Guidance for the Tripartite model Clinical Trial Agreement for Pharmaceutical and Biopharmaceutical Industry sponsored research in NHS Hospitals managed by Contract Research Organisations (CRO mCTA, 2011 version)

This guidance sets out how the NHS-ABPI-BIA Contract Research Organisation model Clinical Trial Agreement (CRO mCTA) was developed and provides advice on how it should be used. For background information on initiatives to improve the UK environment for commercial clinical trials and a general discussion of the model CTAs, please refer to the introduction section of the bipartite mCTA Guidance.

PART 1 - INTRODUCTION

1.1 Background to the development of the CRO mCTA

Like the bipartite mCTA (revised version 2011), the CRO mCTA was developed collaboratively by a group representing the DH, the NHS, and industry (in this case the ABPI, ABPI member companies and CROs). It was developed to supplement the revised NHS-ABPI-BIA mCTA and cover the contractual arrangements needed for contract commercial clinical trials that are managed by Contract Research Organisations (CROs). It was structured to meet the needs of pharmaceutical companies sponsoring and directly managing the trials, CROs that manage them and NHS hospitals accountable for the patients participating in them. It is commended to industry and the NHS as a model for agreements covering arrangements for all CRO-managed contract commercial clinical trials carried out by NHS hospitals.

1.2 Adoption of the 2011 version

When the first version of the CRO mCTA was published in 2007, it was endorsed by the NHS Confederation; Monitor (the independent regulator of Foundation Trusts); the UK Health Departments (of England and the devolved administrations of Wales, Northern Ireland and Scotland); the Medical Schools Council; the NHS R&D Forum; the UK Clinical Research Collaboration (UKCRC); and the pharmaceutical and biopharmaceutical industry associations (the ABPI and BIA). The agreement, negotiated with English law and governance arrangements at its core, was appropriately modified for use under the legal systems and NHS administrative arrangements of Wales, Northern Ireland and Scotland.

The bipartite mCTA was first published in 2003 and it was updated in 2006. A further review was undertaken in 2009 and it was agreed by industry bodies, the NHS, universities and the UK Health Departments that no further changes to the published versions were required at that time.

The version of the CRO mCTA negotiated and published in 2011 is substantively the same as the original 2007 version. It is modified in two areas only: the definition of Agent and the anti-bribery and anti-corruption provisions. The rationale for these changes is outlined at the relevant point in the body of this Guidance. The 2011 version has been adopted after extensive consultation with the ABPI and BIA and their member companies, the NHS, the Medical Schools Council, the National Institute for Health Research, and the UK Health Departments.

1.3 Trials involving medical academics

The Research Governance Framework 2005 clarified contracting arrangements for commercial clinical trials. For governance reasons, commercial trials 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 (RGF 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 has been clarified in

discussions between the UK Health Departments and the Medical Schools Council (MSC). The MSC has also been concerned to ensure that the NHS bodies entering into these contracts will in all cases notify universities about trials in which university employees are to participate and discuss the costs arising from them. The CRO mCTA, like the mCTA, 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 trial contract by inclusion in the financial schedule. On these understandings, the Medical Schools Council also commends the use of the CRO mCTA to its members.

1.4 Categories of trials

Not all clinical trials supported by the pharmaceutical and biopharmaceutical industry are "Contract Clinical Trials". It is important to distinguish "Contract Clinical Trials" from "Collaborative Clinical Research", including investigator-led commercial trials. In this context, "Contract Clinical Trials" are defined as commercial, industry-sponsored trials of investigational medicinal products, involving NHS patients, undertaken in NHS hospitals, usually directed towards pharmaceutical product licensing. "Collaborative Clinical Research" is primarily carried out for academic rather than commercial reasons and is not usually directed towards product licensing. Trials classified as "Collaborative Clinical Research", which include Phases II, III and IV trials and may involve current NHS patients, will continue to be covered by contracts between the company providing resources for the trial (which may for example include funding or the provision of drug supplies) 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 mCTA is designed for use in connection with Phase II to IV trials involving NHS patients undertaken in NHS hospitals, and Phase I trials where these involve NHS patients.

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

The model CTA should NOT be used in connection with commercial clinical trials categorised 'Collaborative Clinical Research', as described in the NHS R&D Partnership with the Pharmaceutical Industry i.e. where industry co-funds but does not sponsor research carried out in the NHS.

1.6 Industry-sponsored Phase I, healthy volunteer studies

The CRO mCTA is NOT to be used for phase I volunteer studies trials and this guidance does not apply to them. When investigators holding substantive employment contracts are with universities carry out such studies, the contracting parties should be the sponsor and the university.

1.6 Use and modification of the CRO mCTA

This guidance has been developed to facilitate the use of the CRO mCTA. It is not mandatory for either NHS hospitals or ABPI or BIA member companies to use the model CTAs when NHS patients are to participate in contract commercial clinical trials 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 mCTA or CRO mCTA is strongly commended by the UK Health Departments; and by the ABPI and the BIA. All these bodies recommend that no modifications are made to the agreements, other than those necessary for correctly identifying the trial, the

contracting parties, and the investigator, and setting out the financial terms and clinical trial subject recruitment arrangements.

The CRO mCTA 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:

- the ICH-GCP harmonised tripartite guideline for good clinical practice,
- good clinical practice guidance contained in or published pursuant to European Directive 2001/20/EC and Commission Directive 2005/28/EC,
- The Medicines for Human Use (Clinical Trials) Regulation 2004, as amended 2006
- the various UK Research Governance Frameworks,
- patient indemnity arrangements and
- accountability through NHS bodies' Chief Executives for clinical research involving NHS patients.

Each time the CRO mCTA is used in connection with a clinical trial, 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 trials. 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 mCTA 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 Trials (in Phases I to IV) 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 clinical trial 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 trial 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 trial involving NHS patients.

2.2 The origin of a tripartite contractual model

The group tasked by the 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.

2.3 Circumstances when the bipartite mCTA (2011 version) may be used for trials involving CROs

Whenever the management of a "Contract Commercial Clinical Trial" undertaken in an NHS hospital, is completely or substantially outsourced to a CRO, the CRO mCTA 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 trial-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 trial, but undertakes a limited range of trial-related duties on the sponsor's behalf, it may be more appropriate for the hospital and sponsor to use the 2011 bipartite mCTA. 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 trials 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 trial and should be agreed by the parties involved.

2.4 Sponsor – CRO outsourcing contracts

The CRO mCTA is the model for contracts between each individual NHS hospital trial 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 trial at all sites.

PART 3 – DIFFERENCES BETWEEN THE CRO mCTA AND THE mCTA

3.1 The CRO mCTA is substantially based on the 2011 version of the bipartite (sponsor-NHS hospital) mCTA 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 trial 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 trials introduces an additional range of interactions to be addressed in the model agreement. The CRO mCTA 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 CTA and the CRO mCTA 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 trial 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 Trial Monitor and in clause 3.2 (last sentence) and 4.8 (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 4.8 (last sentence) or 4.13, 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. 4.14.4, 4.16 etc). In other instances of its use, both the sponsor and CRO have some obligation to the NHS body (e.g. 4.14.2, 6.2.6 etc)

In relation to some trial 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 trial-specific CTA. Examples of this are found in clauses 3.1, 4.1, 4.9, 4.15 and 12.1. Whenever the model agreement says 'delete as appropriate', the trial-specific CTA 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 5. In the model CTA that is a blank template where the sponsor and CRO will set out the sponsor's trial-related duties and functions under 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 ICH GCP, but it will summarise for the benefit of staff of all parties administering the trial site, issues over which the NHS body will liaise with the CRO. Ultimately, under 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 mCTA are the same as those of the bipartite CTA. 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 trial on behalf of the sponsor. These are designed to support the smooth running of the trial but also put in place contingency arrangements so that in these unlikely circumstances, either the sponsor itself or another CRO would carry though the management of the trial. 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 mCTA and the CRO mCTA

For an explanation of the structure of the agreement, readers referred to the fuller Guidance document covering the development and use of the mCTA (2011 version)

Although a number of terms of the original 2007 CRO mCTA are no longer accurate, (for example in regard to ethical approval processes), such clauses have not been renegotiated or revised when (in the view of the UK Health Departments, ABPI and BIA) they do not introduce confusion or delay.

Users should note that there have been two significant modifications to the terms of the original CRO mCTA:

- In the past, some Universities that are the substantive employers of staff involved in clinical trials at NHS Trusts have been concerned that they might not be covered by the terms of the ABPI Form of Indemnity. Universities with these concerns have sometimes requested the industry sponsors of clinical trials to issue them with their own Form of Indemnity, separate from that included in the mCTA between the NHS body and the sponsor. The new definition of Agent makes it clear that in the context of clinical trials, Universities are agents of the NHS body that enters into the clinical trial agreement with the sponsor.
- Clause 3.5 - The anti-bribery and anti-corruption provisions of earlier versions of the mCTAs have been revised to take account of the introduction of the Bribery Act 2010, permitting sponsors to comply with their obligations under US as well as UK legislation. The clause of the agreements that has been modified is Clause 3.5, which in earlier versions referred only to corrupt actions that might be committed by Sponsors. The Bribery Act 2010 and similar US legislation makes it necessary for Sponsors to include in agreements with contractors provisions to discourage any corrupt acts on contractors' parts. The specific difference between the earlier and current versions of the text of Clause 3.5 is that in the current agreements, either party (sponsor or NHS body) can terminate the agreement in

the event that the other party commits any offence covered by the Bribery Act 2010, in relation to the agreement or the clinical study

PART 4 – INFORMATION NEEDED TO COMPLETE THE CRO CTA FOR A SPECIFIC TRIAL

4.1	Title page:	Name of the Clinical Trial, names and addresses of NHS hospital and sponsor.
4.2	Second recital:	Define the disease with which the trial 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 EUDRACT number.
4.5	Clause 1.1:	Insert the trial identification number in the definition of “Clinical Trial”.
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 (twice).
4.9	Clause 4.1:	Select Sponsor or CRO.
4.10	Clause 4.6.3:	Insert the name of the Ethics Committee.
4.11	Clause 4.9:	Select Sponsor or CRO.
4.12	Clause 4.12:	Insert the number of Clinical Trial Subjects.
4.13	Clause 4.15:	Select Sponsor or CRO.
4.14	Clause 5.6:	Insert the minimum amount of clinical trials insurance cover appropriate to the level of risk involved in the trial.
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 Protocol and any amendments made before signature of the Agreement.
4.18	Appendix 2:	Add target dates.
4.19	Appendix 5:	Specify and insert the sponsor’s trial-related duties and functions under 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, ABPI AND BIA ADVICE AND ASSISTANCE

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