Decision Tree for selection of model agreements for collaborative commercial clinical research

1 Research interactions involving industry, universities and the NHS

Industry, universities and the NHS cooperate in preclinical and clinical research in a variety of ways. Depending on the circumstances, such commercial research is executed by companies in association with universities and/or NHS organisation separately and together. Parties contemplating commercial preclinical and clinical research need to consider carefully the governance implications of the research and the form of contracts that are required.

The objective of developing model agreements is to support and encourage expansion of commercial clinical research for the benefit of patients, academic and clinical research and industry in the UK. Each model agreement has been designed to meet the requirements of a specific relationship between the parties involved in the research. Each agreement provides NHS organisations, universities and companies with standard packages of contract terms that are internally consistent and have been developed collaboratively by representatives of research institutions and companies.

The model Industry Collaborative Research Agreement (mICRA) is the first model agreement to support *collaborative* commercial clinical research (as defined below). For its structure, and for many aspects of research governance, it draws extensively on the terms of the NHS-ABPI-BIA model Clinical Trial Agreement (mCTA http://www.ukcrc.org/regulationgovernance/modelagreements/mctaanddownloads/). For provisions covering IPR, the Lambert model research collaboration agreements (http://www.ipo.gov.uk/whyuse/research/lambert/lambert-mrc.htm) provide much of the content. Unlike Contract Clinical Trials, collaborative commercial clinical research is very heterogeneous and studies require a range of contractual provisions to cover Intellectual Property ownership, management and exploitation. The analysis of inputs to that selection process is one of the uses of this Decision Tree.

2 Purpose and use of the Decision Tree

This Decision Tree is firstly designed to help users identify the position of a proposed study involving industry, universities and the NHS on the spectrum of research interactions (which includes pre-clinical research, Contract Clinical Trials, academic clinical research such as investigator-initiated clinical trials, and Industry Collaborative Clinical Research). Its purpose is to identify studies that are Collaborative and for which the mICRA has been negotiated.

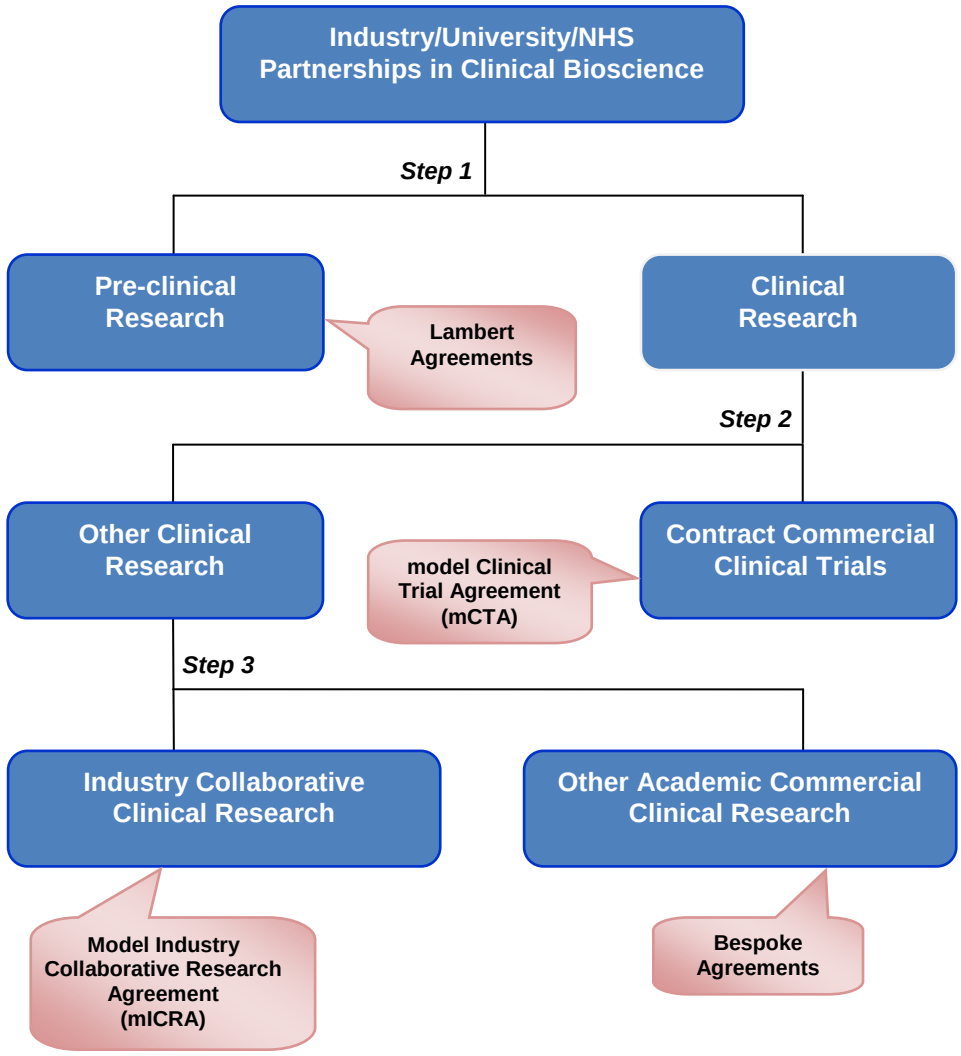
Secondly, when the proposed programme or project meets the criteria characterising Industry Collaborative Clinical Research, for which the mICRA is the appropriate model agreement, this Decision Tree is designed to assist contract negotiators for the three parties to select the appropriate IPR terms from the range available.

The Decision Tree should be employed during preliminary discussions between potential parties to commercial research agreements.

3 Characterising commercial bioscience research in universities and the NHS

Figure 1 illustrates the sequential analysis of Industry/University/NHS partnerships in clinical bioscience and the contracting implications.

Figure 1 Sequential differentiation of categories of commercial research partnerships in pre-clinical and clinical bioscience



Step 1 – Differentiation of pre-clinical research from clinical research.
Pre-clinical commercial studies can readily be differentiated from commercial clinical trials and other clinical research programmes by reference to the involvement, of NHS patients.

- For pre-clinical research carried out collaboratively by industrial companies and universities, five Model Research Collaboration Agreements were developed by the Lambert Working Group on Intellectual Property (http://www.ipo.gov.uk/whyuse/research/lambert.htm).

Steps 2 and 3 of the Decision Tree analyse where overall responsibility and leadership is located: with industry; jointly between industry and the academic/NHS partners; or with one or more of the academic/NHS partners.

Step 2 – Differentiation of Contract Commercial Clinical Trials from other clinical research.
The key feature of Contract Commercial Clinical Trials is that the NHS* provides services to industry for a fee; overall responsibility for the studies lies with the Company. These studies involve NHS patients and are carried out by NHS organisations at the behest of industry. The Company instigates trial development and has full control of trial design and management. The Company also sponsors the trial. NHS organisations have no role in protocol development** and have no discretion in regard to changes to the protocol. Data is owned and analysed by the Company, though for research governance reasons contracts must protect NHS organisations' and Investigators' rights to review all data and publish results of scientific interest.

- For Contract Commercial Clinical Trials as defined above, model Clinical Trial Agreements (mCTAs, http://www.ukcrc.org/regulationgovernance/modelagreements/mctaanddownloads/) have been developed and adopted throughout the UK. Under the terms of the Research Governance Frameworks, these studies are carried out under bilateral agreements between companies and NHS organisations

NB * Investigators undertaking Contract Clinical Trials may be either substantively employed by NHS organisations or university staff carrying out duties in the NHS under honorary contracts. In both cases, the Research Governance Frameworks require Contract Clinical Trials to be contracted by the NHS organisation.

**Investigators sometimes also act in a consultancy role, advising the Company sponsoring the trial on any aspect of trial development including protocol writing and Case Report Form development. Such consultancy should be governed by a separate contract between the Investigator and the Company, or the Investigator's employer and the Company. It is separate from the responsibilities of site Investigators and is not evidence of the studies falling into the category of Industry Collaborative Clinical Research.

Step 3 – Differentiation of Industry Collaborative Clinical Research from other academic commercial clinical research.

At this level of the Decision Tree, proposed studies will either be the joint responsibility of industry and university/NHS partners (i.e. Collaborative) or will be initiated and conducted under the overall responsibility of university/NHS organisations.

The key issue at Step 3 is whether the parties contemplating involvement in the research all agree that they intend to collaborate formally in a joint enterprise to which each party contributes on a continuing basis. This may involve some or all of the following:

- the provision of resources and facilities
- scientific planning;
- ongoing research oversight

Depending on the success of the programme, each party may be rewarded in some form for such contributions. In a collaboration, providing services for a fee to other parties is not the essence of the relationship; the Academic Partners' motivation is not limited to seeking payment in return for the provision of services. If these are a study's characteristics, the study is defined as Industry Collaborative Clinical Research.

Alternatively, the prospective parties involved in the studies may agree that industry will act solely as a supplier of materials or a provider of services for a fee, at the behest of the university/NHS partner or partners that instigate the research and take responsibility for it. The latter studies are placed in the category of 'other academic commercial clinical research'. This term covers a spectrum of research programmes ranging from trials of novel IMPs developed in academia and carried out in universities or NHS organisations, through to investigator-initiated trials of drugs developed by and supplied to the university or NHS organisation by a pharma or biotech company. Although there may be close contact between the research institutions and the Company at all stages of research, in contractual terms the Company is a supplier and the research is driven independently by the academic partners: it is not Collaborative.

- The mICRA is designed as a model contract for use in 'Industry Collaborative Clinical Research'.

4. Optional IPR terms for use in the mICRA

Collaborative studies are very heterogeneous in terms of the range of their aims and objectives, the inputs (financial, material, intellectual and access to facilities) contributed by each of the parties and the rewards sought. Depending on the nature and importance of:

(i) The inputs each of the parties intends to contribute to collaboration
(ii) The new Intellectual Property Rights (IPRs) that it is anticipated may arise in the course of the research

Different contract terms for ownership and management of IPRs would be appropriate. Therefore, the clauses of the mICRA covering IPRs are presented in five different versions, from which prospective parties can select the one appropriate to the circumstances of the proposed studies.

Collaborations may be focused on a variety of different types of research, for example the exploitation of IMPs or drugs owned by either the Company or the Academic Partners, or the development of diagnostic tools to allow better targeting of such IMPs or drugs. From version 1 to version 5 (V1 to V5), the optional clauses reflect an increasing level of control and ownership of resulting IPs on the part of the

Company. This, in some circumstances, might be paralleled by increased conditional financial rewards granted by the Company to one or both of the Academic Partners to reflect the commercial importance and successful exploitation of the IP. The key features of each version of the IPR sub-clauses are summarised below, followed by a vignette exemplifying the position suited by each option. It should be remembered that, for the purposes of efficiency in negotiating a Collaboration-specific contract, the mICRA refers to the Academic Partners collectively owning IPRs, and the vignettes below use the same terminology (see Guidance document for further details). In practice, IPRs generated by the Academic Partners in the course of the Collaboration will be owned, and rewards generated from them will be apportioned, individually as agreed between the Academic Partners.

4.1 Version 1 - *The Academic Partners own IP in the Results and grant the Company a non-exclusive licence to use the Results in a specified Field.*

For example, the Academic Partners do not have the resources to develop and test a novel compound produced in an academic laboratory. The Company has agreed to fund this and in return wishes to have access to the results. In this situation, the Academic Partners' strong negotiating position strengthens their hand in not agreeing to grant the Company exclusivity.

4.2 Version 2 - *The Academic Partners own IP in the Results and grant the Company a non-exclusive licence to use the Results in a specified Field. The Company also has the right to negotiate an exclusive licence or assignment.*

For example, in circumstances similar to those in the vignette in 4.1, the Company recognises the commercial potential of the anticipated IPRs resulting from the Collaboration at the start and wishes to exploit its investment in the programme by securing exclusivity or possible assignment.

4.3 Version 3 - *The Company owns the IP directly related to the IMP alone and the Academic Partners own the remaining IP in the Results. Company grants licence for academic non-commercial research and Academic Partners grant the Company a non-exclusive licence to use the Results in a specified Field. The Company also has the right to negotiate an exclusive licence or assignment.*

For example, the Company offers the Academic Partners a compound to test collaboratively. The Company insists on ownership of all the IP associated with their IMP but is willing to allow the Academic Partners to own all the remaining IP such as that associated with the development of a novel set of biomarkers or the identification of a gene that confers a specific outcome. The Academic Partners are willing to allow the Company access to these data and the option to take out exclusivity over this IPR.

4.4 Version 4 - *The Company owns the IP directly related to the IMP alone and in combination, and the Academic Partners own the remaining IP in the Results. Company grants licence for academic non-commercial research and Academic Partners grant the Company a non-exclusive licence to use the Results in a specified Field. The Company also has the right to negotiate an exclusive licence or assignment***.**

For example, the Academic Partners own the IP associated with a specific treatment-response gene. The Collaboration is focused around the development of a test for bladder cancer based on this IP used in combination with the Company's IMP, or its IMP combined with another IMP or drug. Under this version of the IPR terms, the Company would own all the IP in the results associated with the use of its IMP, both alone and in combination with any other drug shown to expand its effectiveness or range of applications. The Academic Partners would own all IP in the remaining results, (for example related to the specific treatment-response gene and the test based on this IP). The Company grants the Academic Partners a licence to use its IP for non-commercial/academic research. The Academic Partners grant a non-exclusive licence to the Company for their IP (in this case, for example, related to a partner diagnostic test). The latter licence is non-exclusive and restricted to a specific field (which in this case would be bladder cancer). If the diagnostic test proved relevant to a whole class of drugs represented by the IMP, the Academic Partners could issue several licences for testing and subsequently, licence this IP to several companies. Anticipating this scenario and wishing to protect their future exclusive access to the diagnostic test based on the treatment-response gene, under the terms of this IPR option, the Company has the right to negotiate an exclusive licence or assignment so that the test could only be used with their IMP in the field of bladder cancer.

4.5 Version 5 - *The Company owns IP in the Results and grants the Academic Partners the right to use the Results for academic teaching, academic research and clinical patient care.*

For example, the Company allows the Academic Partners access to an IMP for development and, in the course of the Collaboration, novel discoveries are anticipated such as improvements to the drug and the development of diagnostic tests. Although the programme of research is designed collaboratively, in this scenario the Company wishes to own all the foreground IP irrespective of field and not restricted to the IMP. However, as this research is undertaken in collaboration, the Company is willing to grant permission to the academic partners to use the IP for their "primary purpose" (academic research, teaching and patient care). For example, if the research related to the detection of a diagnostic test for heart disease, the new test could be employed at the NHS trust participating in the collaboration on a royalty free basis whereas other hospitals will have to pay the Company for a licence or pay a royalty.

5. Use of the mICRA - selection of IPR terms

The second purpose of this Decision Tree is to support contract negotiators in their selection of IPR terms. One of the five optional versions of the IPR clauses of the mICRA should be selected and inserted in Clause 9 of the model agreement following Clause 9.4.

5.1 It is assumed that the proposed collaborative project has been subjected to the three-step process in stage one of the Decision Tree and that the parties are agreed that they are contemplating a project that meets the criteria for 'Industry Collaborative Clinical Research'.

5.2 It is also assumed that the Collaboration Plan has been developed sufficiently to allow negotiators to answer the questions in the sections below.

If the conditions in 5.1 and 5.2 are met, the following series of questions should be considered:

The questions asked in Section 1 are designed to help in the broad categorisation of suitable contracts. These are, typically, firstly whether the Academic Partners own resulting IPRs (V1, V2). Secondly, whether the Academic Partners own IPRs other than those related to the IMPs and other drugs investigated in the programme (V3, V4, V5). Thirdly, whether IPRs resulting from the programme are owned by the Company (V5).

The questions asked in Section 2 are designed to help with more detailed analysis to suggest where V1 is suitable or V2, V3 or V4 would be more appropriate; whether the Company's participation in the Collaboration is dependent on their right to gain exclusive licenses or assignment of IPRs arising in the course of the Collaboration.

The questions in Section 3 are designed to help with choosing when either V3 or V4 should be used. Typically this will be when the principal objectives of the Collaboration are not directed to studying the effects of IMPs but products such as companion diagnostics.

Section 1

	Question	***Yes or No***
1	Is the Collaboration's research programme critical to the Company's technology acquisition/development strategy?	
2	Does the programme rely substantially on the Company's proprietary materials or Background IP?	
3	Is the Company to supply the IMP described in the Collaboration Plan or Protocol?	
4	Are the Academic Partners to supply the IMP described in the Collaboration Plan or Protocol?	
5	Would the programme be difficult or impossible to conduct without privileged access to the Company's proprietary materials or Background IP?	
6	Is the focus of the programme on the testing or analysis of the Company's proprietary materials or on research based around the Company's materials or Background IP?	
7	Has the Company taken the lead in designing the Collaboration Plan?	
8	Is the probability of achieving scheduled milestones and/or deliverables critical to the Company's participation in the Collaboration?	
9	Can the programme be ring-fenced from the Academic Partners' other research activities?	
10	Is the Company's ownership of IPRs that are not related to their IMP alone or in combination, arising in the course of the Collaboration, irrelevant to the Academic Partners' future research?	
11	Will the Company pay research costs at a profit-bearing rate?	

Possible outcomes to questions in Section 1

Question	*Inferences from Yes or No answers*
1	V1 or V2 are only likely to be suitable if the answer is No. If the answer is Yes, the suitable version is likely to be V3, V4 or V5.
2	If the answer is No, V3, V4 or V5 are unlikely to be suitable. If the answer is Yes, V1 or V2 may be suitable but it is more likely that V3, V4 or V5 are suitable.
3	If the answer is No, V3, V4 or V5 are unlikely to be suitable. If the answer is Yes, V1 or V2 may be suitable, but it is more likely that V3, V4 or V5 are suitable.
4	If the answer is No, V1 or V2 may be suitable, but V3, V4 or V5 are more likely to be suitable. If the answer is Yes, V1 or V2 are most likely to be suitable.
5	If the answer is No, V1 or V2 are likely to be suitable but V3 or V4 may also be suitable. Unless the answer is Yes, V5 is unlikely to be suitable.
6	If the answer is No, V1 or V2 may be suitable. If the answer is Yes, V1 and V2 are unlikely to be suitable. V3, V4 or V5 would be the suitable choice.
7	If the answer is Yes, V5 is most likely to be suitable but V3 or V4 may also be suitable.
8	If the answer is Yes, V5 is most likely to be suitable but V3 or V4 may be suitable.
9	If the answer is No, V5 is unlikely to be suitable.
10	If the answer is No, V5 is unlikely to be suitable. If the answer is Yes, V3, V4 or V5 are most likely to be suitable.
11	If the answer is No, V5 is unlikely to be suitable. If the answer is Yes , V5 is likely to be the suitable choice

Section 2

	Question	***Yes or No***
1	Have the Academic Partners taken the lead in designing the work plan?	
2	Does the programme represent an integral part of the Investigator's overall long-term research activities?	
3	Will the programme receive substantial support from sources other than the Company, for example Research Council grant or other public sector/third party funding?	
4	Does the programme rely substantially on the Academic Partners' proprietary materials or Background?	
5	Can the programme be carried out without privileged access to the Company's proprietary materials or Background?	
6	Will the programme take place entirely on the Academic Partners' premises?	
7	Will all the individuals working on the programme be employees or students of the Academic Partners?	
8	Are the results of the programme likely to be of more interest to the Academic Partners than to the Company?	
9	Is the Academic Partners' ownership of IPRs arising in the course of the programme irrelevant to the Company's future research?	

Possible outcomes to questions in Section 2

Question	***Inferences from Yes or No answers***
1-9	If all the answers are Yes, V1 is the most suitable version.
5	In the context of a pharmaceutical collaborative programme, the answer to question 5 would most often be No, meaning that V1 would be used relatively infrequently. If the collaborative programme is based on the Company's proprietary materials or background and the only No answer is 5, it is likely that V2, V3 or V4 are most suitable.

Section 3

	Question	***Yes or No***
1	In the course of the Collaboration, is it likely that IPRs related to the properties of the Company's IMPs (alone or in combination with other drugs supplied by the Company), ***and*** IPRs not related to the properties of such IMPs and drugs will be generated?	
2	In the course of the Collaboration, are the Company's IMPs likely to be studied in novel combinations with other IMPs and drugs from the same Company?	

Possible outcomes to questions in Section 3

Question	***Inferences from Yes or No answers***
1	If the answer is Yes, V3 or V4 are likely to be most suitable.
2	If the answer is Yes, V4 is likely to be most suitable.

Section 4

In addition to the questions posed in Sections 1 – 3, negotiators should bear in mind more general considerations such as;

- whether proposals for the establishment of the Collaboration originated with the Company or with one of the Academic Partners;
- what the underlying motivations of each of the partners are (for instance, in the case of the Academic Partners, whether scientific objectives such as the understanding of disease etiology or pathophysiology, or therapeutic product development are uppermost);
- which party or parties will take on responsibilities connected with Sponsorship;
- what contributions each party is to make to resourcing the studies.