GUIDANCE RELATING TO THE MODEL AGREEMENT FOR COLLABORATIVE COMMERCIAL CLINICAL RESEARCH CONDUCTED BY COMPANIES IN THE PHARMACEUTICAL AND BIOTECHNOLOGY INDUSTRIES IN ASSOCIATION WITH UNIVERSITIES AND NHS HOSPITALS: THE MODEL AGREEMENT’S TERMS AND ITS USE IN THE DEVELOPMENT OF CONTRACTS FOR COLLABORATIVE STUDIES

The pharmaceutical and biotechnology industries undertake a variety of research and development activities in association with clinical academics and the NHS. To date, industry, academia and the NHS have interacted in three types of clinical research: industry-sponsored contract commercial clinical trials in all phases; investigator-initiated clinical trials and other studies supported by funding and drug supplies from industry; and support for preclinical academic research. Currently, contracts for very few investigator-initiated clinical trials or other types of academic research are structured in terms of formal, multi-party collaborations in which the research is planned and data is analysed jointly, but new models for the organisation and execution of drug development will increase the prevalence of this form of commercial clinical research partnership. It is likely that many studies of the types currently arranged as investigator-initiated clinical trials or academic research will in future be more appropriately designed and executed as collaborative research.

Under the principles of good research governance, all clinical research activities should be carried out in an appropriate contractual framework. The availability of standard templates for such agreements has been shown to speed the completion of contracting and facilitate the initiation of the research programmes. Therefore, over the last 10 years the Government has convened expert groups to develop contract templates for studies with a commercial dimension, addressing jointly all the issues that concern parties from both the commercial and public sectors.

This guidance sets out the background and aims of the first model contract for commercial collaborative clinical studies involving healthy volunteers and/or NHS patients and informs potential users about how the agreement template should be used in the development of contracts for specific clinical research collaborations.

1. What is meant by ‘collaborative’ commercial clinical research?

In future, formally-constituted collaborations will enable UK researchers to build on the recognised potential of open innovation, the closer interaction of industry, academia and the NHS throughout the design, execution and analysis of clinical research.

In clinical research programmes that will now be designated ‘Collaborative Commercial Clinical Research’, industry collaborates with academic clinicians and NHS organisations to develop the research aims and plans, makes a contribution to their funding, supplies materials for them and takes a full and equal part in the analysis of data. Collaborative Commercial Clinical Research involves close engagement, both deep and ongoing, between the parties. At present, collaborative research with industry often involves the staff of a university and NHS organisation executing research
originated and developed by a commercial partner (such as Contract Research or Contract Clinical Trials). In other cases, clinical academics secure resources from a commercial partner to fund a programme of clinical research that is carried out independently from the commercial partner (such as clinical studies that are often called investigator-initiated clinical trials and academic research). The ‘Collaborations’ now envisaged imply a process involving all parties in an ongoing commitment to contribute a variety of inputs – intellectual, material and financial – and this is reflected in the range of potential rewards that may be realised by the participating organisations.

The key feature of Collaborations is the involvement of all parties in the development of the research plan and clinical trial protocols as well as their implementation, and the analysis and interpretation of data. Many Collaborations will include research activities other than clinical trials alone, such as the development of biological markers or diagnostics, and many will be initiated by investigators involved in discussions with industry. When studies meet the criteria for being designated as Collaborative, the participating organisations accept joint responsibility for the research protocol, have equal access to all the Collaboration’s research data and have joint responsibility for data analysis.

Collaborative clinical research programmes are usually tripartite, involving industry, an academic body and an NHS organisation. In many cases, other organisations have a contributory role (such as that played by charities funding academic posts). Rarely, collaborative programmes may be undertaken by NHS organisations and industry without an academic partner.

2. Other forms of industry interaction with the academic research community and the NHS to undertake clinical research

- Through sponsoring and paying all the costs of Contract Clinical Trials of Investigational Medicinal Products (IMPs) at an advanced stage of development. Although investigators have rights and responsibilities in relation to dissemination of research outputs, and may own and be able to exploit certain Intellectual Property Rights (IPRs) arising in the course of undertaking these trials, the principal objective of these studies is the gathering of data related to licensing applications.

- Through support (typically funding and the supply of investigational drug/comparator) for Investigator-initiated Clinical Trials, where the industry involvement is limited to the provision of support and there is no ongoing commitment to involvement in study planning, management or the analysis and interpretation of data. These studies are sponsored by academic institutions, charities, Research Councils or the NHS. While they may generate data of commercial value, the primary interest is academic, contributing to the understanding of disease and therapeutics. These studies are undertaken in academia and the NHS ‘at arms length’ from pharmaceutical and biotech companies, and they are not initiated, executed or managed as collaborations in the terms set out in paragraph 1, above.

- Through providing support (funding and the supply of investigational drug/comparator) for academic clinical research.
3. The NIHR/MRC model Industry Collaborative Research Agreement (mICRA) – background, scope and purpose

- The model Industry Collaborative Research Agreement (mICRA) is an addition to a suite of model agreements developed by the UK Departments of Health in association with the pharmaceutical, biotechnology and medical technology industries and the NHS to facilitate the speedy completion of contracts for specific research projects, clinical trials and translational research programmes (see: http://www.nihr.ac.uk/industry/Pages/industry_model_clinical_trials_agreement.aspx). In the case of mICRA, the development has also involved the Medical Research Council, the Intellectual Property Office, and a number of universities and charities.

- The mICRA was devised by combining, where appropriate, terms drawn from the NHS-ABPI-BIA model Clinical Trial Agreement (mCTA) with terms drawn from the Lambert Agreements (see: http://www.ipo.gov.uk/lambert). In particular, this built on the strengths of the mCTA in terms of NHS research governance provisions and the Lambert Agreements' terms for IPR ownership and management. The Lambert Agreements were designed for contracts between companies in all industrial sectors working in collaboration with universities. However, they were not designed to accommodate the special requirements of research involving human subjects and their confidential information, or work with the NHS. Considerable revision of the terms of the mCTA was also required to accommodate the tripartite nature of clinical research collaborations, so it was not possible or appropriate to merge Lambert IPR terms into the mCTA without revision.

- The use of these model contract templates is in no sense mandatory for companies, universities or NHS organisations. However, UK experience gained over the last ten years has shown that standard terms negotiated by expert managerial and legal representatives of industry and public sector bodies, and endorsed by trade associations and other coordinating bodies, are widely recognised as being fair, even-handed and acceptable to the parties. Their availability usually avoids the lengthy and potentially costly legal review and negotiation that is often required by the use of individual companies’ documents. Model agreements with standard terms are placed in the public domain in full recognition that the circumstances of individual projects may demand the inclusion of special or modified terms.

- The mICRA has been developed for organisations planning collaborative commercial clinical research programmes meeting the criteria outlined above. One of the purposes for which the mICRA has been developed is the support of contracting arrangements for studies being undertaken via Therapeutic Capability Clusters. When used for this purpose, it is intended that the multiple universities and NHS organisations participating in the Cluster should contract with the industrial partner via a Lead University and a Lead NHS Organisation. This arrangement should be underpinned by the universities and NHS organisations entering into consortium agreements using a vehicle, such as a Memorandum of Understanding, which should set out their arrangements for sharing resources provided by the industrial partner and abiding by the mICRA terms signed off by the industrial partner and the lead organisations.

A particular concern of companies exploring opportunities for collaborative research is that universities and NHS organisations recognise the urgency of concluding preparations and initiating research. That is one of the objectives of devising a model
guidance linked to the model industry collaborative research agreement (mICRA)

agreement and it would be greatly facilitated by prospective ‘academic partners’ negotiating with industry through a single point of contact. This is routine in places where research at the NHS organisation and Medical School operate through a shared research office.

- The mICRA would NOT be suitable as a template for a number of types of collaborative commercial clinical research programmes undertaken with the pharmaceutical and biotechnology industries. These include, for example, those involving MORE THAN ONE pharmaceutical or biotechnology company and those NOT involving a university partner. Collaborations of these types will require bespoke contracts that may include many terms similar to those of the mICRA but revised terms for issues such as allocation of responsibilities, liabilities and rights.

- The mICRA is the contractual framework into which intending collaborating parties will insert details identifying the collaboration and its participants (both organisations and investigators), and add appendices or schedules related to the research plans, timelines, allocation of duties and responsibilities. A collaboration agreement using this template could only be finalised after extensive discussions between the parties identifying research aims, participants, costs, resources and their origins, feasibility and timelines, management arrangements and rewards. For this reason, the parties will have to collaborate to a considerable extent before it is possible to frame the Collaboration’s arrangements contractually, other than in terms of Confidentiality and Disclosure Agreements.

4. Key features of the model agreement’s structure

- The mICRA, devised as a template for contracts for Clinical Research Collaborations, has a similar core structure to that of other model agreements jointly developed by the Departments of Health, the NHS and the life sciences industry, such as the mCTA used for Contract Clinical Trials. Many of the explanations and much of the Guidance published with other NIHR contracts (http://www.nihr.ac.uk/industry/Pages/industry_model_clinical_trials_agreement.aspx) is relevant to the mICRA and will not be repeated here. The following important structural differences between model agreements for Contract Clinical Trials and the model Industry Collaborative Research Agreement should be noted:

1. Agreements under which NHS Organisations undertake Contract Clinical Trials are bipartite (or tripartite in the case of CRO-managed trials) for reasons fully explained in Part 2, paragraph 3 of the Guidance at: http://www.nihr.ac.uk/files/pdfs/Guidance%20on%20the%20use%20of%20the%20mCTA%202006.pdf. By contrast, each party in a Research Collaboration (the Company, University and NHS organisation) has rights, responsibilities and liabilities to the other parties and therefore the mICRA is tripartite.

2. Clause 2 in the mCTA, relating to investigators and trial site team members, has been replaced by a clause covering collaborative management arrangements.

3. The major structural difference between the mICRA and other model agreements is in the inclusion of a number of versions of Intellectual Property Rights clauses (clause 9 versions 1 to 5). One that is appropriate to the
Guidance linked to the model Industry Collaborative Research Agreement (mICRA)

circumstances of the collaboration should be selected.

4. The mCTA’s Early Termination clause (clause 12) is replaced by a clause covering Termination, Withdrawal and New Parties.

- The mICRA is a tripartite agreement, as explained above, and in a number of places it is necessary for a particular party to be identified as the one carrying a specific responsibility. For example, in the definition of Investigator and in clauses 4.2 and 4.3. However, on a number of issues covered by the contract, the interests of the university and the NHS organisation that are parties to the agreement are closely aligned and for efficiency in negotiating the contract, the ‘public sector’ parties are, where possible, collectively referred to as the ‘Academic Partners’. Under the various UK administrations’ Research Governance Frameworks, NHS Organisations are required to have agreements setting out the terms of their interactions with regular academic partner organisations. Under such agreements they should negotiate the terms; for example, how Intellectual Property Rights owned by the Academic Partners (e.g. Clause 9 version 1 sub-clause 9.5) are apportioned and managed. The mICRA is structured to avoid the necessity for universities and NHS organisations involved in negotiating collaboration agreements to undertake detailed and, at the time, speculative discussions of the eventual management of any potential IPRs. It was thought that such discussions could delay the initiation of collaborations significantly and to no useful effect. The aggregation of universities’ and NHS organisations’ interests in this way does not carry any implication that universities and NHS organisations accept joint and several liability in any of these agreements. They expressly do not.

Typically, NHS organisations have ‘high level agreements’ with their associated universities. The operation of collaboration agreements will require ‘academic partners’ to negotiate equivalent ‘high level agreements’ for the purpose of industry/university/NHS collaborations. They may support multiple joint endeavours or be study-specific.

- Whereas previous model Agreements have been published in a variety of versions suitable to permit their use in the four different countries of the UK, the mICRA has been drafted in such a way that it can be used without modification throughout the UK.

- In the mICRA, [square-bracketed red text] is used to indicate that material specific to the collaboration needs to be inserted. Sometimes, as on the title page, the required text is information about organisations or addresses. At other points in the agreement, for example the definition of Investigator “on behalf of the [NHS Organisation] [University] [Company]”, a limited range of options are offered in the model agreement. At other points, for example clause 2.6 relating to decision-taking in the Steering Committee, a range of options is offered but collaborating parties may agree to use other alternative arrangements. As adoption of the text of the mICRA is not mandatory for any organisation, collaborating parties may, at the possible cost of extended negotiations, vary any text in the published version.
5. Detailed commentary on clauses in the mICRA

5.1 Parties to the Agreement
The Agreement is designed for use in situations where one pharmaceutical or biotechnology Company, one University and one NHS Organisation are the parties involved in the collaboration or (as in the case of clusters of organisations) where a number of Universities and NHS Organisations can act through their respective lead organisation.

During the negotiation of the model agreement’s terms, it was recognised that in many instances other organisations (such as charities funding research posts or CROs contributing trial management expertise) may play a satellite role in the research collaboration without the need for their being party to the collaboration agreement. The satellite bodies’ relationships are with a particular party to the mICRA, rather than with all the signatory parties. That is why such satellites are not referred to in the core terms of the mICRA, although their roles and contributions would be expected to be fully explained in the Collaboration Plan.

The Sponsor of a clinical trial that is integral to the collaboration’s research plan must always be a party to the collaboration agreement, because the body taking on the role of Sponsor is identified as having responsibilities under the agreement. Therefore, when a collaboration is being established in which it is envisaged that a charity or the MRC, for example, will take on the role of Sponsor, the mICRA in its current form is not a suitable model agreement. A future version of the mICRA will be developed to meet this need.

As the title page of the mICRA states, and this Guidance makes clear, the mICRA is for pharmaceutical and biotechnology collaborations. An agreement for collaborations involving the medical technology industry will be developed.

5.2 Agreement Date
The collaboration agreement date is shown on the title page. The parties must decide whether this date, or a different one, is to be the ‘Effective Date’ (the date the collaboration is deemed to have begun). As it is highly improbable that a collaboration agreement will ever be signed before the prospective parties have had discussions including confidential documents and the possible disclosure of intellectual property, it is strongly recommended that an effective date should be one that coincides with the initiation of discussions leading to the collaboration.

5.3 Definitions
“Collaboration Plan” This is the key document associated with the contract, expressing the collaborating parties’ aims and objectives, the origin and nature of resources to be supplied or made available by the parties to implement the collaboration’s research objectives, management arrangements, milestones and rewards. The Plan is appended to the Agreement as Appendix 1.
The structure and content of the Collaboration Plan will be specific to each collaboration but suggested elements are likely to include, at a minimum, details of the following:

- Background IP underpinning the planned programme
- Work-packages forming the overall collaboration content
- Funding – source, amount, timing, dependencies, relationship to performance milestones. Use of the NIHR Costing template wherever possible and appropriate
- Equipment – availability, supply and loan arrangements
- Responsibility for applications related to Regulatory Approvals
- Responsibility for research ethics applications
- Plans and responsibilities in relation to development of protocols, Case Report Forms and databases
- Conduct of research and SOPs
- Research monitoring arrangements
- Responsibility for pharmacovigilance
- Review and management arrangements
- Research milestones
- Publication policy
- Rewards

“Effective Date” The decision on the Effective Date is a very important one for the collaborating parties, although prospective collaborators would be expected to take appropriate steps to undertake discussions prior to agreement on the terms of the collaboration contract under Confidentiality and Disclosure Agreements. The definition of the Effective Date is to be selected by the parties and alternatives are suggested.

“Field” The definition of this term, used in the IPR clauses, is defined in the same words as are used in the 2nd recital (“Whereas the Company is developing new treatments and therapies in the field of ....”). It has important implications for all parties to the agreement and therefore users are cautioned to consider carefully how wide the field is drawn in the recital. For example, the implications of research in type 1 diabetes being described as in the field of endocrine disorders or autoimmune disease would be much more wide-ranging than if the field comprised diabetes or type 1 diabetes.

5.4 Management arrangements
The arrangements, as described, may be considered ‘best practice’ but the scheme for any particular collaboration should be proportionate to its scale. Collaborating organisations should include in their contract detailed rules of engagement regarding management of the collaboration that support excellence in research governance. For instance, it may not always be necessary to establish a data monitoring and safety committee, depending on the nature of the clinical research proposed. This is an area of the contract that may be expected to be open to revision depending on the scale and complexity of the collaboration.
5.5 Clinical Trial Governance

Clause 3.2 references important laws and statutes but is not intended to be comprehensive.

The reference to the World Medical Association (WMA) ‘Declaration of Helsinki’ does not, unlike other mCTAs and mCIAs, refer to a particular version of the Declaration. As the WMA intends, collaborating parties agree to abide by the principles of the latest version of the Declaration, at present the version agreed in Seoul in 2008.

The final sentence of clause 3.2 requires explanation. The term Investigational New Drug (IND) is a term used by the FDA and refers to clinical trials regulated by the FDA. The sentence means that companies should be aware that UK institutions such as universities and NHS organisations cannot be expected to be aware of, or be competent to judge whether they are compliant with, laws that are written for foreign jurisdictions. Therefore, if research carried out in the UK needs to be undertaken in a way that the company can demonstrate is compliant with an article of US Law, it is not sufficient for them to notify their collaborators that they must, for example, “comply with CFR 21, Part 11”, which concerns electronic records and signatures etc. They would have to provide the collaborators with SOPs, monitor their compliance, and make the judgement on whether the university and NHS organisations were compliant.

The latter issue is particularly important in respect of the US Foreign Corrupt Practices Act. Companies should ensure that their requirements for the prevention of corruption and compliance with both the FCPA and the Bribery Act 2010 are notified to the university and NHS organisation and that use is made of the company’s option to supply Guidelines for the prevention of corruption set out in clause 3.6 of the mICRA.

Clause 3.3 confirms that companies acting as clinical trial Sponsors offer compensation arrangements for clinical trial subjects injured in the course of trials under the customary ABPI Compensation Guidelines. If NHS organisations or universities take on the role of Sponsor, they are not expected to offer subjects similar compensation arrangements.

5.6 Obligations of the Parties and the Investigator

Clause 4.1 is the operative clause relating to Appendix 3 in which the parties set out and allocate their responsibilities relating to each clinical trial undertaken under the terms of the collaboration. Additional responsibilities may be identified and need allocating in the case of specific trials.

Clauses 4.2 and 4.3 and Appendix 4 are very important in regard to the manner in which other clauses in the agreement concerning the duties of the investigator are drafted and neither these nor other clauses referring to the responsibilities of the investigator should be misunderstood. Elsewhere in the agreement, such as in clauses 4.5, 4.9, 4.11, 4.12, 4.14.2 and 12.2, there are references to, for example, “the Investigator shall keep the other Parties fully apprised” (clause 4.5). The investigator does not have these duties as a party to the agreement (and investigators should not be made parties to such agreements). Investigators’ duties are referred to in this way because clause 4.2 identifies the party responsible for
ensuring that the investigator is compliant with his responsibilities “elsewhere in this Agreement”.

5.7 Liabilities and indemnity

The terms of Clauses 5.1 and 5.10 reflect the fact that a collaboration is an equal partnership, unlike the contract clinical trial situation. Therefore, indemnification arrangements between the parties are reciprocal. Some NHS organisations are not able to insure. Nevertheless, they are able to offer indemnities as long as they do so out of their own resources and as long as doing so is necessary or expedient for the normal process of entering into a contract. Foundation Trusts in England are able to take out insurance so the issue is simplified in that circumstance.

Although, in clause 5.1.3, the university indemnifies the other collaborating parties, this does not cover liabilities of its substantively-employed staff who cause harm through clinical negligence and are covered, for the purposes of their clinical duties, by one of the NHS Indemnity schemes, as is made clear in clause 5.6.

Clause 5.2 highlights the fact that the company and university are not obliged to make arrangements for no-fault compensation for Clinical Trial Subjects in trials sponsored by NHS organisations (NHS organisations are not able to provide such cover). However, companies and universities are not prevented from doing so if they chose to make such cover available.

Unlike the comparable clause in the mCTA, where NHS liabilities are capped at a multiple of the contract value, in the mICRA (clause 5.9), all parties’ liabilities may be capped but at a maximum level to be negotiated by the parties. An exception is made in the case of wilful misconduct or fraud, where no cap is put in place.

5.8 Intellectual Property Rights

The key feature of clause 9 are the five packages of terms (versions 1-5) offered to the parties to select sub-clauses that suit the circumstances of the collaboration. The IPR terms in clause 9 are largely drawn from the Lambert model research collaboration agreements designed for industry/university collaborations. The way that mICRA versions relate to Lambert Agreements is as follows:

mICRA version 1 is equivalent to Lambert Agreement 1;

mICRA versions 2, 3 and 4 combine the terms of Lambert Agreements 2 and 3, with additional subdivision of IPR ownership. This is to accommodate the fact that new IPRs may relate to an IMP supplied by the company or that IMP used in combination with another drug or IMP, as well as new IPRs unrelated to the Company’s Background IP;

mICRA version 5 is equivalent to Lambert Agreement 4.

There is no equivalent mICRA version for Lambert Agreement 5 as that agreement supports pre-clinical Contract Research in the same way that the ABPI-BIA-NHS mCTA supports Contract Commercial Clinical Trials.

A Decision Tree similar to the Decision Guide in the Lambert Toolkit
Guidance linked to the model Industry Collaborative Research Agreement (mICRA)

(http://www.ipo.gov.uk/whyuse/research/lambert.htm) is published along with this Guidance to assist collaborating bodies to select the version of the mICRA containing appropriate IPR provisions. The five basic variants cover ownership of IPRs generated in the course of the collaboration and their exploitation. The variety of possible strategies available to the collaborating parties for handling IPR are further expanded by options for licences on royalty-free or royalty-bearing terms.

5.9 Financial Arrangements
Clause 10.2 is the operative clause for the Appendix (6), which describes the financial schedule setting out the collaboration’s financial arrangements.

Clause 10.2 supports the aspiration for a single point of contract for business arrangements between the academic partners and the company. Under this provision, the company should receive invoices from either the university or the NHS organisation.

Appendix 6 should include the amounts to be paid and their purpose; the dependencies between payments and the achievement of milestones set out in the Collaboration Plan. It should also include plans for milestone payments paid as rewards (rather than costs of research) and/or royalty payments. It would be appropriate to set out the principles on which reward arrangements for successful completion of collaboration plans are based.

Negotiators involved in the development of the mICRA agreed that it is reasonable for universities and NHS organisations to harbour expectations that their contributions to significant scientific progress that is commercially exploitable by the company should entitle the organisations conducting the research to rewards in excess of the full costs of the research. Timely delivery of data, by meeting milestones established in the contract, is essential and it is expected that any rewards will be linked to both execution and timely delivery.

5.10 Termination, withdrawal and new parties
Although all parties establishing a collaboration would fully intend to see it through to completion, it is essential that the contract recognises that commercial circumstances may arise that make continuation of the programme pointless. The deadline set in the mICRA (clause 12.3) for withdrawing from a clinical trial or the entire collaboration is the start of a clinical trial (defined as the date of screening the first Clinical Trial Subject). It remains possible to terminate a clinical trial if that is deemed by the Steering Committee to be in the best interests of Clinical Trial Subjects (clause 12.5) or, of course, if regulatory or ethical approval is withdrawn.

Clause 12.2 recognises that the party ‘controlling the investigator’ may not necessarily be either the substantive employer of the investigator or an NHS organisation with which they have an honorary contract. For example, a medical academic from one university may be the investigator without that university being a party to the contract.