Appendix 2
Agreements and Guidelines for Implementation of Clinical Trials

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2.1 Clinical trial agreement for pharmaceutical industry sponsored research in NHS Trusts

This agreement dated day of 20..
is between
[. . . **insert name . . .**] **NHS TRUST, of** [. . . **insert address . . .**]
(Hereinafter known as the 'NHS Trust')
AND
[. . . **insert name . . .**], **of** [. . . **insert address . . .**]
(Hereinafter known as the 'Sponsor')
NOW

WHEREAS the Sponsor is a pharmaceutical company involved in the research, development, manufacture and sale of medicines for use in humans
WHEREAS the Sponsor is developing new treatments for patients with [. . . insert disease . . .]
WHEREAS the NHS Trust is concerned with the diagnosis, treatment and prevention of disease and clinical research for the improvement of health care
WHEREAS the NHS Trust has a particular interest and expertise in [. . . insert disease . . .]
WHEREAS the Sponsor wishes to contract with the NHS Trust to undertake a sponsored clinical trial entitled:
[. . . insert title . . .]
It is agreed that the NHS Trust and Sponsor shall participate in the aforementioned clinical trial in accordance with this Agreement.

1 Definitions

1.1 The following words and phrases have the following meanings:
'Clinical Trial' means the investigation to be conducted at the Trial Site in accordance with the Protocol numbered [. . . insert identification number . . .].
'Clinical Trial Subject' means a person recruited to participate in the Clinical Trial.
'Confidential Information' means in the case of obligations imposed upon the NHS Trust under clauses 6.2 and 12.8 any and all information relating to the

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Clinical Trial including the Investigational Medicinal Product and in the case of obligations imposed upon the Parties under clause 6.2 all information concerning the arrangements contemplated by this Agreement or the business affairs of one Party that it discloses to the other Party pursuant to or in connection with this Agreement.

'ICH GCP' means the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) together with such other good clinical practice requirements as are specified in Directive 2001/ 20/EC of the European Parliament and the Council of 4 April 2001 relating to medicinal products for human use and in guidance published by the European Commission pursuant to such Directive.

'Intellectual Property Rights' means patents, trademarks, copyrights, rights to extract information from a database, design rights and all rights or forms of protection of a similar nature or having equivalent or the similar effect to any of them which may subsist anywhere in the world, whether or not any of them are registered and including applications for registration of any of them.

'Investigational Medicinal Product' means [. . . insert details of study drug/control material . . .] as defined in the Protocol.

'Know How' means all technical and other information which is not in the public domain, including but not limited to information comprising or relating to concepts, discoveries, data, designs, formulae, ideas, inventions, methods, models, procedures, designs for experiments and tests and results of experimentation and testing, processes, specifications and techniques, laboratory records, clinical data, manufacturing data and information contained in submissions to regulatory authorities.

'Monitor' means one or more persons appointed by the Sponsor to monitor compliance of the Clinical Trial with ICH GCP and to conduct source data verification.

'NHS Trust' means the [. . . insert name . . .] NHS Trust that is a signatory to this Agreement.

'Party' means the Sponsor, or the NHS Trust and 'Parties' shall mean both of them.

'Protocol' means the description of the Clinical Trial and all amendments thereto as the Parties may from time to time agree. Such amendments will be signed by the Parties and form a part of this Agreement.

'R&D Office' means the NHS Trust department responsible for the administration of this Clinical Trial on behalf of the NHS Trust.

'Site File' means the file maintained by the Site Principal Investigator containing the documentation specified in section 8 of ICH GCP (edition CPMP/ICH/135/95).

'Site Principal Investigator' means the person who will lead and coordinate the work of the Clinical Trial at the Trial Site on behalf of the NHS Trust or any other person as may be agreed from time to time between the Parties as a replacement.

'Sponsor' means the corporate entity that is a signatory to this Agreement.

'Timelines' means the dates set out in Appendix 2.2 hereto as may be amended by agreement between the Parties and Timeline shall mean any one of such dates.

'Trial Site (s)' means any premises occupied by the NHS Trust.

1.2 Any reference to a statutory provision shall be deemed to include reference to any statutory modification or re-enactment of it.

2 Site Principal Investigator

2.1 The NHS Trust represents that it is entitled to procure and the NHS Trust will procure the Services of [. . . insert name of investigator . . .] to act as Site Principal Investigator and shall ensure the performance of the obligations of the Site Principal Investigator set out in this Agreement.

2.2 The NHS Trust represents that the Site Principal Investigator has the necessary expertise to perform the Clinical Trial and that the Site Principal Investigator meets and will continue to meet the conditions set out at Appendix 2.6 to this Agreement.

2.3 The NHS Trust shall notify the Sponsor if [. . . insert name of investigator . . .] ceases to be employed by or associated with the NHS Trust, and shall use its best endeavours to find a replacement acceptable to both the Sponsor and the NHS Trust. If no mutually acceptable replacement can be found the Sponsor may terminate this Agreement pursuant to clause 12.3 below.

3 Clinical Trial Governance

3.1 The Sponsor shall inform the NHS Trust and the Site Principal Investigator of the name and telephone number of the Monitor and the name of the person who will be available as a point of contact. The

Sponsor shall also provide the Site Principal Investigator with an emergency number to enable adverse event reporting at any time.

3.2 The Parties shall comply with all laws and statutes applicable to the performance of the Clinical Trial including, but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, and with all relevant guidance relating to medicines and clinical trials from time to time in force including, but not limited to the ICH GCP, the World Medical Association Declaration of Helsinki, entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and the NHS Research Governance Framework for Health and Social Care of March 2001, as amended from time to time.

3.3 The Sponsor shall comply with all guidelines from time to time in force and published by the Association of the British Pharmaceutical Industry in relation to clinical trials and in particular those entitled 'Clinical Trial Compensation Guidelines' (1991) a copy of which is set out in Appendix 2.3.

3.4 The Sponsor shall not commit (and warrants that in entering into the Agreement it has not committed) any of the following facts:

3.4.1 Provide or offer to provide to any person in the employment of the NHS Trust any gift or consideration not contemplated by the financial arrangements set out at clause 10 below in relation to the negotiation or performance of this Agreement or any other contract with the NHS Trust.

3.4.2 Make payment or agree to make payment of any commission to any person in the employment of the NHS Trust whether in relation to this Agreement or any other contract with the NHS Trust.

3.5 If the Sponsor or any of his employees, agents or sub-contractors, or any person acting on their behalf, commits any of the acts referred to in clause 3.4 above or commits any offence under the Prevention of Corruption Acts 1889 to 1916, in relation to this or any other agreement with the NHS Trust or an authority that is a health service body within the meaning given by Section 4(2) of the National Health Service and Community Care Act 1990, the NHS Trust shall be entitled, in addition to any other remedy available, to terminate this Agreement with immediate effect.

3.6 Should there be any inconsistency between the Protocol and the other terms of this Agreement the terms of the Protocol shall prevail to the extent of such inconsistency.

4 Obligations of the Parties

4.1 The Site Principal Investigator shall be responsible for obtaining and maintaining all approvals from the relevant local research ethics committee for the conduct of the Clinical Trial and the Site Principal Investigator shall keep the Sponsor fully apprised of the progress of ethics committee submissions and shall upon request provide the Sponsor with all correspondence relating to such submissions. The Site Principal Investigator shall not consent to any change in the Protocol requested by a relevant ethics committee without the prior written consent of the Sponsor.

4.2 The Parties shall conduct the Clinical Trial in accordance with:

(**i**) the Protocol a copy of which for the purposes of identification appears at Appendix 2.1 to this Agreement;

(**ii**) the current marketing authorisation for the Investigational Medicinal Product or, as the case may be, Clinical Trial Certificate or Clinical Trial Exemption Certificate applicable to the Clinical Trial; and

(**iii**) the terms and conditions of the approval of the relevant [. . . insert name . . .] Ethics Committee (s) and the NHS Trust shall ensure that neither administration of the Investigational Medicinal Product to any Clinical Trial Subject nor any other clinical intervention mandated by the Protocol takes place in relation to any such Clinical Trial Subject until it is satisfied that all relevant regulatory and ethics committee approvals have been obtained.

4.3 The Sponsor shall make available to the Site Principal Investigator copies of the documentation referred to in sub-paragraphs (i) and (ii) of clause 4.2 above and the Site Principal Investigator shall include such documents together with the Ethics Committee approvals in the Site File.

4.4 The Site Principal Investigator shall inform the Sponsor immediately upon learning of the existence of any of financial arrangement or interest between the Site Principal Investigator and the Sponsor of the type described at paragraph (f) of Appendix 2.6 hereto and for the purposes of the obligation contained in such paragraph the Sponsor shall advise the Site Principal Investigator in writing of the completion date of the Clinical Trial.

4.5 Neither the NHS Trust nor the Site Principal Investigator shall permit the Investigational Medicinal Product to be used for any purpose other than the conduct of the Clinical Trial and upon termination

or expiration of this Agreement all unused Investigational Medicinal Product shall, at the Sponsor's option, either be returned to the Sponsor or disposed of in accordance with the Protocol.

4.6 The NHS Trust shall recruit [. . . insert number . . .] Clinical Trial Subjects to participate in the Clinical Trial and the Parties shall conduct the Clinical Trial in accordance with the Timelines.

4.7 In the event that the Clinical Trial is part of a multicentre clinical trial (which for the purposes of this Agreement shall mean that at least one other institution is taking part) the Sponsor may amend the number of Clinical Trial Subjects to be recruited pursuant to clause 4.6 above as follows:

4.7.1 if in the reasonable opinion of the Sponsor recruitment of Clinical Trial Subjects is proceeding at a rate below that required to enable the relevant Timeline to be met the Sponsor may by notice to the NHS Trust require recruitment at the Trial Site to cease and the terms of the Agreement shall relate thereafter to the number of Clinical Trial Subjects who have been accepted for treatment in the Clinical Trial at the date of such notice; or

4.7.2 if recruitment of Clinical Trial Subjects is proceeding at a rate above that required to meet the relevant Timeline the Sponsor may with the agreement of the NHS Trust increase the number of Clinical Trial Subjects to be recruited.

4.8 The NHS Trust shall permit the Monitor access to the records of Clinical Trial Subjects for monitoring and source data verification, such access to be arranged at mutually convenient times and on reasonable notice. The Sponsor will report on the Clinical Trial activity to the NHS Trust R&D Office, the frequency of reports to be [. . . insert period as appropriate to the Protocol . . .]. The Sponsor will alert the R&D Director of the NHS Trust promptly to significant issues (in the opinion of the Monitor) relating to the conduct of the Clinical Trial. In the event that the Sponsor reasonably believes there has been any research misconduct in relation to the Clinical Trial the NHS Trust and the Site Principal Investigator shall provide all reasonable assistance to any investigation into any alleged research misconduct undertaken by or on behalf of the Sponsor. At its conclusion, the Sponsor and the R&D Director of the NHS Trust shall review the conduct of the Clinical Trial at the Trial Site, such review to take place within 3 months of Trial Site close-out.

4.9 The NHS Trust shall ensure that any clinical samples required to be tested during the course of the Clinical Trial are tested in accordance with the Protocol and at a laboratory approved by the Sponsor.

4.10 Upon completion of the Clinical Trial (whether prematurely or otherwise) the Site Principal Investigator shall [provide the Sponsor with/cooperate with the Sponsor in producing] a report of the Clinical Trial detailing the methodology, results and containing an analysis of the results and drawing appropriate conclusions.

4.11 Neither the NHS Trust nor the Site Principal Investigator shall during the term of this Agreement conduct any other trial which might adversely affect the NHS Trust's ability to perform its obligations under this Agreement.

5 Liabilities and indemnity

5.1 In the event of any claim or proceeding in respect of personal injury made or brought against the NHS Trust by a Clinical Trial Subject, the Sponsor shall indemnify the NHS Trust, its servants, agents and employees in accordance with the terms of the indemnity set out at Appendix 2.4 hereto.

5.2 The Sponsor shall indemnify the NHS Trust, its servants, agents and employees against all claims, proceedings, costs and expenses (including reasonable legal costs) in respect of loss of or damage to property which is the result of negligence on the part of the Sponsor or of a breach by the Sponsor of any of its obligations under this Agreement, save to the extent that any such loss or damage is the result of negligence on the part of the NHS Trust, its servants, agents or employees or of a breach of the obligations of the NHS Trust under this Agreement.

5.3 The NHS Trust shall indemnify the Sponsor, its servants, agents and employees against all claims, proceedings, costs and expenses (including reasonable legal costs) in respect of loss of or damage to property which is the result of negligence on the part of the NHS Trust or of a breach by the NHS Trust of its obligations under this Agreement, save to the extent that any such loss or damage is the result of negligence on the part of the Sponsor, its servants, agents or employees or of a breach of the obligations of the Sponsor under this Agreement.

5.4 Where a Party is required to provide an indemnity under clause 5.2 or (as the case may be) clause 5.3 above, that Party shall have the right to take over full care and control of the defence to any claim or proceeding by a third party, said defence to be at the sole expense of the indemnifying Party. The indem-

nifying Party shall be entitled to use legal counsel of his choice. The indemnifying Party shall keep the other Party fully informed of the progress of any such claim or proceeding, will consult fully with the other Party on the nature of any defence to be advanced, and will not compromise or settle any such claim or proceeding (whether by admission, statement or payment) nor will it conduct itself in such a way as could prejudice the defence of any such claim or proceeding without the written approval of the other Party, such approval not to be unreasonably withheld. Each Party will give the other written notice of any claim or proceeding brought against it with respect to any matter to which it may be entitled to indemnification under clause 5.2 or (as the case may be) clause 5.3 above and each Party will also use its best endeavours to inform the other Party promptly of any circumstances thought likely to give rise to any such claim or proceeding. Each Party will give to the other Party such help as may reasonably be required for the conduct and prompt handling of any such claim or proceeding.

5.5 In no circumstances shall either Party be liable to the other in contract, tort (including negligence or breach of statutory duty) or otherwise howsoever arising or whatever the cause thereof, for any loss of profit, business, reputation, contracts, revenues or anticipated savings for any special, indirect or consequential damage of any nature, which arises directly or indirectly from any default on the part of either Party. Nothing in this clause shall affect the responsibility of either Party in relation to death or personal injury caused by the negligence of that Party or its servants, agents or employees.

5.6 For the purpose of the indemnity provided in clause 5.2 above, the expression 'agents' shall include, but shall not be limited to, any person providing services to the NHS Trust under a contract for services or otherwise.

5.7 The Sponsor will take out appropriate insurance cover or will provide evidence to the satisfaction of the NHS Trust of self-insurance in respect of its potential liability under clauses 5.1 and 5.2 above and such cover shall be for a minimum of £ [. . . insert amount . . .] in respect of any one occurrence or series of occurrences arising from one event. The Sponsor shall produce to the NHS Trust, on request, copies of insurance policies or other evidence thereof together with evidence that such policies remain in full force and effect. The terms of any insurance or the amount of cover shall not relieve the Sponsor of any liabilities under this Agreement.

6 Confidentiality

6.1 Medical confidentiality

The Parties agree to adhere to the principles of medical confidentiality in relation to Clinical Trial Subjects involved in the Clinical Trial. Personal data shall not be disclosed to the Sponsor by the NHS Trust save where this is required directly or indirectly to satisfy the requirements of the Protocol or for the purpose of monitoring or adverse event reporting. The Sponsor shall not disclose the identity of Clinical Trial Subjects to third parties without prior written consent of the Clinical Trial Subject, in accordance with the requirements of the Data Protection Act 1998 and the principles set out in the Report of the Caldicott Committee on the review of patient identifiable information dated December 1997, a copy of which the NHS Trust shall supply to the Sponsor on request.

6.2 Confidential information

6.2.1 The NHS Trust and the Sponsor shall ensure that only those of its officers and employees directly concerned with the carrying out of this Agreement have access to the Confidential Information and each Party undertakes to treat as strictly confidential and not to disclose to any third party any Confidential Information save where disclosure is required by a regulatory authority or by law and not to make use of any Confidential Information other than in accordance with this Agreement without the prior written consent of the other Party.

6.2.2 In the event of a Party visiting the establishment of the other Party, the visiting Party undertakes that any further information relating to other clinical trials which may come to the visiting Party's knowledge as a result of any such visit, shall be kept strictly confidential and that any such information will not be disclosed to any third party or made use of in any way by the visiting Party without prior written permission of the other Party.

6.2.3 The obligations of confidentiality set out in this clause 6.2 shall not apply to Confidential Information which is (i) published or generally available to the public through no fault of the receiving Party, (ii) in the possession of the receiving Party prior to the date of this Agreement and is not subject to a duty of confidentiality, (iii) independently developed by the receiving Party and is not subject to a duty of confidentiality, (iv) obtained by the receiving Party from a third party not subject to a duty of confidentiality.

6.3 This clause 6 shall continue to apply after the expiry or termination of this Agreement.

7 Publicity

The Sponsor will not use the name of the NHS Trust, nor of any member of the NHS Trust's staff, in any publicity, advertising or news release without the prior written approval of an authorised representative of the NHS Trust, such approval not to be unreasonably withheld. The NHS Trust will not use the name of the Sponsor nor of any of its employees, in any publicity without the prior written approval of the Sponsor.

8 Publication

8.1 The Sponsor recognises that the NHS Trust and Site Principal Investigator have a responsibility under the Research Governance Framework for Health and Social Care to ensure that results of scientific interest arising from the Clinical Trial are appropriately published and disseminated. The Sponsor agrees that employees of the NHS Trust shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the Clinical Trial subject to the publication policy described in the Protocol. If the Clinical Trial is multicentred (as defined in clause 4.7 above), any publication based on the results obtained at the Trial Site (or a group of sites) shall not be made before the first multicentre publication. If a publication concerns the analyses of sub-sets of data from a multicentred Clinical Trial the publication shall make reference to the relevant multicentre publication (s).

8.2 Upon completion of the Clinical Trial, and any prior publication of multicentre data, or when the Clinical Trial data are adequate (in Sponsor's reasonable judgement), the NHS Trust may prepare the data deriving from the Clinical Trial for publication. Such data will be submitted to the Sponsor for review and comment prior to publication. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days (or the time limit specified in the Protocol if longer) prior to submission for publication, public dissemination, or review by a publication committee.

8.3 The NHS Trust agrees that all reasonable comments made by the Sponsor in relation to a proposed publication by the NHS Trust will be incorporated by the NHS Trust into the publication.

8.4 During the period for review of a proposed publication referred to in clause 8.2 above, the Sponsor shall be entitled to make a reasoned request to the NHS Trust that publication be delayed for a period of up to six (6) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its proprietary information and the NHS Trust shall not unreasonably withhold its consent to such a request.

9 Intellectual Property

9.1 All Intellectual Property Rights and Know How owned by or licensed to NHS Trust prior to and after the date of this Agreement other than any Intellectual Property Rights and Know How arising from the Clinical Trial is and shall remain the property of the NHS Trust.

9.2 All Intellectual Property Rights and Know How owned by or licensed to the Sponsor prior to and after the date of this Agreement other than any Intellectual Property Rights and Know How arising out of the Clinical Trial is and shall remain the property of the Sponsor.

9.3 All Intellectual Property Rights and Know How arising from the Clinical Trial shall vest in or be exclusively licensed to the Sponsor in accordance with clauses 9.4 and 9.5 below.

9.4 The NHS Trust hereby assigns its rights in all Intellectual Property Rights and, to the extent possible in all Know How, arising out of the Clinical Trial to the Sponsor and at the request and expense of the Sponsor, the NHS Trust and the Site Principal Investigator shall execute all such documents and do all such other acts and things as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

9.5 NHS Trust and Site Principal Investigator shall promptly disclose to the Sponsor any and all Know How generated pursuant to this Agreement and undertake not to use such Know How other than for the purposes of this Agreement without the prior written consent of the Sponsor, such consent not to

be unreasonably withheld. NHS Trust hereby grants to the Sponsor an exclusive, worldwide, irrevocable, fully paid up royalty free licence under such Know How (to the extent such Know How is not assigned pursuant to clause 9.4 above) to exploit the same for any purpose whatsoever.

10 Financial arrangements

10.1 Arrangements relating to the financing of this Clinical Trial by the Sponsor are set out in Appendix 2.5 hereto.
10.2 All payments will be made according to the schedule contained in Appendix 2.5 on presentation of a VAT invoice to the Sponsor by the NHS Trust.
10.3 The Sponsor shall make payment within thirty (30) days of the date of receipt of the invoice mentioned in clause 10.2 above.
10.4 Any delay in the payment of the payee invoices by the Sponsor will incur an interest charge on any amounts overdue of 2% per month above the National Westminster Bank plc base rate prevailing on the date the payment is due.

11 Term

This Agreement will remain in effect until completion of the Clinical Trial, close-out of the Trial Site and completion of the obligations of the Parties under this Agreement or earlier termination in accordance with this Agreement.

12 Early termination

12.1 Either the Sponsor or the NHS Trust (the Terminating Party) may terminate this Agreement with immediate effect at any time if the other Party (the Defaulting Party) is:
12.1.1 in breach of any of the Defaulting Party's obligations hereunder (including a failure without just cause to meet a Timeline) and fails to remedy such breach where it is capable of remedy within 28 days of a written notice from the Terminating Party specifying the breach and requiring its remedy;
12.1.2 declared insolvent or has an administrator or receiver appointed over all or any part of its assets or ceases or threatens to cease to carry on its business.
12.2 A Party may terminate this Agreement on notice to the other Party with immediate effect if it is reasonably of the opinion that the Clinical Trial should cease in the interests of the health of Clinical Trial Subjects involved in the Clinical Trial.
12.3 The Sponsor may terminate this Agreement on notice to the NHS Trust if [. . . insert name of investigator . . .] is no longer able (for whatever reason) to act as Site Principal Investigator and no replacement mutually acceptable to the NHS Trust and the Sponsor can be found.
12.4 The Sponsor may terminate this Agreement immediately upon notice in writing to the NHS Trust for reasons not falling within clauses 12.1, 12.2 or 12.3 above, save that in such circumstances the provisions of clause 12.6 below shall also apply. In all such circumstances the Sponsor shall confer with the Site Principal Investigator and use its best endeavours to minimise any inconvenience or harm to Clinical Trial Subjects caused by the premature termination of the Clinical Trial.
12.5 In the event of early termination of this Agreement by the Sponsor, pursuant to clauses 12.2, 12.3 and 12.4 and subject to an obligation on the NHS Trust and the Site Principal Investigator to mitigate any loss, the Sponsor shall pay all costs incurred and falling due for payment up to the date of termination, and also all expenditure falling due for payment after the date of termination which arises from commitments reasonably and necessarily incurred by the NHS Trust for the performance of the Clinical Trial prior to the date of termination, and agreed with the Sponsor.
12.6 In the event of early termination pursuant to clause 12.4 above the Sponsor shall make a compensatory payment in accordance with Appendix 2.5.
12.7 In the event of early termination if payment (whether for salaries or otherwise) has been made by the Sponsor to the NHS Trust in advance for work not completed such monies shall be applied to termination related costs and in the case of termination pursuant to clause 12.4 above towards the compensatory payment payable pursuant to clause 12.6 and the remainder of the monies shall be returned forthwith to the Sponsor.
12.8 At close-out of the Trial Site following termination or expiration of this Agreement the NHS Trust shall immediately deliver to the Sponsor all

Confidential Information and any other unused materials provided to the NHS Trust pursuant to this Agreement.

12.9 Termination of this Agreement will be without prejudice to the accrued rights and liabilities of the Parties under this Agreement.

13 Relationship between the Parties

13.1 Neither Party may assign its rights under this Agreement or any part thereof without the prior written consent of the other Party and neither Party may sub-contract the performance of all or any of its obligations under this Agreement without the prior written consent of the other Party. Any party who so sub-contracts shall be responsible for the acts and omissions of its sub-contractors as though they were its own.

13.2 Nothing shall be construed as creating a partnership, contract of employment or relationship of principal and agent between the Parties.

14 Agreement and modification

14.1 Any change in the terms of this Agreement shall be valid only if the change is made in writing, agreed and signed by the Parties.

14.2 This Agreement including its Appendices contains the entire understanding between the Parties and supersedes all other negotiations representations and undertakings whether written or oral of prior date between the Parties relating to the Clinical Trial which is the subject of this Agreement.

15 Force majeure

Neither Party shall be liable to the other Party or shall be in default of its obligations hereunder if such default is the result of war, hostilities, revolution, civil commotion, strike, epidemic, accident, fire, wind, flood or because of any act of God or other cause beyond the reasonable control of the Party affected. The Party affected by such circumstances shall promptly notify the other Party in writing when such circumstances cause a delay or failure in performance ('a Delay') and where they cease to do so. In the event of a Delay lasting for [. . . insert number . . .] weeks or more the non-affected Party shall have the right to terminate this Agreement immediately by notice in writing to the other Party.

16 Notices

Any notices under this Agreement shall be in writing, signed by the relevant Party to this Agreement and delivered personally, by courier or by recorded delivery post.

Notices to the Sponsor shall be addressed to: [. . . insert address . . .]

Notices to the NHS Trust shall be addressed to: [. . . insert address . . .]

17 Rights of Third Parties

Nothing in this Agreement is intended to confer on any person any right to enforce any term of this Agreement which that person would not have had but for the Contracts (Rights of Third Parties) Act 1999.

18 Waiver

No failure, delay, relaxation or indulgence by any Party in exercising any right conferred on such Party by this Agreement shall operate as a waiver of such right, nor shall any single or partial exercise of any such right nor any single failure to do so, preclude any other or future exercise of it, or the exercise of any other right under this Agreement.

19 Dispute resolution

19.1 In the event of a dispute the Parties agree to attempt to settle it by mediation in accordance with the Centre for Effective Dispute Resolution Model Mediation Procedure. To initiate a mediation a Party must give notice in writing (ADR Notice) to the other Party requesting mediation in accordance with this clause. The Parties shall seek to agree the nomination of the mediator, but in the absence of agreement he shall be nominated by the President for the time being of the British Medical Association. The mediation will start no later than [20] days after date of the ADR Notice. If the dispute is not resolved within [30] days of the ADR Notice a Party may by written notice to the other refer the dispute to arbitration in accordance with clause 19.2 below.

19.2 If the Parties are unable to settle a dispute arising out of or in connection with this Agreement by mediation the dispute shall be finally settled by arbitration in accordance with the UNCITRAL Arbitration Rules as at present in force (the 'UNCITRAL Rules'). The Notice of Arbitration shall be served in accordance with Article 3 of the UNCITRAL Rules and a single arbitrator shall be appointed by agreement of the Parties or in the absence of agreement, by the President for the time being of the British Medical Association. The seat of arbitration shall be London and the language of the arbitral proceedings shall be English. All and any awards of the arbitrators shall be made in accordance with the UNCITRAL Rules in writing and shall be binding on the Parties who expressly exclude all and any rights of appeal from all and any awards to the extent that such exclusion may be validly made.

20 Governing law

This Agreement shall be interpreted and governed by English Law.

Signed on behalf of the:

SPONSOR: . . . . . .
. . . . . Date: . . . . . .
(Print name and position)

Signed on behalf of the:

NHS TRUST . . . . . .
. . . . . Date: . . . . . .
(Print name and position)

Authorised signatory (Chief Executive, Director of R&D, or Finance Director)

2.2 ABPI form of Indemnity for Clinical Studies

To: **[Name and address of sponsoring company] ('the Sponsor')**
From: **[Name and address of health authority/health board/NHS Trust] ('the Authority')**
Re: **Clinical study No ( ) with [name of product]**

1. It is proposed that the Authority should agree to participate in the above sponsored study ('the Study') involving [patients of the Authority] [non-patient volunteers] ('the Subjects') to be conducted by [name of investigator (s)] ('the Investigator') in accordance with the protocol annexed, as amended from time to time with the agreement of the Sponsor and the Investigator ('the Protocol'). The Sponsor confirms that it is a term of its agreement with the Investigator that the Investigator shall obtain all necessary approvals of the applicable Local Research Ethics Committee and shall resolve with the Authority any issues of a revenue nature.

2. The Authority agrees to participate by allowing the Study to be undertaken on its premises utilising such facilities, personnel and equipment as the Investigator may reasonably need for the purpose of the Study.

3. In consideration of such participation by the Authority, and subject to paragraph 4 below, the Sponsor indemnifies and holds harmless the Authority and its employees and agents against all claims and proceedings (to include any settlements or ex gratia payments made with the consent of the parties hereto and reasonable legal and expert costs and expenses) made or brought (whether successfully or otherwise).

(**a**) by or on behalf of Subjects taking part in the Study (or their dependants) against the Authority or any of its employees or agents for personal injury (including death) to Subjects arising out of or relating to the administration of the product (s) under investigation or any clinical intervention or procedure provided for or required by the Protocol to which the Subjects would not have been exposed but for their participation in the Study.

(**b**) by the Authority, its employees or agents or by or on behalf of a Subject for a declaration concerning the treatment of a Subject who has suffered such personal injury.

4. The above indemnity by the Sponsor shall not apply to any such claim or proceeding:

4.1 to the extent that such personal injury (including death) is caused by the negligent or wrongful acts or omissions or breach of statutory duty of the Authority, its employees or agents.

4.2 to the extent that such personal injury (including death) is caused by the failure of the Authority, its employees, or agents to conduct the Study in accordance with the Protocol.

4.3 unless as soon as reasonably practicable following receipt of notice of such claim or proceeding, the Authority shall have notified the Sponsor in writing of it and shall, upon the Sponsor's request, and at the Sponsor's cost, have permitted the Sponsor to have full care and control of the claim or proceeding using legal representation of its own choosing.

4.4 if the Authority, its employees, or agents shall have made any admission in respect of such claim or proceeding or taken any action relating to such claim or proceeding prejudicial to the defence of it without the written consent of the Sponsor such consent not to be unreasonably withheld provided that this condition shall not be treated as breached by any statement properly made by the Authority, its employees or agents in connection with the operation of the Authority's internal complaint procedures, accident reporting procedures or disciplinary procedures or where such statement is required by law.

5. The Sponsor shall keep the Authority and its legal advisers fully informed of the progress of any such claim or proceeding, will consult fully with the Authority on the nature of any defence to be advanced and will not settle any such claim or proceeding without the written approval of the Authority (such approval not to be unreasonably withheld).

6. Without prejudice to the provisions of paragraph 4.3 above, the Authority will use its reasonable endeavours to inform the Sponsor promptly of any circumstances reasonably thought likely to give rise to any such claim or proceeding of which it is directly aware and shall keep the Sponsor reasonably informed of developments in relation to any such claim or proceeding even where the Authority decides not to make a claim under this indemnity. Likewise, the Sponsor shall use its reasonable endeavours to inform the Authority of any such circumstances and shall keep the Authority reasonably informed of developments in relation to any such claim or proceeding made or brought against the Sponsor alone.

7. The Authority and the Sponsor will each give to the other such help as may reasonably be required for the efficient conduct and prompt handling of any claim or proceeding by or on behalf of Subjects (or their dependants) or concerning such a declaration as is referred to in paragraph 3(b) above.

8. Without prejudice to the foregoing if injury is suffered by a Subject while participating in the Study, the Sponsor agrees to operate in good faith the Guidelines published in 1991 by The Association of the British Pharmaceutical Industry and entitled 'Clinical Trial Compensation Guidelines' (where the Subject is a patient) and the Guidelines published in 1988 by the same Association and entitled 'Guidelines for Medical Experiments in non-patient Human Volunteers' (where the subject is not a patient) and shall request the Investigator to make clear to the Subjects that the Study is being conducted subject to the applicable Association Guidelines.

9. For the purpose of this indemnity, the expression 'agents' shall be deemed to include without limitation any nurse or other health professional providing services to the Authority under a contract for services or otherwise and any person carrying out work for the Authority under such a contract connected with such of the Authority's facilities and equipment as are made available for the Study under paragraph 2 above.

10. This indemnity shall be governed by and construed in accordance with English/Scots* law.

SIGNED on behalf of the Health Authority/Health Board/NHS Trust

. . . . . .
Chief Executive/District General Manager

SIGNED on behalf of the Company

. . . . . .
Dated . . . . . .

* Delete as appropriate.

2.3 ABPI Guideline on Advertising for Subjects for Clinical Trials

As a result of a number of enquiries to the Medical Affairs Department of the Association of the British Pharmaceutical Industry (ABPI) and the recognition that the media was being increasingly used to advertise for subjects for clinical trials, the ABPI Medical Committee set up a Task Group to develop these guidelines.

The European Commission (EC) have included an appendix on advertising for trial subjects in the detailed guidance on the application to be submitted for an ethics committee opinion on a clinical trial on a medicinal product for human use. The ABPI guideline set out below takes into account the views of the Medical Committee and additional guidance from the EC guideline. Research Ethics Committees (RECs) should be invited to review all materials used to recruit subjects for all phases of clinical trials, including, but not limited to:

1. Television and radio advertisements.
2. Letters, posters, newsletters, etc.
3. Newspaper advertisements.
4. Internet web sites.

1 Essential Information for an Advertisement

1. A statement indicating that the study involves research.
2. A contact name and phone number for the subject to contact.
3. Some of the eligibility criteria.
4. The likely duration of the subject's participation for a specific study.
5. That the advertisement has been approved by an ethics committee.
6. That your general practitioner will be informed that you are taking part in the clinical trial.
7. That any response to the advertisement will be recorded but will not indicate any obligation.

2 Additional Permitted Content

1. The purpose of the research may be described.
2. The location of the research.
3. The company or institution involved may be named if appropriate.

3 Statements That Should Not Be Used

1. Implied or expressed claims of safety or efficacy.
2. Undue emphasis on reimbursement but mention of reimbursement is permitted.
3. Any express or implied claim that the research is FDA or MHRA approved.
4. Use of the term 'new' unless qualified, i.e. 'new research medicine', 'new investigational medicine'.
5. The compound's name.
6. Care should be taken to ensure that advertisements are in no way promotional for the medicine concerned.

The ethics committee approval of any advertising material should be kept with the master study file.

2.4 Guidelines for company-sponsored Safety Assessment of Marketed Medicines (SAMM)

Introduction

It is well-recognised that there is a continuous need to monitor the safety of medicines as they are used in clinical practice. Spontaneous reporting schemes (e.g. the UK yellow card system) provide important early warning signals of potential drug hazards and also provide a means of continuous surveillance. Formal studies to evaluate safety may also be necessary, particularly in the confirmation and characterisation of possible hazards identified at an earlier stage of drug development. Such studies may also be useful in identifying previously unsuspected reactions.

Scope of guidelines

These guidelines apply to the conduct of all company-sponsored studies which evaluate the safety of marketed products. They take the place of previous guidelines on post-marketing surveillance which were published in 1988 (*BMJ* 1998;296:399–400). Studies performed under those guidelines were found to have some notable limitations (*BMJ* 1992;304:1470–2) and these new guidelines have been prepared in response to the problems identified. The major changes may be summarised as follows:

1. The scope of the guidelines has been expanded to include all company-sponsored studies which are carried out to evaluate safety of marketed medicines. It should be emphasised that this includes both studies conducted in general practice and in the hospital setting. The name of the guidelines has been changed to reflect the emphasis on safety assessment rather than merely surveillance.

2. The guidelines have been developed to provide a framework on which a variety of data collection methods can be used to improve the evaluation of the safety of marketed medicines. Whilst it is recognised that the design used needs to be tailored to particular drugs and hazards, the guidelines define the essential principles which may be applied in a variety of situations. The study methods in this field continue to develop and therefore there will be a need to review regularly these guidelines to ensure that they reflect advances made in the assessment of drug safety.

The guidelines have been formulated and agreed by a Working Party which includes representation from the Medicines and Healthcare products Regulatory Agency (MHRA), Commission on Human Medicines (CHM), Association of the British Pharmaceutical Industry (ABPI), British Medical Association (BMA) and the Royal College of General Practitioners (RCGP). Other guidelines exist for the conduct of 'Phase IV clinical trials' where the medication is provided by the sponsoring company (see section 2(b) below). Some of these studies will also meet the definition of a SAMM study (see below) and should therefore also comply with the present guidelines.

1 Definition of Safety Assessment of Marketed Medicines

(**a**) Safety assessment of marketed medicines (SAMM) is defined as 'a formal investigation conducted for the purpose of assessing the clinical safety of marketed medicine (s) in clinical practice'.

(**b**) Any study of a marketed drug which has the evaluation of clinical safety as a specific objective should be included. Safety evaluation will be a specific objective in post-marketing studies either when there is a known safety issue under investigation and/or when the numbers of patients to be included will add significantly to the existing safety data for the product(s). Smaller studies conducted primarily for other purposes should not be considered as SAMM studies. However, if a study which is not conducted for the purpose of evaluating safety unexpectedly identifies a hazard, the manufacturer would be expected to inform the MHRA immediately and the section of these guidelines covering liaison with regulatory authorities would thereafter apply.

In cases of doubt as to whether or not a study comes under the scope of the guidelines the sponsor should discuss the intended study plan with the MHRA.

2 Scope and objectives of SAMM

(**a**) SAMM may be conducted for the purpose of identifying previously unrecognised safety issues

(hypothesis-generation) or to investigate possible hazards (hypothesis-testing).

(**b**) A variety of designs may be appropriate including observational cohort studies, case–surveillance or case–control studies. Clinical trials may also be used to evaluate the safety of marketed products, involving systematic allocation of treatment (e.g. randomisation). Such studies must also adhere to the current guidelines for Phase IV clinical trials.

(**c**) The design to be used will depend on the objectives of the study, which must be clearly defined in the study plan. Any specific safety concerns to be investigated should be identified in the study plan and explicitly addressed by the proposed methods.

3 Design of studies

Observational cohort studies

(**a**) The population studied should be as representative as possible of the general population of users, and be unselected unless specifically targeted by the objectives of the study (e.g. a study of the elderly). Exclusion criteria should be limited to the contraindications stated in the data sheet or summary of product characteristics (SPC). The prescriber should be provided with a data sheet or SPC for all products to be used. Where the product is prescribed outside the indications on the data sheet, such patients should be included in the analysis of the study findings.

(**b**) Observational cohort studies should normally include appropriate comparator group(s). The comparator group(s) will usually include patients with the disease/indication(s) relevant to the primary study drug and such patients will usually be treated with alternative therapies.

(**c**) The product(s) should be prescribed in the usual manner, for example on an FP10 form written by the general practitioner or through the usual hospital procedures.

(**d**) Patients must not be prescribed particular medicines in order to include them in observational cohort studies since this is unethical (see section 15 of the 'Guidelines on the Practices of Ethics Committees in Medical Research involving Human Subjects', Royal College of Physicians, 1990).

(**e**) The prescribing of a drug and the inclusion of the patient in a study are two issues which must be clearly separated. Drugs must be prescribed solely as a result of a normal clinical evaluation, and since such indications may vary from doctor to doctor a justification for the prescription should be recorded in the study documents. In contrast, the inclusion of the patient in the study must be solely dependent upon the criteria for recruitment which have been specifically identified in the study procedures. Any deviation from the study criteria for recruitment could lead to selection bias.

(**f**) The study plan should stipulate the maximum number of patients to be entered by a single doctor. No patient should be prospectively entered into more than one study simultaneously.

Case–control studies

(**g**) Case–control studies are usually conducted retrospectively. In case–control studies comparison is made between the history of drug exposure of cases with the disease of interest and appropriate controls without the disease. The study design should attempt to account for known sources of bias and confounding.

Case–surveillance

(**h**) The purpose of case–surveillance is to study patients with diseases which are likely to be drug-related and to ascertain drug exposure. Companies who sponsor such studies should liaise particularly closely with the MHRA in order to determine the most appropriate arrangements for the reporting of cases.

Clinical trials

(**i**) Large clinical trials are sometimes useful in the investigation of post-marketing safety issues and these may involve random allocation to treatment. In other respects, an attempt should be made to study patients under as normal conditions as possible. Exclusion criteria should be limited to the contraindications in the data sheet or SPC unless they are closely related to the particular objectives of the study. Clinical trials must also adhere to the current guidelines for Phase IV clinical trials (see 2(b) above). Studies which fulfil the definition of SAMM but are performed under a clinical trial exemption (CTX) or under the clinical trial on a marketed product (CTMP) scheme are within the scope of these guidelines.

4 Conduct of studies

(**a**) Responsibility for the conduct and quality of company-sponsored studies shall be vested in the company's medical department under the supervi-

sion of a named medical practitioner registered in the UK, and whose name shall be recorded in the study documents.
(**b**) Where a study is performed for a company by an agent, a named medical practitioner registered in the UK shall be identified by the agent to supervise the study and liaise with the company's medical department.
(**c**) Consideration should be given to the appointment of an independent advisory group(s) to monitor the safety information and oversee the study.

5 Liaison with regulatory authorities

(**a**) Companies proposing to perform a SAMM study are encouraged to discuss the draft study plan with the MHRA at an early state. Particular consideration should be given to specific safety issues which may require investigation.
(**b**) Before the study commences a study plan should be finalised which explains the aims and objectives of the study, the methods to be used (including statistical analysis) and the record keeping which is to be maintained. The company shall submit the study plan plus any proposed initial communications to doctors to the MHRA at least 1 month before the planned start of the study. The MCA will review the proposed study and may comment. The responsibility for the conduct of the study will, however, rest with the sponsoring pharmaceutical company.
(**c**) The company should inform the MHRA when the study has commenced and will normally provide a brief report on its progress at least every 6 months, or more frequently if required by MHRA.
(**d**) The regulatory requirements for reporting of suspected adverse reactions must be fulfilled. Companies should endeavour to ensure that they are notified of serious suspected adverse reactions and should report these to the MHRA within 15 days of receipt. Events which are not suspected by the investigator to be adverse reactions should not be reported individually as they occur. These and minor adverse reactions should be included in the final report.
(**e**) A final report on the study should be sent to the MHRA within 3 months of follow-up being completed. Ideally, this should be a full report but a brief report within 3 months followed by a full report within 6 months of completion of the study would normally be acceptable. The findings of the study should be submitted for publication.
(**f**) Companies are encouraged to follow MHRA guidelines on the content of progress reports and final reports.

6 Promotion of medicines

(**a**) SAMM studies should not be conducted for the purposes of promotion.
(**b**) Company representatives should not be involved in SAMM studies in such a way that it could be seen as a promotional exercise.

7 Doctor participation

(**a**) Subject to the doctor's terms of service, payment may be offered to the doctor in recompense for his time and any expenses incurred according to the suggested scale of fees published by the BMA.
(**b**) No inducement for a doctor to participate in a SAMM study should be offered, requested or given.

8 Ethical issues

(**a**) The highest possible standards of professional conduct and confidentiality must always be maintained. The patient's right to confidentiality is paramount. The patient's identity in the study documents should be codified and only his or her doctor should be capable of decoding it.
(**b**) Responsibility for the retrieval of information from personal medical records lies with the consultant or general practitioner responsible for the patient's care. Such information should be directed to the medical practitioner nominated by the company or agent, who is thereafter responsible for the handling of such information.
(**c**) Reference to a Research Ethics Committee is required if patients are to be approached for information, additional investigations are to be performed or if it is proposed to allocate patients systematically to treatments.

9 Procedure for complaints

A study which gives cause for concern on scientific, ethical or promotional grounds should be referred to the MCA, ABPI and the company concerned.

Concerns regarding possible scientific fraud should be referred to the ABPI. They will be investigated and, if appropriate, referred to the General Medical Council.

10 Review of Guidelines

The Working Party will review these guidelines as necessary.

Association of the British Pharmaceutical Industry (ABPI)
British Medical Association (BMA)
Commission on Human Medicines (CHM)
Medicines and Healthcare products Regulatory Agency (MHRA)
Royal College of General Practitioners (RCGP)