Guidance on the use of Model Clinical Trial Agreement (mCTA) and Clinical Research Organisation Model Clinical Trial Agreement (CRO-mCTA)

May 2022

Contents

Introduction

The first model Clinical Trial Agreement (mCTA) for pharmaceutical research was drawn up and published by the Department of Health and Social Care (DHSC) and The Association of the British Pharmaceutical Industry (ABPI) in 2003, with the intention that a template agreement would make the contracting process more straightforward and efficient.

Since 2003, the mCTA has been refined and developed to take account of a changing regulatory regime and clinical trial environment.

The first version of the clinical research organisation model clinical trial agreement (CRO-mCTA) was published in 2007 and this was updated in 2011, in line with the 2011 version of the mCTA. Both mCTA and CRO-mCTA (the mCTAs) were updated again in 2018, with the most significant update being the replacement of four UK nation-specific templates with a single template applicable to all four UK nations. Revised versions were published in 2021, primarily to account for the end of the transition period following UK exit from the EU, and again in 2022. The May 2022 versions take account of comments and suggestions received by users and align with the UK guidance on the set up of research activity at NHS organisations (interventional research), particularly in adaptations to allow for use, where required, as head agreements from which a 'hub' may subcontract to 'spokes'. More information about the development of the mCTAs is provided below.

The mCTAs have been developed through consultations between the various stakeholder groups, including representatives from the DHSC, the Health Research Authority, the National Institute for Health and Care Research, the Medical Research Council, the Devolved Administrations, the NHS[1], life sciences trade associations and national and global heads of research from bio-pharmaceutical companies and clinical research organisations.

The mCTAs have been devised to meet the needs of the companies Sponsoring clinical trials and clinical research organisations managing sites and to reflect the duty of care that Trial Sites have for their patients and other research participants under their care.

This guidance provides an introduction to the mCTAs, outlining when and how they should be used, summarising some of their key provisions, as well as providing an overview of the change history of the mCTAs.

Structure of the Guidance

This guidance is in three parts:

1. **Section 1 provides an overview of how the mCTAs should be used.**

2. **Section 2 is an overview of some of the provisions within the mCTAs.**

[1] Throughout, references to NHS should be read to include references to Health and Social Care (HSC) in Northern Ireland

3. Section 3 provides background on the development of the mCTAs, including a change history.

Section 1: Use of the mCTAs

1.1 What are the mCTAs?

The mCTA is the standard form contract for use by industry Sponsors and NHS[2] Trial Sites (but see 1.3 below for relationship between the mCTAs and the Hub and Spoke Agreements) running contract clinical trials of investigational medicinal products (CTIMPs).

The CRO-mCTA is the standard form contract used by industry Sponsors, the clinical research organisations separately contracted by them to undertake site management responsibilities, and NHS Trial Sites (but see 1.3 below for relationship between the mCTAs and the Hub and Spoke Agreements) running contract CTIMPs.

Contract CTIMPs in the NHS are industry-Sponsored CTIMPs in which NHS patients, or healthy volunteers under an NHS duty of care, receive Investigational Medicinal Products ("IMPs").

All references in this guidance to "clinical trial" should be read as a reference to a contract CTIMP.

1.2 When should the mCTAs be used?

The mCTA is intended to be used for all phases of contract clinical trials, including Phase I trials in NHS patients or healthy volunteers under an NHS duty of care (NB the May 2022 versions are the first intended for use in Phase I healthy volunteer research in the NHS).

The CRO-mCTA is intended to be used as above but where, in addition, the Sponsor has contracted with a clinical research organisation to be responsible for aspects of trial management at the Trial Site. Where the CRO-mCTA is used, it forms a tri-partite agreement between the Sponsor, CRO and Trial Site.

The mCTAs should be used with NHS Trial Sites undertaking research activities overseen by a Principal Investigator at that Trial Site. Where a Principal Investigator oversees research activity at multiple Trial Sites, the relevant mCTA should be used to contract the Lead Trial Site, with Other trial sites subcontracted by Hub and Spoke Agreements (see 1.3 below).

The mCTAs are not for use in non-commercial studies funded or sponsored by charities, government departments or research councils, whether or not such studies involve NHS patients or healthy volunteers and whether or not they are carried out by NHS organisations. The Model Agreement for Non-Commercial Research in the Health Service (mNCA) or non-commercial Organisation

[2] The mCTAs are intended for use in NHS organisations, not with independent contractors of primary care NHS commissioned services. Primary Care mCTA is provided for such circumstances.

Information Document (as appropriate) should be used for non-commercial studies.

The mCTAs are for managing site arrangements and are not for use to manage the collaboration between organisations in collaborative clinical research trials. NHS, commercial (and, where applicable, academic) collaborations should be managed, as necessary, via a collaborator agreement and the resultant research studies separately contracted between sponsor and site using the appropriate UK template (which would be an mCTA for a commercial CTIMP, the mNCA or Organisation Information Document, for non-commercially sponsored collaborative studies).

The mCTAs are not designed for the purposes of any Contract Clinical Trials (Phases I to IV) performed by private institutions with patients recruited independently of their treatment within the NHS.

The mCTAs are not for use with independent contractors of NHS primary care services. Commercial studies with NHS patients in independent contractor primary care should be contracted using the Primary Care model Clinical Trial Agreement (PC-mCTA).

The mCTAs are not for use in investigator-initiated, non-commercially sponsored, trials. The Model Agreement for Non-Commercial Research in the Health Service (mNCA) should be used for this purpose.

The mCTAs are not for use in clinical investigations of medical devices (commercially sponsored device studies should use mCIA), or for non-interventional studies (for which mNISA should be used if commercial or the organisation information document if non-commercial).

1.3 Investigator Sites, Trial Sites and Hub and Spoke Agreements

The May 2022 version of the mCTA was drafted to take account of and align with UK guidance on the set up of research activity at NHS organisations (interventional research). Accordingly, the Party contracted by the Sponsor to conduct the Clinical Trial is now defined as the Trial Site.

The above referenced set-up guidance defines a Trial Site as “a legal entity responsible for some element of an interventional research study for which PI oversight is required”. It also clarifies that one PI may oversee more than one trial site, or that one trial site may need more than one PI to ensure effective oversight.

The guidance (and the mCTAs) uses the term Investigator Site for “the activities (regardless of their location) with effective oversight by one Principal Investigator”.

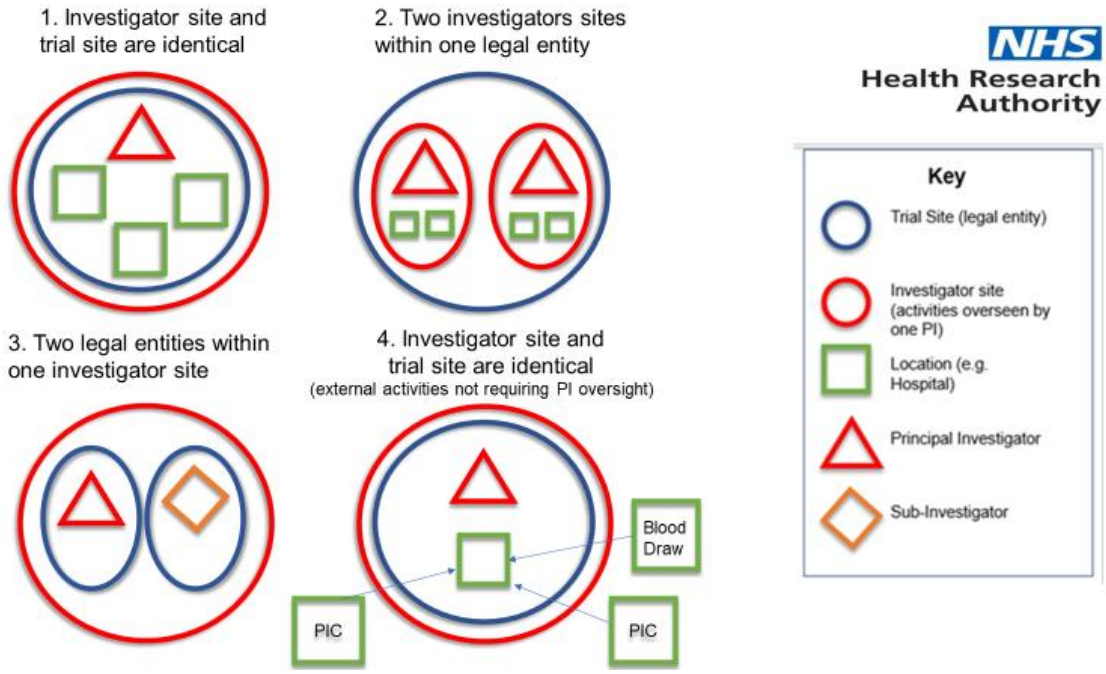
A clinical trial may therefore be delivered with one (or a combination of) the following PI oversight arrangements;

- one Investigator Site per Trial Site. That is to say that there is one PI overseeing research activity at one legal entity (see figure 1.1), or;
- More than one Investigator Site within the one Trial Site. That is to say that there is more than one PI for research activity occurring within the one

legal entity, each PI having oversight for specific activities within that entity (see figure 1.2), or;

- More than one Trial Site within the one Investigator Site. That is to say that one PI oversees research activities occurring within more than one legal entity (see figure 1.3);
- There may also be other legal entities involved in the study that are undertaking activities not needing PI oversight, for example general practices undertaking simple blood draws, Participant Identification Centres and so on (see figure 1.4).

FIGURES 1.1 – 1.4



Where there is more than one Investigator Site within the one Trial Site, one mCTA per Investigator Site should be agreed between the Parties. Whilst this means that the same Trial Site has more than one contract for the same clinical trial, each contract would cover the activities specifically contracted to be overseen by one PI. Clause 16.4 has been updated to facilitate this approach. The mCTA should not be modified to attempt to use one contract to cover more than one Investigator Site within the same Trial Site.

Where there is more than one Trial Site within the one Investigator Site, the mCTAs have been drafted to allow the Lead Trial Site (that which employs the PI) to contract with the Sponsor using the mCTA. The Lead Trial Site then subcontracts to Other Trial Sites the aspects of the Study that they will conduct, overseen by the Lead Trial Site PI. A commercial hub and spoke template has been published for use alongside the mCTA in such circumstances, allowing the Lead Trial Site to subcontract with Other Trial Sites in a consistent manner.

1.4 Modifications to the mCTAs

The mCTAs have been developed through many years of negotiation and discussion between a wide stakeholder group.

Prior to execution of a clinical trial agreement, it is necessary for trial-specific information to be appended to, or options selected within, the mCTAs. The information required/options are identified on the front page of the mCTAs (and throughout the mCTAs in yellow highlight). Other than the need to add or select information as specified, it is strongly recommended by all the UK Health Departments that the mCTAs should be used without modification. Any request by a sponsor or CRO to modify the mCTAs and/or to use any agreement to contract with a site other than the appropriate mCTA, should be disclosed in the IRAS submission (a version of the template proposed for use, with tracked changes and details justification should be provided).

In England and Wales, NHS organisations are required to use only an unmodified mCTA or CRO-mCTA (as appropriate and applicable). In exceptional circumstances this requirement may be waived by the letter of HRA and HCRW Approval for the study. Such waivers require UK agreement from the UK Four Nations Contracting Leads Group. Similarly, proposals for modifications to mCTAs for use with sites in Scotland or Northern Ireland will also be escalated to the UK Group.

Sponsors should be aware that proposing modifications to template agreements is likely to result in significant delay and does not oblige NHS organisations to agree the modified agreement, even where a waiver is centrally agreed for its use. Any waiver issued would allow the NHS organisation to propose and negotiate its own modifications. Unmodified use is strongly recommended.

Section 2: Guidance on the Provisions in the mCTAs

2.1 Contracting Parties

In order to comply with research and clinical governance requirements and expectations, and to establish the correct lines of accountability for clinicians practising in the NHS, all contract clinical trials must be governed by contracts between the Sponsor and NHS organisation (or, where appropriate, a subcontract between NHS organisations). This remains the case even when, for example, the investigator is employed by a university and holds an honorary contract with the NHS organisation.

Where a Sponsor has legally delegated to a corporate affiliate of the Sponsor the power to contractually bind the Sponsor by signing the Agreement on its behalf, evidence of this delegated authority should be attached as Appendix 8 of the mCTA or Appendix 9 of the CRO-mCTA. This evidence is required by the NHS as an assurance that the delegated entity is empowered by the Sponsor to sign on behalf of the Sponsor and thereby bind the Sponsor as Party to the agreement.

Where a Sponsor is not established in the UK or EEA, their UK/EEA Legal Representative for the purposes of the clinical trial regulations should be named in the recitals of the agreement but will not be a separate signatory or Party to the agreement in their capacity as Legal Representative.

Where the Sponsor has contracted a CRO to manage aspects of the clinical trial, the CRO should be a Party to the Agreement and the separation of

responsibilities between the Sponsor and CRO should be set out clearly, including evidence of the delegated activities appended at Appendix 8 of the CRO-mCTA. If the CRO has been legally empowered by the Sponsor to sign on behalf of the Sponsor to bind the Sponsor as party to the Agreement, this should be clearly evidenced in this appendix.

Participating NHS organisations have an obligation to inform medical academics' substantive employers, which are usually universities, about clinical trials in which they are to take part.

The mCTAs should not be modified to form a tripartite agreement with an academic institution as a third party. In the event that a Sponsor has engaged a Contract Research Organisation to recruit and manage trial sites, the CRO-mCTA should be used.

In no case should a clinical trial Sponsor enter into a contract with an individual employee of either an NHS organisation or a university in a personal capacity to undertake a clinical trial involving NHS patients or healthy volunteers under NHS care. This prohibition applies to contracts governing the conduct of clinical trials (including the mCTAs). Chief Investigators may be separately contracted for their services either personally (if acting in a personal, non-NHS capacity), or via their employing organisation.

2.2 Clause 2: Principal Investigator and Personnel

The Principal Investigator is not to be a signatory to the mCTAs. Clause 2 makes clear the obligation of the Trial Site to procure the performance of the Principal Investigator with respect to the Trial Site's obligations under the Agreement. Since the March 2020 version, this obligation has extended to procuring the services of Sub-Investigators and other personnel (which, from the May 2022 version may extend to include those at Other Trial Sites). The mCTAs do not seek to amend the well-understood and established obligations of Principal Investigators. Trial Sites should bring these responsibilities to the attention of Principal Investigators in the course of research governance training.

As the obligations of the Trial Site will be fulfilled through the work of the Principal Investigator, it is important that the Trial Site incorporates the obligations of the Principal Investigator and other investigators set out in the mCTAs, into a separate agreement (in a form that is at the discretion of the Trial Site) between the Trial Site and the Principal Investigator.

It is prudent for the clinical trial activities to be included in the work plans of the Principal Investigator and any Sub-Investigators. The Trial Site may seek assurances from the Principal Investigator and any Sub-Investigators to satisfy the conditions of the mCTAs.

2.3 Clause 2.5: Attendance at Investigator Meetings and Reimbursement of Expenses

Clause 2.5 sets out an obligation on the Principal Investigator and/or the personnel to attend meetings reasonably requested by the Sponsor (or CRO). It should be noted that no compensation will be paid for attendance at such

meetings and any expenses incurred will be paid at the rate of fair market value, subject to documentation evidencing the expenses incurred being in sufficient detail to for the Sponsor's financial reporting purposes (or those of the CRO, as applicable), provided that this is not overly burdensome for the Trial Site.

2.4 **Clause 3.2 and 3.3: Governance**

These Clauses set out the minimum compliance requirements for the conduct of trials, including in respect of domestic law and investigational new drug (IND) in respect of trials conducted by US companies. However, it is essential that Sponsors (or CROs, where applicable) notify Trial Sites of specific requirements that relate to the performance of trials and that arise from such laws.

2.5 **Clause 3.3.7: WHO Ethical Principles**

This reference to the WHO Ethical Principles is intended for use where the clinical trial involves transplantation of human cells, tissue or organs. It is an optional reference, to be deleted if not applicable to the Clinical Trial.

2.6 **Clause 3.6.1: Adverse Event Reporting**

To facilitate use of the mCTAs for Phase I trials in NHS patients or healthy volunteers under NHS care, Clauses setting out obligations in relation to adverse event reporting have been included. These clauses are only applicable where the Clinical Trial is a Phase I clinical trial and should be deleted if not applicable.

2.7 **Clause 3.6.2: Quality Control of Data in Phase I Dose Escalation Trials**

To facilitate use of the mCTAs for Phase I dose escalation trials in NHS patients or healthy volunteers under NHS care, a clause setting out obligations in relation to adverse event reporting has been included. This clause is only applicable where the Clinical Trial is a Phase I dose escalation clinical trial and should be deleted if not applicable.

2.8 **Clause 3.7: Anti-Bribery and Corruption**

Modifications to this clause to reference the Foreign and Corrupt Practises Act of the USA, or any other foreign law, should not be proposed and will not be agreed. Compliance with the Bribery Act 2010 should provide adequate assurance to foreign Sponsors (and CROs) in relation to their own compliance with foreign law.

2.9 **mCTA Clause 4.7 (CRO-mCTA Clause 4.8): No Supply of Investigational Drugs by the Sponsor (or CRO) Prior to Approval**

Clause 4.7 (CRO-mCTA Clause 4.8) requires Sponsors (and CROs, as applicable) to delay supply of investigational drugs supplied by the Sponsor (in addition to the previous requirement in relation to supply of the IMPs), to the Trial Site, until all regulatory and ethics approvals have been obtained. There is an obligation on the Trial Site to ensure that no clinical interventions arising from the Protocol take place before receipt of all relevant approvals.

2.10 **mCTA Clause 4.12 (CRO-mCTA 4.13)**

Reflecting different types of clinical trial and differing Sponsor requirements, mCTA 4.12 (CRO-mCTA 4.13) requires that the Sponsor specifies whether the local recruitment target should be expressed as number(s) enrolled, dosed or randomised. Enrolled means that the clinical trial subject has consented to be a participant in the clinical trial. Dosed means that the clinical trial subject has received their first dose of Investigational Drug. Randomised means that the clinical trial subject has been randomised to an arm of the study, or equivalent, in accordance with the Protocol.

2.11 **mCTA Clause 4.13.2 (CRO-mCTA 4.14.2): Enrolment Targets**

mCTA Clause 4.13.2 (CRO-mCTA Clause 4.14.2) makes clear that payment will only be made for clinical trial subjects who have been enrolled into the clinical trial prior to the date of receipt of the notice.

2.12 **mCTA Clause 4.14 (CRO-mCTA 4.15): Hub and Spoke Agreement**

The May 2022 version of the mCTAs includes this new optional clause, for use when the mCTA is used as a head agreement for subcontracting between the Lead Trial Site and Other Trial Site(s) (that is to say where the PI at the Lead Trial Site is overseeing activities at other legal entities, which are therefore part of the same Investigator Site and subcontracted as such).

2.13 **mCTA Clause 4.15 (CRO-mCTA Clause 4.16): Access, Research Misconduct and Regulatory Authorities**

Reflecting the strict regulatory environment faced by Sponsors (and CROs), representations have been included to confirm that the Trial Site is unaware of any restriction on the Principal Investigator or the Personnel that would prevent that (those) individual(s) from having a role in the Clinical Trial. The March 2020 version clarified that the representation made by the Trial Site must be made only after reasonable due diligence on its part to ensure that the Sponsor may take adequate assurance from this representation.

Detailed provisions covering the Sponsor's (and CROs) access to the Trial Site and handling of possible misconduct have been agreed and these include various reporting requirements.

2.14 **mCTA Clause 4.15.9(a) (CRO-mCTA 4.16.9(a)): Archiving**

This sub-clause allows for circumstances in which archiving is arranged on behalf of the Trial Site, as well as where the archiving is arranged by the Trial Site itself. Costs associated with archiving may be reimbursed by the Sponsor (or CRO, where applicable), provided that those costs are reasonable, agreed in advance and set out in the financial schedule.

2.15 **mCTA Clause 4.15.10 and 4.15.11 (CRO-mCTA Clauses 4.16.10 and 4.16.11): Use of Material**

The mCTAs define "Material" as "…any clinical biological sample, or portion thereof, derived from Clinical Trial Subjects, including information related to such material, analysed by the Trial Site or Other Trial Site in accordance with the Protocol, or otherwise supplied under Appendix 6 to the Sponsor or its nominee."

mCTA Clauses 4.15.10 and 4.15.11 (CRO-mCTA 4.16.10 and 4.16.11) distinguish between the situations where a Trial Site (or Other Trial Site(s) should this be subcontracted) analyses material, and situations where a Sponsor takes that responsibility and it is carried out either in the Sponsor's own laboratory or through a third party laboratory.

mCTA Clause 4.15.10 (CRO-mCTA 4.16.10) should be deleted where no analysis of Material will take place at the Trial Site (or, as applicable, Other Trial Site(s)).

mCTA Clause 4.15.11 (CRO-mCTA 4.16.11) should be deleted where no transfer of Material from the Trial Site (or, as applicable, Other Trial Site(s)) will take place for analysis by the Sponsor or their nominee.

Both clauses should remain where analysis of Material will be undertaken by **BOTH** the Trial Site (and/or, as applicable, Other Trial Site(s)) **AND** by the Sponsor or their nominee.

Appendix 6 sets out general responsibilities with respect to the handling and use of Material transferred to the Sponsor (or their nominee) by the Trial Site/Other Trial Site(s), applicable to both Parties and is applicable only where Clause mCTA 4.15.11 (CRO-mCTA 4.16.11) applies. Otherwise, it should be deleted.

Additional requirements relating to the use of Material in any specific clinical trial are also captured in the Integrated Research Application System (IRAS) application required to obtain approval for the Clinical Trial. Sponsors and Trial Sites (and CROs, where applicable) are strongly encouraged to review both the IRAS question relating to use of Material and Clinical Trial Subjects in order to determine the feasibility (or otherwise) of use/participation in multiple Clinical Trials, as well as the accompanying notes which place restrictions on the use of Material.

2.16 Clause 5: Liabilities and Indemnities

It is essential that Sponsors and Trial Sites (and CROs, where relevant) indemnify each other for any liabilities other than those covered under the ABPI Indemnity Agreement, in case participation in a clinical trial results in damage to a party's property and facilities. Hospitals' non-clinical liabilities in relation to research are not usually covered by existing NHS litigation schemes and it is unlikely that their management would authorise the taking on of unquantified and potentially unlimited liabilities, such as might arise from an intellectual property rights claim.

The liabilities of Trial Sites to Sponsors (and CROs, where applicable) have been capped at two different levels depending on the nature of the breach. The first cap, covering (a) wilful and/or deliberate breaches of the agreement and (b) any breach related to Clauses 6, (Data Protection), 7 (Freedom of Information), 8 (Confidential Information), 10 (Publications) and 11 (Intellectual Property), provides for the Participating Organisation's liability to be limited to a maximum of twice the value of the agreement. The agreement value is the total payment due to be made by the Sponsor (or CRO, as applicable) to the Participating Organisation, if the target number of patients is recruited. The second cap covers all other breaches of the agreement by the Participating Organisation and limits the Participating Organisation's liability to the maximum value of the contract.

While for a number of types of possible breaches these provisions might not fully compensate the Sponsor (or CRO) for their loss, it is considered that the risk of paying compensation on this basis provides an additional incentive for Trial Sites to take every reasonable precaution to prevent a breach of the agreement. These precautions could include: (i) having in place robust research governance arrangements; (ii) instituting training programmes for researchers undertaking commercial trials; (iii) emphasising to staff the importance of protecting the integrity of Sponsors' (and CROs) confidential information; and taking disciplinary action in the event of a wilful or reckless breach of the provisions of clinical trial agreements.

Under The Medicines for Human Use (Clinical Trials) Regulations 2004, Sponsors are not required to take out clinical trials insurance, but Trial Sites will wish to be assured either that sufficient insurance cover has been purchased, or that the Sponsor has provided an indemnity covering potential liabilities to clinical trial subjects participating in the relevant clinical trial. Research ethics committees that provide an opinion on the trial proposal, may therefore take a view, in relation to the risks posed by a specific clinical trial, as to the indemnity and/or the adequacy of the Sponsor's clinical trials insurance.

2.17 Clause 6: Data Protection

The mCTAs include general provisions related to compliance with the relevant data protection laws and guidance. The definition of the term "Data Protection Laws and Guidance" includes "**legally enforceable** NHS requirements, Codes of Practice or Guidance issued by the Information Commissioner's Office, in each case in force from time to time in England, Northern Ireland, Scotland and/or Wales". Oversight of this compliance is provided through the clinical trials approval process, which includes a review of the mechanisms for protecting personal data.

Clause 6 is explicitly concerned with Personal Data as defined in the agreement, that is, only personal data of Clinical Trial Subjects, or potential Clinical Trial Subjects. The Personal Data of the Principal Investigator or Personnel are not dealt with in the template and requests to modify the template to change this will not be accepted. Sponsors are encouraged to fulfil their transparency obligations for processing the personal data of the PI and Personnel via their signature and delegation log, as per the example provided in IRAS.

Clause 6.2, when taken together with the clinical trial protocol, constitutes a GDPR Article 28(3) compliant data processing agreement between Sponsor, as controller of Personal Data processed for the purpose of the clinical trial, and the Participating Organisation, as processor of the Sponsor for this purpose.

Clause 6.2.5(a) explicitly references GDPR Article 28(1) and gives "obligations as an NHS organisation" as the guarantee that the sponsor should take in accordance with 28(1). NHS organisations are held to high standards of data protection in each of the four UK nations. Sponsors should therefore take assurance that the measures taken by the NHS are appropriate when relying upon existing NHS processes, systems, etc. for the processing of personal data (as opposed to when study specific provisions are required by the sponsor, such

as Electronic Case Report Forms (eCRF), where the requirements of the sponsor should be clearly set out in, for example, the protocol, eCRF manual or other relevant document).

Clause 6.2.6 should set out the position of the Sponsor on the use of Participant Identification Centres (PICs) in the clinical trial and, where their use is permitted, whether the Participating Organisation may engage PICs under the general written authorisation of the agreement or only with specific written authorisation from, or on behalf of, the Sponsor.

Clause 6.3 provides for the sharing of Personal Data and or the pseudonymised data of data subjects. The drafting of Clause 6.3 is not intended to directly deal with sponsor responsibilities arising from the Data Protection Laws and Guidance, nor to provide the legal basis for the export of personal data to a country outside of the UK. Instead, the Clause is drafted to provide the Participating Organisation with assurances that NHS organisations are advised, in accordance with Caldicott and NHS policies and best practice, to obtain prior to releasing potentially identifiable confidential patient information to a third party. Modifications to the Clause to form a controller to controller agreement for the export of personal data, or other modifications that fail to reflect the basis of the clause in Caldicott, NHS policy and best practice, should not be proposed and will not be accepted.

2.18 **Clause 7: Freedom of Information**

This Clause imposes obligations on Trial Sites to take timely action to inform Sponsors (and CROs, as applicable) about requests for information, consult fully with them about disclosure, and inform them, where reasonably practicable, in a timely way of any plans they may have to disclose information against the wishes of a Sponsor.

2.19 **Clause 10: Publications**

The mCTAs recognise that Trial Sites have a responsibility to ensure appropriate publication and dissemination of clinical research for the benefit of patients and their peers. Publication should be done in an orderly way, usually in compliance with the publication policy set out in the Protocol, provided such policy is consistent with the Joint Position as defined in the mCTAs.

This Clause sets out conditions governing the way that individual investigators should prepare any publications that they may intend to make, and the opportunities that they should allow Sponsors to comment on them. It also specifies the window of opportunity available to Sponsors in which they can protect proprietary information. It was drafted to ensure that publications based on limited and perhaps unrepresentative data from one site, or a limited number of sites, do not inadvertently misrepresent results, by requiring that the principal report(s) of each clinical trial is (are) published before articles based on subsets of the data.

The terms of the mCTAs allow publication of data derived from the Participating Organisation after the multi-centre publication and subject to the terms of Clause 10.

2.20 Clause 11: Intellectual Property (IP)

Four core principles underlie the mCTAs' IP Clauses. First, each party retains ownership of any pre-existing IP or Know-How owned by it or licensed to it. Second, any IP or Know-How generated at the Participating Organisation that relates to the clinical trial, the IMP or the Protocol (excluding any clinical procedure or related improvements) is the property of the Sponsor. Third, clinical procedures and related improvements are the property of the Participating Organisation and, depending on the inventor's employer (hospital or university), could be protected accordingly. Four, the Participating Organisation also has the right to use know-how gained during the trial in its normal activities, provided it does not result in disclosure of the Sponsor's confidential information. These provisions are designed to protect the Sponsor's IP and give it ownership of anything derived from it, while allowing the investigator's employer to protect and exploit clinical procedures and related improvements, and to use Know-How generated while the Clinical Trial is being undertaken.

Example 1
If an investigator, supplied with information in the investigator brochure about the characteristics of a new drug, identified a possible role for the drug in a different disease, or a potentially more effective combination with a second drug, the rights to that IP would lie with the Sponsor.

Example 2
If a Protocol specified that a certain type of CT scan should be taken, and while analysing the scan, an employee of the Participating Organisation developed a new method of analysing CT scans, the rights to that IP would lie with the Participating Organisation.

Example 3
A Sponsor supplies a case report form for use by an investigator for the Sponsor's clinical trial. In the course of carrying out the Sponsor's clinical trial, the investigator develops, for his/her own convenience and without being requested to or paid to by the Sponsor, a novel database on which to manage the trial subject data. The rights to that IP would lie with the employer of the investigator.

The terms of the mCTAs do not give the Sponsor rights to all IP generated by employees of the Participating Organisation either in the course of the clinical trial or in the field of the clinical trial.

2.21 Clause 12.6: Longstop dates

It is noted that the Sponsor (or CRO, as applicable) has a right to refuse payment of invoices which are not dated within 60 days of site close out (or within sixty (60) days of the Sponsor providing final invoicing data, if that data is requested within forty-five (45) days of the site close out).

2.22 Clause 12.7: Payment Terms

The mCTAs provide a payment term of forty-five (45) days. This payment term should not be revised with respect to any specific Clinical Trial. This payment term

represents a balance between the financial processes of Trial Sites and those of Sponsors and CROs.

2.23 **Clause 16.1: Order of Precedence**

In most respects, the terms of the Protocol will prevail over the other terms of the mCTA. However, in respect of six (6) important Clauses: 5 (Liabilities and Indemnities), 6 (Data Protection), 7 (Freedom of Information), 8 (Confidentiality), 10 (Publications), 11 (Intellectual Property) and 16 (Agreement and Modification), the terms set out in the mCTAs will prevail.

2.24 **Clause 16.3: Changes to the Protocol**

The procedure to be followed when changes are made is set out in Clause 16.3 and if the change requires a revised financial schedule, this should be agreed, signed by the Parties and attached to the Agreement. The implementation of amendments requiring changes to the financial schedule should not be delayed until contract variation is completed. Instead, amendments should be implemented in a timely manner, whilst good faith negotiation between the parties continues to finalise and agree the variation.

2.25 **Clause 17: Force Majeure**

The parties will agree a reasonable time limit after which delays due to an act of God etc., affecting one party's performance of their duties, allow the unaffected party to terminate the contract.

2.26 **Clause 18.1.1: Notices**

It is permitted to serve notice by e-mail, at the discretion of the Sponsor, as set out in this Clause. Where the Sponsor chooses not to allow for notices to be served by e-mail, the Clause should not be modified, the parties should merely refrain from providing email addresses under Clause 18.2.

2.27 **Clause 19: Dispute resolution**

Under the mCTAs, the parties are required, in the first instance, to attempt to resolve any dispute through discussion between senior managers which, if unsuccessful, may proceed to mediation. An informal local procedure is specified, escalating, if necessary, through more formal processes. If mediation fails, the parties can take the dispute to the courts of the jurisdiction in which the Participating Organisation is constituted.

2.28 **Clause 20.4: Governing Law and Jurisdiction**

The Governing law of the mCTA and CRO-mCTA is determined by reference to the nation of the UK within which the Participating Organisation is constituted.

2.29 **Clause 20.5: Counterparts and Signatures**

The signatories to the mCTA and CRO-mCTA will be the authorised representatives of the Sponsor and the Participating Organisation (and CRO, where applicable). In the case of the Participating Organisation, the signatory

might be the Chief Executive, the Director of R&D, the Director of Finance, or another authorised person. In the case of the Sponsor, if the Sponsor has formally delegated authority to contractually bind it, to a corporate affiliate of the Sponsor, this should be evidenced at mCTA Appendix 8 (CRO-mCTA Appendix 9). In the case of CRO-mCTA, if the Sponsor has formally delegated authority to the CRO to sign the Agreement, and thereby bind the Sponsor as a Party to the Agreement, this should be evidenced in Appendix 8 of CRO-mCTA.

The mCTAs allow for execution to be through use of an electronic signature and for execution to be via counterparts.

Sponsors, CROs (as applicable) and Trial Sites are encouraged to discuss execution arrangements early in the contract negotiation, in order to determine the most appropriate arrangements for all parties.

2.30 **Appendix 1: Timelines and Responsibilities of the Parties**

The milestones included in this Appendix are by way of example and the parties may jointly amend the list as they see fit. It is noted that the target dates should be determined in relation to individual sites and not in relation to the relevant clinical trial as a whole. Timelines will require early negotiation involving the Principal Investigator and the Sponsor (and the CRO, where applicable). It will be particularly important that they are realistic with respect to the date that the protocol will be finalised, and should build in as footnotes, contingency plans for changes in the event that there is delay in, for example, regulatory or ethics committee approval. The shared responsibilities indicated on the table in Appendix 1 show that the timing of some events is dependent on good co-ordination between the parties in, for example, scheduling all participants' availabilities for the initiation visit.

2.31 **Appendix 2: ABPI Clinical Trial Compensation Guidelines 2015 and Appendix 3: Form of Indemnity**

Both appendices are the current ABPI documents and no proposed modifications to either will be accepted.

2.32 **Appendix 4: Financial Arrangements**

The financial arrangements for the clinical trial should be appended as Appendix 4 of the mCTAs. Sponsors (and/or CROs, as applicable) and Trial Sites should use the NIHR interactive Costing Tool (iCT) to derive a contract value, in line with the nation-specific processes of the UK nation in which the participating organisation is established.

The financial and other interests of universities that might employ the medical academics and sometimes the research fellows and research nurses involved in clinical trials should be recognised by Trial Sites. The notification arrangements noted above are designed to ensure that universities have the information needed for the protection of their interests. There should be formal agreement between Trial Sites and universities, covering their entire clinical trials portfolio, setting out processes for the identification of the university's direct and indirect costs and overheads, and the apportioning of research income between the institutions. This

issue could be covered in the partnership agreements between Trial Sites and associated academic institutions that are negotiated in the process of implementing research governance arrangements. In the case of clinical trials for which the investigator's or site team members' substantive contract is held by a university, the university should be involved in the calculation of staff costs for the trial and the NHS research managers should agree the content of the financial schedule with the university. Appendix 4 should be populated with details of the financial arrangements of the clinical trial and it should not be used for other matters.

There should not be separate financial arrangements between the Sponsor (or CRO, as applicable) and any Participating Organisation departments such as the pharmacy, nor with the university that employs an investigator.

The staging or scheduling of payments should be negotiated, including any payments to be made before administration of the Investigational Drug(s), or any other clinical intervention mandated by the protocol, (e.g. site set-up costs) and whether such payments are refundable or non-refundable.

Clinical trials are undertaken by Trial Sites under income generation rules and are commercial services supplied under contract to companies. Invoicing arrangements should be via the Participating Organisation's finance department using formal VAT invoices in compliance with NHS Standing Financial Instructions.

2.33 **Appendix 5: Conditions Applicable to the Principal Investigator**

It should be noted that there is an obligation on Trial Sites that are not members of the relevant risk pooling scheme, to ensure that the Principal Investigator carries medical liability insurance.

2.34 **Appendix 6: Material Transfer Provisions**

Where no Material is to be supplied by the Trial Site to the Sponsor or their nominated representative, Appendix 6 should be deleted.

2.35 **Appendix 7: Equipment and Resources**

Where no Equipment or Resources are being provided Appendix 7 should be omitted from the final clinical trial agreement.

Appendix 7 includes tables where equipment and resources that are provided by Sponsors (and/or CROs, as applicable) for the clinical trial should be listed. These tables include a column where the depreciated value of the equipment/resources can be detailed. It is noted that there is no standard method for determining depreciation and therefore, this must be discussed and agreed between Sponsor and Participating Organisation (and CRO, as applicable).

The Sponsor (or CRO, as applicable) should indicate whether alternative 1 or 2 should be used with respect to liability in Clause 7.2 of Appendix 7. The selection should be clearly indicated in the agreement.

It is noted that Northern Ireland does not have any MIA arrangements and that the MIA in England is not applicable to equipment loaned or gifted for the purpose of clinical trials. Alternative #1 must be used where the Participating Organisation is constituted in England or Northern Ireland.

2.36 **Appendix 8 (CRO-mCTA only): Sponsor's Clinical Trial Related Duties and Functions Under ICH-GCP to be Performed by CRO**

This Appendix should clearly set out which Sponsor responsibilities for site management will be performed by the CRO. If the Sponsor has formally empowered the CRO to sign this Agreement and thereby legally bind the Sponsor to its terms as a Party, this must be explicitly evidenced.

2.37 **Appendix 9 (Appendix 8 CRO mCTA): Formal Delegation of Authority from Sponsor to a Corporate Affiliate to Contractually Bind the Sponsor as a Party to this Agreement**

Where applicable, attach here evidence of formal delegation of authority, from the Sponsor to the corporate Affiliate of the Sponsor, to sign this Agreement and thereby legal bind the Sponsor to its terms as a Party.

Contact Points for Advice and Assistance

For queries relating to the use of the mCTAs for trials taking place in England: please contact the Health Research Authority, at alastair.nicholson@hra.nhs.uk.

For queries relating to use in Wales:
please contact the Health and Care Research Wales Support and Delivery Centre at research-contracts@wales.nhs.uk.

For queries relating to use in Scotland:
please contact NHS Research Scotland at enquiries@nrs.org.uk.

For queries relating to use in Northern Ireland:
please contact ResearchContracts@innovations.hscni.net.

Section 3: Background and Change History

Background

The mCTA was published by the Department of Health and the ABPI in 2003.

The mCTA was updated in 2006 to take into account the introduction of the EU clinical trials directive and the directive on good clinical practice in pharmaceutical research. Versions of the mCTA were also created for use in Northern Ireland, Scotland and Wales.

The first CRO-mCTA was published in 2007. Based on mCTA 2006, it allowed unmodified use of a template agreement in circumstances where a CRO undertook site management responsibilities and allowed for the division of responsibilities between Sponsor and CRO to be set out.

A further update, to both the mCTA and CRO-mCTA, took place in 2011. Modifications were made in two areas only: clarification that universities employing staff involved in contract clinical trials at Trial Sites are classed as agents of the Participating Organisation; and anti-bribery and corruption provisions were included.

The 2018 model was the fourth version of the mCTA, and the third version of the CRO-mCTA, and was influenced by the work of the Ministerial Industry Steering Group (MISG), a body which brings together government and the bio-pharmaceutical industry.

In 2016, the MISG Clinical Research Working Group (CRWG) recognised the need to enhance further the UK's position as a great place to do commercially funded research. Following feedback from NHS stakeholders and industry partners, it was decided to develop UK-wide mCTAs as well as bringing the mCTAs up to date with current practice and regulations.

The March 2020 mCTAs built upon the previous versions and reflected significant engagement with both NHS and commercial stakeholders. The most substantial changes took account of the introduction of the General Data Protection Regulation (GDPR) and the Data Protection Act 2018. From this version onwards, the mCTAs have formed GDPR Article 28(3) compliant data processing agreements, as well as incorporating provisions for the transfer of Personal Data and/or pseudonymised data.

The January 2021 mCTAs incorporate further industry feedback on the templates, as well as taking account of the legal situation at the end of the transition period for the UK leaving the EU.

It is anticipated that the mCTAs will be kept under ongoing review.

Change History

Summary of Key Changes in May 2022

General

References to Participating Organisation updated to Trial Site.

Reference to non-applicability in Phase I trials with healthy volunteers removed, as the current template is considered suitable for use in such trials in the NHS.

Recitals

New recital G – for use when it is intended that the Trial Site will be a Lead Trial Site in a hub and spoke delivery model, subcontracting with Other Trial Sites.

Definitions

Revised definition for Data Protection Laws and Guidance (to reflect EU adequacy decision on UK data protection regime).

New definition added for Hub and Spoke Agreement.

New definition added for Investigator Site.

Definition of Site File changed to definition of Investigator Site File.

New definition added for Lead Trial Site.

Revised definition for Multi-Centre Trial, to specify that a Trial is Multi-Centre only if it has more than one Investigator Site (that is to say, more than one Principal Investigator).

New definition added for Other Trial Site.

New Definition added for Participant Identification Centre.

Definition of Site removed and references to Site throughout template updated (e.g. to Trial Site) or removed throughout.

Clause 3

Clause 3.6 removed as referenced to individual sites needing regulatory approval are outdated.

New optional clause 3.6.2 for use in dose escalation CTIMPs, introduced at the request of and drafted collaboratively with the MHRA GCP Inspectorate.

Clause 4

Clause 4.2 (and as applicable throughout the template) addition of reference to ‘potential clinical trial subjects’ added, to emphasise that the Parties responsibilities to respect principles of medical confidentiality and data protection are not limited only to enrolled participants but extend to persons who may be screened, etc. but not then enrolled.

Clause 4.6.1 ‘and as the case me be’ removed, as the mCTA is intended for use only with CTIMPs.

New optional clause 4.14 for use when the Agreement is being used as a Head Agreement, from which the Lead Trial Site may subcontract to Other Trial Sites.

Clause 4.15.4 modified to clarify that monitoring may take place via remote means.

Clause 11

New clause 11.6 intended to provide additional assurance that Material will not be analysed so as to obtain privileged information relating to IMP to which clinical trial subjects may have been exposed in other research studies.

Clause 16

Clause 16.4 modified to allow there to be more than one Investigator Site contracted within the one Trial Site (i.e. for there to be multiple PIs for the study within the one NHS organisation) without the contract signed for the first PI being inadvertently superseded by contracts signed for subsequent PIs.

Appendices

Appendix 4 – additional instruction added to the note.

Appendix 7, clause 7.2 – note added to reiterate that only alternative 1 may be selected for Trial Sites in England or Northern Ireland (where Master Indemnity Agreement schemes do not operate to cover equipment used in research).

Summary of Key Changes in January 2021

Throughout, both mCTAs various minor modifications and errata corrections have been made which are not intended to modify the interpretation of the templates. In addition, the following changes have been made specifically to account for the end of the transition period following the UK exiting the EU:

- **Recital F (CRO-mCTA Recital G)**
  Amended to refer to the sponsor not being established in the UK or another country listed under regulation 3 (11A) of The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019;
- **Definition of Data Protection Laws and Guidance**
  Amended to reference the UK GDPR and the requirements set out or referenced in Part Three, Title VII, Article 71(1) of the Withdrawal Agreement signed by the UK and the EU in December 2019;
- **Definition of GDPR**
  New definition added for UK GDPR;
- **Definition of GMP**
  Replacement of reference to “relevant European Union” regulations with reference to Schedule 2A (and regulation B17(1), if and when applicable) to The Human Medicines Regulations 2012 (for England, Scotland and Northern Ireland) and to any applicable EU standard (for Northern Ireland);
- **Definition of GVP**
  Replacement of reference to “relevant European Union” regulations with reference to UK regulations or standards on good pharmacovigilance practices and in the case of Northern Ireland any applicable EU requirement;
- **Definition of ICH-GCP**
  Replacement of reference to Directive 2001/20/EC, of the European Parliament, and related guidance with reference to such Good Clinical Practice requirements as may apply within the UK from time to time including the requirements of any regulations made under regulation 57 of The Medicines for Human Use (Clinical Trials) Regulations 2004/1031 (as amended by The Medicines for Human Use (Clinical Trials) (Amendment) (EU Exit) Regulations 2019) and any relevant guidance issued under those Regulations and, in the case of Northern Ireland, any applicable EU requirement;
- **Clause 3.2.1**
  Removal of clause referencing laws of the EU;
- **Clauses 3.2.8 and 3.2.9**
  New Clauses respectively referencing relevant law having effect by virtue of sections 2-4 of the European Union (Withdrawal) Act 2018 and (in Northern Ireland) laws of the European Union having effect as a result of the Protocol on Ireland/Northern Ireland;

- **Clause 4.7.1**
  Addition of reference to IMP marketing authorisation "within the relevant part of the UK" to reflect the position of Northern Ireland under the Protocol on Ireland/Northern Ireland;
- **Clause 6.2.9(b)**
  Clause modified to refer to "UK and the EEA";
- **Clause 6.2.10**
  Clause modified to refer to "UK and the EEA".

In addition to the above, the following modifications have been made following consideration by the UK Four Nations Contracting Leads of comments and requests from stakeholders:

- **Definition of Agreement**
  Amended to explicitly reference amendments to the Agreement;
- **Definition of Joint Position**
  Reference updated to latest published version;
- **Clause 2.7**
  New Clause added to further clarify the responsibilities of the Participating Organisation for the appropriate appointment of Personnel;
- **Clause 3.7.1**
  The Clause has been made optional, for inclusion only in agreements for Phase I clinical trials in NHS patients. The definition of SUSAR has been removed from the main definitions section and defined at its single occurrence, at 3.7.1(a);
- **Clause 6.1.2**
  Clause modified to clarify that the responsibility is for one Controller to notify the other Controller of any data breach only when the breach is of data of which both parties are at that time separate Controllers. For example, the Clause obliges the Participating Organisation to notify the Sponsor of a breach of medical records which contain data processed for the purpose of the Clinical Trial, as both Participating Organisation and Sponsor are separate Controllers of this data. It does not oblige the Sponsor to notify the Participating Organisation of breaches that may occur to data for which the Participating Organisation is no longer a Controller;
- **Clause 6.2.4**
  Clause modified to clarify responsibility of the Participating Organisation to notify the Controller of processing undertaken other than in accordance with the Sponsor instructions, BEFORE undertaking such processing, unless prohibited from doing so, but to emphasise that notification should take place after the processing as soon as possible after such prohibition is lifted, if it is lifted;
- **Clause 6.2.6**
  Clause modified to allow the Sponsor/CRO to propose a duration other than five (5) business days in this optional part of the Clause;

- **Clause 6.3.6**
  Clause modified to clarify that it is the responsibility of the Sponsor (and CRO) **TO TAKE REASONABLE STEPS** to proactively prevent Personal Data Breaches;
- **Clause 7.2**
  Scope of Clause broadened to apply not only to information that belongs to the Sponsor (CRO) or Affiliate but also to any information that relates to the agreement, to clarify that the Clause would apply to information not owned by the Sponsor but, for example, provided to the Sponsor by a Non-Affiliate third party;
- **Clause 8**
  Scope of Clause broadened again to clarify applicability to information provided by or on behalf of Affiliates or related persons;
- **Clause 10.4.1**
  Clause modified to be explicitly more permissive for the Sponsor (CRO) in determining parties with whom it may share data to present or publish, in line with transparency expectations;
- **Clause 10.7**
  Clause modified so that it is not restricted to only the Sponsor protecting its proprietary information, thereby enabling the Clause to apply to circumstances when the Sponsor has brought the proprietary information of third parties to the clinical trial;
- **Clause 15.2**
  Modified to allow for the Sponsor (or CRO) to assign the Agreement, without prior consent, to a successor entity by virtue of merger, consolidation, sale, etc. whilst placing an obligation on the Sponsor (or CRO) to notify the participating organisation of such assignment/assignation in good time in writing;
- **Clause 16.3.2**
  Days, within which the participating organisation shall communicate with the Sponsor as to the impact of any proposed amendment, reduced to fourteen (14), to better align with the expectation that amendments are implemented no later than thirty-five (35) days after notification (although it should be noted that it is expected that amendment implementation is not delayed by contract negotiation, which should continue in good faith parallel and subsequent to amendment implementation);
- **Appendix 6, Section 4.3**
  Clarification made such that research ethics committee (REC) approval is needed only for use in research that itself requires a REC opinion;
- **Appendix 7**
  Modified to allow for applicable sections to be selected and enacted by check-box.