



GUIDANCE ON USE OF THE MODEL CLINICAL TRIAL AGREEMENT FOR PHARMACEUTICAL AND BIOPHARMACEUTICAL INDUSTRY SPONSORED RESEARCH IN NHS HOSPITALS (2006 VERSION)

Background to the development of the 2006 version

Following the publication of the DH/ABPI model Clinical Trial Agreement (mCTA) for pharmaceutical research in 2003, most pharmaceutical and biopharmaceutical companies operating in the UK adopted it as the core template for their CTA. To address particular corporate needs or concerns, or the circumstances of specific studies, pharmaceutical companies and NHS hospitals have incorporated a variety of modifications into the terms of the model agreement. The need for legal review of such changes has slowed the initiation of trials, increased costs and thereby reduced the mCTA's value in facilitating commercial clinical trials in the UK.

With three years experience of using the mCTA, and following the introduction of the EU Clinical Trials Directive and the Directive on Good Clinical Practice in pharmaceutical research, a decision was taken by the Pharmaceutical Industry Competitiveness Task Force (PICTF) Clinical Research Working Group to review and revise the Agreement. Negotiations between representatives of the various stakeholder interests were undertaken with the objective of devising a model agreement that would be accepted, without modification, by all pharmaceutical and biopharmaceutical companies and all NHS hospitals throughout the UK. The resulting mCTA would carry an authority equivalent to that of the ABPI Form of Indemnity, without its use being legally mandatory.

Adoption of the 2006 version

The mCTA has been renegotiated, and the revised model agreement has been endorsed by the NHS Confederation; Monitor (the independent regulator of Foundation Trusts); the Department of Health for England and the devolved administrations of Wales, Northern Ireland and Scotland; the Council of Heads of Medical Schools (CHMS); 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, has been appropriately modified for use under the legal systems and administrative arrangements of Wales, Northern Ireland and Scotland.

Trials involving medical academics

The Research Governance Framework 2005 clarified contracting arrangements for commercial clinical trials. For governance reasons, commercial trials classified as “Contract Clinical Trials”, must in all cases take place under an agreement between the commercial Sponsor and the NHS body responsible for the trial site (RGF v2, paragraph 3.2.4). This contracting arrangement is required whether the investigator is substantively employed by the NHS body or by an associated academic body. The exact meaning of “Contract Clinical Trial” in this context has been clarified in discussions between the Department of Health and the Council of Heads of Medical Schools (CHMS). CHMS has also been concerned to ensure that the NHS bodies entering into these contracts will in all cases notify universities about trials in which university employees are to participate and discuss the costs arising from them. The mCTA now contains provisions that require such notifications to be made and discussions about costs and reimbursements to take place. The basis for reimbursement of universities should be made explicit in the trial contract by inclusion in the financial schedule. On these understandings, the CHMS commends the use of the mCTA to its members.

Categories of trials

Not all clinical trials supported by the pharmaceutical and biopharmaceutical industry are “Contract Clinical Trials”. It is important to distinguish “Contract Clinical Trials” from “Collaborative Clinical Research”, including investigator-led commercial trials. In this context, “Contract Clinical Trials” are defined as commercial, industry-sponsored trials of investigational medicinal products, involving NHS patients, undertaken in NHS hospitals, usually directed towards pharmaceutical product licensing. “Collaborative Clinical Research” is primarily carried out for academic rather than commercial reasons and is not usually directed towards product licensing. Trials classified as “Collaborative Clinical Research”, which include Phases II, III and IV trials and may involve current NHS patients, will continue to be covered by contracts between the company providing resources for the trial (which may for example include funding or the provision of drug supplies) and the holder of the investigator’s substantive employment contract, whether that be a university or NHS body. See paragraph 4.4 in Part 2 of this guidance.

Use of the mCTA

This model agreement is for use whenever a “Contract Clinical Trial” is to be undertaken. The mCTA is for use in these circumstances whether the investigator’s substantive employment contract is with the NHS body itself, or with an associated university. A number of modifications to the agreement (highlighted in this guidance) have been designed to ensure that the NHS bodies inform medical academics’ substantive employers (usually universities) about trials in which they are to take part. Important guidance is included here that hospital research managers should consider at an early stage when commercial clinical trials involving university employees are being planned. This guidance is directed towards ensuring firstly that the correct contracting parties are identified for different types of trials undertaken in NHS hospitals and secondly that there is agreement with medical academics’ employers on trial costs and pass-through reimbursements.

Industry-sponsored Phase I, healthy volunteer studies

The mCTA is not used for these trials and this guidance does not apply to them. When investigators whose substantive employment contracts are with universities carry out these studies, the contracts should be between the Sponsor and the university.

Structure of the Guidance

This guidance has been developed to facilitate the use of the model Clinical Trial Agreement (mCTA). It is not mandatory for either NHS hospitals or member companies of either The Association of the British Pharmaceutical Industry (ABPI), or the Bio Industry Association (BIA) to use the model CTA. 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 3 parts:

Part 1 summarises the observations made by the Pharmaceutical Industry Competitiveness Task Force (PICTF) Clinical Research Working Group concerning the performance of clinical trials in the UK and the UK's international competitiveness and the national and international regulatory framework for clinical trials. The PICTF Working Group's conclusions and recommendations for clinical trials in the UK are set out.

Part 2 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 mCTA. It also contains guidance on the issues that need to be negotiated in the process of developing a CTA specific to the trial under discussion. It explains the discussions that should take place with universities employing medical academics who take on the role of investigator in Contract Clinical Trials.

Part 3 identifies a recommended sequence of steps in the process of negotiating terms for NHS hospitals' corporate approval of industry-sponsored clinical trials, and contact points for enquiries about the model CTA.

Terminology

In this guidance, the research site is referred to as 'NHS hospital' or 'NHS body', which are generic terms for the corporate bodies that undertake clinical trials. In England and Wales, this will have the meaning of NHS Trusts and NHS Foundation Trusts; in Northern Ireland, it means Hospitals Trusts and Health and Social Services Trusts; and in Scotland, it means Health Boards. The national versions of the mCTA include text options for the different corporate terms.

PART 1

Background to the formulation of guidance on Clinical Trial Agreements (CTAs)

1. International competitiveness

As part of a wide-ranging investigation of the international competitiveness of the Pharmaceutical Industry in the UK, the Pharmaceutical Industry Competitiveness Task Force (PICTF), a joint Government and Industry body, studied the performance of commercially sponsored clinical trials in the NHS. PICTF showed that the Pharmaceutical Industry has invested in research in the UK to a disproportionately large extent compared with the UK's record as a market for the drugs developed. This reflects the long-standing perception in the industry of the high quality of the UK's research skills base and facilities, and its research output, particularly in basic science and translational studies, together with the comprehensive health service and well-organised medical research infrastructure. The Task Force identified a number of problems with UK sites' performance as a host of industry sponsored clinical trials.

In setting up the PICTF Clinical Research Working Group (comprising representatives from major pharmaceutical companies based in the UK, the ABPI, the BIA, the DH, the MHRA and the NHS), the main objective was to identify actions necessary to maintain and improve the international competitiveness of industry-sponsored clinical research in the UK. The Working Group documented and analysed the factors that determine the competitiveness of UK sites involved in international trials. In recent years, the performance of UK sites involved in these international clinical trials has declined in terms of the speed of trial site initiation, patient recruitment, and quality of data generated, while trial costs have, in general, risen faster than in comparable countries. With increasing competition from research sites in the developing world and states in Eastern Europe, it has become more difficult for pharmaceutical companies to justify the inclusion of UK sites. Unless their performance improves, the extent of UK participation in international trials will continue to decline, with possible adverse consequences for the UK Pharmaceutical Industry more generally, as well as the status of the UK as a centre of medical and research excellence.

The UKCRC, established in 2004 in response to these challenges, has initiated a multi-faceted work programme designed to harness the capacity of the NHS to establish the UK as a world leader in clinical research, implementation of the Government's new strategy for R&D in England, Best Research for Best Health (<http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/fs/en>) will be critical to achieving this vision. It sets out a programme of investment and reforms which should enable high quality, cost effective medical advances to be discovered and developed more quickly, cheaply and reliably. One aspect of this is the national roll out of the mCTA by trusts and companies for multi-centre trials as highlighted in the Chancellor's pre-budget statement (http://www.hm-treasury.gov.uk/pre_budget_report/prebud_pbr05/report/prebud_pbr05_repinde_x.cfm December 2005, ch 3, p 59).

2. Improved Research Governance

A number of changes have taken place in recent years aimed at ensuring that clinical research is of the highest achievable scientific and ethical standard. Several of these changes relate specifically to research connected to drug development and have been introduced at the international level, including the

International Committee on Harmonisation Good Clinical Practice Guideline (ICH GCP) and the EU Directive relating to the implementation of good clinical practice in the conduct of clinical trials (Directive 2001/20/EC) and the Commission GCP Directive (Commission Directive 2005/28/EC).

In the UK, the introduction of the Research Governance Framework for Health and Social Care set in place a comprehensive set of principles for the organisation, management and corporate governance of research within healthcare. In April 2005 a revised version was published in England and revisions are planned or have been published by the devolved administrations elsewhere in the UK.

The importance of appropriate lines of accountability for all researchers undertaking studies involving NHS patients and clinical samples obtained from them was emphasised in the Follett Report 'A Review of Appraisal, Disciplinary and Reporting Arrangements for Senior NHS and University Staff with Academic and Clinical Duties' (www.dfes.gov.uk/follettreview). That Report's conclusions on reporting arrangements for academic staff with clinical responsibilities are of particular importance. They underlie the recognition that the contractual arrangements for clinical trials sponsored by industry most appropriately lie in the domain of the Chief Executive of the NHS body responsible for the clinical care of the patients involved in the trial.

3. PICTF recommendations relating to clinical trials in the NHS

To remedy the observed problems with trial initiation, recruitment, data quality and cost, noted above, the Working Group recommended the collaborative development of a programme to improve clinical trial performance at sites in the UK. This focused on three areas of governance and site management.

- Ensuring that contractual arrangements made between companies sponsoring trials and the hospitals carrying them out conform to all relevant Research Governance arrangements.
- Providing the companies sponsoring clinical trials with consistent and explicit guidance on the NHS's approach to corporate management of trials by NHS hospitals.
- Avoiding one of the greatest impediments to quick and efficient initiation of UK trials that have secured both regulatory and ethical approval: the site-by-site review and re-negotiation of clinical trial agreements.

PART 2

Commentary on the structure and use of the model CTA

1. Development of the revised mCTA

As set out on page 1 of this document, a large number of stakeholder organisations have been involved in the development and review of the revised version of the model CTA. These include the DH, NHS hospitals (including Foundation Trusts), the NHS Confederation, the ABPI and BIA and their member companies and regulatory bodies. Universities have also been involved. The views of the Council of Heads of Medical Schools and research managers in universities have been taken into account. It is a revised and updated version of the document first published in February 2003. It has been structured to meet the needs of the companies sponsoring the trials and the NHS bodies accountable for the patients participating in them. It is commended to pharmaceutical and biopharmaceutical companies and NHS bodies as a model for agreements covering arrangements for all clinical trials categorised 'Contract Research' in the NHS R&D Partnership with the Pharmaceutical Industry:

(<http://www.advisorybodies.doh.gov.uk/pictf/pictfclinicalresearch.pdf>)

2. Voluntary use of the model CTA

The model CTA 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 and
- accountability through NHS bodies' Chief Executives for clinical research involving NHS patients.

The use of the mCTA is recommended by all the Departments of Health throughout the UK, organisations representing NHS hospitals, and the industry, but its adoption by any individual company or NHS body is at their own discretion.

3. Contracting parties

- 3.1 In order to comply with research and clinical governance requirements, and establish the correct lines of accountability for the work of clinicians practising in the NHS, all commercial Contract Clinical Trials (in Phases I to IV) involving subjects recruited by virtue of their being current NHS patients, carried out in NHS hospitals, must be governed by contracts between the Sponsor and the NHS body responsible for the clinical care of the clinical trial subjects, irrespective of the institution that employs the investigator. This includes the situation where, for example, the investigator's substantive employment contract is with a university and the investigator holds an honorary contract with the NHS body.
- 3.2 In no case should a clinical trial Sponsor enter into a contract with an individual employee of either an NHS body or a university in a personal capacity to undertake a clinical trial involving NHS patients.

- 3.3 In connection with many trials, Sponsors employ a Contract Research Organisation (CRO) to recruit and manage sites. In these cases, there should be a tripartite clinical trial agreement between the Sponsor, CRO and NHS body (the contracting parties). The CTA should reference certain aspects of trial governance that involve the Sponsor specifically (e.g. the ABPI Indemnity). A version of the model CTA, modified to take account of differences in the roles of Sponsor companies and CROs, will also be published.

4. Applicability of the model CTA

- 4.1 The mCTA is designed for use in connection with Phase II to IV trials involving NHS patients undertaken in NHS hospitals, and Phase I trials where these involve NHS patients.
- 4.2 The mCTA is NOT designed for use in connection with Phase I trials involving healthy volunteers. This guidance does not concern those trials.
- 4.3 The mCTA is NOT for use in connection with non-commercial studies sponsored by charities, government departments or Research Councils, whether or not such trials involve NHS patients and whether or not they are carried out in NHS hospitals.
- 4.4 The model CTA should NOT be used in connection with commercial clinical trials categorised 'Collaborative Clinical Research', as described in the NHS R&D Partnership with the Pharmaceutical Industry i.e. where industry co-funds research carried out in the NHS. The terms of the Partnership are set out at: <http://www.advisorybodies.doh.gov.uk/pictf/pictfclinicalresearch.pdf>
- 4.5 The mCTA is NOT designed for the purposes of any Contract Clinical Trials (Phases I to IV) performed by private institutions with patients recruited independent of their treatment within the NHS. This will include, 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.

5. Objectives of the 2006 revision of the mCTA

Discussions in PICTF and with individual pharmaceutical and biopharmaceutical companies and NHS hospitals suggested an extensive range of issues that needed addressing by clarification or modification of the relevant terms of the mCTA. These included:

- Clarity about the need for a single bipartite agreement covering each site including all services and personnel. There should not be separate agreements with pharmacies, laboratories etc or partner bodies such as universities.
- Changes to European legislation required updating of references to the EU and Commission Good Clinical Practice Directives and UK Regulations.
- In line with industry undertakings and government requirements, provisions relating to the registration of trials and publication of trial data.
- Insurance and indemnity arrangements for trial subjects and other corporate liabilities.
- Removal of references to foreign laws, while retaining the capacity to ensure compliance with their requirements
- Fuller treatment of provisions relating to Confidentiality, Data Protection and Freedom of Information Act legislation.
- Revision of Intellectual Property and Know How provisions to simplify and clarify ownership and exploitation rights.
- Changes reflecting the range of corporate structures in the NHS such as Trusts, Foundation Trusts and Health Boards.

- Arrangements for efficient liaison between the Sponsor and either the investigator or R&D managers, over variations to the agreement required by protocol changes.
- Simplification of the dispute resolution procedures.

6. Modification of the model CTA

Every time it is used, the mCTA will require completion 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.

7. The terms of the updated mCTA

7.1 Definitions (Clause 1.1): Additional definitions have been added to cover a number of terms used throughout the Agreement and some definitions have been revised.

7.2 Investigator and Trial Site Team Members (Clause 2): This concerns the need for NHS hospitals to take appropriate steps to ensure that the investigator is aware of his/her obligations under the CTA and agrees to abide by the requirements of Appendix 6. The CTA specifies a number of investigator obligations, many of which (e.g. 4.1, 4.10, 4.11, 4.15, 8.1, 8.2, 8.3, 8.4, Appendix 3 paragraph 5.4, Appendix 4 paragraph 6, and Appendix 6) are well-understood duties of investigators. Other investigator responsibilities (e.g. 2.4, 4.3, 4.9, 4.16, 7.1, 7.2, 9.4, and 9.5) may be less familiar. NHS bodies should bring all these responsibilities to the attention of investigators in the course of training in research governance. It is particularly important that investigators not *substantively* employed by NHS bodies (i.e. those who have honorary employment contracts to cover their work in the hospital) fulfil the obligation to inform their employer (usually an associated university) of their plans to participate in trials, and secure their permission to do so (Appendix 6, paragraph b).

The investigator’s identity and role is specified in the CTA and is central to the NHS hospital fulfilling the work specified in the CTA. The NHS hospital should incorporate the obligations of the investigator under the CTA in any employment contract or other contract under which the services of the investigator are obtained. Therefore, it would be prudent if each trial on which he/she takes a leading role were included in his/her job plan. The NHS hospital may seek warranties to satisfy the conditions in Appendix 6.

When the investigator (usually a medical academic) is substantively employed by a body other than the NHS hospital, the hospital’s research managers must then give the investigator’s employer timely notification of the academic’s proposed involvement. The two organisations must liaise to identify and agree appropriate costs and overheads to be included in the trial’s financial schedule (Appendix 5) (see also paragraph 7.16.3 of this guidance). Arrangements must be made for these amounts to be passed through to the university on their receipt from the Sponsor.

7.3 Governance (Clause 3.2): Reference is made in this section to the 1996 version of the Declaration of Helsinki in order to maintain consistency with Directive 2001/20/EC, which similarly refers to this version of the Declaration.

An important addition to this clause is the reference to trials conducted as part of an IND (i.e. connected to an application for licensing by the FDA). As the contract does not now include references to foreign laws, it is essential that Sponsors notify NHS hospitals of specific requirements related to their performance of trials that arise from such laws.

7.4 Governance (Clause 3.6): In negotiating the trial-specific aspects of the CTA, both parties should try to ensure that none of its provisions are in conflict with the Protocol. Because the Protocol sets out arrangements for the trial across

all countries and sites, it is agreed that, in most respects, the terms of the Protocol will prevail over the other terms of the CTA. However, in respect of four important clauses: 5 – Liabilities and Indemnities, 6 – Confidentiality, Data Protection and Freedom of Information, 8 – Publication and 9 – Intellectual Property, the terms set out in the CTA will prevail.

These precedence arrangements must not in any way undermine the obligation on investigators to undertake the trial in compliance with the terms of the favourable opinion given by the Ethics Committee.

- 7.5 Obligations of the Parties - Clinical Trial initiation (Clauses 4.6): One of the objectives of developing the mCTA is to facilitate the initiation of trials. The availability of signatories can lead to delays, and there are advantages to trial contracts being signed off as soon as their trial-specific terms are finalised, before regulatory approval has been obtained and before a favourable opinion has been obtained from the ethics committee. However, it is crucial that the trial does not start before those approvals have been obtained. To provide reassurance to the hospital that signing the agreement before the approvals have been granted will not create a risk of trial initiation occurring too early, clause 4.6 requires Sponsors to delay supply of the IMP to the site until it has received all approvals. Similarly, there is an obligation on the hospital to ensure that no non-routine clinical interventions mandated by the Protocol take place before receipt of final, written ethical and regulatory approval.
- 7.6 Obligations of the Parties – Substantial amendments to the Protocol (Clause 4.7 and 14): It is important that substantial amendments to the protocol are implemented expeditiously. Liaison between the investigator and the Sponsor is the most efficient way to ensure this. However, without involvement and approval of the R&D Office, it could also create a risk that the financial or service implications of the change might not be recognised or appropriately reflected in a change in the financial schedule. Therefore, provisions have been negotiated that allow the investigator to sign off and implement the change (clause 4.7), but require the Sponsor simultaneously to initiate the ‘change protocol’ procedures set out in clause 14, and in due course reach agreement on a new financial schedule. As substantial changes are mandatory for the site, the trial would have to be terminated if the site were unable to accommodate them.
- 7.7 Obligations of the Parties - Financial disclosure (Clause 4.9): Financial disclosures are required to be made by the investigator under FDA rules. Because the relevant US laws are no longer written into the contract, the Sponsor must specify to the investigator what disclosures are necessary.
- 7.8 Obligations of the Parties - Recruitment (Clauses 4.11 and 4.12): Prior to agreeing the target numbers of patients to be recruited, the investigator should, in collaboration with the R&D Office, undertake an assessment of the feasibility of the clinical trial at the site. This should take account of the predicted availability of patients meeting inclusion and exclusion criteria and access to all support services required under the Protocol. Focusing effort on the practicalities of participation in the clinical trial will help to ensure that the recruitment target is realistic and that the Timelines (as inserted in Appendix 2) can be met. In order to emphasise how seriously hospitals should attempt to fulfil the recruitment target, they are required by clause 4.11 to use their ‘best endeavours’.

Some clinical trials undertaken by NHS Trusts will be multinational with competitive recruitment. If recruitment is proceeding slowly and the target number of subjects specified in Clause 4.11 is not being achieved, clause 12 permits the Sponsor to scale back the target to allow other sites to fill the gap, and conversely, if recruitment is ahead of target, a higher number of subjects may be allowed to enter the trial. The NHS Trust is not, however, under an

obligation to recruit more than the target number specified. See also paragraph 7.16 below.

- 7.9 Obligations of the Parties - Access (Clause 4.13): Detailed provisions covering the Sponsor's access to the hospital and handling of possible misconduct have been agreed and these include various reporting requirements. The revised mCTA does not require Sponsors to report to the hospital on trial progress, and it does not require the Sponsor and the hospital's R&D Director to review the site's performance at the end of the trial.
- 7.10 Competing trials (Clause 4.16): Hospitals' R&D Offices should, through their knowledge of their research portfolio, be aware of any potential for conflicts to arise involving recruitment to competing trials. These possibilities should be discussed with investigators and the R&D Office should not proceed with arrangements for trials that might prejudice the Trust's ability to perform existing contractual obligations. However, the primary obligation of hospitals is the care of their patients, so this obligation (like several others in the agreement, such as clauses 2.3 and 3.5), is qualified by an over-riding duty to consider the best interests of patients.
- 7.11 Liabilities and Indemnities (Clause 5.4 and 5.5): It is essential that Sponsors indemnify hospitals (and *vice versa*) in respect of liabilities other than those covered under the ABPI Indemnity because of the possibilities that exist for participation in the clinical trial to result in damage to either party's property and facilities. Hospitals' non-clinical liabilities in relation to research are not usually covered by NHSLA-administered schemes and it is unlikely that either their Boards, or in the case of Foundation Trusts, the regulator (Monitor) would authorise their taking on unquantified and potentially unlimited liabilities, such as might arise from an Intellectual Property Rights claim. Therefore, hospitals' liabilities to Sponsors have been capped, and the caps are 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 (Confidentiality, Data Protection and Freedom of Information), 8 (publication) and/or 9 (Intellectual Property), provides for the hospital's liability to be limited to a maximum of twice the value of the contract. The contract value would be the total payments to be made by the Sponsor to the hospital if all the target number of patients were recruited. The second cap, covering all other breaches of the agreement by the hospital, provides for the hospital's liability to be limited to a maximum of the contract value. It is recognised that for a number of possible types of breach (for example, the loss of important Intellectual Property Rights or the release of strategically important information) it is arguable that these provisions might not fully compensate the Sponsor to the extent of their loss. However, it is considered that paying compensation on the basis negotiated would be an additional incentive to encourage hospitals to take every reasonable precaution to prevent a breach. These precautions could include: having in place robust research governance arrangements; instituting training programmes for researchers undertaking commercial trials; publicising to researchers and their staff the crucial importance of protecting the integrity of Sponsors' confidential information; and taking disciplinary action in the event of a wilful or reckless breach of the provisions of clinical trial agreements.
- 7.12 Liabilities and Indemnities (Clause 5.6): Under the EU Clinical Trials Directive, Sponsors must provide evidence of insurance cover, or provide an indemnity covering their potential liabilities to subjects participating in the trial. Under the Regulations, Sponsors are not required to take out clinical trials insurance, but hospitals will wish to be assured either that sufficient insurance cover has been purchased, or that the Sponsor has provided an indemnity. Hospitals, and the Research Ethics Committees that provide an opinion on the trial proposal, may

therefore take a view as to the indemnity and/or the adequacy of their clinical trials insurance, in relation to the risks posed by the specific trial.

7.13 Freedom of Information (Clause 6.2.6 – 6.2.9): These new clauses impose obligations on hospitals to take timely action to inform Sponsors about requests for information related to contract clinical trials, 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.

7.14 Publications (Clause 8): The model CTA recognises that hospitals in the UK 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. In line with clause 3.6, however, clause 8 does take precedence over the publication policy set out in the Protocol.

This clause sets out conditions governing the way that individual investigators should prepare their publications, and the opportunities they should allow trial Sponsors to comment on them. It also specifies the window of opportunity available to Sponsors in which they can protect proprietary information.

This clause was drafted to ensure that publications based on limited and perhaps unrepresentative data from one or a limited number of Trial Sites do not inadvertently misrepresent results, by requiring that the principal report(s) of each clinical trial are published before articles based on sub-sets of the data.

The terms of the model CTA allow publication of a dissenting interpretation of the clinical trial's data after the principal reports have been published, provided the procedures in Clause 8 of the CTA are adhered to.

7.15 Intellectual Property (Clause 9): The principles underlying the drafting of the new IP clauses are that, firstly, each party retains ownership of any pre-existing IP or Know How owned by it or licensed to it. Secondly, any IP or Know How generated at the trial site that relates to the Clinical Trial, the IMP or the Protocol (but excluding any clinical procedure or related improvements) is the property of the Sponsor. Thirdly, clinical procedures and related improvements are the property of the site and depending on the inventor's employer (hospital or university), could be protected and exploited accordingly. Fourthly, the site also has the right to use Know How gained in the course of the trial in its normal clinical work, 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 the Sponsor ownership of anything derived from it, but allow the investigator's employer to protect and exploit clinical procedures and related improvements and to use Know How generated while the 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, under the terms of the mCTA, 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 at the trial site developed a new method of analysing CT scans, under the terms of the mCTA, the rights to that IP would lie with the site.

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 trial, the investigator develops, for his own convenience and without being requested to or paid to by the Sponsor, a novel database on which to manage the data from his trial subjects. Under the terms of the mCTA, the rights to that IP would lie with the site.

The terms of the mCTA do not give the Sponsor rights to all IP generated by employees at the site either in the course of the clinical trial or in the field of the clinical trial.

7.16 Financial arrangements (Clause 10 and Appendix 5):

7.16.1 A financial schedule must be negotiated for each clinical trial. This should cover all financial issues related to the Trial Site including the costs associated with medical, scientific and nursing staff, and the costs of all services including clinics, hotel charges (e.g. bed days), laboratories, imaging, medical records, pharmacy services.

7.16.2 Clinical trials should be costed in keeping with NHS requirements and the NHS Partnership Agreement with the Pharmaceutical Industry. Guidance has been published by the NHS R&D Forum: http://www.rdforum.nhs.uk/docs/commercial_research_guidance_2005.pdf

If, in all the circumstances, facilitating the clinical trial is the best use of resources, Sponsors may only be charged for costs (research costs and the costs of clinical services, including service support and excess treatment costs), that are *additional* to the costs that the NHS would have incurred in the normal course of the care of the patients in the clinical trial. Overhead charges specific to the cost item should be included; a general overhead should not be applied.

7.16.3 The financial and other interests of universities that employ the medical academics and sometimes the research fellows and research nurses involved in clinical trials should be recognised by NHS Trusts. The notification arrangements noted in paragraph 7.2, above are designed to ensure that universities have the information needed for the protection of their interests. There should be formal agreement between trusts 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 NHS Trusts and associated academic institutions that are negotiated in the process of implementing research governance arrangements. In the case of 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 5 suggests text that should be included in the schedule in these cases.

7.16.4 There should not be separate financial arrangements between the Sponsor and any NHS Trust departments such as the pharmacy or the university that employs an investigator (but see paragraph 7.16.3 and 7.16.4c).

7.16.5 The precise format of the financial schedule will depend on the nature of the trial, but it is suggested that it should include sections covering:

- (a) central administrative and set up costs (e.g. R&D Office and Pharmacy set-up)
- (b) 'per visit' costs (disaggregated into grades of staff, time and unit costs, and costs of services and facilities, each item inclusive of an appropriate overhead rate)
- (c) 'pass-through' costs (expenses incurred by and reimbursed to third parties) such as universities, or in respect of patient travel etc.

7.16.6 The staging or scheduling of payments should be negotiated, including any payments to be made before administration of the Investigational Medicinal Product, or any other clinical intervention mandated by the

- Protocol, (e.g. site set-up costs) and whether such payments are refundable or non-refundable.
- 7.16.7 Payment of VAT should be included where appropriate and invoicing arrangements should be via the Trust Finance Department using formal VAT invoices in compliance with NHS Standing Financial Instructions.
- 7.16.8 Changes to the Protocol required by the Sponsor should be negotiated as set out in Clause 14 and a revised Financial Schedule signed by the Parties and attached to the agreement.
- 7.17 Early termination (Clause 12.4): A number of specific grounds for early termination of the Clinical Trial at the site are set out in Clause 12. Even when a site is recruiting at the rate required in the CTA, over-recruitment by other sites and early achievement of the total numbers of Clinical Trial Subjects required under the protocol may create circumstances in which early termination of recruitment at the site is unavoidable. Clause 12.4 explains the Sponsors obligations in such circumstances.
- 7.18 Changes to the Protocol (Clause 14.2): The procedure to be followed when 'substantial' changes are made is set out in Clause 14.2 and if these require a revised Financial Schedule this should be agreed, signed by the Parties and attached to the Agreement.
- 7.19 Force Majeure (Clause 15): 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.
- 7.20 Dispute resolution (Clause 19): Under the model CTA the parties are required, in the first instance, to attempt to resolve any dispute by way of 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 site is located.
- 7.21 Signatures (Clause 20): The signatories to the CTA will be the authorised representatives of the Sponsor and the NHS Trust. In the case of the NHS hospital, the signatory must have legal authority to bind the NHS Trust. This might be the Chief Executive, the Director of R&D or the Director of Finance. The investigator is not to be a signatory to the CTA, which is between the corporate bodies. As provided in Clause 13.1, the NHS hospital takes on responsibility for the acts and omissions of its sub-contractors. These include the warranties relating to the investigator given by the hospital in Appendix 6 to the agreement. See also paragraph 7.2 above. The NHS hospital should keep on file a copy of Appendix 6, signed by the investigator at the initiation of each trial. The Sponsor may require the investigator to sign a copy of the Protocol and he/she will be the applicant for the purposes of ethical approval of locality issues.
- 7.22 Timelines (Appendix 2): The milestones included in the Appendix are by way of example and the parties may amend the list as they see fit. Timelines will require early negotiation involving the investigator and the Sponsor. 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 2 show that the timing of some events is dependent on good co-ordination between the Trial Site and the Sponsor e.g. in scheduling all participants' availabilities for the initiation visit. (See also paragraph 6.5, above). Pursuant to GCP, the responsibility for local ethics committee submission lies with the Trial Site but it is recognised that in practice assistance is often provided by the Sponsor and accordingly parties may wish to assign shared responsibility in relation to this milestone.

8. Information needed to develop the CTA

- 8.1 Title page: Name of the Clinical Trial, names and addresses of NHS hospital and Sponsor
- 8.2 Second recital: Define the disease with which the trial is concerned.
- 8.3 Fourth recital: Define the disease in which the NHS Trust has expertise.
- 8.4 Fifth recital: Insert the title of the study and EUDRACT number.
- 8.5 Clause 1.1: Insert the trial identification number in the definition of “Clinical Trial”.
- 8.6 Clause 1.1: Insert the legal name of the NHS hospital in the definition of “Trust” or “Board” (Scotland).
- 8.7 Clause 1.1: Insert the study drug/control material in the definition of “Investigational Medicinal Product”.
- 8.8 Clause 2.1: Insert the name of the investigator.
- 8.9 Clause 4.5.3: Insert the name of the Ethics Committee.
- 8.10 Clause 4.11: Insert the number of Clinical Trial Subjects.
- 8.11 Clause 5.6: Insert the minimum amount of clinical trials insurance cover appropriate to the level of risk involved in the trial (see paragraph 7.12 of this Guidance).
- 8.12 Clause 16: insert the addresses to which notices should be sent.
- 8.13 Appendix 1: Attach the Protocol and any amendments made before signature of the Agreement.
- 8.14 Appendix 2: Add target dates (see paragraph 6.19 of this Guidance).
- 8.15 Appendix 3: Insert a copy of the ABPI Clinical Trial Compensation Guidelines.
- 8.16 Appendix 5: Insert a copy of the Financial Agreement (see paragraph 7.16 of this Guidance).
- 8.17 Appendix 6: The investigator should sign a copy of Appendix 6, which should then be kept in the project file

PART 3

Negotiating the CTA and securing approval of the trial at individual NHS hospitals

The revised model CTA, the formulation of guidance on its use and the identification of a pathway that can be followed to expedite arrangements for the initiation of trials draw on the experience of a collaborative relationship operating between the Pharmaceutical and Biopharmaceutical Industries and the NHS. Contract Clinical Trials are commercial, and while they should be undertaken at the expense and risk of the sponsoring company, the opportunity to participate in the process of drug development offers benefits to research-active NHS Trusts, to the UK as a country with a dynamic knowledge based economy and industrial sector and to the development of improved treatments for current and future NHS patients. Therefore, the process of negotiating the specific details of contracts covering clinical trials should be undertaken with an awareness of operating within a collaborative environment. NHS Trusts undertake Contract Clinical Trials sponsored by the Pharmaceutical and Biopharmaceutical Industries in accordance with NHS income generation rules. They are not expected to undertake such clinical trials 'at cost' but, particularly in the area of support services, the wider development agenda and the full range of benefits that arise from participation should be given appropriate consideration. In general, sites should price their participation realistically and transparently. Higher volumes of clinical trial activity are likely to result in efficiencies and increased security of trial income flows. NHS Managers should read and apply this Guidance in conjunction with "NHS Income Generation" Guidance and the NHS Forum Guidance on costing trials (http://www.rdforum.nhs.uk/docs/commercial_research_guidance_2005.pdf).

Research-active NHS hospitals that value participation in contract research as an element of their clinical research portfolio should ensure that their management arrangements can support the necessary work involved in negotiations and trial co-ordination, including having appropriate agreements in place with their academic partner institutions.

1. Management Systems

The essential features of management systems that ensure efficient progress towards the development of a satisfactory CTA and result in timely approval of initiation of the clinical trial at the site would usually include ensuring that:

- early contact is established between the Sponsor and the R&D Office,
- the parties where appropriate agree to share information and assumptions about the clinical trial's costs and the Trial Site's potential performance,
- the R&D Office has a good understanding of unit costs for the additional activities driven by the clinical trial,
- there is good liaison and understanding between investigators, managers of support services (such as pharmacy, radiology etc) and the hospital's R&D Managers and
- Investigators and managers make available sufficient time for identification of additional clinical and other costs.
- appropriate account is taken of universities' costs when trial site staff are employed by them.

2. Notification, negotiation and approval process

- 2.1 Once a trial Sponsor has identified a potential investigator for a Contract Research trial, the Trial Monitor or other appropriate Sponsor personnel should make contact with the hospital's R&D Director.
- 2.2 The hospital needs access to a copy of the Protocol (which may be the subject of a confidentiality agreement) and the R&D Office will wish to discuss the Sponsor's view of the clinical activities that are additional-to-routine.
- 2.3 There should be agreement on who will initially draft the application for either Local Research Ethics Committee (LREC) approval or the consideration of local issues in a Multi-centre Research Ethics Committee (MREC) application.
- 2.4 There needs to be discussion of the hospital's costing/pricing/overhead arrangements.
- 2.5 When the investigator is not its own employee, the NHS body should notify his or substantive employer with a view to their being involved in the costing and pricing of the trial.
- 2.6 The Sponsor or the hospital should forward to the other party a draft CTA, with details of the trial, the investigator, REC etc added, confirming that it is the standard 2006 version of the mCTA.
- 2.7 All business arrangements should be negotiated by the Sponsor and the hospital's R&D Office. Speed and efficiency of replies are the keys to rapid progress.
- 2.8 All regulatory, ethics and NHS Trust corporate negotiations should be moved forward in parallel.
- 2.9 Final approval of the completed CTA should be obtained from the person or corporate function to whom the hospital delegates the responsibility, and the CTA signed off.

3. DH and ABPI advice and assistance

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

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