



GUIDANCE ON USE OF THE TRIPARTITE MODEL CLINICAL INVESTIGATION AGREEMENT FOR MEDICAL TECHNOLOGY INDUSTRY SPONSORED RESEARCH IN NHS HOSPITALS MANAGED BY CONTRACT RESEARCH ORGANISATIONS (CRO mCIA, 2009 VERSION)

This guidance concerns the way the NHS-ABHI CRO mCIA was developed and how it should be used. For background information on initiatives to improve the UK environment for commercial clinical investigations and a general discussion of the model CIAs, the reader is referred to the introduction to earlier guidance published on the background and use of the bipartite mCIA:

<http://www.nihr.ac.uk/files/pdfs/mCIA%20Guidance.pdf>

PART 1 - INTRODUCTION

1.1 Background to the development of the CRO mCIA

Like the bipartite mCIA (published in 2008), the CRO mCIA was developed by collaborative work involving the Departments of Health of England, Scotland, Northern Ireland and Wales, NHS bodies and the medical technology industry, in association with Contract Research Organisations (CROs). The modifications made to the mCIA to allow it to be used in a tripartite format for investigations managed by CROs followed the approach adopted in the conversion of the bipartite mCIA to the tripartite CRO mCIA:

http://www.nihr.ac.uk/industry/Pages/industry_model_clinical_trials_agreement.aspx

It has been structured to meet the needs of medical technology companies sponsoring and directly managing the investigations, the CROs that manage them and NHS hospitals accountable for the patients participating in them. It is commended to industry and the NHS throughout the UK as a model for

agreements covering arrangements for all CRO-managed contract commercial clinical investigations carried out by NHS hospitals.

1.2 Adoption of the 2009 version

As with previous model agreements, the CRO mCIA has been reviewed by a number of representative bodies including the NHS Confederation; the Medical Schools Council (MSC, formerly called the Council of Heads of Medical Schools, CHMS); the NHS R&D Forum; and the UK Clinical Research Collaboration (UKCRC) and they all either endorse or do not object to its use as a standard agreement template for investigations of medical technology devices. Versions of the agreement, which was negotiated with English law and governance arrangements at its core, have been developed for use under the legal systems and NHS administrative arrangements of Wales, Northern Ireland and Scotland.

1.3 Investigations involving medical academics

The Research Governance Framework 2005 clarified contracting arrangements for commercial clinical investigations carried out in NHS hospitals. For governance reasons, clinical research involving NHS patients, classified as “Contract Clinical Trials”, must in all cases take place under an agreement between the commercial sponsor and the NHS body responsible for the trial site (Research Governance Framework v2, paragraph 3.2.4). This contracting arrangement is required whether the investigator is substantively employed by the NHS body or by an associated academic body. The exact meaning of “Contract Clinical Trial” in this context was clarified in discussions between the Department of Health and the Council of Heads of Medical Schools (CHMS). CHMS was concerned to ensure that the NHS bodies entering into these contracts will in all cases notify universities about trials (and investigations) in which university employees are to participate and discuss the costs arising from them. The CRO mCIA, like the previous model agreements, contains provisions that require such notifications to be made and discussions about costs and reimbursements to take place. The basis for reimbursement of universities should be made explicit in the investigation contract by inclusion in the financial schedule. On these understandings, the Medical Schools Council (formerly called the Council of Heads of Medical Schools) commends the use of the CRO mCIA to its members.

1.4 Categories of investigations

Not all clinical investigations supported by the medical technology industry are “Contract Clinical Investigations”. It is particularly important in the case of medical technology research to distinguish “Contract Clinical Investigations” from “Collaborative Clinical Research”. In this context, “Contract Clinical Investigations” are defined as commercial, industry-sponsored investigations of investigational medical devices, involving NHS patients, undertaken in NHS hospitals, often directed towards CE marking. These investigations are carried out following a precisely specified Clinical Investigation Plan and are not iterative device improvement programmes into which the clinical researchers contribute developmental expertise. Developmental studies, i.e. “Collaborative Clinical Research”, which may involve current NHS patients, will continue to be covered by contracts between the company providing resources for the investigation and the holder of the investigator’s substantive employment contract, whether that be a university or NHS body.

1.5 Applicability of the model CTA

The CRO mCIA is NOT for use in connection with non-commercial studies sponsored by charities, government departments or Research Councils, whether or not such investigations involve NHS patients and whether or not they are carried out in NHS hospitals.

1.6 Use and modification of the CRO mCIA

This guidance has been developed to facilitate the use of the CRO mCIA. It is not mandatory for either NHS hospitals or ABHI member companies to use the model CIAs when NHS patients are to participate in contract commercial clinical investigations and its adoption by any individual company or NHS body as their preferred contract template is at their own discretion. However, the routine use of either the mCIA or CRO mCIA is strongly commended by the UK Departments of Health in England and the devolved administrations of Wales, Northern Ireland and Scotland; and by the ABHI. All these bodies recommend that no modifications are made to the agreements, other than those necessary for correctly identifying the investigation, the contracting parties, and the investigator, and setting out the financial terms and clinical investigation subject recruitment arrangements.

The CRO mCIA contains references to national and international standards of good practice in clinical research and governance, and compliance with a number of these is mandatory. They include:

- EN ISO 14155, the harmonised standard for good clinical practice in clinical investigations of medical devices,
- ICH-GCP, the harmonised tripartite guideline for good clinical practice,
- the Medical Devices Regulations 2002 (and subsequent amendments) implementing the EU medical devices directives,
- the UK Research Governance Frameworks that are relevant to England and each of the Devolved Administrations (Scotland, Wales and Northern Ireland),
- patient indemnity arrangements (specifically the ABHI Compensation Guidelines and ABHI Form of Indemnity),
- accountability through NHS bodies' Chief Executives for clinical research involving NHS patients.

Each time the CRO mCIA is used in connection with a clinical investigation, it will require addition of the information specified in part 8 of this Guidance.

1.7 Terminology

In this guidance, the research site is referred to as 'NHS hospital' or 'NHS body', which are generic terms for the corporate bodies that undertake clinical investigations. In England and Wales, this will have the meaning of NHS Trusts and NHS Foundation Trusts; in Northern Ireland, it means Hospitals Trusts and Health and Social Services Trusts; and in Scotland, it means Health Boards. The national versions of the CRO mCIA include appropriate text variants.

PART 2 - COMMENTARY ON THE STRUCTURE AND USE OF THE CRO MCTA

2.1 Contracting Parties

In order to comply with research and clinical governance requirements, and establish the correct lines of accountability for the work of clinicians practising in the NHS, the company or companies sponsoring and managing commercial Contract Clinical Investigations involving subjects recruited by virtue of their being current NHS patients, carried out in NHS hospitals, must contract with the NHS body responsible for the clinical care of the subjects, irrespective of the institution that employs the investigator. This includes the situation where, for example, the investigator's substantive employment contract is with a university and the investigator holds an honorary contract with the NHS body.

In no case should a clinical investigation sponsor enter into a contract with an individual employee of either an NHS body or a university in a personal capacity to undertake a clinical investigation involving NHS patients.

2.2 The origin of a tripartite contractual model

This was developed in connection with pharmaceutical clinical trials and is now applied to investigations of products of the medical technology industry.

The group tasked by the Pharmaceutical Industry Competitiveness Task Force (PICTF) Clinical Research Working Group with developing an agreement for trials managed by CROs considered the suitability of a variety of different contract formats. These included the NHS body signing an agreement with the CRO alone; the NHS body signing an agreement with the sponsor alone; the NHS body signing individual agreements with both the CRO and the sponsor; and the NHS body, the sponsor and the CRO signing a tripartite agreement. These options raised the following issues:

- A bipartite agreement between the NHS body and the CRO would be insufficient to cover all aspects of the governance of the trial or the relationship between the NHS body and both the sponsor and the CRO. A contract between the sponsor company and the NHS Trust is needed to cover issues related to publications and the management of intellectual property, over which Pharma companies usually wish to retain direct control; and responses to Freedom of Information Act enquiries, in the process of which sponsor's wish to liaise with the NHS body. In addition, there needs to be a contract between the sponsor and the NHS body to cover patient and non-patient liabilities and indemnity arrangements, publicity, confidentiality and actions to be taken in the event that the CRO is replaced or the trial terminated.
- Similarly, when the sponsor entirely or substantially delegates management of the trial to the CRO, a bipartite agreement between the sponsor and the NHS body which identified the CRO as the sponsor's agent would not reflect the importance of the relationship between the NHS body and the CRO. However, see also paragraph 2.3 which deals with lower levels of delegation of sponsors' responsibilities.
- It would be possible for the NHS body to have bipartite contracts with both the sponsor and the CRO, but these would need to be developed in parallel for each trial and they would need careful scrutiny to ensure that the agreements were consistent and covered all the responsibilities that lie with either the sponsor or the CRO.
- A single tripartite agreement signed by the NHS body, the sponsor and the CRO could cover all issues involved in the tripartite relationship between the parties without the possibility of conflicts and inconsistencies.

The working group's conclusion was that a tripartite agreement, signed by all three parties, was the most satisfactory contracting model for trials managed by CROs. The template published with this guidance, with versions for use in hospitals accountable to the Devolved Administrations of Scotland, Wales and Northern Ireland, was negotiated.

Exactly the same arguments apply to medical technology industry investigations and so a tripartite contracting format is recommended.

2.3 Circumstances when the bipartite mCIA (2008 version) may be used for investigations involving CROs

Whenever the management of a "Contract Commercial Clinical Investigation" undertaken in an NHS hospital, is completely or substantially outsourced to a CRO, the CRO mCIA should be used. However, the term CRO is defined in GCP as "a person or organisation contracted by the sponsor to perform one or more of a sponsor's investigation-related duties and functions" and therefore includes individual freelance staff (e.g. CRAs and project managers) as well as full service companies. When the 'CRO' (which may therefore in practice be one freelance CRA) does not manage the whole investigation, but undertakes a limited range of investigation-related duties on the sponsor's behalf, it may be more appropriate for the hospital and sponsor to use the 2008 bipartite mCIA. Examples of such limited CRO involvement might be undertaking only one of the following: drafting the ethics submission; identifying potential investigators; running the initiation visit; source data verification; GCP compliance. If the bipartite agreement is used, the sponsor will be liable to the trust for the acts and omissions of the CRO.

Most investigations involving CROs will require the use of the tripartite agreement but when the CRO has a limited role, the decision on whether to use the bi- or tripartite model agreement should be determined by the particular circumstances of the investigation and should be agreed by the parties involved.

2.4 Sponsor – CRO outsourcing contracts

The CRO mCIA is the model for contracts between each individual NHS hospital investigation site, the sponsor and the CRO. It does not, for example, concern the business relationship between the sponsor and CRO under which the CRO manages the investigation at all sites.

PART 3 – DIFFERENCES BETWEEN THE CRO mCTA AND THE mCTA

3.1 The CRO mCIA is based on the 2008 version of the bipartite (sponsor-NHS hospital) mCIA and many of the clauses are identical. As explained in paragraph 2.2, this is a tripartite agreement, to which the signatories are the sponsor, CRO and NHS body responsible for the patients who consent to participate. Although the carrying out of the investigation protocol is unaffected by the involvement of a CRO, the reporting and accountability arrangements of the sponsor and the NHS body may be significantly affected by the involvement of a CRO.

3.2 References to Sponsor and CRO

The inclusion of a third party (the CRO) into arrangements for carrying out investigations introduces an additional range of interactions to be addressed in the model agreement. The CRO mCIA is structured and worded in such a way as to make clear the obligations of each of the parties. In general, the differences between the bipartite CIA and the CRO mCIA reflect the way that the sponsor's obligations are either retained by the sponsor or delegated to the CRO, and the text identifies the party (sponsor or CRO) with which the NHS body has to interact on each issue.

Some investigation responsibilities can, at the sponsor's discretion, be undertaken either by the sponsor or the CRO. Where reference is made in the agreement to 'either the Sponsor or the CRO', there is no need for the responsible party to be specified more definitively. For example, this wording is found in the definitions (clause 1.1) of Auditor and Investigation Monitor and in clause 3.2 (last sentence) and 4.10 (first sentence). In these cases, the use of the phrase 'Sponsor or CRO' means that the NHS body can be given an instruction by either the sponsor or the CRO. In other places, for example clause 4.10 (last sentence) or 4.15, it means that either the sponsor or CRO can act in the way specified. Other examples are found in throughout the agreement.

Sometimes, the agreement refers to the 'Sponsor and CRO'. This can be in connection with the NHS body being required to notify both the sponsor and CRO (e.g. as in clause 2.3, 4.14.2, 4.14.3, 6.2.7 etc). In other examples, it refers to an NHS obligation to cooperate with both the sponsor and CRO over some action (e.g. 4.16.4, 4.18 etc). In other instances of its use, both the sponsor and CRO have some obligation to the NHS body (e.g. 4.16.2, 6.2.6 etc)

In relation to some investigation responsibilities that may at the sponsor's discretion be delegated to the CRO, it is very important for the NHS body to be informed whether the sponsor or the CRO is in practice to be responsible. In references to those situations, the agreement offers options: '[Sponsor] [CRO] (delete as appropriate)' to be selected when the parties are developing the investigation-specific CTA. Examples of this are found in clauses 3.1, 4.1, 4.11, 4.17 and 12.1. Whenever the model agreement says 'delete as appropriate', the investigation-specific CIA should have no ambiguity about who is to supply the information, provide the name etc. Only where the model agreement says '[Sponsor] [CRO] (delete as appropriate)' does the choice of sponsor or CRO need to be made explicit.

3.3 CRO's duties

Clause 4.2 refers to Appendix 4. In the model CIA that is a blank template where the sponsor and CRO will set out the sponsor's investigation-related duties and functions under EN ISO 14155 or ICH GCP that will be performed by

the CRO. The level of detail given in this appendix will be at the discretion of the parties to the agreement. It is NOT intended that it will reproduce EN ISO 14155 or ICH GCP, but it will summarise for the benefit of staff of all parties administering the investigation site, issues over which the NHS body will liaise with the CRO. Ultimately, under EN ISO 14155 or ICH GCP, the sponsor is accountable for the execution of sponsor duties, even if they are delegated to a CRO.

3.4 Intellectual Property Rights

In general, the IPR provisions of the CRO mCIA are the same as those of the bipartite CIA. These include the right of the NHS body to use the sponsor's Know How in furtherance of its normal business activities. However, the CRO's Know How, which was thought unlikely to be of value in patient care, is excluded from this.

3.5 Relationship between the Parties

A number of changes have been made to the original text of clause 13 to deal with the situation that could arise if the CRO were no longer to manage the continuing investigation on behalf of the sponsor. These are designed to support the smooth running of the investigation but also put in place contingency arrangements so that in these unlikely circumstances, either the sponsor itself or another CRO would carry through the management of the investigation. They would thus ensure as far as is possible that patients would neither be inconvenienced nor their care prejudiced.

3.6 Text common to the bipartite mCIA and the CRO mCIA

For an explanation of the structure of the agreement readers are reminded that guidance on the bipartite CIA is at:
<http://www.nihr.ac.uk/files/pdfs/mCIA%20Guidance.pdf>

PART 4 – INFORMATION NEEDED TO COMPLETE THE CRO CIA FOR A SPECIFIC INVESTIGATION

- 4.1 Title page: Name of the Clinical Investigation, names and addresses of NHS hospital, sponsor and CRO.
- 4.2 Second recital: Define the disease with which the investigation is concerned.
- 4.3 Fifth recital: Define the disease in which the NHS Trust has expertise.
- 4.4 Sixth recital: Insert the title of the study and Sponsor's Unique Identifier number.
- 4.5 Clause 1.1: Insert the investigation identification number in the definition of "Clinical Investigation".
- 4.6 Clause 1.1: Insert the legal name of the NHS hospital in the definition of "Trust" or "Board" (Scotland).
- 4.7 Clause 2.1: Insert the name of the investigator.
- 4.8 Clause 3.1: Select Sponsor or CRO.
- 4.9 Clause 4.1: Select Sponsor or CRO.
- 4.10 Clause 4.7.5: Insert the name of the Ethics Committee.
- 4.11 Clause 4.11: Select Sponsor or CRO.
- 4.12 Clause 4.14: Insert the number of Clinical Investigation Subjects.
- 4.13 Clause 4.17: Select Sponsor or CRO.
- 4.14 Clause 5.6: Insert the minimum amount of clinical investigations insurance cover appropriate to the level of risk involved in the investigation (This may equal the *maximum* amount of cover provided under the sponsor's insurance policy).
- 4.15 Clause 12.1: Select Sponsor or CRO.
- 4.16 Clause 16: Insert the addresses to which notices should be sent.
- 4.17 Appendix 1: Attach the Clinical Investigation Plan and any amendments made before signature of the Agreement.
- 4.18 Appendix 2: Add target dates.
- 4.19 Appendix 4: Specify and insert the sponsor's investigation-related duties and functions under EN ISO 14155 or ICH GCP to be performed by the CRO.
- 4.20 Appendix 6: Insert a copy of the financial agreement.
- 4.21 Appendix 7: The investigator should sign a copy of Appendix 7, which should then be kept in the project file.

PART 5 – DH and ABHI ADVICE AND ASSISTANCE

The Research and Development Directorate of the DH and the ABHI can be contacted on the use of the model CTA and this guidance.

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