthermore, it is recommended that a consistent methodology be used for the data collection and evaluation throughout a clinical trial program in order to facilitate the combining of data from different trials. The use of a common adverse event dictionary is particularly important. This dictionary has a structure which gives the possibility to summarise the adverse event data on three different levels; system-organ class, preferred term or included term (see Glossary). The preferred term is the level on which adverse events usually are summarised, and preferred terms belonging to the same system-organ class could then be brought together in the descriptive presentation of data (see ICH M1).

6.3 Set of Subjects to be Evaluated and Presentation of Data

For the overall safety and tolerability assessment, the set of subjects to be summarised is usually defined as those subjects who received at least one dose of the investigational drug. Safety and tolerability variables should be collected as comprehensively as possible from these subjects, including type of adverse event, severity, onset and duration (see ICH E2B). Additional safety and tolerability evaluations may be needed in specific subpopulations, such as females, the elderly (see ICH E7), the severely ill, or those who have a common concomitant treatment. These evaluations may need to address more specific issues (see ICH E3).

All safety and tolerability variables will need attention during evaluation, and the broad approach should be indicated in the protocol. All adverse events should be reported, whether or not they are considered to be related to treatment. All available data in the study population should be accounted for in the evaluation. Definitions of measurement units and reference ranges of laboratory variables should be made with care; if different units or different reference ranges appear in the same trial (e.g. if more than one laboratory is involved), then measurements should be appropriately standardised to allow a unified evaluation. Use of a toxicity grading scale should be prespecified and justified.

The incidence of a certain adverse event is usually expressed in the form of a proportion relating number of subjects experiencing events to number of subjects at risk. However, it is not always self-evident how to assess incidence. For example, depending on the situation the number of exposed subjects or the extent of exposure (in person-years) could be considered for the denominator. Whether the purpose of the calculation is to estimate a risk or to make a comparison between treatment groups it is important that the definition is given in the protocol. This is especially important if long-term treatment is planned and a substantial proportion of treatment withdrawals or deaths are expected. For such situations survival analysis methods should be considered and cumulative adverse event rates calculated in order to avoid the risk of underestimation.

In situations when there is a substantial background noise of signs and symptoms (e.g. in psychiatric trials) one should consider ways of accounting for this in the estimation of risk for different adverse events. One such method is to make use of the 'treatment emergent' (see Glossary) concept in which adverse events are recorded only if they emerge or worsen relative to pretreatment baseline.

Other methods to reduce the effect of the background noise may also be appropriate such as ignoring adverse events of mild severity or requiring that an event should have been observed at repeated visits to qualify for inclusion in the numerator. Such methods should be explained and justified in the protocol.

6.4 Statistical Evaluation

The investigation of safety and tolerability is a multidimensional problem. Although some specific adverse effects can usually be anticipated and specifically monitored for any drug, the range of possible adverse effects is very large, and new and unforeseeable effects are always possible. Further, an adverse event experienced after a protocol violation, such as use of an excluded medication, may introduce a bias. This background underlies the statistical difficulties associated with the analytical evaluation of safety and tolerability of drugs, and means that conclusive information from confirmatory clinical trials is the exception rather than the rule.

In most trials the safety and tolerability implications are best addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals wherever this aids interpretation. It is also valuable to make use of graphical presentations in which patterns of adverse events are displayed both within treatment groups and within subjects.

The calculation of p-values is sometimes useful either as an aid to evaluating a specific difference of interest, or as a 'flagging' device applied to a large number of safety and tolerability variables to highlight differences worth further attention. This is particularly useful for laboratory data, which otherwise can be difficult to summarise appropriately. It is recommended that laboratory data be subjected to both a quantitative analysis, e.g. evaluation of treatment means, and a qualitative analysis where counting of numbers above or below certain thresholds are calculated.

If hypothesis tests are used, statistical adjustments for multiplicity to quantify the type I error are appropriate, but the type II error is usually of more concern. Care should be taken when interpreting putative statistically significant findings when there is no multiplicity adjustment.

In the majority of trials investigators are seeking to establish that there are no clinically unacceptable differences in safety and tolerability compared with either a comparator drug or a placebo. As is the case for non-inferiority or equivalence evaluation of efficacy the use of confidence intervals is preferred to hypothesis testing in this situation. In this way, the considerable imprecision often arising from low frequencies of occurrence is clearly demonstrated.

6.5 Integrated Summary

The safety and tolerability properties of a drug are commonly summarised across trials continuously during an investigational product's development and in particular at the time of a marketing application. The usefulness of this summary, however, is dependent on adequate and well-controlled individual trials with high data quality.

The overall usefulness of a drug is always a question of balance between risk and benefit and in a single trial such a perspective could also be considered, even if the assessment of risk/benefit usually is performed in the summary of the entire clinical trial program. (See section 7.2.2)

For more details on the reporting of safety and tolerability, see Chapter 12 of ICH E3.

VII.REPORTING

7.1 Evaluation and Reporting

As stated in the Introduction, the structure and content of clinical study reports is the subject of ICH E3. That ICH guidance fully covers the reporting of statistical work, appropriately integrated with clinical and other material. The current section is therefore relatively brief.

During the planning phase of a trial the principal features of the analysis should have been specified in the protocol as described in Section 5. When the conduct of the trial is over and the data are assembled and available for preliminary inspection, it is valuable to carry out the blind review of the planned analysis also described in Section 5. This pre-analysis review, blinded to treatment, should cover decisions concerning, for example, the exclusion of subjects or data from the analysis sets; possible transformations may also be checked, and outliers defined; important covariates identified in other recent research may be added to the model; the use of parametric or non-parametric methods may be reconsidered. Decisions made at this time should be described in the report, and should be distinguished from those made after the statistician has had access to the treatment codes, as blind decisions will generally introduce less potential for bias. Statisticians or other staff involved in unblinded interim analysis should not participate in the blind review or in making modifications to the statistical analysis plan. When the blinding is compromised by the possibility that treatment induced effects may be apparent in the data, special care will be needed for the blind review.

Many of the more detailed aspects of presentation and tabulation should be finalised at or about the time of the blind review so that by the time of the actual analysis full plans exist for all its aspects including subject selection, data selection and modification, data summary and tabulation, estimation and hypothesis testing. Once data validation is complete, the analysis should proceed according to the pre-defined plans; the more these plans are adhered to, the greater the credibility of the results. Particular attention should be paid to any differences between the planned analysis and the actual analysis as described in the protocol, protocol amendments or the updated statistical analysis plan based on a blind review of data. A careful explanation should be provided for deviations from the planned analysis.

All subjects who entered the trial should be accounted for in the report, whether or not they are included in the analysis. All reasons for exclusion from analysis should be documented; for any subject included in the full analysis set but not in the per protocol set, the reasons for exclusion from the latter should also be documented. Similarly, for all subjects included in an analysis set, the measurements of all important variables should be accounted for at all relevant time-points.

The effect of all losses of subjects or data, withdrawals from treatment and major protocol violations on the main analyses of the primary variable(s) should be considered carefully. Subjects lost to follow up, withdrawn from treatment, or with a severe protocol violation should be identified, and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

Descriptive statistics form an indispensable part of reports. Suitable tables and/or graphical presentations should illustrate clearly the important features of the primary and secondary variables and of key prognostic and demographic variables. The results of the main analyses relating to the objectives of the trial should be the subject of particularly careful descriptive presentation. When reporting the results of significance tests, precise p-values (e.g.'p=0.034') should be reported rather than making exclusive reference to critical values.

Although the primary goal of the analysis of a clinical trial should be to answer the questions posed by its main objectives, new questions based on the observed data may well emerge during the unblinded analysis. Additional and perhaps complex statistical analysis may be the consequence. This additional work should be strictly distinguished in the report from work which was planned in the protocol.

The play of chance may lead to unforeseen imbalances between the treatment groups in terms of baseline measurements not pre-defined as covariates in the planned analysis but having some prognostic importance nevertheless. This is best dealt with by showing that an additional analysis which accounts for these imbalances reaches essentially the same conclusions as the planned analysis. If this is not the case, the effect of the imbalances on the conclusions should be discussed.

In general, sparing use should be made of unplanned analyses. Such analyses are often carried out when it is thought that the treatment effect may vary according to some other factor or factors. An attempt may then be made to identify subgroups of subjects for whom the effect is particularly beneficial. The potential dangers of over-interpretation of unplanned subgroup analyses are well known (see also Section 5.7), and should be carefully avoided. Although similar problems of interpretation arise if a treatment appears to have no benefit, or an adverse effect, in a subgroup of subjects, such possibilities should be properly assessed and should therefore be reported.

Finally statistical judgement should be brought to bear on the analysis, interpretation and presentation of the results of a clinical trial. To this end the trial statistician should be a member of the team responsible for the clinical study report, and should approve the clinical report.

7.2 Summarising the Clinical Database

An overall summary and synthesis of the evidence on safety and efficacy from all the reported clinical trials is required for a marketing application (Expert report in EU, integrated summary reports in USA, Gaiyo in Japan). This may be accompanied, when appropriate, by a statistical combination of results.

Within the summary a number of areas of specific statistical interest arise: describing the demography and clinical features of the population treated during the course of the clinical trial programme; addressing the key questions of efficacy by considering the results of the relevant (usually controlled) trials and highlighting the degree to which they reinforce or contradict each other; summarising the safety information available from the combined database of all the trials whose results contribute to the marketing application and identifying potential safety issues. During the design of a clinical programme careful attention should be paid to the uniform definition and collection of measurements which will facilitate subsequent interpretation of the series of trials, particularly if they are likely to be combined across trials. A common dictionary for recording the details of medication, medical history and adverse events should be selected and used. A common definition of the primary and secondary variables is nearly always worthwhile, and essential for meta-analysis. The manner of measuring key efficacy variables, the timing of assessments relative to randomisation/entry, the handling of protocol violators and deviators and perhaps the definition of prognostic factors, should all be kept compatible unless there are valid reasons not to do so.

Any statistical procedures used to combine data across trials should be described in detail. Attention should be paid to the possibility of bias associated with the selection of trials, to the homogeneity of their results, and to the proper modelling of the various sources of variation. The sensitivity of conclusions to the assumptions and selections made should be explored.

7.2.1 Efficacy Data

Individual clinical trials should always be large enough to satisfy their objectives. Additional valuable information may also be gained by summarising a series of clinical trials which address essentially identical key efficacy questions. The main results of such a set of trials should be presented in an identical form to permit

comparison, usually in tables or graphs which focus on estimates plus confidence limits. The use of meta-analytic techniques to combine these estimates is often a useful addition, because it allows a more precise overall estimate of the size of the treatment effects to be generated, and provides a complete and concise summary of the results of the trials. Under exceptional circumstances a meta analytic approach may also be the most appropriate way, or the only way, of providing sufficient overall evidence of efficacy via an overall hypothesis test. When used for this purpose the meta-analysis should have its own prospectively written protocol.

7.2.2 Safety Data

In summarising safety data it is important to examine the safety database thoroughly for any indications of potential toxicity, and to follow up any indications by looking for an associated supportive pattern of observations. The combination of the safety data from all human exposure to the drug provides an important source of information, because its larger sample size provides the best chance of detecting the rarer adverse events and, perhaps, of estimating their approximate incidence. However, incidence data from this database are difficult to evaluate because of the lack of a comparator group, and data from comparative trials are especially valuable in overcoming this difficulty. The results from trials which use a common comparator (placebo or specific active comparator) should be combined and presented separately for each comparator providing sufficient data.

All indications of potential toxicity arising from exploration of the data should be reported. The evaluation of the reality of these potential adverse effects should take account of the issue of multiplicity arising from the numerous comparisons made. The evaluation should also make appropriate use of survival analysis methods to exploit the potential relationship of the incidence of adverse events to duration of exposure and/or follow-up. The risks associated with identified adverse effects should be appropriately quantified to allow a proper assessment of the risk/benefit relationship.

GLOSSARY

Bayesian Approaches

Approaches to data analysis that provide a posterior probability distribution for some parameter (e.g. treatment effect), derived from the observed data and a prior probability distribution for the parameter. The posterior distribution is then used as the basis for statistical inference.

Bias (Statistical & Operational)

The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as 'operational' bias. The other sources of bias listed above are referred to as 'statistical'.

Blind Review

The checking and assessment of data during the period of time between trial completion (the last observation on the last subject) and the breaking of the blind, for the purpose of finalising the planned analysis.

Content Validity

The extent to which a variable (e.g. a rating scale) measures what it is supposed to measure.

Double-Dummy

A technique for retaining the blind when administering supplies in a clinical trial, when the two treatments cannot be made identical. Supplies are prepared for Treatment A (active and indistinguishable placebo) and for Treatment B (active and indistinguishable placebo). Subjects then take two sets of treatment; either A (active) and B (placebo), or A (placebo) and B (active).

Dropout

A subject in a clinical trial who for any reason fails to continue in the trial until the last visit required of him/her by the study protocol.

Equivalence Trial

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

Frequentist Methods

Statistical methods, such as significance tests and confidence intervals, which can be interpreted in terms of the frequency of certain outcomes occurring in hypothetical repeated realisations of the same experimental situation.

Full Analysis Set

The set of subjects that is as close as possible to the ideal implied by the intention-to-treat principle. It is derived from the set of all randomised subjects by minimal and justified elimination of subjects.

Generalisability, Generalisation

The extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings.

Global Assessment Variable

A single variable, usually a scale of ordered categorical ratings, which integrates objective variables and the investigator's overall impression about the state or change in state of a subject.

Independent 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.

Intention-To-Treat Principle

The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e. the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment.

Interaction (Qualitative & Quantitative)

The situation in which a treatment contrast (e.g. difference between investigational product and control) is dependent on another factor (e.g. centre). A quantitative interaction refers to the case where the magnitude of the contrast differs at the different levels of the factor, whereas for a qualitative interaction the direction of the contrast differs for at least one level of the factor.

Inter-Rater Reliability

The property of yielding equivalent results when used by different raters on different occasions.

Intra-Rater Reliability

The property of yielding equivalent results when used by the same rater on different occasions.

Interim Analysis

Any analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to the formal completion of a trial.

Meta-Analysis

The formal evaluation of the quantitative evidence from two or more trials bearing on the same question. This most commonly involves the statistical combination of summary statistics from the various trials, but the term is sometimes also used to refer to the combination of the raw data.

Multicentre 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.

Non-Inferiority Trial

A trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent (active or placebo control).

Preferred and Included Terms

In a hierarchical medical dictionary, for example MedDRA, the included term is the lowest level of dictionary term to which the investigator description is coded. The preferred term is the level of grouping of included terms typically used in reporting frequency of occurrence. For example, the investigator text “Pain in the left arm” might be coded to the included term “Joint pain”, which is reported at the preferred term level as “Arthralgia”.

Per Protocol Set (Valid Cases, Efficacy Sample, Evaluable Subjects Sample)

The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations.

Safety & Tolerability

The safety of a medical product concerns the medical risk to the subject, usually assessed in a clinical trial by laboratory tests (including clinical chemistry and haematology), vital signs, clinical adverse events (diseases, signs and symptoms), and

other special safety tests (e.g. ECGs, ophthalmology). The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject.

Statistical Analysis Plan

A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

Superiority Trial

A trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent (active or placebo control).

Surrogate Variable

A variable that provides an indirect measurement of effect in situations where direct measurement of clinical effect is not feasible or practical.

Treatment Effect

An effect attributed to a treatment in a clinical trial. In most clinical trials the treatment effect of interest is a comparison (or contrast) of two or more treatments.

Treatment Emergent

An event that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state.

Trial Statistician

A statistician who has a combination of education/training and experience sufficient to implement the principles in this guidance and who is responsible for the statistical aspects of the trial.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS

TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

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ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

ICH E9(R1)

ICH Consensus Guideline

TABLE OF CONTENTS

A.1. PURPOSE AND SCOPE

To properly inform decision making by pharmaceutical companies, regulators, patients, physicians and other stakeholders, clear descriptions of the benefits and risks of a treatment (medicine) for a given medical condition should be made available. Without such clarity, there is a concern that the reported "treatment effect" will be misunderstood. This addendum presents a structured framework to strengthen the dialogue between disciplines involved in the formulation of clinical trial objectives, design, conduct, analysis and interpretation, as well as between sponsor and regulator regarding the treatment effect(s) of interest that a clinical trial should address.

Precision in describing a treatment effect of interest is facilitated by constructing the "estimand" (see Glossary; A.3.) corresponding to a clinical question of interest. Clarity requires a thoughtful envisioning of "intercurrent events" (see Glossary; A.3.1.) such as discontinuation of assigned treatment, use of an additional or alternative treatment and terminal events such as death. The description of an estimand should reflect the clinical question of interest in respect of these intercurrent events, and this addendum introduces strategies to reflect different questions of interest that might be posed. The choice of strategies can influence how more conventional attributes of a trial are reflected when describing the clinical question, for example the treatments, population or the variable (endpoint) of interest.

The statistical analysis of clinical trial data should be aligned to the estimand. This addendum clarifies the role of "sensitivity analysis" (see Glossary) to explore robustness of conclusions from the main statistical analysis.

Throughout the addendum, references to the original ICH E9 are made using x.y. References within this addendum are made using A.x.y.

This addendum clarifies and extends ICH E9 in respect of the following topics. Firstly, ICH E9 introduced the Intention-To-Treat (ITT) principle in connection with the effect of a treatment policy in a randomised controlled trial, whereby subjects are followed, assessed and analysed irrespective of their compliance to the planned course of treatment, indicating that preservation of randomisation provides a secure foundation for statistical tests. Multiple consequences arising from the ITT principle can be distinguished. Firstly, that the trial analysis should include all subjects relevant for the research question. Secondly, that subjects should be included in the analysis as randomised. Taken directly from the definition of the ITT principle (see ICH E9 Glossary), a third consequence is that subjects should be followed-up and assessed regardless of adherence to the planned course of treatment and that those assessments should be used in the analysis. It remains undisputed that randomisation is a cornerstone of controlled clinical trials and that analysis should aim at exploiting the advantages of randomisation to the greatest extent possible. However, the question remains whether estimating an effect in accordance with the ITT principle always represents the treatment effect of greatest relevance to regulatory and clinical decision making. The framework outlined in this addendum gives a basis for describing different treatment effects

and some points to consider for the design and analysis of trials to give estimates of these treatment effects that are reliable for decision making.

Secondly, issues considered generally under data handling and "missing data" (see Glossary) are re-visited. Two important distinctions are made. Firstly, the addendum distinguishes discontinuation of randomised treatment from study withdrawal. The former represents an intercurrent event, to be addressed in the precise specification of the trial objective through the estimand. The latter gives rise to missing data to be addressed in the statistical analysis. Consider, for example, a subject switching treatments in an oncology trial, and a subject for whom no outcome event can be observed because the trial is completed. The former represents an intercurrent event and the clinical question of interest in respect of that should be clear. The latter is administrative censoring which needs to be addressed as a missing data problem in the statistical analysis. Having clarity in the estimand gives a basis for planning which data need to be collected and hence which data, when not collected, present a missing data problem to be addressed in the statistical analysis. In turn, methods to address the problem presented by missing data can be selected to align with the estimand. Secondly, the addendum highlights the distinct consequences of different intercurrent events. Events such as discontinuation of treatment, switching between treatments, or use of an additional medication may render the later measurements of the variable irrelevant or difficult to interpret even when they can be collected. Measurements after a subject dies do not exist.

Thirdly, issues related to the concept of analysis sets are considered in the framework. Section 5.2. strongly recommends that analysis of superiority trials be based on the full analysis set, defined to be as close as possible to including all randomised subjects. However, trials often include repeated measurements on the same subject. Elimination of some planned measurements on some subjects, perhaps because the measurement is considered irrelevant or difficult to interpret, can have similar consequences to excluding subjects altogether from the full analysis set, i.e. that the initial randomisation is not fully preserved. A consequence of this is that the theoretical benefits that randomisation confers on testing hypotheses about treatment effects and the practical benefits of balancing confounding factors at baseline can be diminished. In addition, a meaningful value of the outcome variable might not exist, as when the subject dies. Section 5.2. does not directly address these issues. Clarity is introduced by carefully defining the treatment effect of interest in a way that determines both the population of subjects to be included in the estimation of that treatment effect and the observations from each subject to be included in the analysis considering the occurrence of intercurrent events. The meaning and role of an analysis of the per protocol set is also re-visited in this addendum; in particular whether the need to explore the impact of protocol violations and deviations can be addressed in a way that is less biased and more interpretable than naïve analysis of the per protocol set.

Finally, the concept of robustness (see 1.2.) is given expanded discussion under the heading of sensitivity analysis. A distinction is made between the sensitivity of inference to the assumptions of a chosen method of analysis and the sensitivity to the choice of analytic approach more broadly. With precise specification of an agreed estimand and a method of

analysis that is both aligned to the estimand and pre-specified to a level of detail that it can be replicated precisely by a third party, regulatory interest can focus on sensitivity to deviations from assumptions and limitations in the data in respect of a particular analysis.

The principles outlined in this addendum are relevant whenever a treatment effect is estimated, or a hypothesis related to a treatment effect is tested, whether related to efficacy or safety. While the main focus is on randomised clinical trials, the principles are also applicable for single arm trials and observational studies. The framework applies to any data type, including longitudinal, time-to-first event, and recurrent event data. Regulatory interest in the application of the principles outlined will be greater for confirmatory clinical trials and, where used to generate confirmatory conclusions, for data integrated across trials.

A.2. A FRAMEWORK TO ALIGN PLANNING, DESIGN, CONDUCT, ANALYSIS AND INTERPRETATION

Trial planning should proceed in sequence (Figure 1). Clear trial objectives should be translated into key clinical questions of interest by defining suitable estimands. An estimand defines the target of estimation for a particular trial objective (i.e. "what is to be estimated", see A.3.). A suitable method of estimation (i.e. the analytic approach, referred to as the main "estimator", see Glossary) can then be selected (see A.5.1.). The main estimator will be underpinned by certain assumptions. To explore the robustness of inferences from the main estimator to deviations from its underlying assumptions, a sensitivity analysis should be conducted, in the form of one or more analyses, targeting the same estimand (see A.5.2.).

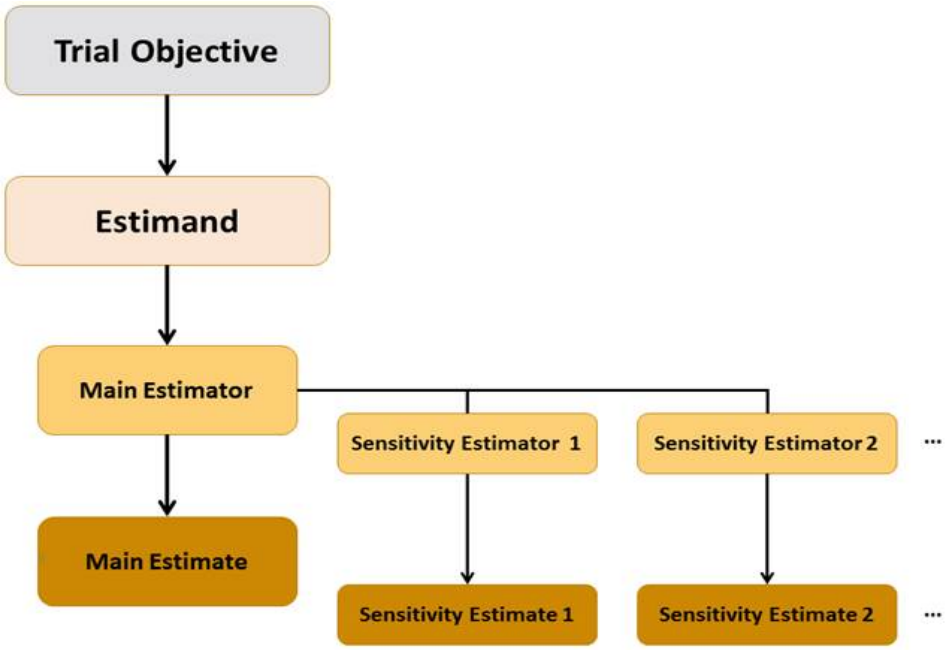

Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

This framework enables proper trial planning that clearly distinguishes between the target of estimation (trial objective, estimand), the method of estimation (estimator), the numerical result ("estimate", see Glossary), and a sensitivity analysis. This will assist sponsors in planning trials, regulators in their reviews, and will enhance the interactions between these parties when discussing the suitability of clinical trial designs, and the interpretation of clinical trial results.

The specification of appropriate estimands (see A.3.) will usually be the main determinant for aspects of trial design, conduct (see A.4.) and analysis (see A.5.).

A.3. ESTIMANDS

Central questions for drug development and licensing are to establish the existence, and to estimate the magnitude, of treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under alternative treatment (i.e. had they not received the treatment, or had they received a different treatment). An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarises at a population level what the outcomes would be in the same patients under different treatment conditions being compared. The targets of estimation are to be defined in advance of a clinical trial. Once defined, a trial can be designed to enable reliable estimation of the targeted treatment effect.

The description of an estimand involves precise specifications of certain attributes, which should be developed based not only on clinical considerations but also on how intercurrent events are reflected in the clinical question of interest. Section A.3.1. introduces intercurrent events. Section A.3.2. introduces strategies to describe the question of interest in respect of intercurrent events. Section A.3.3. describes the attributes of an estimand and Section A.3.4. gives considerations for its construction. It is critically important to understand the differences between the strategies and to precisely articulate which are used in constructing the estimand.

A.3.1. Intercurrent Events to be Reflected in the Clinical Question of Interest

Intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

Intercurrent events need to be considered in the description of a treatment effect because measurements of the variable can be influenced by the intercurrent event and the occurrence of the intercurrent event may depend on treatment. For example, two patients might be exposed initially to the same treatment and provide the same measure of outcome, but if one patient has received additional medication, the information that the two measures give about the treatment differs between the two patients. Furthermore, whether a patient needs to take additional

medication, and whether or not a patient can continue taking treatment, may depend on the treatment to which they are exposed. Unlike missing data, intercurrent events are not to be thought of as a drawback to be avoided in clinical trials. Discontinuation of prescribed treatment, use of additional medication, and other such events may occur in clinical practice as they do in clinical trials, and their occurrence needs to be considered explicitly when defining the clinical question of interest.

Examples of intercurrent events that can affect interpretation of the measurements include discontinuation of assigned treatment and use of an additional or alternative therapy. Use of an additional or alternative therapy can take multiple forms, including change to background or concomitant therapy and switching between treatments of interest. Examples of intercurrent events that would affect the existence of the measurements include terminal events such as death and leg amputation (when assessing symptoms of diabetic foot ulcers), when these events are not part of the variable itself. Certain clinical events can also be intercurrent events, when their occurrence, or non-occurrence, defines a principal stratum of interest (see A.3.2.). Examples include tumour shrinkage defining objective response when assessing a treatment effect on duration of response in oncology and occurrence of infection when assessing a treatment effect on severity of infections occurring after vaccination of initially uninfected subjects.

An intercurrent event might be identified solely by the event itself, such as discontinuation of treatment, or might be more granular. For example, the reason for the event might be specified, such as discontinuation of treatment due to toxicity, or due to lack of efficacy; the event might require to be of certain magnitude or degree, such as use of additional medication exceeding a specified duration or dose; or the timing of the event might be specified, perhaps in relation to its proximity to the assessment of the variable. Some events will affect interpretation of the outcome measurements indefinitely, such as discontinuation of treatment, whilst others will affect interpretation only temporarily, such as short-term use of additional treatment. Indeed, additional or alternative treatments can be diverse; either replacing or supplementing a treatment on which the subject is experiencing inadequate benefit, as an alternative where a subject is not tolerating their assigned treatment, or as a short-term acute treatment to manage a temporary flare in disease symptoms. In a clinical trial, additional or alternative treatments are often identified as e.g. background treatment, rescue medication, prohibited medication, distinguishing their different roles and allowing them to be considered separately. The additional granularity, identifying different intercurrent events, is required if different strategies are to be used. If the intercurrent event for which a strategy needs to be selected depends not only on, for example, failure to continue with treatment, but also on the reason, magnitude or timing associated with that failure, this additional information should be defined and recorded accurately in the clinical trial. The description of intercurrent events might in theory reflect very specific details of treatment and follow-up, such as a single missed dose of a chronic treatment or a dose taken at the wrong time of day. Where such specific criteria are not expected to affect interpretation of the variable, they would not need to be addressed as intercurrent events.

As indicated above, consideration of intercurrent events is required when constructing the estimand. Because the estimand is to be defined in advance of trial design, neither study withdrawal nor other reasons for missing data (e.g. administrative censoring in trials with survival outcomes) are in themselves intercurrent events. Subjects who withdraw from the trial may have experienced an intercurrent event before withdrawal.

A.3.2. Strategies for Addressing Intercurrent Events when Defining the Clinical Question of Interest

Descriptions of various strategies are listed below, each reflecting a different clinical question of interest in respect of a particular intercurrent event. Whether or not the naming convention is used, it is required that the choices of strategy are unambiguously clear once the estimand is constructed. It is not necessary to use the same strategy to address all intercurrent events. Indeed, different strategies will often be used to reflect the clinical question of interest in respect of different intercurrent events. Section A.3.4. gives some considerations on selecting strategies to construct an estimand.

Treatment policy strategy

The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs. For example, when specifying how to address use of additional medication as an intercurrent event, the values of the variable of interest are used whether or not the patient takes additional medication.

If applied in relation to whether or not a patient continues treatment, and whether or not a patient experiences changes in other treatments (e.g. background or concomitant treatments), the intercurrent event is considered to be part of the treatments being compared. In that case, this reflects the comparison described in the ICH E9 Glossary (under ITT Principle) as the effect of a treatment policy.

In general, the treatment policy strategy cannot be implemented for intercurrent events that are terminal events, since values for the variable after the intercurrent event do not exist. For example, an estimand based on this strategy cannot be constructed with respect to a variable that cannot be measured due to death.

Hypothetical strategies

A scenario is envisaged in which the intercurrent event would not occur: the value of the variable to reflect the clinical question of interest is the value which the variable would have taken in the hypothetical scenario defined.

A wide variety of hypothetical scenarios can be envisaged, but some scenarios are likely to be of more clinical or regulatory interest than others. For example, it may be of clinical or regulatory importance to consider the effect of a treatment under different conditions from those of the trial that can be carried out. Specifically, when additional medication must be

made available for ethical reasons, a treatment effect of interest might concern the outcomes if the additional medication was not available. A very different hypothetical scenario might postulate that intercurrent events would not occur, or that different intercurrent events would occur. For example, for a subject that will suffer an adverse event and discontinue treatment, it might be considered whether the same subject would not have the adverse event or could continue treatment in spite of the adverse event. The clinical and regulatory interest of such hypotheticals is limited and would usually depend on a clear understanding of why and how the intercurrent event or its consequences would be expected to be different in clinical practice than in the clinical trial.

If a hypothetical strategy is proposed, it should be made clear what hypothetical scenario is envisaged. For example, wording such as "if the patient does not take additional medication" might lead to confusion as to whether the patient hypothetically does not take additional medication because it is not available or because the particular patient is supposed not to require it.

Composite variable strategies

This relates to the variable of interest (see A.3.3.). An intercurrent event is considered in itself to be informative about the patient's outcome and is therefore incorporated into the definition of the variable. For example, a patient who discontinues treatment because of toxicity may be considered not to have been successfully treated. If the outcome variable was already success or failure, discontinuation of treatment for toxicity would simply be considered another mode of failure. Composite variable strategies do not need to be limited to dichotomous outcomes, however. For example, in a trial measuring physical functioning, a variable might be constructed using outcomes on a continuous scale, with subjects who die being attributed a value reflecting the lack of ability to function. Composite variable strategies can be viewed as implementing the intention-to-treat principle in some cases where the original measurement of the variable might not exist or might not be meaningful, but where the intercurrent event itself meaningfully describes the patient's outcome, such as when the patient dies.

Terminal events, such as death, are perhaps the most salient examples of the need for the composite strategy. If a treatment saves lives, its effect on various measures in surviving patients may be of interest, but it would be inappropriate to say that the summary measure of interest was only the average value of some numerical measure in survivors. The outcome of interest is survival along with the numerical measures. For example, progression-free survival in oncology trials measures the treatment effect on a combination of the growth of the tumour and survival.

While on treatment strategies

For this strategy, response to treatment prior to the occurrence of the intercurrent event is of interest. Terminology for this strategy will depend on the intercurrent event of interest; e.g. "while alive", when considering death as an intercurrent event.

If a variable is measured repeatedly, its values up to the time of the intercurrent event may be considered relevant for the clinical question, rather than the value at the same fixed timepoint

for all subjects. The same applies to the occurrence of a binary outcome of interest up to the time of the intercurrent event. For example, subjects with a terminal illness may discontinue a purely symptomatic treatment because they die, yet the success of the treatment can be measured based on the effect on symptoms before death. Alternatively, subjects might discontinue treatment and, in some circumstances, it will be of interest to assess the risk of an adverse drug reaction while the patient is exposed to treatment.

Like the composite variable strategy, the while on treatment strategy can hence be thought of as impacting the definition of the variable, in this case by restricting the observation time of interest to the time before the intercurrent event. Particular care is required if the occurrence of the intercurrent event differs between the treatments being compared (see A.3.3.).

Principal stratum strategies

This relates to the population of interest (see A.3.3.). The target population might be taken to be the "principal stratum" (see Glossary) in which an intercurrent event would occur. Alternatively, the target population might be taken to be the principal stratum in which an intercurrent event would not occur. The clinical question of interest relates to the treatment effect only within the principal stratum. For example, it might be desired to know a treatment effect on severity of infections in the principal stratum of patients becoming infected after vaccination. Alternatively, a toxicity might prevent some patients from continuing the test treatment, but it would be desired to know the treatment effect among patients who are able to tolerate the test treatment.

It is important to distinguish "principal stratification" (see Glossary), which is based on potential intercurrent events (for example, subjects who would discontinue therapy if assigned to the test product), from subsetting based on actual intercurrent events (subjects who discontinue therapy on their assigned treatment). The subset of subjects who experience an intercurrent event on the test treatment will often be a different subset from those who experience the same intercurrent event on control. Treatment effects defined by comparing outcomes in these subsets confound the effects of the different treatments with the differences in outcomes possibly due to the differing characteristics of the subjects.

A.3.3. Estimand Attributes

The attributes below are used to construct the estimand, defining the treatment effect of interest.

The **treatment** condition of interest and, as appropriate, the alternative treatment condition to which comparison will be made (referred to as "treatment" through the remainder of this document). These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. (see Treatment Policy and Hypothetical strategies under A.3.2.).

The **population** of patients targeted by the clinical question. This will be represented by the entire trial population, a subgroup defined by a particular characteristic measured at baseline, or a principal stratum defined by the occurrence (or non-occurrence, depending on context) of a specific intercurrent event (see Principal Stratum strategies under A.3.2.).

The **variable** (or endpoint) to be obtained for each patient that is required to address the clinical question. The specification of the variable might include whether the patient experiences an intercurrent event (see Composite Variable and While on Treatment strategies under A.3.2.).

Precise specifications of treatment, population and variable are likely to address many of the intercurrent events considered in sponsor and regulator discussions of the clinical question of interest. The clinical question of interest in respect of any **other intercurrent events** will usually be reflected using the strategies introduced as treatment policy, hypothetical or while on treatment.

Finally, a **population-level summary** for the variable should be specified, providing a basis for comparison between treatment conditions.

When defining a treatment effect of interest, it is important to ensure that the definition identifies an effect due to treatment and not due to potential confounders such as differences in duration of observation or patient characteristics.

A.3.4. Considerations for Constructing an Estimand

The clinical questions of interest and associated estimands should be specified at the initial stages of planning any clinical trial. Precise specification of objectives for most trials will need to reflect discontinuation of treatment and use of additional or alternative treatments. In some settings terminal events, such as death, should be addressed. Some trial objectives can only be described with reference to clinical events, for example the duration of response in subjects who achieve a response.

The construction of an estimand should consider what is of clinical relevance for the particular treatment in the particular therapeutic setting. Considerations include the disease under study, the clinical context (e.g. the availability of alternative treatments), the administration of treatment (e.g. one-off dosing, short-term treatment or chronic dosing) and the goal of treatment (e.g. prevention, disease modification, symptom control). Also important is whether an estimate of the treatment effect can be derived that is reliable for decision making. For example, a clinical question on the treatment effect on clinical outcome regardless of which other therapies are to be used before that outcome is experienced differs to a clinical question on the treatment effect had no additional medication been available. Depending on the setting, either might represent a clinical question of interest. However, in both cases, a clinical trial designed to estimate these treatment effects will often include the possibility to use additional medications if medically required. For the former question, values after the use of additional treatment will be relevant. For the latter question, values after the additional treatment are not

directly relevant since the values also reflect the impact of that additional medication. It should be agreed that reliable estimation is possible before the choice of estimand is finalised. This includes, for the latter question, the methods to replace observations that are not to be used in the analysis.

When constructing the estimand it is necessary to have a clear understanding of the treatment to which the clinical question of interest pertains (see A.3.3.). Clear specifications for the treatments of interest might already reflect multiple relevant intercurrent events. Specifically, a treatment might already reflect the clinical question of interest in respect of changes in background treatment, concomitant medications, use of additional or later-line therapies, treatment-switching and conditioning regimens. For example, it is possible to specify treatment as *intervention A added to background therapy B, dosed as required*. In that case, changes to the dose of background therapy B would not need to be considered as an intercurrent event. However, the use of an additional therapy would need to be considered as an intercurrent event. If use of any additional medication is also reflected, using the treatment policy strategy for example, then treatment might be specified as *intervention A added to background therapy B, dosed as required, and with additional medication, as required*. Alternatively, if the treatment is specified as *intervention A,* then both changes in background therapy and use of additional therapy would be addressed as intercurrent events.

Discussions should also consider whether specifications for the population and variable attributes should be used to reflect the clinical question of interest in respect of any intercurrent events. Strategies can then be considered for any other intercurrent events. Usually an iterative process will be necessary to reach an estimand that is of clinical relevance for decision making, and for which a reliable estimate can be made. Some estimands, in particular those for which the measurements taken are relevant to the clinical question, can often be robustly estimated making few assumptions. Other estimands may require methods of analysis with more specific assumptions that may be more difficult to justify and that may be more sensitive to plausible changes in those assumptions (see A.5.1.). Where significant issues exist to develop an appropriate trial design or to derive an adequately reliable estimate for a particular estimand, an alternative estimand, trial design and method of analysis would need to be considered.

Avoiding or over-simplifying the process of discussing and constructing an estimand risks misalignment between trial objectives, trial design, data collection and method of analysis. Whilst an inability to derive a reliable estimate might preclude certain choices of strategy, it is important to proceed sequentially from the trial objective and an understanding of the clinical question of interest, and not for the choice of data collection and method of analysis to determine the estimand.

The experimental situation should also be considered. If the management of subjects (e.g. dose adjustment for intolerance, rescue treatment for inadequate response, burden of clinical trial assessments) under a clinical trial protocol is justified to be different to that which is anticipated in clinical practice, this might be reflected in the construction of the estimand.

Once constructed, the estimand should define a target of estimation clearly and unambiguously. Consider an intercurrent event of discontinuation of treatment; it is of utmost importance to distinguish between treatment effects of interest based on the principal stratum of patients who would be able to continue if administered the test treatment and the effect during continued treatment. Furthermore, neither of these should be taken to represent an effect if all patients can continue with treatment.

As stated above, when using the hypothetical strategy, some conditions are likely to be more acceptable for regulatory decision making than others. The hypothetical conditions described should therefore be justified for the quantification of an interpretable treatment effect that is relevant to inform the decisions to be taken by regulators, and use of the medicine in clinical practice. The question of what the values for the variable of interest would have been if rescue medication had not been available may be an important one. In contrast, the question of what the values for the variable of interest would have been under the hypothetical condition that subjects who discontinued treatment because of adverse drug reaction had in fact continued with treatment, might not be justifiable as being of clinical or regulatory interest. A clinical question of interest based on the effect if all subjects had been able to continue with treatment is not well-defined without a thorough discussion of the hypothetical conditions under which it is supposed that they would have continued. The inability to tolerate a treatment may constitute, in itself, evidence of an inability to achieve a favourable outcome.

Characterising beneficial effects using estimands based on the treatment policy strategy might also be more generally acceptable to support regulatory decision making, specifically in settings where estimands based on alternative strategies might be considered of greater clinical interest, but main and sensitivity estimators cannot be identified that are agreed to support a reliable estimate or robust inference. An estimand based on the treatment policy strategy might offer the possibility to obtain a reliable estimate of a treatment effect that is still relevant. In this situation, it is recommended to also include those estimands that are considered to be of greater clinical relevance and to present the resulting estimates along with a discussion of the limitations, in terms of trial design or statistical analysis, for that specific approach. When constructing estimands based on the treatment policy strategy, inference can be complemented by defining an additional estimand and analysis pertaining to each intercurrent event for which the strategy is used; for example, contrasting both the treatment effect on a symptom score and the proportion of subjects using additional medication under each treatment. Similarly, an estimand using a while on treatment strategy should usually be accompanied by the additional information on the time to intercurrent event distributions, and an estimand based on a principal stratum would usefully be accompanied by information on the proportion of patients in that stratum, if available.

The considerations informing the construction of estimand to support regulatory decision making based on a non-inferiority or equivalence objective may differ to those for the choice of estimand for a superiority objective. As explained in ICH E9, the problem facing the regulator in their decision making is different when based on non-inferiority or equivalence studies compared to superiority studies. In Section 3.3.2. it is stated that such trials are not

conservative in nature and the importance of minimising the number of protocol violations and deviations, non-adherence and study withdrawals is indicated. In Section 5.2.1. it is described that the result of the Full Analysis Set (FAS) is generally not conservative and that its role in such trials should be considered very seriously. Estimands that are constructed with one or more intercurrent events accounted for using the treatment policy strategy present similar issues for non-inferiority and equivalence trials as those related to analysis of the FAS under the ITT principle. Responses in both treatment groups can appear more similar following discontinuation of randomised treatment or use of another medication for reasons that are unrelated to the similarity of the initially randomised treatments. Estimands could be constructed to directly address those intercurrent events which can lead to the attenuation of differences between treatment arms (e.g. discontinuations from treatment and use of additional medications). When selecting strategies, it might be important to distinguish between trials designed to detect whether differences exist between treatments containing the same or similar active substance (e.g. comparison of a biosimilar to a reference treatment) and trials where a non-inferiority or equivalence hypothesis is used in order to establish and quantify evidence of efficacy. An estimand can be constructed to target a treatment effect that prioritises sensitivity to detect differences between treatments, if appropriate for regulatory decision making.

A.4. IMPACT ON TRIAL DESIGN AND CONDUCT

The design of a trial needs to be aligned to the estimands that reflect the trial objectives. A trial design that is suitable for one estimand might not be suitable for other estimands of potential importance. Clear definitions for the estimands on which quantification of treatments effects will be based should inform the choices that are made in relation to trial design. This includes determining the inclusion and exclusion criteria that identify the target population, the treatments, including the medications that are allowed and those that are prohibited in the protocol, and other aspects of patient management and data collection. If interest lies, for example, in understanding the treatment effect regardless of whether a particular intercurrent event occurs, a trial in which the variable is collected for all subjects is appropriate. Alternatively, if the estimands that are required to support regulatory decision making do not require the collection of the variable after an intercurrent event, then the benefits of collecting such data for other estimands should be weighed against any complications and potential drawbacks of the collection.

Efforts should be made to collect all data that are relevant to support estimation, including data that inform the characterisation, occurrence and timing of intercurrent events. Data cannot always be collected. Certainly, subjects cannot be retained in a trial against their will, and in some trials missing data for some subjects is inevitable by design, such as administrative censoring in trials with survival outcomes. On the contrary, the occurrence of intercurrent events such as discontinuation of treatment, treatment switching, or use of additional medication, does not imply that the variable cannot be measured thereafter, though the measures may not be relevant. For terminal events such as death, the variable cannot be

measured after the intercurrent event, but neither should these data generally be regarded as missing.

Not collecting any data needed to assess an estimand results in a missing data problem for subsequent statistical inference. The validity of statistical analyses may rest upon untestable assumptions and, depending on the proportion of missing data, this may undermine the robustness of the results (see A.5.). A prospective plan to collect informative reasons for why data intended for collection are missing may help to distinguish the occurrence of intercurrent events from missing data. This in turn may improve the analysis and may also lead to a more appropriate choice of sensitivity analysis. For example, "loss to follow-up" may more accurately be recorded as "treatment discontinuation due to lack of efficacy". Where that has been defined as an intercurrent event, this can be reflected through the strategy chosen to account for that intercurrent event and not as a missing data problem. To reduce missing data, measures can be implemented to retain subjects in the trial. However, measures to reduce or avoid intercurrent events that would normally occur in clinical practice risk reducing the external validity of the trial. For example, selection of the trial population or use of titration schemes or concomitant medications to mitigate the impact of toxicity might not be suitable if those same measures would not be implemented in clinical practice.

Randomisation and blinding remain cornerstones of controlled clinical trials. Design techniques for avoiding bias are addressed in Section 2.3. Certain estimands may necessitate, or may benefit from, use of trial designs such as run-in or enrichment designs, randomised withdrawal designs, or titration designs. It might be of interest to identify the principal stratum of subjects who can tolerate a treatment using a run-in period, in advance of randomising those subjects between test treatment and control. Dialogue between regulator and sponsor would need to consider whether the proposed run-in period is appropriate to identify the target population, and whether the choices made for the subsequent trial design (e.g. washout period, randomisation) supports the estimation of the target treatment effect and associated inference. These considerations might limit the use of these trial designs, and use of that particular strategy.

A precise description of the treatment effects of interest should inform sample size calculations. Particular care should be taken when making reference to historical studies that might, implicitly or explicitly, have reported estimated treatment effects or variability based on a different estimand. Where all subjects contribute information to the analysis, and where the impact of the strategy to reflect intercurrent events is included in the effect size that is targeted and the expected variance, it is not usually necessary to additionally inflate the calculated sample size by the expected proportion of subject withdrawals from the trial.

Section 7.2. addresses issues related to summarising data across clinical trials. The need to have consistent definitions for the variables of interest is highlighted and this can be extended to the construction of estimands. Hence, in situations when synthesising evidence from across a clinical trial programme is envisaged at the planning stage, a suitable estimand should be constructed, included in the trial protocols, and reflected in the choices made for the design of

the contributing trials. Similar considerations apply to the design of a meta-analysis, using estimated effect sizes from completed trials to determine non-inferiority margins, or the use of external control groups for the interpretation of single-arm trials. A naïve comparison between data sources, or integration of data from multiple trials without consideration and specification of the estimand that is addressed in each data presentation or statistical analysis, could be misleading.

More generally, a trial is likely to have multiple objectives translated into multiple estimands, each associated with statistical testing and estimation. The multiplicity issues arising should be addressed.

A.5. IMPACT ON TRIAL ANALYSIS

A.5.1. Main Estimation

An estimand for the effect of treatment relative to a control will be estimated by comparing the outcomes in a group of subjects on the treatment to those in a similar group of subjects on the control. For a given estimand, an aligned method of analysis, or estimator, should be implemented that is able to provide an estimate on which reliable interpretation can be based. The method of analysis will also support calculation of confidence intervals and tests for statistical significance. An important consideration for whether an interpretable estimate will be available is the extent of assumptions that need to be made in the analysis. Key assumptions should be stated explicitly together with the estimand and accompanying main and sensitivity estimators. Assumptions should be justifiable and implausible assumptions should be avoided. The robustness of the results to potential departures from the underlying assumptions should be assessed through an estimand-aligned sensitivity analysis (see A.5.2.). Estimation that relies on many or strong assumptions requires more extensive sensitivity analysis. Where the impact of deviations from assumptions cannot be comprehensively investigated through sensitivity analysis, that particular combination of estimand and method of analysis might not be acceptable for decision making.

All methods of analysis rely on assumptions, and different methods may rely on different assumptions even when aligned to the same estimand. Nevertheless, some kinds of assumption are inherent in all methods of analysis aligned to estimands that use each of the different strategies outlined; for example, the methodology for predicting the outcomes that would have been observed in the hypothetical scenario, or for identifying a suitable target population in a principal stratum strategy. Some examples are given below related to the different strategies used to reflect the occurrence of intercurrent events. The issues highlighted will be key components of discussion between sponsor and regulator in advance of an estimand, main analysis and sensitivity analysis being agreed.

Analysis aligned with a treatment policy strategy to address a given intercurrent event may entail stronger or weaker assumptions depending on the design and conduct of the trial. When most subjects are followed-up even after the respective intercurrent event (e.g. discontinuation

of treatment), the remaining problem of missing data may be relatively minor. In contrast, when observation is terminated after an intercurrent event, which is obviously undesirable in respect of this strategy, the assumption that (unobserved) outcomes for discontinuing subjects are similar to the (observed) outcomes for those who remain on treatment will often be implausible. An alternative approach to handle the missing data would need to be justified and sensitivity analysis will be expected.

Analysis aligned to a hypothetical strategy involves outcomes different from those actually observed; for example, outcomes if rescue medication had not been given when in fact it was. Observations before the rescue medication and observations on subjects who did not require rescue medication may be informative, but only under strong assumptions.

A composite variable strategy can avoid statistical assumptions about data after an intercurrent event by considering occurrence of the intercurrent event as a component of the outcome. The potential concern relates less to assumptions for estimation, and more to the interpretation of the estimated treatment effect. For the estimand to be interpretable, if scores are assigned for failure because the intercurrent event occurs, these should meaningfully reflect the lack of benefit to the patient (e.g. death may be reflected differently than discontinuation of treatment due to adverse event).

Estimands constructed based on a while on treatment strategy can be estimated provided outcomes are collected up to the time of the intercurrent event. Again, the crucial assumptions concern interpretation. Take discontinuation of treatment by way of example. Outcomes while on treatment may be improved but the treatment may also shorten, or lengthen, the treatment period by provoking, or delaying, discontinuations, and both these effects should be considered in interpretation and assessment of clinical benefit.

Analysis aligned to a principal stratum strategy usually requires strong assumptions. For example, some principal stratification methods infer this from baseline characteristics of the subjects, but the correctness of this inference may be difficult to assess. This difficulty cannot be avoided by simplified methods, however. For example, simply comparing subjects who do not have an intercurrent event on the test treatment to those who do not have an event on control, assuming intercurrent events are unrelated to treatment, is very difficult to justify.

Even after defining estimands that address intercurrent events in an appropriate manner and making efforts to collect the data required for estimation (see A.4.), some data may still be missing, including e.g. administrative censoring in trials with survival outcomes. Failure to collect relevant data should not be confused with the choice not to collect, or to collect and not to use, data made irrelevant by an intercurrent event. For example, data that were intended to be collected after discontinuation of trial medication to inform an estimand based on the treatment policy strategy are missing if uncollected; however, the same data points might be irrelevant for another strategy, and thus, for the purpose of that second estimand, are not missing if uncollected. Where those efforts to collect data are not successful it becomes necessary to make assumptions to handle the missing data in the statistical analysis. Handling of missing data should be based on clinically plausible assumptions and, where possible, guided

by the strategies employed in the description of the estimand. The approach taken may be based on observed covariates and post-baseline data from individual subjects and from other similar subjects. Criteria to identify similar subjects might include whether or not the intercurrent event has occurred. For example, for subjects who discontinue treatment without further data being collected, a model may use data from other subjects who discontinued treatment but for whom data collection has continued.

A.5.2. Sensitivity Analysis

A.5.2.1. Role of Sensitivity Analysis

Inferences based on a particular estimand should be robust to limitations in the data and deviations from the assumptions used in the statistical model for the main estimator. This robustness is evaluated through a sensitivity analysis. Sensitivity analysis should be planned for the main estimators of all estimands that will be important for regulatory decision making and labelling in the product information. This can be a topic for discussion and agreement between sponsor and regulator.

The statistical assumptions that underpin the main estimator should be documented. One or more analyses, focused on the same estimand, should then be pre-specified to investigate these assumptions with the objective of verifying whether or not the estimate derived from the main estimator is robust to departures from its assumptions. This might be characterised as the extent of departures from assumptions that change the interpretation of the results in terms of their statistical or clinical significance (e.g. tipping point analysis).

Distinct from sensitivity analysis, where investigations are conducted with the intent of exploring robustness of departures from assumptions, other analyses that are conducted in order to more fully investigate and understand the trial data can be termed “supplementary analysis” (see Glossary; A.5.3.). Where the primary estimand(s) of interest is agreed between sponsor and regulator, the main estimator is pre-specified unambiguously, and the sensitivity analysis verifies that the estimate derived is reliable for interpretation, supplementary analyses should generally be given lower priority in assessment.

A.5.2.2. Choice of Sensitivity Analysis

When planning and conducting a sensitivity analysis, altering multiple aspects of the main analysis simultaneously can make it challenging to identify which assumptions, if any, are responsible for any potential differences seen. It is therefore desirable to adopt a structured approach, specifying the changes in assumptions that underlie the alternative analyses, rather than simply comparing the results of different analyses based on different sets of assumptions. The need for analyses varying multiple assumptions simultaneously should then be considered on a case by case basis. A distinction between testable and untestable assumptions may be useful when assessing the interpretation and relevance of different analyses.

The need for sensitivity analysis in respect of missing data is established and retains its importance in this framework. Missing data should be defined and considered in respect of a particular estimand (see A.4.). The distinction between data that are missing in respect of a specific estimand and data that are not directly relevant to a specific estimand gives rise to separate sets of assumptions to be examined in sensitivity analysis.

A.5.3. Supplementary Analysis

Interpretation of trial results should focus on the main estimator for each agreed estimand providing that the corresponding estimate is verified to be robust through the sensitivity analysis. Supplementary analyses for an estimand can be conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect. They generally play a lesser role for interpretation of trial results. The need for, and utility of, supplementary analyses should be considered for each trial.

Section 5.2.3. indicates that it is usually appropriate to plan for analyses based on both the FAS and the Per Protocol Set (PPS) so that differences between them can be the subject of explicit discussion and interpretation. Consistent results from analyses based on the FAS and the PPS is indicated as increasing confidence in the trial results. It is also described in Section 5.2.2. that results based on a PPS might be subject to severe bias. In respect of the framework presented in this addendum, it may not be possible to construct a relevant estimand to which analysis of the PPS is aligned. As noted above, analysis of the PPS does not achieve the goal of estimating the effect in any principal stratum, for example, in those subjects able to tolerate and continue to take the test treatment, because it may not compare similar subjects on different treatments.

Protocol violations and deviations might exclude subjects from the PPS, for example by having a visit outside a time window, without an intercurrent event necessarily having occurred. Likewise, subjects could experience an intercurrent event, such as death, without having deviated from the protocol. Notwithstanding the differences between violations and deviations from the protocol and intercurrent events, events likely to affect the interpretation or existence of measurements are considered in the description of the estimand. Estimands might be constructed, with aligned method of analysis, that better address the objective usually associated with the analysis of the PPS. If so, analysis of the PPS might not add additional insights.

A.6. DOCUMENTING ESTIMANDS AND SENSITIVITY ANALYSIS

A trial protocol should define and specify explicitly a primary estimand that corresponds to the primary trial objective. The protocol and the analysis plan should pre-specify the main estimator that is aligned with the primary estimand and leads to the primary analysis, together with a suitable sensitivity analysis to explore the robustness under deviations from its assumptions. Estimands for secondary trial objectives (e.g. related to secondary variables) that

are likely to support regulatory decisions should also be defined and specified explicitly, each with a corresponding main estimator and a suitable sensitivity analysis. Additional exploratory trial objectives may be considered for exploratory purposes, leading to additional estimands.

The choice of the primary estimand will usually be the main determinant for aspects of trial design, conduct and analysis. Following usual practices, these aspects should be well documented in the trial protocol. If secondary estimands are of key interest, these considerations may be extended to support these as needed and should be documented as well. Beyond these aspects, the conventional considerations for trial design, conduct and analysis remain the same.

While it is to the benefit of the sponsor to have clarity on what is being estimated, it is not a regulatory requirement to document an estimand for each exploratory objective.

Results from the main, sensitivity and supplementary analyses should be reported systematically in the clinical trial report, specifying whether each analysis was pre-specified, introduced while the trial was still blinded, or performed post hoc. Summaries of the number and timings of each intercurrent event in each treatment group should be reported.

Changes to the estimand during the trial can be problematic and can reduce the credibility of the trial. Addressing intercurrent events that were not foreseen at the design stage, and are identified during the conduct of the trial, should discuss not only the choices made for the analysis, but the effect on the estimand, i.e. on the description of the treatment effect that is being estimated, and the interpretation of the trial results. A change to the estimand should usually be reflected through amendment to the protocol.

GLOSSARY

Estimand:
A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared.

Estimate:
A numerical value computed by an estimator.

Estimator:
A method of analysis to compute an estimate of the estimand using clinical trial data.

Intercurrent Events:
Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. It is necessary to address intercurrent events when describing the clinical question of interest in order to precisely define the treatment effect that is to be estimated.

Missing Data:
Data that would be meaningful for the analysis of a given estimand but were not collected. They should be distinguished from data that do not exist or data that are not considered meaningful because of an intercurrent event.

Principal Stratification:
Classification of subjects according to the potential occurrence of an intercurrent event on all treatments. With two treatments, there are four principal strata with respect to a given intercurrent event: subjects who would not experience the event on either treatment, subjects who would experience the event on treatment A but not B, subjects who would experience the event on treatment B but not A, and subjects who would experience the event on both treatments. In this document a **principal stratum** refers to any of the strata (or combination of strata) defined by principal stratification.

Sensitivity Analysis:
A series of analyses conducted with the intent to explore the robustness of inferences from the main estimator to deviations from its underlying modelling assumptions and limitations in the data.

Supplementary Analysis:
A general description for analyses that are conducted in addition to the main and sensitivity analysis with the intent to provide additional insights into the understanding of the treatment effect.

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

ADDENDUM TO ICH E11: CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11 (R1)

Final version
Adopted on 18 August 2017

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the ICH regulatory bodies.

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ICH HARMONISED GUIDELINE

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

E11(R1)

ICH Consensus Guideline

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CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PEDIATRIC POPULATION

1. INTRODUCTION

1.1 Objectives of the Guidance

The number of medicinal products currently labeled for pediatric use is limited. It is the goal of this guidance to encourage and facilitate timely pediatric medicinal product development internationally. The guidance provides an outline of critical issues in pediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the pediatric population.

1.2 Background

Other ICH documents with relevant information impacting on pediatric studies include:

- E2: Clinical Safety Data Management
- E3: Structure and Content of Clinical Study Reports
- E4: Dose-Response Information to Support Drug Registration
- E5: Ethnic Factors in the Acceptability of Foreign Clinical Data
- E6: Good Clinical Practice: Consolidated Guideline
- E8: General Considerations for Clinical Trials
- E9: Statistical Principles for Clinical Trials
- E10: Choice of Control Group in Clinical Trials
- M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals
- Q1: Stability Testing
- Q2: Validation of Analytical Procedures
- Q3: Impurity Testing

1.3 Scope of the Guidance

Specific clinical study issues addressed include: (1) considerations when initiating a pediatric program for a medicinal product; (2) timing of initiation of pediatric studies during medicinal product development; (3) types of studies (pharmacokinetic, pharmacokinetic/pharmacodynamic (PK/PD), efficacy, safety); (4) age categories; and (5) ethics of pediatric clinical investigation. This guidance is not intended to be comprehensive; other ICH guidances, as well as documents from regional regulatory authorities and pediatric societies, provide additional detail.

1.4 General Principles

Pediatric patients should be given medicines that have been appropriately evaluated for their use. Safe and effective pharmacotherapy in pediatric patients requires the timely development of information on the proper use of medicinal products in pediatric patients of various ages and, often, the development of pediatric formulations of those products. Advances in formulation chemistry and in pediatric study design will help facilitate the development of medicinal products for pediatric use. Drug development programs should usually include the pediatric patient population when a product is being developed for a disease or condition in adults and it is anticipated the product will be used in the pediatric population. Obtaining knowledge of the effects

of medicinal products in pediatric patients is an important goal. However, this should be done without compromising the well-being of pediatric patients participating in clinical studies. This responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole.

2. GUIDANCE

2.1 Issues When Initiating a Pediatric Medicinal Product Development Program

Data on the appropriate use of medicinal products in the pediatric population should be generated unless the use of a specific medicinal product in pediatric patients is clearly inappropriate. The timing of initiation of clinical studies in relation to studies conducted in adults, which may be influenced by regional public health and medical needs, is discussed in section 2.3. Justification for the timing and the approach to the clinical program needs to be clearly addressed with regulatory authorities at an early stage and then periodically during the medicinal product development process. The pediatric development program should not delay completion of adult studies and availability of a medicinal product for adults.

The decision to proceed with a pediatric development program for a medicinal product, and the nature of that program, involve consideration of many factors, including:

- The prevalence of the condition to be treated in the pediatric population
- The seriousness of the condition to be treated
- The availability and suitability of alternative treatments for the condition in the pediatric population, including the efficacy and the adverse event profile (including any unique pediatric safety issues) of those treatments
- Whether the medicinal product is novel or one of a class of compounds with known properties
- Whether there are unique pediatric indications for the medicinal product
- The need for the development of pediatric-specific endpoints
- The age ranges of pediatric patients likely to be treated with the medicinal product
- Unique pediatric (developmental) safety concerns with the medicinal product, including any nonclinical safety issues
- Potential need for pediatric formulation development

Of these factors, the most important is the presence of a serious or life-threatening disease for which the medicinal product represents a potentially important advance in therapy. This situation suggests relatively urgent and early initiation of pediatric studies.

Information from nonclinical safety studies to support a pediatric clinical program is discussed in ICH M3, section 11. It should be noted that the most relevant safety data for pediatric studies ordinarily come from adult human exposure. Repeated dose toxicity studies, reproduction toxicity studies and genotoxicity tests would generally be available. The need for juvenile animal studies should be considered on a case-by-case basis and be based on developmental toxicology concerns.

2.2 Pediatric Formulations

There is a need for pediatric formulations that permit accurate dosing and enhance patient compliance. For oral administration, different types of formulations, flavors and colors may be more acceptable in one region than another. Several formulations, such as liquids, suspensions, and chewable tablets, may be needed or desirable for pediatric patients of different ages. Different

drug concentrations in these various formulations may also be needed. Consideration should also be given to the development of alternative delivery systems.

For injectable formulations, appropriate drug concentrations should be developed to allow accurate and safe administration of the dose. For medicinal products supplied as single-use vials, consideration should be given to dose-appropriate single-dose packaging.

The toxicity of some excipients may vary across pediatric age groups and between pediatric and adult populations, e.g., benzyl alcohol is toxic in the preterm newborn. Depending on the active substance and excipients, appropriate use of the medicinal product in the newborn may require a new formulation or appropriate information about dilution of an existing formulation. International harmonization on the acceptability of formulation excipients and of validation procedures would help ensure that appropriate formulations are available for the pediatric population everywhere.

2.3 Timing of Studies

During clinical development, the timing of pediatric studies will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of alternative treatments. Since development of pediatric formulations can be difficult and time consuming, it is important to consider the development of these formulations early in medicinal product development.

2.3.1 Medicinal Products for Diseases Predominantly or Exclusively Affecting Pediatric Patients

In this case, the entire development program will be conducted in the pediatric population except for initial safety and tolerability data, which will usually be obtained in adults. Some products may reasonably be studied only in the pediatric population even in the initial phases, e.g., when studies in adults would yield little useful information or expose them to inappropriate risk. Examples include surfactant for respiratory distress syndrome in preterm infants and therapies targeted at metabolic or genetic diseases unique to the pediatric population.

2.3.2 Medicinal Products Intended to Treat Serious or Life-Threatening Diseases, Occurring in Both Adults and Pediatric Patients, for Which There Are Currently No or Limited Therapeutic Options

The presence of a serious or life-threatening disease for which the product represents a potentially important advance in therapy suggests the need for relatively urgent and early initiation of pediatric studies. In this case, medicinal product development should begin early in the pediatric population, following assessment of initial safety data and reasonable evidence of potential benefit. Pediatric study results should be part of the marketing application database. In circumstances where this has not been possible, lack of data should be justified in detail.

2.3.3 Medicinal Products Intended to Treat Other Diseases and Conditions

In this case, although the medicinal product will be used in pediatric patients, there is less urgency than in the previous cases and studies would usually begin at later phases of clinical development or, if a safety concern exists, even after substantial postmarketing experience in adults. Companies should have a clear plan for pediatric studies and reasons for their timing. Testing of these medicinal products in the pediatric population would usually not begin until Phase 2 or 3. In most cases, only limited pediatric data would be available at the time of submission of the application, but more would be expected after marketing. The development of many new chemical entities is discontinued during or following Phase 1 and 2 studies in adults for lack of efficacy or an unacceptable side effect profile. Therefore, very early initiation of testing in pediatric patients might needlessly expose these patients to a compound that will be of no benefit. Even for a

nonserious disease, if the medicinal product represents a major therapeutic advance for the pediatric population, studies should begin early in development, and the submission of pediatric data would be expected in the application. Lack of data should be justified in detail. Thus, it is important to carefully weigh benefit/risk and therapeutic need in deciding when to start pediatric studies.

2.4 Types of Studies

The principles outlined in ICH E4, E5, E6, and E10 apply to pediatric studies. Several pediatric-specific issues are worth noting. When a medicinal product is studied in pediatric patients in one region, the intrinsic (e.g., pharmacogenetic) and extrinsic (e.g., diet) factors[1] that could impact on the extrapolation of data to other regions should be considered.

When a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and pediatric patients, and the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of pediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults. If this approach is taken, adult pharmacokinetic data should be available to plan the pediatric studies.

When a medicinal product is to be used in younger pediatric patients for the same indication(s) as those studied in older pediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger pediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of pediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for pediatric use.

An approach based on pharmacokinetics is likely to be insufficient for medicinal products where blood levels are known or expected not to correspond with efficacy or where there is concern that the concentration-response relationship may differ between the adult and pediatric populations. In such cases, studies of the clinical or the pharmacological effect of the medicinal product would usually be expected.

Where the comparability of the disease course or outcome of therapy in pediatric patients is expected to be similar to adults, but the appropriate blood levels are not clear, it may be possible to use measurements of a pharmacodynamic effect related to clinical effectiveness to confirm the expectations of effectiveness and to define the dose and concentration needed to attain that pharmacodynamic effect. Such studies could provide increased confidence that achieving a given exposure to the medicinal product in pediatric patients would result in the desired therapeutic outcomes. Thus, a PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies.

In other situations where a pharmacokinetic approach is not applicable, such as for topically active products, extrapolation of efficacy from one patient population to another may be based on studies that include pharmacodynamic endpoints and/or appropriate alternative assessments. Local tolerability studies may be needed. It may be important to determine blood levels and systemic effects to assess safety.

[1] In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors which may result in different drug responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively.

When novel indications are being sought for the medicinal product in pediatric patients, or when the disease course and outcome of therapy are likely to be different in adults and pediatric patients, clinical efficacy studies in the pediatric population would be needed.

2.4.1 Pharmacokinetics

Pharmacokinetic studies generally should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations. Relative bioavailability comparisons of pediatric formulations with the adult oral formulation typically should be done in adults. Definitive pharmacokinetic studies for dose selection across the age ranges of pediatric patients in whom the medicinal product is likely to be used should be conducted in the pediatric population.

Pharmacokinetic studies in the pediatric population are generally conducted in patients with the disease. This may lead to higher intersubject variability than studies in normal volunteers, but the data better reflect clinical use.

For medicinal products that exhibit linear pharmacokinetics in adults, single-dose pharmacokinetic studies in the pediatric population may provide sufficient information for dosage selection. This can be corroborated, if indicated, by sparse sampling in multidose clinical studies. Any nonlinearity in absorption, distribution, and elimination in adults and any difference in duration of effect between single and repeated dosing in adults would suggest the need for steady state studies in the pediatric population. All these approaches are facilitated by knowledge of adult pharmacokinetic parameters. Knowing the pathways of clearance (renal and metabolic) of the medicinal product and understanding the age-related changes of those processes will often be helpful in planning pediatric studies.

Dosing recommendations for most medicinal products used in the pediatric population are usually based on milligram (mg)/kilogram (kg) body weight up to a maximum adult dose. While dosing based on mg/square meter body surface area might be preferred, clinical experience indicates that errors in measuring height or length (particularly in smaller children and infants) and calculation errors of body surface area from weight and height are common. For some medications (e.g., medications with a narrow therapeutic index, such as those used in oncology), surface-area-guided dosing may be necessary, but extra care should be taken to ensure proper dose calculation.

Practical considerations to facilitate pharmacokinetic studies

The volume of blood withdrawn should be minimized in pediatric studies. Blood volumes should be justified in protocols. Institutional Review Boards/Independent Ethics Committees (IRB's/IEC's) review and may define the maximum amount of blood (usually on a milliliters (mL)/kg or percentage of total blood volume basis) that may be taken for investigational purposes. Several approaches can be used to minimize the amount of blood drawn and/or the number of venipunctures.

- Use of sensitive assays for parent drugs and metabolites to decrease the volume of blood required per sample
- Use of laboratories experienced in handling small volumes of blood for pharmacokinetic analyses and for laboratory safety studies (blood counts, clinical chemistry)
- Collection of routine, clinical blood samples wherever possible at the same time as samples are obtained for pharmacokinetic analysis
- The use of indwelling catheters, etc., to minimize distress as discussed in section 2.6.5.
- Use of population pharmacokinetics and sparse sampling based on optimal sampling theory to minimize the number of samples obtained from each patient. Techniques include:

- Sparse sampling approaches where each patient contributes as few as 2 to 4 observations at predetermined times to an overall "population area-under-the-curve"
- Population pharmacokinetic analysis using the most useful sampling time points derived from modeling of adult data

2.4.2 Efficacy

The principles in study design, statistical considerations and choice of control groups detailed in ICH E6, E9, and E10 generally apply to pediatric efficacy studies. There are, however, certain features unique to pediatric studies. The potential for extrapolation of efficacy from studies in adults to pediatric patients or from older to younger pediatric patients is discussed in section 2.4. Where efficacy studies are needed, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. Measurement of subjective symptoms such as pain requires different assessment instruments for patients of different ages. In pediatric patients with chronic diseases, the response to a medicinal product may vary among patients not only because of the duration of the disease and its chronic effects but also because of the developmental stage of the patient. Many diseases in the preterm and term newborn infant are unique or have unique manifestations precluding extrapolation of efficacy from older pediatric patients and call for novel methods of outcome assessment.

2.4.3 Safety

ICH guidances on E2 topics and ICH E6, which describe adverse event reporting, apply to pediatric studies. Age-appropriate, normal laboratory values and clinical measurements should be used in adverse event reporting. Unintended exposures to medicinal products (accidental ingestions, etc.) may provide the opportunity to obtain safety and pharmacokinetic information and to maximize understanding of dose-related side effects.

Medicinal products may affect physical and cognitive growth and development, and the adverse event profile may differ in pediatric patients. Because developing systems may respond differently from matured adult organs, some adverse events and drug interactions that occur in pediatric patients may not be identified in adult studies. In addition, the dynamic processes of growth and development may not manifest an adverse event acutely, but at a later stage of growth and maturation. Long-term studies or surveillance data, either while patients are on chronic therapy or during the posttherapy period, may be needed to determine possible effects on skeletal, behavioral, cognitive, sexual, and immune maturation and development.

2.4.4 Postmarketing Information

Normally the pediatric database is limited at the time of approval. Therefore, postmarketing surveillance is particularly important. In some cases, long-term follow-up studies may be important to determine effects of certain medications on growth and development of pediatric patients. Postmarketing surveillance and/or long-term follow-up studies may provide safety and/or efficacy information for subgroups within the pediatric population or additional information for the entire pediatric population.

2.5 Age Classification of Pediatric Patients

Any classification of the pediatric population into age categories is to some extent arbitrary, but a classification such as the one below provides a basis for thinking about study design in pediatric patients. Decisions on how to stratify studies and data by age need to take into consideration developmental biology and pharmacology. Thus, a flexible approach is necessary to ensure that studies reflect current knowledge of pediatric pharmacology. The identification of which ages to study should be medicinal product-specific and justified.

If the clearance pathways of a medicinal product are well established and the ontogeny of the pathways understood, age categories for pharmacokinetic evaluation might be chosen based on any "break point" where clearance is likely to change significantly. Sometimes, it may be more appropriate to collect data over broad age ranges and examine the effect of age as a continuous covariant. For efficacy, different endpoints may be established for pediatric patients of different ages, and the age groups might not correspond to the categories presented below. Dividing the pediatric population into many age groups might needlessly increase the number of patients required. In longer term studies, pediatric patients may move from one age category to another; the study design and statistical plans should prospectively take into account changing numbers of patients within a given age category.

The following is one possible categorization. There is, however, considerable overlap in developmental (e.g., physical, cognitive, and psychosocial) issues across the age categories. Ages are defined in completed days, months, or years.

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years (dependent on region))

2.5.1 Preterm Newborn Infants

The study of medicinal products in preterm newborn infants presents special challenges because of the unique pathophysiology and responses to therapy in this population. The complexity of and ethical considerations involved in studying preterm newborn infants suggest the need for careful protocol development with expert input from neonatologists and neonatal pharmacologists. Only rarely will it be possible to extrapolate efficacy from studies in adults or even in older pediatric patients to the preterm newborn infant.

The category of preterm newborn infants is not a homogeneous group of patients. A 25-week gestation, 500-gram (g) newborn is very different from a 30-week gestation newborn weighing 1,500 g. A distinction should also be made for low-birth-weight babies as to whether they are immature or growth retarded. Important features that should be considered for these patients include: (1) gestational age at birth and age after birth (adjusted age); (2) immaturity of renal and hepatic clearance mechanisms; (3) protein binding and displacement issues (particularly bilirubin); (4) penetration of medicinal products into the central nervous system (CNS); (5) unique neonatal disease states (e.g., respiratory distress syndrome of the newborn, patent ductus arteriosus, primary pulmonary hypertension); (6) unique susceptibilities of the preterm newborn (e.g., necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity); (7) rapid and variable maturation of all physiologic and pharmacologic processes leading to different dosing regimens with chronic exposure; and (8) transdermal absorption of medicinal products and other chemicals. Study design issues that should be considered include: (1) weight and age (gestational and postnatal) stratification; (2) small blood volumes (a 500-g infant has 40 mL of blood); (3) small numbers of patients at a given center and differences in care among centers; and (4) difficulties in assessing outcomes.

2.5.2 Term newborn infants (0 to 27 days)

While term newborn infants are developmentally more mature than preterm newborn infants, many of the physiologic and pharmacologic principles discussed above also apply to term infants. Volumes of distribution of medicinal products may be different from those in older pediatric

patients because of different body water and fat content and high body-surface-area-to-weight ratio. The blood-brain barrier is still not fully mature and medicinal products and endogenous substances (e.g., bilirubin) may gain access to the CNS with resultant toxicity. Oral absorption of medicinal products may be less predictable than in older pediatric patients. Hepatic and renal clearance mechanisms are immature and rapidly changing; doses may need to be adjusted over the first weeks of life. Many examples of increased susceptibility to toxic effects of medicinal products result from limited clearance in these patients (e.g., chloramphenicol grey baby syndrome). On the other hand, term newborn infants may be less susceptible to some types of adverse effects (e.g., aminoglycoside nephrotoxicity) than are patients in older age groups.

2.5.3 Infants and toddlers (28 days to 23 months)

This is a period of rapid CNS maturation, immune system development and total body growth. Oral absorption becomes more reliable. Hepatic and renal clearance pathways continue to mature rapidly. By 1 to 2 years of age, clearance of many drugs on a mg/kg basis may exceed adult values. The developmental pattern of maturation is dependent on specific pathways of clearance. There is often considerable inter-individual variability in maturation.

2.5.4 Children (2 to 11 years)

Most pathways of drug clearance (hepatic and renal) are mature, with clearance often exceeding adult values. Changes in clearance of a drug may be dependent on maturation of specific metabolic pathways.

Specific strategies should be addressed in protocols to ascertain any effects of the medicinal product on growth and development. Children achieve several important milestones of psychomotor development that could be adversely affected by CNS-active drugs. Entry into school and increased cognitive and motor skills may affect a child's ability to participate in some types of efficacy studies. Factors useful in measuring the effects of a medicinal product on children include skeletal growth, weight gain, school attendance, and school performance. Recruitment of patients should ensure adequate representation across the age range in this category, as it is important to ensure a sufficient number of younger patients for evaluation. Stratification by age within this category is often unnecessary, but it may be appropriate to stratify patients based on pharmacokinetic and/or efficacy endpoint considerations.

The onset of puberty is highly variable and occurs earlier in girls, in whom normal onset of puberty may occur as early as 9 years of age. Puberty can affect the apparent activity of enzymes that metabolize drugs, and dose requirements for some medicinal products on a mg/kg basis may decrease dramatically (e.g., theophylline). In some cases, it may be appropriate to specifically assess the effect of puberty on a medicinal product by studying pre- and postpubertal pediatric patients. In other cases, it may be appropriate to record Tanner stages of pubertal development or obtain biological markers of puberty and examine data for any potential influence of pubertal changes.

2.5.5 Adolescents (12 to 16-18 years (dependent on region))

This is a period of sexual maturation; medicinal products may interfere with the actions of sex hormones and impede development. In certain studies, pregnancy testing and review of sexual activity and contraceptive use may be appropriate.

This is also a period of rapid growth and continued neurocognitive development. Medicinal products and illnesses that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt and, by changing the pattern of growth, may affect final height. Evolving cognitive and emotional changes could potentially influence the outcome of clinical studies.

Many diseases are also influenced by the hormonal changes around puberty (e.g., increases in insulin resistance in diabetes mellitus, recurrence of seizures around menarche, changes in the frequency and severity of migraine attacks and asthma exacerbations). Hormonal changes may thus influence the results of clinical studies.

Within this age group, adolescents are assuming responsibility for their own health and medication. Noncompliance is a special problem, particularly when medicinal products (for example, steroids) affect appearance. In clinical studies compliance checks are important. Recreational use of unprescribed drugs, alcohol and tobacco should be specifically considered.

The upper age limit varies among regions. It may be possible to include older adolescents in adult studies, although issues of compliance may present problems. Given some of the unique challenges of adolescence, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centers knowledgeable and skilled in the care of this special population.

2.6 Ethical Issues in Pediatric Studies

The pediatric population represents a vulnerable subgroup. Therefore, special measures are needed to protect the rights of pediatric study participants and to shield them from undue risk. The purpose of this section is to provide a framework to ensure that pediatric studies are conducted ethically.

To be of benefit to those participating in a clinical study, as well as to the rest of the pediatric population, a clinical study must be properly designed to ensure the quality and interpretability of the data obtained. In addition, participants in clinical studies are expected to benefit from the clinical study except under the special circumstances discussed in ICH E6, section 4.8.14.

2.6.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The roles and responsibilities of IRB's/IEC's as detailed in ICH E6 are critical to the protection of study participants. When protocols involving the pediatric population are reviewed, there should be IRB/IEC members or experts consulted by the IRB/IEC who are knowledgeable in pediatric ethical, clinical, and psychosocial issues.

2.6.2 Recruitment

Recruitment of study participants should occur in a manner free from inappropriate inducements either to the parent(s)/legal guardian or the study participant. Reimbursement and subsistence costs may be covered in the context of a pediatric clinical study. Any compensation should be reviewed by the IRB/IEC.

When studies are conducted in the pediatric population, an attempt should be made to include individuals representing the demographics of the region and the disease being studied, unless there is a valid reason for restricting enrollment.

2.6.3 Consent and Assent

As a rule, a pediatric subject is legally unable to provide informed consent. Therefore pediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand. Where appropriate, participants should assent to enroll in a study (age of assent to be determined by IRB's/IEC's or be consistent with local legal requirements). Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form or the written informed consent. In all cases, participants should be made aware of their rights to decline

to participate or to withdraw from the study at any time. Attention should be paid to signs of undue distress in patients who are unable to clearly articulate their distress. Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parent(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study. Emancipated or mature minors (defined by local laws) may be capable of giving autonomous consent.

Information that can be obtained in a less vulnerable, consenting population should not be obtained in a more vulnerable population or one in which the patients are unable to provide individual consent. Studies in handicapped or institutionalized pediatric populations should be limited to diseases or conditions found principally or exclusively in these populations, or situations in which the disease or condition in these pediatric patients would be expected to alter the disposition or pharmacodynamic effects of a medicinal product.

2.6.4 Minimizing Risk

However important a study may be to prove or disprove the value of a treatment, participants may suffer injury as a result of inclusion in the study, even if the whole community benefits. Every effort should be made to anticipate and reduce known hazards. Investigators should be fully aware before the start of a clinical study of all relevant preclinical and clinical toxicity of the medicinal product. To minimize risk in pediatric clinical studies, those conducting the study should be properly trained and experienced in studying the pediatric population, including the evaluation and management of potential pediatric adverse events.

In designing studies, every attempt should be made to minimize the number of participants and of procedures, consistent with good study design. Mechanisms should be in place to ensure that a study can be rapidly terminated should an unexpected hazard be noted.

2.6.5 Minimizing Distress

Repeated invasive procedures may be painful or frightening. Discomfort can be minimized if studies are designed and conducted by investigators experienced in the treatment of pediatric patients.

Protocols and investigations should be designed specifically for the pediatric population (not simply re-worked from adult protocols) and approved by an IRB/IEC as described in section 2.6.1.

Practical considerations to ensure that participants' experiences in clinical studies are positive and to minimize discomfort and distress include the following:

- Personnel knowledgeable and skilled in dealing with the pediatric population and its age-appropriate needs, including skill in performing pediatric procedures
- A physical setting with furniture, play equipment, activities, and food appropriate for age
- The conduct of studies in a familiar environment such as the hospital or clinic where participants normally receive their care
- Approaches to minimize discomfort of procedures, such as:
    - Topical anesthesia to place IV catheters
    - Indwelling catheters rather than repeated venipunctures for blood sampling
    - Collection of some protocol-specified blood samples when routine clinical samples are obtained

IRB's/IEC's should consider how many venipunctures are acceptable in an attempt to obtain blood samples for a protocol and ensure a clear understanding of procedures if an indwelling catheter fails to function over time. The participant's right to refuse further investigational procedures must be respected except as noted in section 2.6.3.

3. ADDENDUM to ICH E11

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Scope and Objective of the ICH E11 Guideline Addendum (R1)

Pediatric drug development has evolved since the original ICH E11 Guideline (2000), requiring consideration of regulatory and scientific advances relevant to pediatric populations. This addendum does not alter the scope of the original guideline which outlines an approach to the safe, efficient, and ethical study of medicinal products in the pediatric population. ICH E11 (2000), including the present addendum (R1) is not intended to be comprehensive; other ICH guidelines, as well as documents from regulatory authorities worldwide, the World Health Organization (WHO) and pediatric societies, provide additional detail.

The purpose of this addendum is to complement and provide clarification and current regulatory perspective on topics in pediatric drug development. The use of the word "should" means that something is suggested or recommended, but not required, unless specific regulatory or statutory requirements are specified as advised by regulatory authorities worldwide.

In this addendum, section 2 on ETHICAL CONSIDERATIONS**,** section 4 on AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS INCLUDING NEONATES**,** and section 7 on PEDIATRIC FORMULATIONS, supplement the content in ICH E11 (2000). Section 3 on COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS addresses issues to aid scientific discussions at various stages of pediatric drug development in different regions. Section 5 on APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT includes enhancement to the topic of pediatric extrapolation, and introduces modelling and simulation (M&S). Section 6 on PRACTICALITIES IN THE DESIGN AND EXECUTION OF PEDIATRIC CLINICAL TRIALS includes discussion of feasibility, outcome assessments, and long-term clinical aspects. These sections describe essential considerations intended to provide high level guidance on the implementation of these important approaches in pediatric drug development, reflecting the evolving nature of these topics. This harmonized addendum will help to define the current recommendations and reduce the likelihood that substantial differences will exist among regions for the acceptance of data generated in pediatric global drug development programs and ensure timely access to medicines for children.

2. ETHICAL CONSIDERATIONS

ICH E11 (2000) Section 2.6 addresses relevant principles for the ethical conduct of pediatric studies, including the roles and responsibilities of the Institutional Review Board/Independent Ethics Committee (IRB/IEC), recruitment of study participants, parental (legal guardian) consent/permission and child assent (See Glossary), and minimization of risk and distress. These ethical principles are also defined in the current legal and regulatory framework of health authorities worldwide responsible for ensuring safeguards for the protection of children participating in research.

A fundamental principle in pediatric drug development requires that children should not be enrolled in a clinical study unless necessary to achieve an important pediatric public health need. When clinical studies are required to obtain information relevant to the use of a medicinal product, such studies should be conducted in pediatric populations having the disease or condition for which the investigational product is intended, unless an exception is justified. Without a prospect of direct clinical benefit from an experimental intervention or procedure, the foreseeable risks and burdens to which pediatric participants would be exposed must be low, i.e., comparable to those risks and burdens encountered in their routine clinical care. The burden of trial-related activities

should also be minimized. Experimental interventions or procedures that present greater than low risk to participants must offer a sufficient prospect of clinical benefit to justify or outweigh exposure of a pediatric population to such risk. Likewise, the balance of risk and anticipated clinical benefit must be at least comparable to the available alternative treatments, such that the child is not disadvantaged by enrollment in the research study. There should be a reasonable expectation that knowledge resulting from the clinical study will contribute to the health of the pediatric population.

The general principles of ethical considerations for parental (legal guardian) consent/permission and child assent are outlined in ICH E11 (2000) Section 2.6.3 and continue to apply. Information regarding participation in the clinical study and the process of parental (legal guardian) consent/permission and child assent must be clearly provided to the parent (legal guardian) and as appropriate to the child participant, at the time of enrollment. When obtaining child assent, relevant elements of informed consent should be provided that are appropriate to the child's capability to understand. Refusal to assent or withdrawal of assent by a child should be respected.

Over the course of a clinical study, it may be necessary to reassess the assent of a child in recognition of their advancing age, evolving maturity and competency, especially for long-term studies or studies that may require sample retention. During clinical studies there is a requirement for obtaining adequate informed consent for continued participation from pediatric participants once a child reaches the age of legal consent. Local regulations related to confidentiality and privacy of pediatric participants must be followed.

The transparency of clinical research in pediatric drug development includes the registration of clinical trials on publicly accessible and recognized databases, and the public availability of clinical trial results. Objective and unbiased information thus made available can benefit pediatric populations through enhancing clinical research, reducing unnecessary clinical trials, and informing clinical decisions in pediatric practice.

3. COMMONALITY OF SCIENTIFIC APPROACH FOR PEDIATRIC DRUG DEVELOPMENT PROGRAMS

General principles outlined in ICH E11 (2000) Sections 1.4 and 2.1 continue to apply. Pediatric drug development programs are increasingly multiregional, and these programs face specific challenges due to regional differences in pediatric regulatory requirements, operational practicalities, standards of care, and cultural expectations. These regional differences in some instances limit the ability of health authorities to align requirements for pediatric product development. To address such differences, timely and efficient drug development requires a common scientific approach for which the following questions should be considered:

- What is the medical need in one or more pediatric populations that the drug could address?
- Who are the appropriate pediatric populations or subgroups that could be considered? (See Section 4)
- What are the key issues in the drug development program that need to be addressed based on the intended pediatric use of the drug?
- Based on the existing knowledge, including developmental physiology, disease pathophysiology, nonclinical data, data in adult or pediatric populations, or data from

related compounds, what are the knowledge gaps that should be addressed to establish the safe and effective use of the drug? (See Section 5.1)

- What specific nonclinical studies could be considered?
- What clinical studies and/or methodological approaches could be considered? (See Section 5)
- What pediatric-specific clinical study design elements could be considered? (See Section 5)
- What practical and operational issues should be considered? (See Section 4 and Section 6)
- Are there different formulations/dosage forms or delivery devices that will be needed for specific pediatric subgroups, both to facilitate an optimal dose-finding strategy, and for treatment of pediatric patients in different subgroups? (See Section 7)

A common scientific approach should consider input from stakeholders (e.g., clinicians, patients, experts from academia), and should be based on scientific advances and up-to-date knowledge.

Early consideration of pediatric populations during drug development planning, along with early interactions between drug developers and regulatory authorities worldwide can facilitate agreement on a common scientific approach to a pediatric development program. When differences are identified, established regulatory pathways to minimize the impact of these differences can be utilized. Therefore, a common scientific approach, not common regional requirements, is at the cornerstone of efficient pediatric drug development and timely delivery of safe and effective medicines for children.

4. AGE CLASSIFICATION AND PEDIATRIC SUBGROUPS, INCLUDING NEONATES

General principles outlined in ICH E11 (2000) Section 2.5 continue to apply. A rationale for the selection of the pediatric population to be included in clinical studies should be provided. Chronological age alone may not serve as an adequate categorical determinant to define developmental subgroups in pediatric studies. Physiological development and maturity of organs, pathophysiology and natural history of the disease or condition, available treatment options, and the pharmacology of the investigational product are factors to be considered in determining the subgroups in pediatric studies. Further, the arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study. Depending on factors such as the condition, the treatment, and the study design, it may be justifiable to include pediatric subpopulations in adult studies (See Section 6) or adult subpopulations in pediatric studies.

Advances in medical care have led to better survival of high risk newborn infants, especially preterm newborn infants, which makes drug development research in newborn infants or “neonates” increasingly important for certain conditions. Neonates include term, post-term and preterm newborn infants. The neonatal period for term and post-term newborn infants is defined as the day of birth plus 27 days. The neonatal period for preterm newborn infants is defined as the day of birth through the expected date of delivery plus 27 days. As the neonatal population represents a broad maturational range, the conditions that affect this population can vary considerably; therefore, it is important to carefully consider the rationale for the selection of a neonatal population or subpopulation to be studied.

5. APPROACHES TO OPTIMIZE PEDIATRIC DRUG DEVELOPMENT

The concepts presented in ICH E11 (2000) Section 2.4 continue to apply. The principles outlined in ICH E4, E5, E6, E9, and E10 should be consulted. The number of pediatric studies and knowledge in the field of pediatrics has increased since ICH E11 (2000). Respective regulations for pediatric drug development worldwide have also evolved. However, drug development in pediatrics continues to present challenges and opportunities. In some cases, there are difficulties with generating data across a pediatric population due to a variety of ethical considerations and feasibility issues. Alternative approaches may provide opportunities to address these issues when structured and integrated into the drug development program as per the principles outlined in this addendum. Proactive multi-disciplinary dialogue regarding the acceptability of such approaches with regulatory authorities is recommended. The planning for pediatric development of the drug should be integrated into overall product development. Waiting to begin planning until adult development has concluded can limit the opportunity to generate meaningful data for pediatric drug development.

5.1. The Use of Existing Knowledge in Pediatric Drug Development

To better inform the design of a pediatric drug development program, there is an opportunity to utilize existing knowledge. Existing knowledge about a drug under development includes evidence already or concurrently generated in adult and pediatric populations with similar or other relevant diseases or conditions. Existing knowledge also integrates nonclinical data, data about related compounds, disease pathophysiology, consideration of the developmental physiology, and clinical data from the pediatric population or subgroup. Use of such information may optimize pediatric drug development programs without reducing standards for pediatric authorization. Safety and risk considerations based on existing knowledge should guide the decision whether specific risk mitigation, such as staggered enrollment based on age group, is necessary. However, any uncertainties related to the use of existing knowledge must be identified and managed prospectively. As data are generated through the drug development cycle, it is possible that the assumptions behind the parameters that have gone into the development strategy and methodology may need to be revisited to take new information into account. This new information will continue to inform the strategy and present an opportunity to further address uncertainties.

Additional approaches to optimize pediatric drug development may include, but are not limited to, statistical and pharmacometric methods, including M&S (see Glossary) that integrate and leverage existing knowledge, as well as extrapolation of information from other populations (adults or pediatric subgroups). The following subsections provide general considerations on the use of extrapolation and M&S in pediatric drug development.

5.1.1. The Use of Extrapolation in Pediatric Drug Development

The concept of “extrapolation” is used in different ways in drug development. “Pediatric extrapolation” is defined as an approach to providing evidence in support of effective and safe use of drugs in the pediatric population when it can be assumed that the course of the disease and the expected response to a medicinal product would be sufficiently similar in the pediatric and reference (adult or other pediatric) population.

When a drug is studied in a pediatric population, one should consider all factors which may result in different drug responses, such as intrinsic (e.g., developmental) and extrinsic (e.g., geographic) factors that could impact on the extrapolation of data from one population to the other.

The process of pediatric extrapolation examines several factors that support the assumptions of similarity of disease and similarity of response to therapy between the pediatric and the reference populations, including disease pathogenesis, criteria for disease diagnosis and classification, measures of disease progression, and pathophysiological, histopathological, and pathobiological characteristics. A thorough understanding of the differences between pediatric and reference populations is required relative to the pathophysiology of the disease, available biomarker/endpoints, organ systems physiology (i.e., renal, hepatic, central nervous system, skeletal, and immune systems), as well as clinical context of available therapeutics, the mechanism of action of the drug and its pharmacological behavior. As new information is generated, the process of pediatric extrapolation should be reviewed and confirmed.

Support for the assumptions of similarity of disease and response to therapy, including exposure-response relationship and prediction of an effective dose and regimen for the intended population, may be derived from existing data about the use of the drug; published literature; expert panels and consensus documents; or previous experience with other products in the same therapeutic class. All data and information gathered can either confirm the extrapolation approach or inform how it might be improved. Ultimately, the exercise should identify if there are sufficient data to support pediatric extrapolation, or if additional clinical information is needed.

When efficacy in the pediatric population can be extrapolated from data obtained in the reference populations, leveraging of safety data from the reference to the pediatric population may be utilized; however, additional pediatric safety data are usually required, as existing data may only provide some information about potential safety concerns related to the use of a drug in the pediatric population [See ICH E11 (2000) Section 2.4].

When pediatric extrapolation is considered in a pediatric drug development strategy, the following framework of questions should be assessed to identify what additional supportive data are needed:

1. What evidence supports a common pathophysiology of disease, natural history, and similarity of the disease course between the reference and pediatric population(s)?

2. What is the strength of the evidence of efficacy in the reference populations?

3. Is there a biomarker or surrogate endpoint in the reference populations that is relevant in the pediatric population?

4. What evidence supports a similar exposure-response between the reference and intended populations?

5. What uncertainties and/or limitations do the existing data (e.g., clinical or historical data and published literature) have, and what uncertainties about the pediatric population remain?

6. If uncertainties remain, what additional information should be generated (e.g., information from M&S, animal, adult, pediatric subgroup studies) in order to inform the acceptability of the extrapolation approach?

As evidence builds, the acceptability of the proposed extrapolation approach should be reassessed and it may be appropriate to change the extrapolation approach.

5.1.2. The Use of Modelling and Simulation in Pediatric Drug Development

Advancement in clinical pharmacology and quantitative M&S techniques has enabled progress in utilizing model-informed approaches (e.g., mathematical/statistical models and simulations based on physiology, pathology and pharmacology) in drug development. M&S can help quantify available information and assist in defining the design of pediatric clinical studies and/or the dosing strategy. Considering the limited ability to collect data in the pediatric population, pediatric drug development requires tools to address knowledge gaps. M&S is one such tool that can help avoid unnecessary pediatric studies and help ensure appropriate data are generated from the smallest number of pediatric patients. The usefulness of M&S in pediatric drug development includes, but is not limited to, clinical trial simulation, dose selection, choice and optimization of study design, endpoint selection, and pediatric extrapolation. With M&S, quantitative mathematical models are built with all available and relevant sources of existing knowledge. Well conducted M&S can inform on the pharmacokinetics, pharmacodynamics, efficacy and safety of a drug.

The incorporation of M&S into pediatric drug development should be based on a strategic plan established through multidisciplinary discussions outlining objectives, methods, assumptions, deliverables and timelines.

When building a model, it is important to consider several elements, including the context of use of the model, the quality and the extent of the existing data, and the assumptions made. Assumptions are usually structured around five main areas: pharmacology, physiology, disease considerations, existing data, as well as the mathematical and statistical assumptions underpinning the model.

Complexity in M&S requires a careful assessment of the impact of each of the above assumptions because the impact of each one on model building can vary between populations. In pediatrics, it is particularly critical to consider the maturation of organ systems with the understanding that data from older subgroups may not necessarily be informative for the younger subgroups. Once assumptions are set, different scenarios should be defined and tested to support the analysis of the impact of potential uncertainty in existing knowledge.

Emerging knowledge is incorporated into the model in an iterative approach to revisit and improve the model. A series of “learn and confirm” cycles should be used for model building and simulation/prediction, and be confirmed as soon as new information is generated. Several models may be needed to support a given pediatric drug development program depending on the question(s) to be addressed, the credibility of the model, and the emerging data generated.

Risk assessment is a critical part of M&S. The clinical and statistical consequences of a specific approach should be discussed with experts to define the risks to be handled. The risks associated with accepting the model depend on the relative contribution of the model in making a decision during product development and its consequences. These risks should be assessed and weighed against the credibility of the model for the context of use.

6. PRACTICALITIES IN THE DESIGN AND EXECUTION OF PEDIATRIC CLINICAL TRIALS

Before deciding which types of methodological approaches are to be used in clinical trial design and execution, one should consider several practical factors that influence the design and

execution of pediatric clinical trials. Three key practical factors to consider are feasibility, outcome assessments, and long-term clinical aspects, including safety.

6.1. Feasibility

Pediatric drug development faces unique feasibility issues, including a small number of eligible children for clinical research, limited pediatric specific resources at research centers, and the scarcity of dedicated pediatric trial networks. Consideration should be given to the available centers that are willing to participate, have access to eligible pediatric participants, and are appropriately staffed in research and clinical care of pediatric patients. When studying pediatric conditions, it may be necessary to consider implementing clinical trial operational strategies, including, but not limited to, the use of pediatric research coordinating centers; the development of master protocols for pediatric clinical trials or registries, planned and conducted in a collaborative manner to evaluate multiple therapies for the same disease or condition with a common control arm; and the enhancement of pediatric clinical research networks. These operational strategies and adherence to Good Clinical Practice (ICH E6) should result in improved feasibility and increase timely and efficient pediatric drug development.

The foreseeable experience of children and their parent(s)/legal guardian should be considered, including the emotional and physical burden and the convenience of participation. Current standards of care can influence physician/patient treatment choices that may impact the design and conduct of pediatric clinical trial. Strategies that foster input from children, their caregivers, and the advocacy communities can facilitate participation, recruitment, and acceptability of a clinical study.

6.2. Outcome Assessments

As stated in the ICH E11 (2000) Section 2.4.2, it may be necessary to develop, validate, and employ different endpoints for specific age and developmental subgroups. The relevant endpoints and outcome measures for the pediatric population should be identified as early as possible. The standardized measurement, collection, analysis, and reporting of outcome assessments are encouraged to optimize pediatric drug development [See ICH E11 (2000) Section 2.4 and ICH E11 (R1) Section 5]. It is important to include protocol design features that allow pediatric participants at appropriate ages to contribute directly in these measures when possible. Where relevant, it may be prudent to initiate the evaluation of potential pediatric endpoints as part of the adult development program prior to their incorporation into the pediatric program.

6.3. Long-term Clinical Aspects

The concepts on safety presented in ICH E11 (2000) Section 2.4.3 and Section 2.4.4; ICH E6 and ICH E2 topics continue to apply. It is acknowledged that rare events may not be identifiable in pre-registration development, and that pediatric-specific adverse events are unlikely to be detected in development programs that are limited in size and duration. Planned collection of safety data in nonclinical studies, adult clinical studies regardless of dose or indication, or information from other sources (e.g., M&S), should serve to improve the design of pediatric studies and pharmacovigilance activities to address specific pediatric safety concerns.

Long-term effects of drug treatment in children can include impacts on development, growth, and/or maturation of organ/system function. Therefore, adequate baseline assessments of growth/development and organ function, and regular follow-up measurements should be planned and discussed with regulatory authorities, as appropriate. Early planning for follow-up in a drug

development program offers the opportunity to systematically capture and evaluate long-term effects in a disease or condition, and increase data interpretability.

7. PEDIATRIC FORMULATIONS[2]

Principal considerations for the development of age-appropriate pediatric formulations to allow for safe and accurate use of pediatric medicines as outlined in ICH E11 (2000) Section 2.2 continue to apply. Additional considerations for pediatric formulations to optimize efficacy and reduce the risk for medication and dosing errors should include age-appropriate dosage forms, ease of preparations and instructions for use for caregivers, acceptability (e.g., palatability, tablet size), choice and amount of excipients, as well as use of alternative delivery systems and appropriate packaging.

Adult dosage forms are not always appropriate for use in the pediatric population, and if a product for adults is used, it may pose a safety risk. When pediatric considerations are not addressed early during drug development, the final medicinal product(s) may require such modification for use in children that the risk is increased for inaccurate dosing, changes in stability, bioavailability, or suboptimal patient acceptability. Examples of this include multiple small volume acquisitions from a vial designed for a single adult use; use of an opened adult capsule formulation or crushed tablets to mix with food for administration of a pediatric dose; and breaking tablets for dose reductions that do not have a functional score line. When modifications of the available preparations are unavoidable, measures to minimize the impact on dose accuracy, stability, bioavailability and safety must be addressed.

Planning for development of age-appropriate dosage forms for pediatric populations should be incorporated into the earliest stages of drug development. If modifications to the available forms are necessary to allow earlier inclusion of pediatric patients in clinical trials during drug development, an age-appropriate product and the applicable bridging studies in support of its use should be planned.

7.1. Dosage and Administration

In order to achieve the targeted drug exposure, more than one dosage form of the active pharmaceutical ingredient (API) and/or strengths may be needed to cover the range of pediatric populations intended to receive the medicinal product. For pediatric drugs, the setting where the product is likely to be administered should be considered when selecting the formulation for development. For example, long acting formulations may be beneficial in settings where the caregiver is not always available (e.g., school, nursery). Further, certain dosage forms that reduce the requirements for handling and storage may be more appropriate than others.

In developing a formulation for pediatric use, considerations should include the ease of accurate dose measurement and the capability to deliver small volumes of liquids to minimize the risk for dosing errors, especially in neonates, infants and young children. Such approaches could include clearly marked administration devices, and/or devices with scaling capability designed for accurate measurement of the smallest dose volume and dose increments.

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[2] For purposes of this document, the term "pediatric formulations" includes design considerations for the dosage form, route of administration, packaging, measuring or administration device of a pediatric medicine (drug).

7.2. Excipients

Excipients may lead to adverse reactions in children that are not observed (or not to the same extent) in adults. Thus, the use of excipients in pediatric medicines should take into account factors such as age, weight, maturity (e.g., term and preterm newborns related to their physiologic development), frequency of dosing, intended duration of treatment, and potential for additional excipient exposure from commonly co-administered medicines. The use of excipients and their quantity in a formulation should minimize risk and ensure product performance, stability, palatability, microbial control, and dose uniformity. Alternatives to excipients that pose a significant risk to children should always be considered, and the risk posed by the excipient weighed against the severity of the disease and availability of alternative treatments. When selecting excipients, one should always consider the potential impact on absorption and bioavailability of the API.

7.3. Palatability and Acceptability

Orally administered pediatric medicines must be palatable to ensure dose acceptance and regimen adherence. A formulation strategy for developing palatable drug preparations includes minimizing/eliminating aversive attributes of the API and considering favorable flavor attributes. Taste masking is often needed to improve the palatability of the API. As pediatric drug development can benefit global populations, the target for taste masking should not only be focused on ensuring that the preparation does not taste unpleasant. Ideally, the preparation should have a neutral taste or a taste with broad cultural acceptance.

Alternative dose administration strategies should be considered for pediatric populations who cannot be accommodated by the intended dosage form (e.g., segmenting or crushing tablets, co-administration with food or liquids). Appropriateness of the alternative strategy for a pediatric population, including patient and caregiver aspects (e.g., taste/palatability, ease and accuracy of modification, and potential changes in bioavailability due to a variety of factors) should be investigated prior to selection of the final market image formulation. Understanding real-world use behaviors in administering pediatric drugs and the mitigation of associated risks will contribute to the development of a drug product that allows for safe dose administration.

7.4. Neonates

Formulation requirements for neonates warrant special attention, such as its effects on electrolyte, fluid or nutritional balance. Intramuscular preparations should be avoided where possible due to pain, risk of over-penetration (e.g., bone, vasculature), and unpredictable drug absorption. Likewise, the tolerability of subcutaneous and intravenous preparations should be evaluated. For neonates, environmental conditions (e.g., temperature, light) and equipment used for drug administration (e.g., enteral feeding tubes) may have an effect on drug delivery and bioavailability. When developing a parenteral dosage form, compatibility with other commonly administered parenteral medicines or parenteral nutrition should also be considered and investigated as necessary, since intravenous access is often limited in neonates. While parenteral formulations may be used in neonates, it should be considered that their use often necessitates careful monitoring to minimize the risk of fluid and electrolyte disturbance.

8. GLOSSARY

Parental (legal guardian) consent/permission:

Expression of understanding and agreement by fully informed parent(s) or legal guardian to permit the investigator/sponsor of a clinical study to enroll a child in a clinical investigation. The choice of the terms parental consent or parental permission in different regions may reflect local legal/regulatory and ethical considerations.

Child assent:

The affirmative agreement of a child to participate in research or to undergo a medical intervention. Lack or absence of expression of agreement or disagreement must not be interpreted as assent.

Modelling and Simulation (M&S):

A range of quantitative approaches, including pharmacometrics/systems pharmacology and other mathematical/statistical approaches based on physiology, pathology and pharmacology to quantitatively characterize the interactions between a drug and an organ system which could predict quantitative outcomes of the drug and/or system's behavior in future experiments. In modelling and simulation, existing knowledge is often referred to as "prior" knowledge.

WMA DECLARATION OF HELSINKI – ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN PARTICIPANTS

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
and by the 75th WMA General Assembly, Helsinki, Finland, October 2024

PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human participants, including research using identifiable human material or 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. While the Declaration is adopted by physicians, the WMA holds that these principles should be upheld by all individuals, teams, and organizations involved in medical research, as these principles are fundamental to respect for and protection of all research participants, including both patients and healthy volunteers.

GENERAL PRINCIPLES

3. The WMA Declaration of Geneva binds the physician with the words, “The health and well-being of my patient will be my first consideration,” and the WMA International Code of Medical Ethics declares “The physician must commit to the primacy of patient health and well-being and must offer care in the patient’s best interest.”

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 participants.

Even well-proven interventions should be evaluated continually through research for their safety, effectiveness, efficiency, accessibility, and quality.

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

   Since medical research takes place in the context of various structural inequities, researchers should carefully consider how the benefits, risks, and burdens are distributed.

   Meaningful engagement with potential and enrolled participants and their communities should occur before, during, and following medical research. Researchers should enable potential and enrolled participants and their communities to share their priorities and values; to participate in research design, implementation, and other relevant activities; and to engage in understanding and disseminating results.

7. The primary purpose of medical research involving human participants is to generate knowledge to understand the causes, development and effects of diseases; improve preventive, diagnostic and therapeutic interventions; and ultimately to advance individual and public health.

   These purposes can never take precedence over the rights and interests of individual research participants.

8. While new knowledge and interventions may be urgently needed during public health emergencies, it remains essential to uphold the ethical principles in this Declaration during such emergencies.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, autonomy, privacy, and confidentiality of personal information of research participants. The responsibility for the protection of research participants must always rest with physicians or other researchers and never with the research participants, even though they have given consent.

10. Physicians and other researchers must consider the ethical, legal and regulatory norms and standards for research involving human participants in the country or countries in which the research originated and where it is to be performed, 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 participants set forth in this Declaration.

11. Medical research should be designed and conducted in a manner that avoids or minimizes harm to the environment and strives for environmental sustainability.

12. Medical research involving human participants must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Such research requires the supervision of a competent and appropriately qualified physician or other researcher.

    Scientific integrity is essential in the conduct of medical research involving human participants. Involved individuals, teams, and organizations must never engage in research misconduct.

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 will not adversely affect the health of the patients who serve as research participants.

15. Appropriate compensation and treatment for participants 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 participants may only be conducted if the importance of the objective outweighs the risks and burdens to the research participants.

17. All medical research involving human participants 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 minimize the risks and burdens must be implemented. The risks and burdens must be continuously monitored, assessed, and documented by the researcher.

18. Physicians and other researchers may not engage in research involving human participants unless they are confident that the risks and burdens have been adequately assessed and can be satisfactorily managed.

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

Individual, Group, and Community Vulnerability

19. Some individuals, groups, and communities are in a situation of more vulnerability as research participants due to factors that may be fixed or contextual and dynamic, and thus are at greater risk of being wronged or incurring harm. When such individuals, groups, and communities have distinctive health needs, their exclusion from medical research can potentially perpetuate or exacerbate their disparities. Therefore, the harms of exclusion must be considered and weighed against the harms of inclusion. In order to be fairly and responsibly included in research, they should receive specifically considered support and protections.

20. Medical research with individuals, groups, or communities in situations of particular vulnerability is only justified if it is responsive to their health needs and priorities and the individual, group, or community stands to benefit from the resulting knowledge, practices, or interventions. Researchers should only include those in situations of particular vulnerability when the research cannot be carried out in a less vulnerable group or community, or when excluding them would perpetuate or exacerbate their disparities.

Scientific Requirements and Research Protocols

21. Medical research involving human participants must have a scientifically sound and rigorous design and execution that are likely to produce reliable, valid, and valuable knowledge and avoid research waste. The research 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 all medical research involving human participants 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 aims, methods, anticipated benefits and potential risks and burdens, qualifications of the researcher, sources of

funding, any potential conflicts of interest, provisions to protect privacy and confidentiality, incentives for participants, provisions for treating and/or compensating participants who are harmed as a consequence of participation, and any other relevant aspects of the research.

In clinical trials, the protocol must also describe any post-trial provisions.

Research Ethics Committees

23. The protocol must be submitted for consideration, comment, guidance, and approval to the concerned research ethics committee before the research begins. This committee must be transparent in its functioning and must have the independence and authority to resist undue influence from the researcher, the sponsor, or others. The committee must have sufficient resources to fulfill its duties, and its members and staff must collectively have adequate education, training, qualifications, and diversity to effectively evaluate each type of research it reviews.

    The committee must have sufficient familiarity with local circumstances and context, and include at least one member of the general public. It must take into consideration the ethical, legal, and regulatory norms and standards of the country or countries in which the research is to be performed as well as applicable international norms and standards, but these must not be allowed to reduce or eliminate any of the protections for research participants set forth in this Declaration.

    When collaborative research is performed internationally, the research protocol must be approved by research ethics committees in both the sponsoring and host countries.

    The committee must have the right to monitor, recommend changes to, withdraw approval for, and suspend ongoing research. Where monitoring is required, the researcher must provide information to the committee and/or competent data and safety monitoring entity, especially 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 research, the researchers must submit a final report to the committee containing a summary of the findings and conclusions.

Privacy and Confidentiality

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

Free and Informed Consent

25. Free and informed consent is an essential component of respect for individual autonomy. Participation by individuals capable of giving informed consent in medical research must be voluntary. Although it may be appropriate to consult family members or community representatives, individuals capable of giving informed consent may not be enrolled in research unless they freely agree.

26. In medical research involving human participants capable of giving informed consent, each potential participant must be adequately informed in plain language of the aims, methods, anticipated benefits and potential risks and burdens, qualifications of the researcher, sources of funding, any potential conflicts of interest, provisions to protect privacy and confidentiality, incentives for participants, provisions for treating and/or compensating participants who are harmed as a consequence of participation, and any other relevant aspects of the research.

    The potential participant must be informed of the right to refuse to participate in the research or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information and communication needs of individual potential participants as well as to the methods used to deliver the information.

    After ensuring that the potential participant has understood the information, the physician or another

qualified individual must then seek the potential participant's freely given informed consent, formally documented on paper or electronically. If the consent cannot be expressed on paper or electronically, the non-written consent must be formally witnessed and documented.

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

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

28. In medical research involving human participants incapable of giving free and informed consent, the physician or other qualified individual must seek informed consent from the legally authorized representative, considering preferences and values expressed by the potential participant.

    Those persons incapable of giving free and informed consent are in situations of particular vulnerability and are entitled to the corresponding safeguards. In addition to receiving the protections for the particularly vulnerable, those incapable of giving consent must only be included if the research is likely to either personally benefit them or if it entails only minimal risk and minimal burden.

29. When a potential research participant who is incapable of giving free and informed consent is able to give assent to decisions about participation in research, the physician or other qualified individual must seek that assent in addition to the consent of the legally authorized representative, considering any preferences and values expressed by the potential participant. The potential participant's dissent should be respected.

30. Research involving participants 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 or other qualified individual must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the research may proceed without informed consent provided that the specific reasons for involving participants with a condition that renders them unable to give informed consent have been stated in the research protocol and the research has been approved by a research ethics committee.

    Free and informed consent to remain in the research must be obtained as soon as possible from a legally authorized representative or, if they regain capacity to give consent, from the participant.

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

32. Physicians or other qualified individuals must obtain free and informed consent from research participants for the collection, processing, storage, and foreseeable secondary use of biological material and identifiable or re-identifiable data. Any collection and storage of data or biological material from research participants for multiple and indefinite uses should be consistent with requirements set forth in the WMA Declaration of Taipei, including the rights of individuals and the principles of governance. A research ethics committee must approve the establishment and monitor ongoing use of such databases and biobanks.

    Where consent is impossible or impracticable to obtain, secondary research on stored data or biological material 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:

    - If no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
    - If for compelling and scientifically sound methodological reasons the use of any intervention other than the best proven one(s), the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention; and the participants who receive any intervention other than the best proven one(s), 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, post-trial provisions must be arranged by sponsors and researchers to be provided by themselves, healthcare systems, or governments for all participants who still need an intervention identified as beneficial and reasonably safe in the trial. Exceptions to this requirement must be approved by a research ethics committee. Specific information about post-trial provisions must be disclosed to participants as part of informed consent.

Research Registration, Publication, and Dissemination of Results

35. Medical research involving human participants must be registered in a publicly accessible database before recruitment of the first participant.

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 participants and are accountable for the timeliness, 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. When an unproven intervention is utilized in an attempt to restore health or alleviate suffering for an individual patient because approved options are inadequate or ineffective and enrollment in a clinical trial is not possible, it should subsequently be made the object of research designed to evaluate safety and efficacy. Physicians participating in such interventions must first seek expert advice, weigh possible risks, burdens, and benefits, and obtain informed consent. They must also record and share data when appropriate and avoid compromising clinical trials. These interventions must never be undertaken to circumvent the protections for research participants set forth in this Declaration.