The University of Nottingham

SPONSORSHIP AGREEMENT

SPONSOR and CHIEF INVESTIGATOR CLINICAL RESEARCH (CLINICAL TRIALS)

Version 1.0, July 2007

This **AGREEMENT** is made between

The University of Nottingham (the Sponsor) of University Park, Nottingham, NG7 2RD,

and **the Chief Investigator** (collectively the '**Parties**') of the clinical research identified below:

Chief Investigator name: Professor Philip Bath

University of Nottingham job title: Stroke Association Professor of Stroke Medicine

Title of research project: Determining the potential of ambulance-based randomised controlled trials in patients with hyperacute stroke; assessment of glyceryl trinitrate in lowering blood pressure.

Project ID: 08022

With effect from 1st May 2004, Statutory Instrument 2004, no. 1031, *The Medicines for Human Use (Clinical Trials) Regulations 2004* enacting *EU Directive 2001/20/EC*

and

with effect from 29th August 2006, Statutory Instrument 2006, no. 1928, *The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006*

and

with effect from 12th December 2006, Statutory Instrument 2006, no. 2984, *The Medicines for Human Use (Clinical Trials) Amendment (no. 2) Regulations 2006*

hereafter known as the '**Regulations**', came into effect in the UK governing the conduct of clinical trials involving the use of investigational medicinal products (IMPs) and superseding previous clinical trial legislations.

In addition the Department of Health Research Governance Framework for Health and Social Care, second edition, 2005 (RGF) set out a framework for the conduct of all clinical research within the NHS.

The Regulations define a 'Sponsor' with regard to clinical trials as being the organisation or organisations taking responsibility for the 'initiation, management and financing (or arranging the financing) of that trial'.

The Regulations define a Chief Investigator as 'the authorised health professional, whether or not he is an investigator at any particular site, who takes primary responsibility for the conduct of the trial'.

The RGF defines a Sponsor as the 'Individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study' and also make provision for joint sponsorship.

The RGF defines a Chief Investigator as 'the person who takes overall responsibility for the design, conduct and reporting of a study if it is at one site; or if the study involves researchers at more than one site, the person who takes responsibility for the design, conduct and reporting of the study, whether or not that person is an investigator at any particular site'.

This agreement defines the roles and responsibilities of both the Sponsor and Chief Investigator for the named clinical research falling within these Regulations and / or the RGF.

While the Regulations pertain to the use of investigational medicinal products (IMP) within clinical trials, the RGF covers all clinical research within the NHS. For the purposes of this agreement 'clinical research' is taken to mean any research whose participants are human beings *and* who are patients or users of the NHS *and* the research is conducted within NHS, Primary Care Trust (PCT) or associated premises, including non-NHS premises such as universities and study participants' homes regardless of whether that research uses IMPs.

For the purposes of this agreement the Chief Investigator shall be an employee of the University of Nottingham or, where the University is not the substantive employer, the proposed Chief Investigator shall hold an Honorary Contract with the University of Nottingham.

IT IS HEREBY AGREED that the following terms and conditions shall apply to the Parties' collaboration on the clinical research identified:-

1 GENERAL OPERATING AGREEMENTS

1.1 In undertaking clinical research, the Parties shall do so in line with the Regulations and the Research Governance Framework for Health and Social Care as applicable and any subsequent amendment or re-issue thereof.

1.2 In undertaking clinical research, the Parties shall do so in line with the all other Regulations, Codes of Practice and guidance documents that pertain to the research and are issued by relevant authorities such as the Department of Health.

1.3 The Chief Investigator shall be responsible for the overall day-to-day running of the research and shall report to the Sponsor accordingly. The responsibilities of being a Chief Investigator in whole or part may not be devolved to or expected to be delivered by a third party without prior written agreement from the Sponsor. In such cases the third party shall be an employee of or hold an honorary contract with the University of Nottingham

1.4 No clinical research shall be permitted to start [at a particular site] without first obtaining all [the relevant] ethics committee and regulatory approvals for that research. These include the national ethical and competent authority approvals and each Site Specific Assessment and R&D approvals where applicable. The Chief Investigator shall retain and be required to produce evidence to the Sponsor of all approvals for the clinical research upon request.

1.5 The Chief Investigator shall obtain all necessary approvals, indemnities and agreements from organisations with which they are collaborating on the research. This includes any NHS Trusts, PCTs or associated organisations where aspects of the research may be carried out.

1.6 Where the Parties are collaborating on an international multi-centre clinical trial, none of them shall accept Sponsorship responsibilities for activity outside the United Kingdom without prior written agreement from the University of Nottingham. This agreement may be required at an early stage of the research development and must be sought before any funding application is made.

2 SPONSOR DUTIES AND OBLIGATIONS

The Sponsor or its representatives shall:

2.1 Ensure research agreement(s) are in place with other participating organizations

2.2 Assess the quality of the research using the protocol and submitted peer review reports as guidance.

2.3 Assess overall corporate risk to the University of Nottingham based on the research protocol risk assessment, own experience and in consultation with relevant in-house experts

2.4 Ensure that the Chief Investigator has sufficient experience and expertise to carry out the research as evidenced by his or her previous involvement at a high level in all aspects of research development and management

2.5 Ensure that there is provision for adequate trial insurance, indemnity and financial management of the research

2.6 Ensure arrangements are in place for overall monitoring of the research

2.7 Ensure arrangements are in place for the conduct of the research in accordance with the principles of Good Clinical Practice with appropriate documented management systems and Standard Operating Procedures (SOPs)

2.8 Provide CI with authorization letter for the Medicine and Healthcare products Regulatory Authority (MHRA) to complete a Clinical Trial Authorization (CTA) on behalf of the Sponsor

2.9 Provide CI with authorization letter for the NHS Research Ethics Committee to which the application for ethical permission is sought on behalf of the Sponsor

2.10 Provide payment of initial and annual CTA fee to the MHRA, and payment of any audit inspection fee as required. Payment may be recovered from the research or School funding

2.11 Ensure arrangements are in place to review any change to the protocol or research developments and to review sponsorship accordingly

2.12 Monitor serious adverse events and in particular those that are sudden, unexpected and serious adverse reactions to an IMP. In accordance with regulatory requirements shall ensure that these events are reported to the competent authority and ethics committee as required

2.13 Be responsible for the management of Intellectual Property and publication rights

2.14 Ensure arrangements are in place for the archiving of trial source data, essential documents and the Trial Master File

2.15 Provide for and partake in statutory inspections by the competent authority

2.16 Take the decision and retain the right to temporarily halt or stop the research where:

- there is reason to do so such that the University of Nottingham's interests are protected
- or where there is sufficient reason to believe that the research is not being conducted in accordance with any Regulations, Codes of Practice or the RGF
- or where there is a real or perceived unforeseen or unacceptable danger to the participants of the research
- or where advised to do so by any Trial Steering Committee or Data Monitoring Committee

and shall do so by withdrawal of its sponsorship

3 CHIEF INVESTIGATOR DUTIES AND OBLIGATIONS

The Chief Investigator shall:

3.1 Research Protocol

3.1.1 Devise, with appropriately qualified advice, the clinical research proposal and develop into a full written protocol and associated documents
3.1.2 Seek, where appropriate, independent expert review of the protocol and provide reports to the Sponsor
3.1.3 Seek, and incorporate within the protocol, statistical advice from a qualified statistician for the analysis of the research data and outcomes
3.1.4 Seek advice from and liaise with an appropriately qualified Pharmacist and/or QP to write and develop an Investigator Brochure where required
3.1.5 Seek advice from and liaise with a qualified information technology expert for development of computer based collection, storage and manipulation, including transfer where applicable, of the research data.
3.1.6 Carry out a full risk/benefit analysis of the research and incorporate into the protocol. Use this analysis to determine the risk to the research participants, the research staff and to the University of Nottingham. Submit a risk assessment report to the Sponsor.

3.2 Competent Authority, Ethics Committee and R&D Authorisations

3.2.1 Obtain a EudraCT number and submit the Clinical Trials Authorisation (CTA) request to the Medicines and Healthcare products Regulatory Agency (MHRA) where applicable; and respond to queries and amendments as required
3.2.2 Complete and submit the application to the NHS Research Ethics Service (NRES) for approval to conduct the research; attend the designated Research Ethics Committee (REC) meeting as required and respond to and act upon any recommendations then made.
3.2.3 Complete and submit the NHS R&D application form for local permission to conduct the research. Liaise with the local R&D Department to meet their expectations of the research conduct
3.2.4 For multi-centre research assist local researchers in completion and submission of their R&D applications and advise accordingly
3.2.5 Submit for permission and give notice of trial management and protocol amendments to the MHRA and REC
3.2.6 Cooperate with and allow statutory inspection of trial-sites by the competent authority
3.2.7 Produce and submit quarterly, annual and final reports, including safety reports to the MHRA
3.2.8 Give notice of the end of the trial to the MHRA and REC

3.3 Research Funding and Terms and Conditions

3.3.1 Liaise with University of Nottingham staffs to procure funding from a suitable source for the costs of the research.
3.3.2 Complete and submit any research funding proposal to the appropriate body and respond to any call for clarification and / or amendment
3.3.3 Ensure that the terms and conditions of the funding are met throughout the research and that the research conduct can meet those terms without jeopardising its integrity and the welfare of the research participants

3.4 Good Clinical Practice and Trial Conduct

3.4.1 Ensure that management systems are in place to assure the quality of the trial conduct to meet GCP standard
3.4.2 Ensure that all aspects of data collection, storage and manipulation comply with the Data Protection Act 1998 and any subsequent amendments or additions to this Act
3.4.3 Ensure that sufficient monitoring of the research data and conduct is carried out in accordance with the level identified within the research risk assessment and identified within the protocol
3.4.4 Ensure that there are documented systems with audit trails for the supply, storage, delivery and disposal of IMPs and that IMPs are made available to participants free of charge
3.4.5 Recruit only suitable qualified and experienced researchers to undertake any research duties and demonstrable by retention of evidence. The CI must be satisfied that all those expected to play a role in the execution of the research are capable through qualification, expertise and

experience to take on their roles including those at dispersed sites in a multi centre trial

3.4.6 Ensure that all other researchers involved in the research are trained in aspects of this research and are fully versed in their requirements and responsibilities within the research

3.4.7 Ensure that local logs are completed and retained for delegation of research duties

3.5 **Pharmacovigilance** (research involving IMPs)

3.5.1 Take appropriate urgent safety measures to assure the welfare of research participants

3.5.2 Assess all serious adverse events (SAEs) for seriousness and causality and report accordingly

3.5.3 Report all Suspected Unexpected Serious Adverse Reactions (SUSARs) in an expedited fashion to the MHRA according to the Regulations. Report to the Sponsor within the same timeframes.

3.5.4 Keep records of all SAEs and continually monitor the research for ongoing risk/benefit and take appropriate measures accordingly to protect the welfare of research participants

3.5.5 Ensure that all other researchers involved are promptly informed of SUSARs and any changes to the research protocol in light of ongoing risk/benefit analyses of safety data

3.5.6 Complete and submit safety reports to the MHRA, REC and R&D according to the Regulations and local requirements

3.5.7 Complete and submit safety reports to the Sponsor on a frequency determined by the research risk assessment and by prior agreement. This shall be no less than yearly.

4 CONFIDENTIALITY

4.1 The Parties shall ensure that information supplied to or deriving from the clinical research is exchanged between themselves on a confidential basis and in accordance with the Data Protection Act 1998. The Chief Investigator shall ensure that any of the researchers within this research, employed by the University of Nottingham or otherwise; students, consultants, sub-contractors or agents who participate in the research are made aware of, and abide by, this requirement.

4.2 The Parties shall ensure that the publication and dissemination of the results of the clinical research on which they collaborate is managed in a co-ordinated manner and in accordance with the protocol. All publications arising from such clinical research shall give due credit to the Parties involved, unless requested to the contrary by either Party.

5 DATE AND TERM

5.1 This Agreement shall be effective from 8th April 2009 and shall initially run until 31st December 2011 on which date it shall automatically expire unless it is specifically renewed.

5.2 The Parties intend that before its expiry this Agreement shall be reviewed in light of the continuation of the named research, renewed where appropriate and that it shall be amended as appropriate to reflect their working relationship and any changes in relevant laws or regulations. To this end, the Parties shall meet to consider the renewal of this Agreement no later than three months before its expiry date.

SIGNATURES

Signed for and on behalf of the University of Nottingham:

Signature: _____ Date: 20/4/09

Name: Paul Cartledge Position: Head of Research Grants and Contracts

Chief Investigator:

Signature: _____ Date: 23/4/09

Name: P BATH Position: Professor of Stroke