National Institute for Health Research

GOOD CLINICAL PRACTICE (GCP)

REFERENCE GUIDE

Version 3.1 August 2016

Delivering research to make patients, and the NHS, better

National Institute for Health Research
Clinical Research Network (NIHR CRN)
http://www.crn.nihr.ac.uk/learning-development/

Contents

The Clinical Research Network, together with the Coordinating Centre, are key parts of the National Institute for Health Research.

The National Institute for Health research was established by the Department of Health to create a world-class health research system within the NHS, as part of the government health research strategy. The networks support and deliver high quality clinical research studies. The NIHR Clinical Research Network delivers research to make patients, and the NHS, better.

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NIHR Clinical Research Network

Delivering research to make patients, and the NHS, better

We provide the infrastructure (people, funding and practical help) that allows high quality clinical research to take place in the NHS, so that patients can benefit from new and better treatments. We help researchers to set up clinical studies quickly and effectively; support the life-sciences industry to deliver their research programmes; provide health professionals with research training; and work with patients to ensure their needs are at the very centre of all research activity.

In practice this means:

- We fund research support posts in the NHS, and provide training, so that researchers have access to experienced “front-line” staff, who can carry out the additional practical activities required by their study such as obtaining patient consent for participation, carrying out extra tests, and collecting the clinical data required for the research.
- We provide funding to meet the costs of using facilities such as scanners and x-rays that are needed in the course of the study, so that research activity adds value to patient care.
- We also provide practical help in identifying and recruiting patients onto Portfolio studies, so that researchers can be confident of completing the study on time, and on target.

Find out more at www.crn.nihr.ac.uk

NIHR CRN Good Clinical Practice training

Good Clinical Practice (GCP) is the international ethical, scientific and practical standard to which all clinical research is GCP training conducted. Compliance with GCP provides public assurance that the rights, safety and wellbeing of research participants are protected and that research data are reliable.

We offer a range of high quality GCP training courses. All our courses have a practical focus, with the key aim that participants know what to do to practise excellent GCP when they return to their workplace to ensure the rights, safety and well-being of patients and the quality of the research data. All NIHR CRN GCP courses are appropriate for people conducting clinical trials, non-clinical trials and other kinds of research.

Find out more at
https://www.crn.nihr.ac.uk/learning-development/good-clinical-practice/

Conditions and Principles which apply to all Clinical Trials

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
Schedule 1 Part 2

Principles based on Articles 2 to 5 of the GCP Directive

1. The rights, safety and well-being of the trial subjects shall prevail over the interests of science and society.
2. Each individual involved in conducting a trial shall be qualified by education, training and experience to perform his tasks.
3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.
4. The necessary procedures to secure the quality of every aspect of the trial shall be complied with.
5. The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.
6. Clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.
7. The protocol shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.
8. The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.
9. All clinical information shall be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

Conditions based on Article 3 of the Directive

10. Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.
11. The medical care given to, and medical decisions made on behalf of, subjects shall always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.
12. A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.
13. The rights of each subject to physical and mental integrity, to privacy and to the protection of the data concerning him in accordance with the Data Protection Act 1998 are safeguarded.
14. Provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor, which may arise in relation to the clinical trial.

Details of the laws which govern clinical trials in the UK can be found on the MHRA's website: https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

Excerpt from ICH E6 Guideline for Good Clinical Practice: 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 non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

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

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

The E6 Guideline for Good Clinical Practice can be found on the ICH website:
http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

World Medical Association Declaration of Helsinki

1996 Version

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission. The Declaration of Geneva of the World Medical Assembly binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act only in the patient’s interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient.”

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civic and ethical responsibilities under the laws of their own countries.

I. Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interest of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation.
Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.
Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with clinical care (clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

II. Non-therapeutic biomedical research involving human subjects (non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

The Declaration of Helsinki can be found on the WMA website:
http://www.wma.net/en/30publications/10policies/b3/

Excerpt from ICH E6 Guideline for Good Clinical Practice: Informed Consent Explanation

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 authorising 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.

The E6 Guideline for Good Clinical Practice can be found on the ICH website:
http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

Excerpt from ICH E6 Guideline for Good Clinical Practice: Essential Documents for the Conduct of a Clinical Trial

The E6 Guideline for Good Clinical Practice can be found on the ICH website: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html

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).

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:

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ 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		X	X
	– INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent		
	– ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
	– ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:	To document agreements		
	– 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

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ Institution**	**Sponsor**
8.2.7	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:	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
	– 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			
8.2.8	INSTITUTIONAL REVIEW COARD/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

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ Institution**	**Sponsor**
8.2.12	MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
	– certification or			
	– accreditation or			
	– established quality control and/or external quality assessment or			
	– other validation (where required)			
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)
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

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ 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:	To document revisions of these trial related documents that take effect during trial	X	X
	– protocol/amendment(s) and CRF			
	– informed consent form			
	– any other written information provided to subjects			
	– advertisement for subject recruitment (if used)			
8.3.3	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:	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
	– 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)			

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ Institution**	**Sponsor**
8.3.4	REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:	To document compliance with applicable regulatory requirements	X (where required)	X
	– protocol amendment(s) and other documents			
8.3.5	CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	(see 8.2.10)	X	X
8.3.6	UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL / LABORATORY/ TECHNICAL PROCEDURE(S)/ TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	UPDATES OF MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
	– certification or			
	– accreditation or			
	– established quality control and/or external quality assessment or			
	– other validation (where required)			
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	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
	– letters			
	– meeting notes			

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ Institution**	**Sponsor**
8.3.12	SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
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	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

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ Institution**	**Sponsor**
8.3.19	INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)
8.3.20	SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	X	
8.3.22	SUBJECT ENROLMENT LOG	To document chronological enrolment of subjects by trial number	X	
8.3.23	INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	SIGNATURE SHEET	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

			Located In Files of	
	Title of Document	**Purpose**	**Instigator/ 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
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

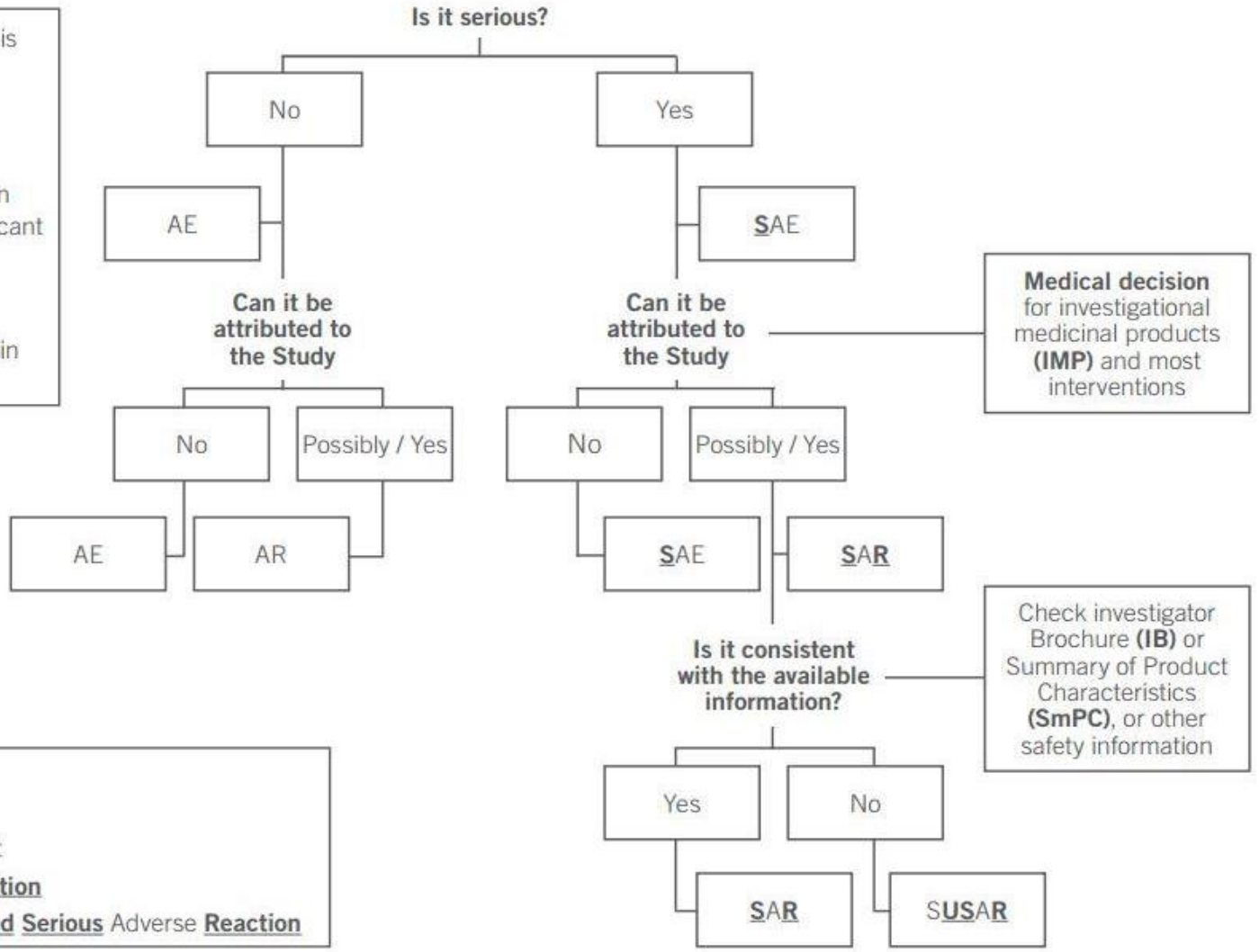
National Institute for Health Research

Safety Reporting Decision Tree

A Serious Adverse Event (SAE) is any adverse event that:

- results in death
- is a life-threatening situation
- requires hospitalisation or prolongation of hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital abnormality or birth defect

Check the definition of Serious in each Protocol.



AE	Adverse Event
AR	Adverse Reaction
SAE	**Serious** Adverse Event
SAR	**Serious** Adverse **Reaction**
SUSAR	Suspected **Unexpected Serious** Adverse **Reaction**

Commonly Used Research Abbreviations and Terms

ABPI	Association of the British Pharmaceutical Industry: A trade association for UK pharmaceutical companies
AE	Adverse Event
Amendment	A written description of a change to the protocol or supporting documents. All amendments should be submitted to HRA for ongoing HRA Approval.
AMRC	Association of Medical Research Charities
AR	Adverse Reaction (also known as ADR)
ARSAC	Administration of Radioactive Substances Advisory Committee: Research studies wishing to administer radioactive medicinal products to human subjects need to obtain ARSAC approval before NHS R&D approval
ASR	Annual Safety Report: For studies involving the use of an Investigational Medicinal Product, this is the annual report which must be submitted to the MHRA detailing all SUSARs and SARs that have occurred in subjects on that study in the past year
ATMP	Advanced Therapy Medicinal Products
BRC	Biomedical Research Centre: larger centre covering a number of topics with facilities and research active clinicians/academics/research nurses to run clinical projects
BRU	Biomedical Research Unit: topic-focused centre which usually combines facilities and research active clinicians/academics/research nurses to run clinical projects, e.g. respiratory BRU
CA	Competent Authority: organisation approving the testing of new drugs/devices or approving the marketing licences, in the UK this is the MHRA
CC	Coordinating Centre
CCF	NIHR Central Commissioning Facility. The CCF manages the following research funding programmes.
CF	Consent Form (also ICF, Informed Consent Form)
CFR	Code of Federal Regulations (US)
CI (i)	Chief Investigator: The lead investigator with overall responsibility for the research. In a multi-site study, the CI has coordinating responsibility for research at all sites. The CI may also be the PI at the site in which they work. In the case of a single-site study, the CI and the PI will normally be the same person and are referred to as PI.
CI (ii)	Coordinating investigator
CPMS	Central Portfolio Management System: a national system that will enable the NIHR CRN to capture high quality study information and produce a range of detailed reports to help manage and deliver studies. CPMS will replace the Portfolio Database, Industry Application Gateway and interim Industry Tracker
CRA	Clinical Research Associate: usually a commercially employed person supporting the management of clinical studies, helps with obtaining R&D approval, site initiation, study monitoring and close out
CRF (i)	Case Report Forms: data collection tools provided by a sponsor on which the clinical data is recorded for each participant, such as weight, lab results, symptoms
CRF (ii)	Clinical Research Facility: hospital-like facility with consulting rooms, standard patient beds, ward medical equipment, research nurses supporting only research
CRN	Clinical Research Network
CRO	Clinical Research Organisation or Contract Research Organisation: A person or an organisation (commercial, academic or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions
CSAG	Clinical Studies Advisory Group
CSG	Clinical Studies Group
CSP	Coordinated System for gaining NHS Permissions (no longer in use, see HRA Approval)

CTA (i)	Clinical Trials Administrator: person providing coordinating/secretarial support for running clinical studies
CTA (ii)	Clinical Trials Agreement: contract between the legal Sponsor and the hosting research sites
CTA (iii)	Clinical Trials Associate (similar to CRA): person involved in the management of a study from initiation, through conduct/monitoring to close-out
CTA (iv)	Clinical Trials Authorisation: The regulatory approval for a clinical trial of a medicinal product issued by the MHRA
CTAAC	Clinical Trials Advisory and Awards Committee
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit: Design and manage CTIMPs, sometimes in specialist clinical areas, such as Cancer, or types of trial, such as RCTs
Delegation of Duties log	Document detailing who has been delegated each duty by the Principal Investigator.
DH	Department of Health (for England)
DPA	Data Protection Act
DQ	Data query
DSMB	Data and Safety Monitoring Board: An independent committee composed of clinical research experts and community representatives that reviews data whilst a clinical trial is in progress to ensure that participants are not being exposed to undue risk
DSUR	Development Safety Update Report: In addition to the expedited reporting required for SUSARs, Sponsors are required to submit a safety report (DSUR) to the MHRA and Research Ethics Committee, once a year throughout the clinical trial or on request
ECMC	Experimental Cancer Medicine Centre
eCRF	An electronic CRF
Eligibility	A clinical assessment of whether the potential participant meets the inclusion and exclusion criteria for the study as described in the protocol
EMA	The European Medicines Agency: A body of the European Union which has responsibility for the protection and promotion of public health through the evaluation and supervision of medicines for human use
EPAP	European Patient Ambassador Programme
eTMF	An electronically stored TMF
EU	European Union
EudraCT	European Clinical Trials Database: A database of all clinical trials in Europe, held since 1994 in accordance with EU directive 2001/20/EC
FDA	Food and Drug Administration: the Competent Authority in the United States, giving authorisation to conduct clinical trials and issuing marketing licences
Feasibility	The process of reviewing the protocol to determine whether or not a study can be safely and effectively delivered
GAfREC	Governance Arrangements for Research Ethics Committees
GCP	Good Clinical Practice: GCP is an international ethical and scientific quality standard for designing, recording and reporting studies. The aim of GCP is to ensure the rights, safety and wellbeing of study participants are protected and research data is high quality
GLP	Good Laboratory Practice: standard for laboratories involved in pre-clinical analyses (e.g. animal, in vitro); does not apply to Laboratories analysing samples from clinical trials involving humans
GMP	Good Manufacturing Practice: quality assurance standard for producing IMP, medicinal products
GTAC	Gene Therapy Advisory Committee: the ethics committee for clinical studies using genetically modified products; usually no REC approval required
HEI	Higher Education Institution

HFEA	Human Fertilisation and Embryological Authority
HRA	Health Research Authority
HRA Approval	The process for the NHS in England that brings together the assessment of governance and legal compliance, undertaken by dedicated HRA staff, with the independent REC opinion provided through the UK Health Departments' Research Ethics Service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England. This allows participating organisations to focus their resources on assessing, arranging and confirming their capacity and capability to deliver the study.
HRC	Honorary Research Contract
HSE	Health and Safety Executive
HTA	Human Tissue Act or Human Tissue Authority
HTA	Health Technology Assessment – one of the NIHR research funding streams
IB	Investigator's Brochure: A compilation of clinical and pre-clinical pharmacological/biological data relevant to the use of that IMP(s) in human subjects (one single IB for all trials using the same IMP)
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation (Europe, USA, Japan): Defined standards for the terminology, design, conduct, monitoring, recording, analysis and reporting of a study. Section E6 of ICH defines principles of Good Clinical Practice (referred to as ICH-GCP)
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product: an unlicensed new drug, an existing drug tested outside its licence, or existing drugs tested against each other for their efficacy/safety. The MHRA provide advice to help you decide if your product is an investigational medicinal product (IMP).
Indemnity	Compensation for damage, loss or injury
Investigator	Researcher conducting the (clinical) study, those researchers leading the team are referred to as CI or PI
IRAS	Integrated Research Application System: A single, web-based system for completing applications for the permissions and approvals required for health and social care research in the UK. The various applications can be printed or submitted for this single system (includes REC, R&D, MHRA, GTAC, NIGB, ARSAC)
IRB	Independent Review Boards: US equivalent of authorised REC
IRMER	Ionising Radiation Medical Exposure Regulations: part of NHS R&D approval, usually done by the local hospital experts
ISF	Investigator Site File: A file designed for use in organising and collating all essential documentation required to conduct a study in accordance with the principles of GCP and the applicable regulatory requirements (e.g. REC approval letter/correspondence, MHRA approval, blank CRF, staff CVs, delegation of duties log etc.)
ISRCTN	International Standard Randomised Control Trial Number: A simple numeric system for the identification of randomised controlled clinical trials worldwide. Allows the identification of trials and provides a unique number that can be used to track all publications and reports resulting from each trial.
LCRN	Local Clinical Research Network
LPMS	Local Portfolio Management System: local systems which capture high quality study information and integrate with CPMS
MCA	Mental Capacity Act
mCIA	model Clinical Investigation Agreement: for medical devices, covers the running of the study, not design of prototype or design of protocol; standard template for the UK (use is not obligatory)
mCTA	model Clinical Trial Agreement: for IMP studies with commercial sponsor/CRO conducted; standard template for the UK (use is not obligatory)

MfHU (CT)	Medicines for Human Use (Clinical Trials) Regulations: SI 2004:1031 and subsequent amendments 2006:1928, 2006:2984 ,2008:941, 2009:1164 and 2010:1882 are the UK Statutory Instruments translating EU directives 2001/20/EC and 2005/28/EC into UK law, laying down the legal requirements for conducting CTIMPs in the UK
MHRA	Medicines and Healthcare products Regulatory Agency: The UK Competent Authority (CA) and licensing authority for medicines and medical devices. It replaced both the Medical Devices Agency (MDA) and the Medicines Control Agency (MCA) in April 2003
mNCA	model Non-Commercial Agreement: for clinical research studies; standard template for the UK (use is not obligatory)
Monitor	The person designated by the sponsor to perform site visits and conduct the monitoring process; eg check whether there are any deviations from the protocol and that all source data was transferred into the Case Report Forms correctly
MRC	Medical Research Council
Multi Centre Study	A study conducted according to a single protocol but carried out at more than one site and by more than one investigator; one CI oversees several local PIs
ND	Not done (in CRFs)
NHS	National Health Service
NICE	National Institute for health and Clinical Excellence: develop evidence-based guidelines on the most effective ways to diagnose, treat and prevent disease and ill health
NIHR	National Institute for Health Research: established by Department of Health for England in 2006 to provide the framework through which DH will position, manage and maintain the research, research staff and infrastructure of the NHS in England as a virtual national research facility
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMP (or non-IMP)	Non-Investigational Medicinal Product: product used alongside IMP but not directly under investigation in the research study, e.g. a challenge agent
NK	Not known (in CRFs)
NOCRI	National Office for Clinical Research Infrastructure
Non-substantial amendments	Changes to the details of a study that have no significant implications for the subjects, the conduct, the management or the scientific value of the study (sometimes referred to as administrative amendments).
NRES	National Research Ethics Service: umbrella organisation responsible for all REC across the UK (replaced COREC in 2007)
ODP	Open Data Platform: an online, open platform which provides secure access to collated study and recruitment data
PI	Principal Investigator: The lead person at a single site designated as taking responsibility within the research team for the conduct of the study
PIC	Participant Identification Centre: NHS or other organisation which only identifies participants from a database etc, but recruitment/receiving consent and study conduct are managed elsewhere
PIS	Participant or Patient Information Sheet: An information leaflet given to those who have been invited to participate in a research study. The sheet is designed to provide the potential participant with sufficient information to allow that person to make an informed decision on whether or not they want to take part
PPIE (or PPI)	Patient and Public Involvement and Engagement
QA	Quality Assurance
QC	Quality Control
QLQ	Quality of Life Questionnaire
R&D	Research and Development: often name of Department within NHS hospitals giving permission to conduct projects on those facilities with patients/staff

RCT	Randomised Controlled Trial: A randomised controlled trial (RCT) is a clinical study in which two (or more) forms of care are compared; the participants are allocated to one of the forms of care in the study, in an unbiased way
RDS	Research Design Service: organisation with a number of experts who can help write the protocol/documents for NIHR grant applications
REC	Research Ethics Committee: authorised by NRES to review study documents for research taking place in the NHS, or social services. Some REC specialise in Clinical Trials, or topics such as research in children, MCA. See NRES website for more detail and other types of research http://www.nres.npsa.nhs.uk/ All Research in NHS/social services must have been reviewed by a UK REC
Research Passport	A system for HEI employed researchers/postgraduate students who need to undertake their research within NHS organisations, which provides evidence of the pre-engagement checks undertaken on that person in line with NHS Employment Check Standards (among them CRB and occupational health checks)
RfPB	Research for Patient Benefit: NIHR research funding stream
RGF	Research Governance Framework: DH guidance for the conduct of research within the NHS in England (use 2nd edition, 2005)
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
Screening	The process of identifying eligible patients prior to approaching them to determine if they are willing to consent to participate in the study
SDV	Source Data Verification: checking the original data record, such as lab reports, patient medical notes against what was transferred onto the CRF/into a database
SI (i)	Statutory Instruments: document which defines UK law in on a specific topic, e.g. how to manage a clinical trial
SI (ii)	Sub-Investigator (as in ICH-GCP, ICH does not use the term Co-investigator)
Site	The NHS organisation in which study activities and assessment are performed or the location(s) where trial-related activities are actually conducted. Each site/Trust needs to give R&D approval
SIV	Site initiation visit
SLA	Service Level Agreement
SMO	Site Management Organisation
SmPC	Summary of Product Characteristics: smaller version of Investigator Brochure with details on pharmacological effects, side effects, but issued for a product that already holds a marketing licence
SOP	Standard Operating Procedure: detailed written instructions designed to achieve uniformity of the performance of a specific function
Substantial Amendment	An amendment to the protocol or any other study specific documentation, the terms of the REC application or the terms of the CTA application (as applicable) that is likely to affect to a significant degree the safety or physical or mental integrity of the participants or the scientific value of the trial.
SUSAR	Suspected Unexpected Serious Adverse Reaction: A Serious Adverse Reaction (SAR) which is Unexpected (i.e. its nature and severity is not consistent with the known information about that product from the Investigator's Brochure or the SmPC) and suspected, as it is not possible to be certain of causal relationship with the IMP
TMF	Trial Master File (file with essential documents held by the Chief Investigator/Sponsor organisation)
UKCRC	United Kingdom Clinical Research Collaboration
WHO	World Health Organisation
WMA	World Medical Association

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