

Health Products and Food Branch
Inspectorate
250 Lanark Avenue
Address Locator: # 2003A
OTTAWA, Ontario
K1A 0K9

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To: Associations, Pharmaceutical Sponsors, Clinical Research Investigators, Research Ethics Boards, and all other interested parties

Health Canada is pleased to inform you that the document entitled "Guidance for Records Related to Clinical Trials" Guide 0068 - Interpretation of section C.05.012 of the *Food and Drug Regulations* - Division 5 "*Drugs for clinical trials involving human subjects*" is now available on the Health Canada's Compliance and Enforcement website at:

http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index_e.html

This guide is in effect as of June 15, 2006. Inquiries about this document can be addressed in writing to the GCP Coordinator, Good Clinical Practices Compliance Unit, by telephone at (613) 952-8173, by fax (613) 952-9805, or by e-mail at: GCP_BPC@hc-sc.gc.ca

Yours sincerely,

Original signed by

Diana Dowthaite
A/Director General



Health Canada
Health Products and Food Branch

OUR MANDATE:

To promote good nutrition and informed use of drugs, food, medical devices and natural health products, and to maximize the safety and efficacy of drugs, food, natural health products, medical devices, biologics and related biotechnology products in the Canadian marketplace and health system.

Health Products and Food Branch Inspectorate

GUIDANCE FOR RECORDS RELATED TO CLINICAL TRIALS

Guide 0068

Interpretation of section C.05.012 of the *Food and Drug Regulations - Division 5* *“Drugs for Clinical Trials Involving Human Subjects”*

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document may be acceptable. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

This document should be read in conjunction with the relevant regulations, guidelines and any other regional, institutional or local requirements.

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1.0 PURPOSE

This is a guidance document for the interpretation of section C.05.012 on clinical trial records under the *Food and Drug Regulations* Amendment (Schedule No. 1024) “*Drugs for Clinical Trials Involving Human Subjects*” [SOR/2001-203] (also referred to as the *Regulations*). This document outlines the interpretation of the specific requirements for records and record retention related to the conduct of clinical trials in Canada for Sponsors, Qualified Investigators (QI), and Research Ethics Boards (REB) involved in clinical trials under the purview of the *Regulations*.

This interpretation for the requirement of records and record retention is meant to be harmonized with the International Conference on Harmonization on Good Clinical Practice (ICH-GCP, Topic Efficacy E6). However, the *Regulations* can exceed these requirements. ICH Guideline should be used in conjunction with the relevant regulations, guidelines and any other regional, institutional or local requirements.

This document does not constitute part of the *Regulations* and in the event of any inconsistency or conflict, the *Regulations* take precedence over this guidance document.

2.0 BACKGROUND

As of September 1st, 2001, regulatory requirements for the conduct of clinical trials in Canada were amended. The new *Regulations* established the requirements for Sponsors to file an application with Health Canada before selling or importing a drug for use in a clinical trial. Integrated in these *Regulations* is the requirement to comply with good clinical practices (GCP). This standard is also generally a worldwide requirement for the conduct of clinical trials submitted to other regulatory authorities. The guideline includes the requirements for records, how these are to be kept and the conditions under which they are to be made available for monitoring, auditing and inspection.

3.0 SCOPE

This guideline document applies to all records created during the conduct of clinical trials and includes the records of Sponsors, Qualified Investigators, Research Ethics Boards which approved clinical trials, as well as those other stakeholders involved in the conduct of clinical trials that are the subject of the *Regulations*. As it is a Sponsor that requests an authorization, it is ultimately the Sponsor’s responsibility to comply with the *Regulations*.

When an independent investigator initiates a clinical trial under his/her own sponsorship, he or she becomes responsible for all aspects of that trial, both as a Qualified Investigator and a Sponsor.

4.0 DEFINITIONS

The definitions below can be found mainly in Division 5 of the *Food and Drug Regulations*, (FDR-Div. 5)⁽¹⁾ or the ICH Guidance Documents *E6: Guideline for Good Clinical Practice: Consolidated Guideline* (GCP)⁽²⁾.

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, analysed and accurately reported according to the protocol, Sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s). (GCP, 1.6)

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. (GCP, 1.11)

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. (GCP, 1.20)

Clinical Trial: An investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug. (FDR-Div. 5)

Date of Commencement of a Clinical Trial: The date when the clinical trial site will be ready to enrol patients in the clinical trial.⁽³⁾

Direct Access: Permission to examine, analyse, 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. (GCP, 1.21)

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. (GCP, 1.22)

Drug: Means a drug for human use that is to be tested in a clinical trial. (source: FDR-Div. 5)

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

Good Clinical Practices: Generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons, and the good clinical practices referred to in section C.05.010 of Division 5 of the *Food and Drug Regulations*. (FDR-Div. 5)

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). (GCP, 1.29)

Original Medical Record: See Source Documents (GCP, 1.43)

Qualified Investigator: The person responsible to the Sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

- a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and
- b) in any other case a physician and a member in good standing of a professional medical association. (FDR-Div. 5)

Research Ethics Board: A body that is not affiliated with the Sponsor, and

- a) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being; and
- b) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents under the *Immigration Act*, that is composed of both men and women and that includes at least:
 - (i) two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline,
 - (ii) one member knowledgeable in ethics,
 - (iii) one member knowledgeable in Canadian laws relevant to the biomedical research to be approved,
 - (iv) one member whose primary experience and expertise are in a non-scientific discipline, and
 - (v) one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the Sponsor or the site where the clinical trial is to be conducted. (FDR-Div. 5)

Senior Medical or Scientific Officer: A scientific or medical officer residing in Canada, representing the Sponsor, who is responsible for providing an attestation with respect to the Clinical Trial Application / Amendment at the time of filing.⁽³⁾

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). (GCP, 1.51)

Source Document: 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). (GCP, 1.52)

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (GCP 1.53)

Trial Site: The location(s) where trial-related activities are actually conducted. (GCP, 1.59)

5.0 REGULATIONS

5.1 OVERVIEW

The *Food and Drugs Act* and *Regulations* provide the authority for Health Canada to regulate the sale and importation of drugs for the purposes of use in human clinical trials in Canada. Part C, Division 5 of the *Regulations* defines specific requirements for the sale and importation of these drugs. Other guidance documents have been issued to facilitate the application of the *Regulations* including a guidance for clinical trial Sponsors to explain how to apply to obtain an authorization⁽³⁾ and a guidance on Good Manufacturing Practices (GMP) requirements for drugs used in clinical trials⁽⁴⁾.

The terminology used in the *Regulations* on clinical trials is consistent with the definitions used in Health Canada / International Conference on Harmonisation (ICH) Guidance Document *E6: Good Clinical Practice: Consolidated Guideline*⁽²⁾. This guidance document, developed through the process of the International Conference on Harmonisation, was adopted by Health Canada in 1997. The guideline provides the international ethical and scientific quality standard for designing, conducting, recording and reporting of clinical trials involving the participation of human subjects. However, the *Regulations* can exceed these requirements. The ICH Guideline should therefore be used in conjunction with the relevant regulations, guidelines and any other regional, institutional or local requirements.

Sponsors conducting Phase IV clinical trials (as defined at sub-section C.05.002(2)) of the *Regulations*, should comply with GCP and the record requirements, even if these are not required to file an application with Health Canada. These trials involve the use of marketed products where the proposed use of the product is within the approved indication of the Notice of Compliance (NOC) or Drug Identification Number (DIN), (reference C.05.002(2)).

5.2 REGULATIONS

Part C, Division 5 of the Food and Drug Regulations [C.05.012] under the heading of “Sponsor’s Obligations - Records” states:

Records

C.05.012 (1) The sponsor shall record, handle and store all information in respect of a clinical trial in a way that allows its complete and accurate reporting as well as its interpretation and verification.

(2) The sponsor shall maintain complete and accurate records to establish that the clinical trial is conducted in accordance with good clinical practices and these *Regulations*.

(3) The sponsor shall maintain complete and accurate records in respect of the use of a drug in a clinical trial, including:

- (a) a copy of all versions of the Investigator's Brochure for the drug;
- (b) records respecting each change made to the Investigator's Brochure, including the rationale for each change and documentation that supports each change;
- (c) records respecting all adverse events in respect of the drug that have occurred inside or outside Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;
- (d) records respecting the enrolment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the sale of the drug may endanger the health of the clinical trial subjects or other persons;
- (e) records respecting the shipment, receipt, disposition, return and destruction of the drug;
- (f) for each clinical trial site, an undertaking from the qualified investigator that is signed and dated by the qualified investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that:
 - (i) the qualified investigator will conduct the clinical trial in accordance with good clinical practices, and
 - (ii) the qualified investigator will immediately, on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the Research Ethics Board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial subjects or other persons;
- (g) for each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the Research Ethics Board for that clinical trial site; and
- (h) for each clinical trial site, an attestation, signed and dated by the Research Ethics Board for that clinical trial site, stating that it has reviewed and approved the protocol and informed consent form and that the board carries out its functions in a manner consistent with good clinical practices.

(4) The sponsor shall maintain all records referred to in this Division for a period of 25 years.

In addition and in accordance with section C.05.013 of the *Regulations*, information shall be made available within 2 days if there is a concern regarding the use of the drug for the purposes of a clinical trial, including a risk to health of the subjects involved in that trial. In other cases, records shall be provided within 7 days of a request.

Records shall be made available for inspection by Inspectors of Health Canada, in accordance with section 23 of the *Food and Drugs Act* and as described in the *Inspection Strategy for Clinical Trials*⁽⁶⁾.

6.0 SPONSORS

The *Regulations* clearly establish that the Sponsor is the responsible party to whom an authorization to sell or import a drug for use in a clinical trial is issued. As Sponsors delegate many of the functions to third parties, including Research Ethics Boards, Qualified Investigators, Contract Research Organizations and others, agreements with these third parties should be secured by Sponsors to ensure full compliance with the regulatory requirements including record retention. Sponsors must be diligent in their dealings with third parties, including REBs to ensure that their record keeping obligations are met.

Should there be significant deviations from regulatory requirements, the Health Products and Food Branch (HPFB) could initiate actions to suspend or cancel an authorization issued to the Sponsor. Other actions could be initiated, as required and appropriate, and in accordance with the Compliance and Enforcement Policy⁽⁷⁾.

All records created during the conduct of clinical trials are subject to inspection. Essential documents, including protocols, protocol amendments, adverse events, adverse drug reactions, chemistry and manufacturing information, drug accountability records, Research Ethics Board attestations⁽³⁾, Qualified Investigator undertakings⁽³⁾, communications with Qualified Investigators are all examples of essential documents. These records should be kept in secure locations and accessible only by personnel who have been appropriately trained in the management of these records. As the responsible party for the conduct of a clinical trial, the Sponsor should relay these expectations to third parties and should expect due diligence, from all involved in the management of clinical trial records.

The location of these records should be in accordance with section 8 of the GCP Guideline “Essential Documents for the Conduct of a Clinical Trial”. This section provides guidance for the location of essential documents, based on the stage of the clinical trial, from before the trial commences, during the conduct of the trial, and after the completion or termination of the trial. This section is attached as Annex 1.

Only specific and unique documents that belong solely to the Sponsor, the REB, the QI or other entities, must be kept at the conclusion or termination of a trial. Retention of copies of original documents is not a requirement. For example;

- Sponsors are to keep: Adverse events as per C.05.012(3)(c), REB attestation form, QI undertakings form;
- QI’s are to keep: records that identify clinical trial subjects, medical records of subjects;
- REB’s are to keep: membership, qualifications of members, minutes of the meetings.

Essential documents should be retained as per GCP Guideline (REB: section 3.4, QI: section 4.9.5 and Sponsor: section 5.5.11). Once these requirements are satisfied and the final report of the trial is issued, only the original records need to be kept for 25 years. Duplication of documents and multiple copies are not necessary.

Retention of all records created during the conduct of a clinical trial is 25 years as per the *Regulations*. This retention period will allow for patient follow-up throughout the subsequent stages of drug development, assessment and marketing as well as provide the ability to assess the impact on second generation.

The starting time to calculate the retention time is the date when a record is created. For example, when an informed consent is signed, the date of the signature by the subject is the starting date. In practice, it may be easier to calculate the starting date for record retention, as the date of completion or termination of the trial.

Essential documents should be kept for the entire retention period and in their original medium. Transfer of essential documents from their original medium to a secondary medium may be acceptable, preferably at the completion of a trial, and only if:

- the corrections to the original data can be clearly captured in the secondary medium,
- the person that performs the task of transferring from the original to the secondary medium attest (sign and date an attestation), that the secondary documents are true copies of their respective primary documents, and,
- the transfer process has been fully validated. Evidence of validation should be available for inspection.

In addition, the following guidance on computerized systems can be consulted: Annex 11 to the PIC/s Good Manufacturing Practices (GMP) Guide: Computerized Systems ⁽⁵⁾.

When transferring from an original medium to a secondary medium, a standard, such as the "Microfilm and Electronic Images as Documentary Evidence CAN/CGSB-72.11-93" developed by the Canadian General Standard Board, or equivalent, should be utilized. This should apply to any transfer of essential documents for all parties involved in a trial (e.g. REB, QI and others).

Audit reports will not normally be accessed other than to verify that audits are taking place as required, their scope and their frequency. The records may however be requested under exceptional circumstances.

6.1 QUALIFIED INVESTIGATORS

All records created by and under the supervision of the Qualified Investigator should be maintained in accordance with the requirements of the *Regulations* and the GCP Guideline. The Qualified Investigator is responsible for the conduct of the clinical trial at the trial site. Tasks delegated from Qualified Investigator to others (Sub-Investigator, Clinical Research Coordinator, Pharmacist and others) should be documented, signed and dated by the Qualified Investigator and the person to whom the functions were delegated. The extent of delegation should be clearly stated; e.g. who will be responsible for assessing, and reporting of serious adverse drug reactions / serious unexpected adverse drug reactions, and the reporting of these

reactions within the specified time limits. Tasks not specified as being delegated are deemed to remain under the direct responsibility of the Qualified Investigator.

The informed consent forms shall include a statement to relay that regulatory authorities such as Inspectors of Health Canada will be granted direct access to subjects' original medical records for verification of compliance (reference GCP 4.8.10(n)). This statement, when signed by subjects enrolled in a clinical trial, provides access to original medical records for inspection by Inspectors.

The Qualified Investigator should ensure compliance with the *Regulations* and the GCP Guideline from every person involved in the conduct of the clinical trial at the site. The essential processes should be described in a standard operating procedure (SOP) and evidence of satisfactory training of personnel involved in these processes should be documented. Essential SOP's should include a procedure to explain, obtain and maintain the consent of subjects to participate in a clinical trial, a procedure for reporting adverse events and drug reactions, a procedure for drug accountability and others as required if these procedures are not explicitly described in the protocol.

All records created during the conduct of clinical trials are all subject to inspection. Source documents, including signed informed consent forms, medical records, office charts, laboratory reports, X-rays, subject diaries, appointment / scheduling records, adverse events and drug reactions records, pharmacy records, and other essential documents including communications with Sponsors and Research Ethics Board, qualifications and evidence of training of staff involved in the trial are all examples. These records should be kept in a secure location to maintain their integrity and confidentiality. Access to these records should be restricted to personnel who have been appropriately trained in the management of these records.

The Qualified Investigator should always consult the Sponsor prior to destruction of records created during the conduct of clinical trials.

6.2 RESEARCH ETHICS BOARDS

Sponsors of clinical trials are required to obtain an approval of a properly constituted Research Ethics Board prior to the initiation of a trial. Sponsors are also required to have an REB approve amendments, informed consent forms and conduct periodic reviews of the trial. The Board should also attest that it carries out its functions in a manner consistent with good clinical practices (reference: C.05.012(3)(h)⁽¹⁾).

Records relevant to clinical trials and to the roles and responsibilities of the Research Ethics Boards are subject to the provisions of the record requirements. Records, such as membership, qualifications of members, procedures for the conduct of reviews for approval of biomedical research and communications with Qualified Investigators should be retained for 25 years. Other essential documents that are not unique to the REB, such as records of drug reactions and reviewed documents, should be retained for a period of at least three years after completion of the trial as per GCP Guideline.

7.0 REFERENCES

1. *Food and Drugs Act and Regulations*. Clinical Trial Regulations, available at:
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/1024_e.pdf

2. Good Clinical Practice: Consolidated Guideline, International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use - Topic E6, commonly referred to as ICH-Good Clinical Practices- Topic E6, available at:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/e6_e.pdf

3. Guidance for Clinical Trial Sponsors - Clinical Trial Applications - Health Products and Food Branch - Guidance Document, available at:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/ctdcta_ctddec_e.pdf

Qualified Investigator Undertaking:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/qi_qc_e.pdf

Research Ethics Board Attestation:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/reba_acdr_e.pdf

4. Good Manufacturing Practices for drugs used in clinical trial drugs (Annex 2 to the current edition of the Good Manufacturing Practices Guidelines: Manufacture of drugs used in clinical trials), available at:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/cln_trials-essais_cln_e.pdf

5. Annex 11 to the PIC/S Good Manufacturing Practices (GMP) Guide: Computerised Systems, available at:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/comput-inform_e.pdf

6. Inspection Strategy for Clinical Trials. Health Products and Food Branch Inspectorate. Policy. POL-0030, available at:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/insp_strat_e.pdf

7. Compliance and Enforcement Policy. No. POL-0001, Health Products and Food Branch, available at:

http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/insp_strat_e.pdf

Useful Internet Website Addresses

Compliance and Enforcement - Good Clinical Practices

http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/index_e.html

Guidance for Clinical trials Applications

http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/index_e.html

Health Canada www.hc-sc.gc.ca

International Conference on Harmonization www.ich.org

Annex 1

Section 8 of the ICH GCP Guideline - This section includes the corrections of typographical errors noted in the earlier version, namely at section 8.2.6, 8.2.7, 8.2.9, 8.3.20. Other than these corrections, the content of this Annex has not been modified in any way.

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 guidance may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
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
	-ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:	To document agreements		
	- investigator/institution and sponsor		X	X
	- investigator/institution and CRO		X	X (where required)
	- sponsor and CRO			X
	- investigator/institution and authority(ies) (where required)		X	X
8.2.7	DATED, DOCUMENTED APPROVAL/ FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
8.2.8	INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
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
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
8.2.16	CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.19	PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the 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				
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
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
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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.7	UPDATES OF MEDICAL / LABORATORY / TECHNICAL PROCEDURES/TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	(see 8.2.15)	X	X
8.3.9	CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	(see 8.2.16)		X
8.3.10	MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		X
8.3.11	RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS - letters - meeting notes - 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
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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.18	NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	SUBJECT IDENTIFICATION CODE LIST	To document that investigator/ institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator / institution to reveal identity of any subject	X	
8.3.22	SUBJECT ENROLLMENT LOG	To document chronological enrollment 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				
8.4.1	INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To document 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

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.4.5	FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial	X	
8.4.8	CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X