GUIDANCE ON USE OF THE MODEL CLINICAL TRIAL AGREEMENT FOR PHARMACEUTICAL AND BIOPHARMACEUTICAL INDUSTRY SPONSORED RESEARCH IN PRIMARY CARE (PRIMARY CARE mCTA, 2013 VERSION)

Background to the development of the Primary Care mCTA

The first DH/ABPI model Clinical Trial Agreement (mCTA) for pharmaceutical research in NHS hospitals was published in 2003, and most pharmaceutical and biopharmaceutical companies operating in the UK adopted it as the core template for their CTA. Revised versions were negotiated at intervals thereafter, as experience with the use of the template grew and to accommodate changes in the clinical research environment (such as the EU Clinical Trials Directive and the Directive on Good Clinical Practice in pharmaceutical research). The mCTA became the default option for hospital commercial clinical trial contracts throughout the UK.

The model agreement for hospital-based studies was endorsed by the NHS Confederation; Monitor (the independent regulator of Foundation Trusts); the UK Health Departments (for England, Northern Ireland, Scotland and Wales); 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 also appropriately modified for use under the legal systems and administrative arrangements of Wales, Northern Ireland and Scotland.

The different governance arrangements for research in Primary Care and the differences in hospitals' and General Practices' corporate legal arrangements make the current mCTA for hospital-based clinical trials unsuitable for use in Primary Care. Therefore, taking the 2011 version of the mCTA as the starting point, a modified version of the mCTA suitable for use in Primary Care (the Primary Care mCTA) has now been developed by the National Institute for Health Research (NIHR) following extensive consultations with: the pharmaceutical and biopharmaceutical industry (via the ABPI and BIA); a number of highly research-active GPs; the British Medical Association; the Medical Protection Society; and the Department of Health.

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, 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.

Use of the Primary Care mCTA

This model agreement is for use whenever a "Contract Clinical Trial" is to be undertaken in a General Practice.

Industry-sponsored Phase I, healthy volunteer studies
The Primary Care mCTA is not used for Phase 1 trials and this guidance does not apply to them.

Structure of the Guidance
This guidance has been developed to facilitate the use of the model Clinical Trial Agreement (mCTA) for pharmaceutical and biopharmaceutical industry sponsored research in general practice. It is not mandatory for either General Practices or member companies of either The Association of the British Pharmaceutical Industry (ABPI), or the Bio Industry Association (BIA) or other companies to use the Primary Care mCTA. However, its routine use is strongly commended by the UK Departments of Health in England and the devolved administrations of Wales, Northern Ireland and Scotland; the ABPI and the BIA. These bodies recommend that no modifications are made to the agreement, other than those necessary to correctly identify the trial, the contracting parties, and the investigator, and set out the financial terms and clinical trial subject recruitment arrangements.

This guidance is in 2 parts:

Part 1 contains a commentary, drafted collaboratively by the NHS, DH and its industry partners explaining the importance and implications of a number of the key terms of the Primary Care mCTA.

Part 2 contains guidance on the issues that need to be negotiated by Practices (and Investigators) and sponsor companies in the process of developing a CTA specific to the trial under discussion

Part 1

1. Voluntary use of the Primary Care mCTA

Although the use of the Primary Care mCTA is voluntary, it contains references to standards for the management and governance of commercial clinical trials that are either mandatory or reflective of good practice. These 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.

The use of the Primary Care mCTA is recommended by all the Departments of Health throughout the UK, and the industry, and organisations representing general practitioners have been involved in its development, but its adoption by any individual company or general practice is at their own discretion.

2. Contracting parties

2.1 This model agreement is structured as a template for use **either** by three contracting parties: a pharmaceutical or biotechnology company, a General Practice and a General Practitioner who is the Investigator at that site; **or** by two contracting parties: a pharmaceutical or biotechnology company and a General Practice. Tripartite use is recommended.

2.2 In connection with many trials, Sponsors employ a Contract Research Organisation (CRO) to recruit and manage sites. In these cases, there should be a clinical trial agreement between the Sponsor, CRO and the General Practice (or the General Practice and the General Practitioner who is the Investigator at the site). A model agreement for CRO–managed trials in Primary Care is under development.

3. Applicability of the Primary Care mCTA

3.1 The Primary Care mCTA is designed for use in connection with Phase II to IV trials involving NHS patients undertaken in General Practices.

3.2 The Primary Care mCTA is NOT designed for use in connection with Phase I trials involving either patients or healthy volunteers. This guidance does not concern those trials.

3.3 The Primary Care 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 General Practices.

3.4 The Primary Care mCTA should NOT be used in connection with commercial clinical trials categorised 'Collaborative Clinical Research', as described in http://www.nihr.ac.uk/files/mICRA%20Guidance.pdf

3.5 The Primary Care mCTA is NOT designed for the purposes of any Contract Clinical Trials (Phases I to IV) performed by private institutions with clinical trial subjects recruited independent of their treatment within the NHS. This exclusion extends to, for example, independent practitioners (GPs) running trials in private facilities, when the subjects have consented in the knowledge that the trial is outside the NHS.

4. The revised terms of the mCTA designed specifically for use in Primary Care

The Primary Care mCTA is based on the 2011 revision of the mCTA, which has in most respects only been amended to address the specific differences in the governance of research carried out by General Practitioners in General Practices from research carried out in NHS hospitals. In regard to certain terms, however, the opportunity has also been taken to correct long-standing anomalies and references to out-of-date arrangements that remain in the 2011 version of the mCTA for hospital-based studies. For example, the 2011 mCTA refers (clause 4.1) to Investigators being responsible for obtaining ethical review of research protocols. This, and several similar anachronisms, as noted in the paragraphs below, have been corrected in the Primary Care mCTA. The negotiation of revised terms for use in Primary Care situations was led by the NIHR and involved pharmaceutical companies, coordinated by the ABPI; biopharmaceutical companies, coordinated by the BIA; the Department of Health; the NIHR Primary Care Research Network and a number of research-active General Practitioners; the BMA; and the Medical Protection Society. Modified versions of the Primary Care mCTA suitable for use in Scotland, Wales and Northern Ireland were developed by the Devolved Administrations making only such changes as were needed to address the different legal systems, statutes and NHS organisational arrangements that exist in those countries.

5. Development of a trial-specific CTA

Every time it is used, the Primary Care mCTA will require selection of text options (usually set out in red in square brackets with the instruction to 'delete as appropriate') and completion by the addition of the information specified in paragraph 8 of this Guidance. References to "the CTA" hereafter refer to an agreement tailored for a specific clinical trial.

6. The key differences between the terms of the 2011 mCTA for hospital-based studies and those of the Primary Care mCTA 2013

This commentary does not set out to identify and explain each and every difference between the two types of mCTA; only those that are considered to require explanation.

6.1 Title page: Investigators are generally independent contractors rather than employees of Practices. Therefore, they can choose to be contracting parties in their own right

6.2 Definitions (Clause 1.1): The definition of Agent has been amended to make clear that third parties involved in the identification of clinical trial subjects (such as GPs in Practices operating as Participant Identification Centres[1] (PICs), often referred to as 'Spokes' in 'Hub and Spoke' arrangements), act as Agents of the Practice and Investigator.

Practices acting as Participant Identification Centres, whose interests are protected by being Agents of the Trial Site, are not research sites in their own right. Any activities undertaken by a 'Spoke' Practice other than identifying and contacting potential clinical trial subjects and providing information mean that the Practice has to be managed as a research site. It will not be able to operate under another Practice's (the 'Hub's') contract and the 'Spoke' Practice will need to have its own CTA.

6.3 Investigator and Trial Site Team Members (Clause 2): This clause now provides a declaration by the Practice that entering into the contract to

[1] See paper on Participant Identification Centres published by the NIHR Clinical Research Network Coordinating Centre:
www.crncc.nihr.ac.uk/Resources/NIHR%20CRN%20CC/CSP/PICS%20leaflet%20Final.pdf

undertake the trial is consistent with the terms of such things as the Practice's partnership arrangements.

6.4 Alternative versions of clause 2.2 are set out so as to mitigate the complexity of selecting and combining text for the different options for a declaration concerning the Investigator's registration, expertise etc.

6.5 Clause 2.3 is a new clause addressing Sponsors' enhanced needs, arising from legislation such as the US Foreign Corrupt Practices Act and the FDA Amendment Act, to have assurance concerning Investigators' good research standing.

6.6 Clause 2.4 (replacing the 2011 mCTA's clause 2.3) now has an option addressing the possibility that it might be necessary for an Investigator who is a signatory to the agreement to be replaced. The first option, for use when the Investigator is *NOT* a signatory, allows the Practice to find a replacement and continue the trial under the same agreement. The second option, for when the Investigator *IS* a signatory, allows the Sponsor to terminate the agreement, in which case a new agreement would usually be signed off between the Practice, the Sponsor and the new Investigator. See also the changes to clause 12.3 which concern the same issue.

6.7 Obligations of the Parties (Clause 4): Clause 4.1 now correctly refers to obtaining and maintaining favourable ethical opinions as a Sponsor responsibility. As a result, it is no longer necessary for there to be a clause preventing Investigators from accepting changes to trial protocols without obtaining permission from the Sponsor.

6.8 Liabilities and Indemnity (Clause 5): The addition of clause 5.7 reflects the difference between arrangements for clinical negligence cover in hospitals and General Practice. Practices are not members of the Clinical Negligence Scheme for Trusts and obtain either an indemnity or liability insurance. It is important that Practices and Investigators assure themselves that their cover is sufficient for their risk from participation in clinical trials.

6.9 Confidentiality, Data Protection and Freedom of Information (Clause 6): Clause 6.5.1 makes clear that in the case of Practices that act as 'Hubs' and use 'Spokes' to assist in recruitment of clinical trial subjects, they must ensure that only people directly concerned with carrying out the trial have access to the confidential material.

6.10 Dispute Resolution (Clause 19): This has been amended to reflect the fact that Practices are organisationally 'flat' bodies and it would be impractical to propose referring disputes to a senior management level, as is possible in a hospital with more hierarchical management structure.

Part 2
Information needed to develop the trial-specific CTA

1.1 Title page: Insert the name of the Clinical Trial, and the names and addresses of the Practice (and Investigator where the Investigator is to be a party to the agreement) and Sponsor.

1.2 Third recital: State the form of Practice's legal structure and include reference to Investigator if appropriate. Select options for site party/ies and insert area of expertise

1.3 Fourth recital and elsewhere throughout the agreement: select option for contracting parties at the site – either Practice or Practice and Investigator. These must be consistent throughout the agreement. In some clauses when both Practice and Investigator are mentioned, the inclusion of the reference to the Investigator is not optional e.g. the objective of clause 3.1 is to require the Sponsor to inform both the Practice and the Investigator of the name etc of the Trial Monitor, whether or not the Investigator is a party to the agreement. The

same applies in clause 3.4.1 and in other places where the words Practice and Investigator are not in red and square brackets in the Primary Care mCTA.

1.4 Fifth recital: Delete if Investigator is not to be a party to the agreement.
1.5 Sixth recital; Insert Title and etc.
1.6 Definition of Clinical Trial; Complete text.
1.7 Definition of Practice; Complete text.
1.8 Clause 2.2: Select option and delete alternative.
1.9 Clause 2.4; Select option and delete alternative.
1.10 Clause 4.11; Insert number of clinical trial subjects to be recruited.
1.11 Clause 12.3: Select option and delete alternative.
1.12 Clause 16: Insert addresses; delete Investigator details if appropriate.
1.13 Draft financial appendix (Appendix 5), being sure to include details of payments to be made to 'Spoke' sites if the Practice is using a 'Hub and Spoke' arrangement to assist with clinical trial subject recruitment.

Advice and assistance in using the Primary Care mCTA

The NIHR, the ABPI, and the BIA can be contacted for advice on the use of the Primary Care mCTA and this Guidance.