

31044 – Institutional review board

The study was reviewed and approved by the following bodies

1. Institute for Science and Technology in Medicine, Keele University Medical School: approval for publication (Professor N Forsyth, Director of the Institute) - **Document 1.**
2. National Research Ethics Service (West Midlands Ethics Service) 08/H1208/30 – **Document 2**
3. National Institute for Health Research (Birmingham and the Black Country Comprehensive Local Research Network), RM&G reference Number 1268 – **Document 3**
4. Warwickshire Primary Care Trust (West Midlands (South) Comprehensive Local Research Network), reference WAR230909 – **Document 4**
5. Institute of Diabetes for Older People, Beds and Herts Postgraduate Medical School, University of Bedfordshire (ref: SOP ID: BSP-SOP-040) – **Document 5**
6. Bayer plc (ref: SOP ID: BSP-SOP-040): funding organisation – **Document 5**

All the documents quoted above are attached below



Professor Sudarshan Ramachandran

Institutional Review Board Statement:

Document 1

Institute for Science and Technology in Medicine, Keele University Medical School

The manuscript titled '**Statin, testosterone and phosphodiesterase 5-inhibitor treatments and age related mortality in diabetes**' was reviewed by Professor N Forsyth, Director of the Institute for Science and Technology in Medicine, Keele University Medical School on the 06.12.2016 and approved for publication.



Professor S Ramachandran (author for correspondence)

Institutional Review Board Statement:

Institute for Science and Technology in Medicine, Keele University Medical School

Statin, testosterone and phosphodiesterase 5-inhibitor treatments and age related mortality in diabetes

Original Study: Approved by the West Midlands Research Ethics Committee, R&D committee (Warwickshire Primary Care Trust)

Extended Audit: Approved by The Institute of Diabetes for Older People (IDOP), Beds and Herts Postgraduate Medical School, Putteridge Bury Campus, Hitchin Road, Luton LU2 8LE

Principal Investigator: Professor Geoffrey Hackett, University of Bedfordshire, Heart of England Foundation NHS Trust

Planning of the Study: Professor Geoffrey Hackett, University of Bedfordshire, Heart of England Foundation NHS Trust

Statistics: Professor Peter Jones, Keele University Medical School, Professor S Ramachandran, Heart of England Foundation NHS Trust, University Hospitals of North Midlands, Staffordshire University

Manuscript Preparation:

Professor Richard Strange, Institute of Science and Technology in Medicine, Keele University

Professor S Ramachandran, Heart of England Foundation NHS Trust, University Hospitals of North Midlands, Staffordshire University

Professor Geoffrey Hackett, University of Bedfordshire, Heart of England Foundation NHS Trust

Funding: Bayer Healthcare (for the independent conduct of the study)

Data Storage: Heart of England Foundation NHS Trust (Professor S Ramachandran)

I have been through the above manuscript and am happy for it to be submitted to the World Journal of Diabetes on behalf of the Institute for Science and Technology in Medicine, Keele University Medical School.



Professor N Forsyth

Director of the Institute for Science and Technology in Medicine, Keele University Medical School


e. mail: n.r.forsyth@keele.ac.uk

31044 - Institutional Review Board Statement:

Document 2

National Research Ethics Service (West Midlands Ethics Service)



08/H1208/30.

		
		National Research Ethics Service
		West Midlands Research Ethics Committee
		Osprey House Albert Street Redditch Worcestershire, B97 4DE anna.mccullough@westmidlands.nhs.uk Chairman: Mr Paul Hamilton
		Telephone: 01527 587573 Facsimile: 01527 587501
 02 October 2008		
Dr G I Hackett Consultant in Urology (Sexual Medicine) Good Hope Hospital Holly Cottage Clinic Fisherwick Rd Lichfield WS14 9JL		
 Dear Dr Hackett		
Full title of study:	Clinical and biochemical improvement in Type 2 diabetic parameters in type 2 diabetic men with symptomatic testosterone deficiency syndrome (TDS). A double blind, placebo controlled study of depot testosterone undecanoate (NEBIDO) versus placebo	
REC reference number:	08/H1208/30	
Protocol number:	23 May 2008	
EudraCT number:	2008-000931-16	
 The REC gave a favourable ethical opinion to this study on 22 July 2008.		
Further notification(s) have been received from local site assessor(s) following site-specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s). I attach an updated version of the site approval form, listing all sites with a favourable ethical opinion to conduct the research.		
R&D approval		
The Chief Investigator or sponsor should inform the local Principal Investigator at each site of the favourable opinion by sending a copy of this letter and the attached form. The research should not commence at any NHS site until approval from the R&D office for the relevant NHS care organisation has been confirmed.		
Statement of compliance		
This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.		
<hr/>		
This Research Ethics Committee is an advisory committee to West Midlands Strategic Health Authority		

West Midlands Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

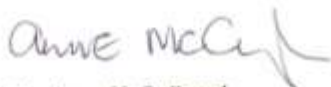
REC reference number:	08/H1208/30	Issue number:	1	Date of issue:	02 October 2008
Chief Investigator:	Dr G I Hackett				
Full title of study:	Clinical and biochemical improvement in Type 2 diabetic parameters in type 2 diabetic men with symptomatic testosterone deficiency syndrome (TDS). A double blind, placebo controlled study of depot testosterone undecanoate (NEBIDO) versus placebo				
<p><i>This study was given a favourable ethical opinion by West Midlands Research Ethics Committee on 22 July 2008. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.</i></p>					
Principal Investigator	Post	Research site	Site assessor	Date of favourable opinion for this site	Notes ⁽¹⁾
Dr Arup Deshpande	GP Principal	Aldergate Medical Practice, Sallers Lane, Tamworth B78 8BH	South Staffordshire Local Research Ethics Committee	02/10/2008	
Dr Nigel Cole	GP Principal	Cloisters Practice, Greenhill Health Centre Church St, Lichfield WS13 8JL	South Staffordshire Local Research Ethics Committee	02/10/2008	
<p>Approved by the Chair on behalf of the REC:</p> <p>  (delete as applicable)  (Name) </p>					

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

08/H1208/30**Please quote this number on all correspondence**

Yours sincerely



Mrs Anne McCullough
Committee Co-ordinator

Email: anne.mccullough@westmidlands.nhs.uk

Enclosure: *Site approval form*

Copy to: *Clinical Trials Unit, MHRA*

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Document 3

National Institute for Health Research (Birmingham and the Black Country Comprehensive Local Research Network), RM&G reference Number 1268.



Dr G I Hackett
Consultant in Urology (Sexual Medicine)
Good Hope Hospital
Holly Cottage Hospital
Fisherwick Road
Lichfield
WS14 9JL

Thursday, 25 June 2009



Birmingham and the Black Country
Comprehensive Local Research Network
Unit 1, West Wing
Institute of Research and Development
Birmingham Research Park
Vincent Drive
Birmingham
B15 2SQ

Tel: 0121 627 2843
Fax: 0121 627 2178

Website: <http://bbc.ukcrn.org.uk>
Email: BBCCLRN@bb.nhs.uk

LETTER OF RESEARCH MANAGEMENT AND GOVERNANCE (RM&G) PERMISSION

Research Management and Governance Permission has been granted by the Consortium RM&G Office on behalf of the Birmingham and the Black Country RM&G Consortium Trusts. The Chief Investigator named in this letter has permission to undertake the following research activity in the NHS Trust(s) identified below.

Chief Investigator Name: Dr G I Hackett

Date of Issue: 25/06/09

Project Title:	Clinical and biochemical improvement in type 2 diabetic parameters in type 2 diabetic men with symptomatic testosterone deficiency syndrome (TD6). A double blind, placebo controlled study of depot testosterone undecanoate (NEBIDO) versus placebo	
Consortium RM&G Ref ID:	1268	
Start/End Dates:	Start Date: 25/06/09	End date: 31/12/2010
Chief Investigator:	Dr G I Hackett	
Chief Investigator Employer:	Self Employed	
Funding & Funding amount:	Bayer plc £325,000	
Sponsor:	Dr G I Hackett	

Trust Registered:
Birmingham East and North Primary Care Trust (BENPCT)

Principal Investigator	Research Site
Dr Robert Flacks	Manor Practice
Dr Peter Ingham	Tudor Medical Practice

Trust Service/Directorate: Primary Care / GP Practices

Thank you for informing the BBC CLRN RM&G Consortium of the above research.

Confirmation of RM&G Permission

On behalf of the BBC CLRN RM&G Consortium, I am please to confirm RM&G Permission has been granted for the Consortium Trust(s) and Research Site(s) as stated above.

Conditions of RM&G Permission

This permission is given provided that you comply with the conditions as set out in the attached. You are advised to study the conditions carefully.

If you require any further assistance, please call the Consortium RM&G Office stating your RM&G Reference Number 1268.

Directors: Professor Robert Stockley, Professor Brendan Delaney
Hosted by: University Hospital Birmingham NHS Foundation Trust



Birmingham and the Black Country Comprehensive Local Research Network is part of the National Institute for Health Research and the UK Clinical Research Network.

We wish you success on completing your research.

Yours Sincerely,



Susie Fisher
CLRN RM&G Operational Manager (Consortium)
BBC CLRN RM&G Consortium

Documents Enclosed:

- (1) RM&G Permission Letter
- (2) Standard Conditions of RM&G Permission for the BBC CLRN RM&G Consortium & RM&G Reporting Form for Research Incidents

Scanned copy of Documents sent to:

Dr G I Hackett - Chief Investigator
Chris Zohari - R&D Lead for BEN PCT

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Document 4

Warwickshire Primary Care Trust (West Midlands (South)
Comprehensive Local Research Network), reference WAR230909.



West Midlands (South) Comprehensive Local Research Network
CLRN Office
Fourth Floor Rotunda (ADA40017)
University Hospitals Coventry & Warwickshire NHS Trust
University Hospital
Clifford Bridge Road
Coventry
CV2 2DX

19th November 2009

Dr Trevor Gooding
Atherstone Surgery
1 Ratcliffe Road
Atherstone
CV9 1EU

Dear Dr Gooding,

***Project Title: Clinical and Biochemical Improvement in Type 2 Diabetic
Parameters Men with Symptomatic Testosterone Deficiency Syndrome (TDS).
A Double Blind, Placebo Controlled Study of Depot Testosterone Undecanoate
(NEBIDO) versus Placebo.***

R&D Ref: WAR230909
REC Ref: 08/H1208/30

I am pleased to inform you that the R&D review of the above project is complete and has been formally approved to be undertaken at Warwickshire Primary Care Trust. Your research activity is now covered by NHS indemnity as set out in HSG (96) 48, and your trial has been entered onto the Trust's database.

The following documents were reviewed:

- **Protocol** 23rd May 2008
- **Patient Information Sheet** 12th July 2008
- **Consent Form** 12th July 2008
- **R&D NRES Application Form** Lock Code: AB/137541/1 Signed 27th May 2008
- **R&D Site Specific Information Form** Lock Code: 3702/64558/6/832/32571/152294 Signed 1st October 2009
- **NRES Approval Letter** Approval letter 5th August 2008
- **MHRA Notice of Acceptance** Approval Letter 9th May 2009
- **International Index of Erectile Function (IIEF)[115] Questionnaire**
- **Hospital Anxiety & Depression Scale – Scoring Sheet**
- **AMS Questionnaire**
- **CV Dr Geoff Hackett**
- **CV Dr Trevor Gooding**

Your responsibilities are set out in the attached agreement, which must be signed and returned to the R&D Office. You should keep a copy for your records.

All research must be managed in accordance with the requirements of the Department of Health's Research Governance Framework (RGF) and to ICH-GCP standards. In order to ensure that research is carried out to these standards, the Trust employs the services of an external monitoring organisation to provide assurance. Your study may be randomly selected for audit at any time, and you must co-operate with the auditors.

The duration of Trust approval extends to the date specified in the NRES application form. Action may be taken to suspend Trust approval if the research is not run in accordance with RGF or ICH-GCP standards, or following recommendations from the auditors. Research must commence within two years of the REC approval date, and within six months of R&D approval.

I wish you well with your project. Please do not hesitate to contact me should you need any guidance or assistance.

Yours sincerely



Luke Chaplin
R&D Facilitator

Enc: PI agreement

Cc: Geoff Hackett, Chief Investigator

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Document 5

Bayer plc (ref: SOP ID: BSP-SOP-040): funding organisation.

Institute of Diabetes for Older People, Beds and Herts Postgraduate Medical School, University of Bedfordshire (ref: SOP ID: BSP-SOP-040).

SOP ID: BSP-SOP-040
Generic non-interventional ISS Agreement Template
Associated Document Date: 2011-Jan-21



CONTRACT FOR THE SUPPORT OF AN INVESTIGATOR INITIATED NON-INTERVENTIONAL STUDY

between

Bayer plc,
Bayer House,
Strawberry Hill,
Newbury,
Berks RG14 1JA

(hereinafter referred to as „BAYER“)

And

Institute of Diabetes for Older People (IDOP)
Beds and Herts Postgraduate Medical School,
Putteridge Bury Campus
Hitchin Rd,
Luton LU2 8LE

(hereinafter referred to as "INSTITUTION")

and

Professor Geoffrey Hackett,
Holly Cottage,
Fisherwick Road,
Lichfield
WS14 9JL

(hereinafter referred to as "PRINCIPAL INVESTIGATOR")

(INSTITUTION and PRINCIPAL INVESTIGATOR hereinafter jointly referred to as "CONTRACT PARTNERS")

(all parties to the Agreement hereinafter jointly or individually referred to as "Parties" or "Party")

Preamble

WHEREAS, CONTRACT PARTNERS are undertaking, on their own initiative and responsibility, the following non-interventional study entitled: **Clinical Audit in Type 2 diabetes and Hypogonadism** (hereinafter referred to as "STUDY");

WHEREAS, CONTRACT PARTNERS have requested BAYER to provide support for the conduct of the STUDY;

WHEREAS, BAYER is interested in increasing its knowledge about Nebido (testosterone undecanoate) (hereinafter referred to as the "BAYER PRODUCT") and has agreed to provide such support under the terms and conditions as defined in this Agreement.

NOW THEREFORE, the Parties agree as follows:

§ 1 – Subject of the Agreement

The subject of the Agreement is the support rendered by BAYER to INSTITUTION for the independent conduct of the STUDY.

CONTRACT PARTNERS are responsible for the initiation, management and financing of the STUDY. This includes but is not limited to all regulatory obligations there may be in connection with the performance of the STUDY. In particular, this also comprises responsibilities as required pursuant to Good Clinical Practice as well as Good Epidemiological Practice, as far as applicable. Such obligations and responsibilities are with CONTRACT PARTNERS entirely.

BAYER will have no role in the planning or conduct of the STUDY other than providing the supportive tasks set forth in this Agreement.

§ 2 – Responsibilities of the CONTRACT PARTNERS for the STUDY conduct

2.1 The STUDY shall be conducted under the responsibility and supervision of the PRINCIPAL INVESTIGATOR.

2.2 CONTRACT PARTNERS declare and represent that

- will conduct the STUDY in accordance with the study outline-information as provided in the Assessment Form dated 12th November 2012 attached hereto as **Appendix 1** (hereinafter referred to as the "Assessment Form"). CONTRACT PARTNERS will generate a protocol based on the information provided in the ISS Assessment Form (hereinafter referred to as the "PROTOCOL"). CONTRACT PARTNERS will conduct the STUDY in accordance with such PROTOCOL. The Assessment Form and the PROTOCOL and any amendments thereto will form an integral part of this Agreement.
- the STUDY will be conducted in accordance with (a) the ethical principles that have their origin in the Declaration of Helsinki, (b) the principles of ICH-GCP Guideline as amended from time to time, and (c) the laws and regulations and codes of practice applicable in the country/countries where the STUDY is performed. Should a participating investigator be suspected of non-compliance therewith, CONTRACT PARTNERS shall take immediate corrective action, which may include termination of such investigator's participation in the STUDY.
- for the conduct of the STUDY will not use the services in any capacity of anyone debarred by the US Food and Drug Administration (FDA) or any other competent authority. Furthermore, CONTRACT PARTNERS represent and warrant that neither INSTITUTION nor its employees, agents or representatives have been debarred by the FDA or any other competent authority, nor that they are currently, to the best of CONTRACT PARTNERS' knowledge, the subject of such a debarment proceeding. During the term of this Agreement, CONTRACT PARTNERS shall promptly notify BAYER should INSTITUTION or any of its employees, agents or representatives become subject of such debarment proceeding.

- any regulatory or legal authorizations necessary for the performance of the STUDY will be obtained prior to the commencement of the STUDY and that the performance of the STUDY fully complies with any and all authorizations.
 - The BAYER PRODUCT supplied by or through BAYER, if any, is exclusively used for the STUDY. The CONTRACT PARTNERS are accountable for the use of the BAYER PRODUCT and must ensure to keep an up to date written record of the BAYER PRODUCT supplied.
- 2.3 CONTRACT PARTNERS shall use their best efforts to commence the STUDY (first patient first visit) within three months after the effective date of this Agreement. BAYER shall have the right to terminate this Agreement by giving written notice to the CONTRACT PARTNERS in case this timeline is not met in accordance with the termination section below.
- 2.4 In case the STUDY is not or not solely performed on the INSTITUTION'S own premises (e.g. in multi-centre studies), CONTRACT PARTNERS are responsible for the involvement of the centers participating in the conduct of the STUDY (participating centers and investigators hereinafter jointly referred to as "PARTICIPATING CENTER/S"), coordination between them as well as the consolidation of the results of the STUDY generated at the PARTICIPATING CENTERS.
- 2.5 If applicable, CONTRACT PARTNERS shall be responsible for the contracting of the PARTICIPATING CENTERS as well as clinical research organizations or other third parties involved to support the STUDY (hereinafter jointly referred to as "CRO"), if any. CONTRACT PARTNERS shall require the PARTICIPATING CENTERS and/or CRO to comply with equal terms as set forth herein, including without limitation regarding confidentiality, publication and rights to results. To ensure this, CONTRACT PARTNERS shall enter into a written agreement with each PARTICIPATING CENTER and/or CRO that (a) contains obligations of confidentiality not less protective of BAYER's CONFIDENTIAL INFORMATION as set forth in Section 8; (b) contains terms requiring such PARTICIPATING CENTER and/or CRO to assign ownership of deliverables to CONTRACT PARTNERS or BAYER in a manner consistent with the terms set forth in Section 7; and (c) contains terms requiring such PARTICIPATING CENTER and/or CRO to comply with applicable regulatory requirements. CONTRACT PARTNERS shall be responsible for ensuring compliance of the PARTICIPATING CENTER and/or CRO with the terms set forth in (a) to (c) above and shall be liable for any breach thereof.
- 2.6 In the event that the PRINCIPAL INVESTIGATOR resigns from his job at the INSTITUTION, INSTITUTION shall provide written notice to BAYER immediately upon gaining knowledge thereof and shall designate a duly qualified replacement. The new principal investigator shall be requested to agree to the terms and conditions of this Agreement in writing. In the event BAYER does not approve of the new principal investigator or such new principal investigator does not agree to the terms of this Agreement in writing, BAYER may terminate this Agreement in accordance with the termination section below.

§ 3 – Support of the STUDY by BAYER

- 3.1 Provision of Financial Support
- 3.1.1 BAYER will support the STUDY with a total amount of **£50,000 (fifty thousand GBP)**.
- 3.1.2 The above amount will be paid to INSTITUTION as follows:
- The first payment: £25,000 (twenty five thousand GBP) upon receipt of a fully executed agreement;
 - The second payment: £20,000 no earlier than January 2014 and after three practices complete data entry;
 - The third and final payment: £5,000 (five thousands GBP) upon receipt of a final study report/publication as described in this contract.
- The first milestone is exclusively meant to cover start-up costs actually incurred by the CONTRACT PARTNERS. CONTRACT PARTNERS agree to provide BAYER with detailed

documentation shortly after the conclusion of the Agreement on how the first milestone payment is or has been used.

As far as the first milestone payment exceeds the costs actually incurred for the start-up of the STUDY, CONTRACT PARTNERS will notify BAYER without delay and either pay back the exceeding amount or set it off against the next milestone payment.

If a milestone has not been fully reached when the Agreement, for whatever reason, terminates, BAYER shall not be obliged to any further milestone payments.

- 3.1.3 BAYER will pay the due support to INSTITUTION within 60 days upon receipt of a proper and undisputed invoice or similar written documentation to the following account of INSTITUTION:

Bank:

Bank code:40-30-32.....

Account owner:University Main Account

Account No.:81276360.....

Reference:RES12154.....

- 3.1.4 All amounts under this Agreement are net of value-added-tax (VAT). If any payments are subject to VAT by law, BAYER will pay the relevant amount subject to the receipt of an invoice which meets the requirements of the competent tax authority. Any other tax with respect to the payments under this Agreement will be borne by the CONTRACT PARTNERS.

- 3.1.5 BAYER shall be entitled to deduct and withhold from the amount payable the tax which BAYER is liable under any provisions of tax law.

- 3.1.6 CONTRACT PARTNERS shall be responsible for the remuneration of the PARTICIPATING CENTRES and/or CRO, if any, with regard to their involvement in the STUDY and CONTRACT PARTNERS agree to indemnify and hold harmless BAYER against any claims for remuneration for their participation in the STUDY.

- 3.1.7 The above agreed-upon financial support of the STUDY is all the financial support granted by BAYER to CONTRACT PARTNERS for the STUDY. If, in the course of the STUDY, the CONTRACT PARTNERS request from BAYER further financial support for the STUDY, CONTRACT PARTNERS will explain the need for such support in writing and will lay out in detail the reasons why the initially agreed-upon payments were insufficient.

3.1.8 Invoicing

Invoices relating to this contract and subsequent amendments must quote our Purchase Order number 2210226212. Invoices which do not display a valid Purchase Order number cannot be processed for payment and will be returned as disputed.

To expedite payment Bayer suggest that you send your invoices electronically. To do this you must first register by sending an e-mail to vendors.uk@bayer.com

Once your registration is confirmed your invoices may be sent in an unzipped PDF format (1 invoice per email) to invoice.bayer.plc@bayer.com. A copy must also be sent to invoices.bayer.plc@bayer.es & local.study.unit@bayerhealthcare.com

You may send a 'hard copy' of your invoice to our Accounts Payable department at
Bayer Plc
C/O Euroservices Bayer S.L.
Department Accounts Payable
PO Box 1078

08080 Barcelona, Spain

A copy of this invoice must also be sent to
Local Study Unit
Bayer plc
Bayer House
Strawberry Hill
Newbury
RG14 1JA

- 3.2 Further support granted by BAYER
BAYER takes on further tasks to support the STUDY solely to the extent and as explicitly set forth in the Responsibility Matrix attached hereto as Appendix 2. Appendix 2 forms an integral part of this Agreement.
- 3.3 CONTRACT PARTNERS will use the support received from BAYER exclusively for the performance of the STUDY.

§ 4 – Pharmacovigilance

- 4.1 CONTRACT PARTNERS are responsible for all pharmacovigilance obligations and safety reporting pursuant to the applicable laws and regulations in the country/countries where the STUDY is performed.
Additionally, CONTRACT PARTNERS shall immediately within 24 hours at the latest, report to BAYER by fax and/or e-mail:
- | | |
|---------------------|---------------------|
| Electronic Mailbox: | phdsduk@bayer.co.uk |
| Telephone: | 01635 563500 |
| Fax: | 01635 563703 |
- Non Safety ISS: all Serious Adverse Reactions with a potential relationship to BAYER product(s);
- any other relevant safety information including but not limited to reports on pregnancy and lactation including their outcome, drug interaction, overdose, drug abuse or misuse, and lack of drug effect (LODE) occurring at any time during the treatment phase; and
 - communication concerning safety related information of a Bayer product including but not limited to:
 - any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees;
 - Non Safety ISS: annual line listing of all Serious Adverse Reactions with a potential relationship to BAYER product(s);
- 4.2 CONTRACT PARTNERS commit to promptly respond to any query from BAYER regarding adverse event documentation.

§ 5 – Audits and Inspections

- 5.1 BAYER retains the right to audit CONTRACT PARTNERS's records and any other documentation and facilities relating to the STUDY at any time during or following the STUDY. CONTRACT PARTNERS agrees to maintain accurate and detailed records of information pertaining to the STUDY and agrees to grant access to BAYER (or its nominees) at INSTITUTION's and any other STUDY related facility upon request. Such audit(s) will require reasonable prior written notice by BAYER. As such audit would potentially include direct

access to STUDY subject data the informed consent obtained from the STUDY subject must cover this eventuality, if feasible.

- 5.2 Should any health authority conduct or give notice of intent to conduct any inspection at any investigation site, or at the site of INSTITUTION, or take any other action with respect to the STUDY, CONTRACT PARTNERS will promptly give BAYER notice thereof, and supply all information pertinent thereto. For inspections at any investigation site, BAYER may support such inspections.

§ 6 – Provision of Data & Reports

- 6.1 In case the PROTOCOL is not yet finalized at the time this Agreement is signed, CONTRACT PARTNERS will send the draft and the final version of the PROTOCOL to BAYER for information.
- 6.2 CONTRACT PARTNERS shall transmit to BAYER within two weeks of knowledge the following information related to the STUDY:
- A copy of the first approval for the conduct of the STUDY from the relevant regulatory authority, including the applicable identifier of the STUDY, if applicable;
 - A copy of the main ethics approval letter within the UK;
 - The actual date of the first patient recruitment;
 - Any significant planned changes to the design and conduct of the STUDY, including protocol amendments. In case BAYER, in its sole discretion, deems that in respect of such changes it does not wish to support the changed STUDY any longer, BAYER has the right to terminate this Agreement in accordance with the termination section set forth below;
 - The actual date of completion of the STUDY (last patient last visit);
 - The actual number of patients recruited in the course of the STUDY.
- 6.3 CONTRACT PARTNERS shall inform BAYER within 24 hours upon gaining knowledge of any issues, positive or negative, raised by the regulatory authorities or ethics committees with regard to the STUDY.
- 6.4 CONTRACT PARTNERS shall inform BAYER of any confirmed case of misconduct of an investigator at any PARTICIPATING CENTRE immediately upon gaining knowledge thereof.
- 6.5 CONTRACT PARTNERS shall report to BAYER at any time upon BAYER's request, at least every quarter, on the state of advancement of the STUDY. CONTRACT PARTNERS shall send BAYER a final written report summarizing any and all results of the STUDY within 6 months upon completion of the STUDY (last patient last visit). This also applies in case the STUDY has been terminated before its originally scheduled end. The following specifics shall apply to such report:
- Summary of Baseline demographic data:
 - Age
 - Duration of diabetes
 - Percentage male /
 - Ethnicity
 - Summary of the following outcomes:
 - HbA1c
 - Total cholesterol
 - HDL cholesterol
 - LDL cholesterol
 - Triglycerides
 - Adverse events
 - BMI

- In addition BAYER would also be interested in the following outcomes if collected as part of routine practice:
 - Systolic blood pressure
 - Hypoglycaemia rates
 - Treatment changes over time (e.g. insulin dose)
 - Resource use (e.g. number of hospitalisations, healthcare visits including telephone consultations)
 - Smoking status
 - Alcohol consumption
 - Comorbid risk factors (e.g. LVH)

§ 7 – Rights to results

- 7.1 As far as not otherwise set forth herein, all data and intellectual property generated in connection with the performance of the STUDY (hereinafter referred to as the "RESULTS") will belong to CONTRACT PARTNERS. BAYER and its AFFILIATES shall have a non-exclusive perpetual, irrevocable, sub-licensable, royalty-free, worldwide right to access, transfer and use, without limitation in any manner in its discretion, the RESULTS.
- "AFFILIATE" in this Agreement shall mean any entity or company which directly or indirectly, through one or more intermediaries, controls, is controlled by or is under common control with a Party.
- 7.2 The intellectual property in any patentable RESULT that relates to the BAYER PRODUCT, or is derived from proprietary information provided in relation to it by or on behalf of BAYER or an AFFILIATE of BAYER, (hereinafter referred to as "INVENTION") will belong to BAYER. CONTRACT PARTNERS ensure that all INVENTIONS will be notified to BAYER in writing without delay. The CONTRACT PARTNERS hereby assign in advance all right, title and interest in any such INVENTION and agree to execute or procure the execution of any document required to vest in BAYER (or its nominee) the full legal and beneficial title in and, at BAYER'S expense, to apply for and to obtain patents to any INVENTION.
- 7.3 Each Party will remain the owner of any proprietary rights or inventions made prior to the commencement of the STUDY. The CONTRACT PARTNERS will inform BAYER prior to the commencement of and during the STUDY of any proprietary rights or inventions owned by INSTITUTION and/or PRINCIPAL INVESTIGATOR (collectively "INSTITUTION IP") if such INSTITUTION IP is related to the use of the RESULTS. In the event and to the extent that the use of the RESULTS requires a license under the INSTITUTION IP, CONTRACT PARTNERS hereby grant BAYER and its AFFILIATES a perpetual, irrevocable, worldwide, sub-licensable, royalty-free non-exclusive right to access, transfer and use, without limitation in any manner and in its sole discretion such INSTITUTION IP as contained in the RESULTS in accordance with the terms of this Agreement.
- CONTRACT PARTNERS will furthermore to the best of their knowledge inform BAYER prior to the commencement of and during the STUDY of any proprietary rights or inventions owned by third Parties if such rights are related to the use of the RESULTS.
- 7.4 Except for, and limited to, the right to use for the conduct of the STUDY, BAYER grants CONTRACT PARTNERS no express or implied intellectual property in the BAYER PRODUCT or in any methods of making or using the BAYER PRODUCT.

§ 8 – Confidentiality

The Parties shall treat all information received by or on behalf of the disclosing Party or any of its AFFILIATES relating to the STUDY or the BAYER PRODUCT and all RESULTS (hereinafter called "CONFIDENTIAL INFORMATION") strictly confidential. The Parties shall use the CONFIDENTIAL INFORMATION only for the purposes of the conduct of the STUDY and shall not disclose such

CONFIDENTIAL INFORMATION to any third Party without the disclosing Party's prior written consent. Such obligations of confidentiality and non-use shall not apply to CONFIDENTIAL INFORMATION which (a) is published in accordance with the terms set forth in section 9 hereof; (b) the receiving Party has the right to use pursuant to the terms of this Agreement; (c) the receiving Party can demonstrate was already in its possession at the time of its disclosure to it; (d) is or becomes public knowledge other than by an act or omission on the part of the receiving Party; (e) is legally acquired by the receiving Party from a third party not bound to the disclosing Party by any express or implied obligation of secrecy; (f) the receiving Party can prove was developed independently by it without reference to or use of the CONFIDENTIAL INFORMATION.

Furthermore the receiving Party may disclose CONFIDENTIAL INFORMATION to the extent that such disclosure is required to comply with law or an enforceable judicial order, provided, however, that the receiving Party shall give reasonable advance notice to the disclosing Party and, at its request, shall cooperate with the disclosing Party to seek a protective order or other appropriate remedy. The receiving Party will use reasonable efforts to secure confidential treatment of any CONFIDENTIAL INFORMATION that will be disclosed.

The obligation of secrecy and non-use provided hereunder shall survive for a period of ten (10) years upon early termination or expiration of this Agreement.

§ 9 – Publication

- 9.1 BAYER acknowledges the interest of CONTRACT PARTNERS to publish the findings of the STUDY and is supportive towards such activity.
- 9.2 To ensure against inadvertent disclosure of unprotected INVENTIONS and CONFIDENTIAL INFORMATION, the CONTRACT PARTNERS agree to comply with the following terms on publication:
- 9.2.1 CONTRACT PARTNERS shall provide to BAYER any proposed publication or oral presentation relating to the STUDY or the BAYER PRODUCT or the RESULTS (hereinafter called "PUBLICATION") at least sixty (60) days prior to the intended submission or presentation of the PUBLICATION in order to allow BAYER to review it. BAYER has the right to terminate this Agreement in accordance with clause 14.2 if this declaration of support is not included.
- If BAYER does not notify CONTRACT PARTNERS within sixty (60) days of BAYER's receipt of the intended PUBLICATION, CONTRACT PARTNERS shall be free to publish.
- 9.2.2 BAYER may recommend any changes to the PUBLICATION it reasonably believes are necessary for scientific purposes. CONTRACT PARTNERS agree that the implementation of such recommended changes shall not be unreasonably refused.
- 9.2.3 If BAYER informs CONTRACT PARTNERS that such PUBLICATION could be expected to have an adverse effect on the confidentiality of any of the CONFIDENTIAL INFORMATION, CONTRACT PARTNERS shall prevent the PUBLICATION, unless the CONFIDENTIAL INFORMATION can be deleted from the PUBLICATION without detriment effect on the scientific correctness of the PUBLICATION.
- 9.2.4 If the PUBLICATION could in BAYER'S view have an adverse effect on the ability to obtain patent protection for any INVENTION, BAYER may request a delay of the PUBLICATION for a reasonable period of time in order to permit the preparation and filing of any desired patent application by or on behalf of BAYER, such period, however, not to exceed 60 days.
- 9.2.5 CONTRACT PARTNERS shall include a statement in any PUBLICATION that creation of the data was supported in part by BAYER and shall refer to BAYER's support whenever they write or speak in public about a matter that is the subject of this Agreement. BAYER has the right to terminate this Agreement in accordance with clause 13.2 if this declaration of support is not included.
- 9.3 The obligations set forth in Section 9.2 hereof shall survive for a period of ten (10) years upon early termination or expiration of this Agreement.

§ 10 – Results Posting

As far as CONTRACT PARTNERS are not already obliged by law to post the results of the STUDY, BAYER encourages CONTRACT PARTNERS to post the results of the STUDY.

In the latter case, BAYER encourages CONTRACT PARTNERS to post the STUDY within twelve months of completion of the STUDY as defined in the PROTOCOL. In case of a premature termination of the STUDY, results should be posted within twelve months after the date of the last observation of the last patient who remains enrolled in the STUDY or after the date the decision has been made to terminate the STUDY, whichever happens first. Has the STUDY been prematurely terminated due to safety reasons, information describing reasons for terminating the STUDY, especially noting any discernable threat (not previously disclosed on the label) to patient health should be posted within 30 days after termination of the STUDY.

The summary of the posting should conform to ICH E3 principles. The summary of the posting should also reflect not only the generic and brand names of the BAYER product(s) involved, but also a listing of all aliases under which the BAYER product(s) may be known at the time of posting, including serial numbers, code names and chemical descriptions.

CONTRACT PARTNERS shall give BAYER the opportunity to review the posting prior to its publications and grant BAYER the opportunity to comment.

§ 11 – Liability, Indemnification, Insurance

- 11.1 The Parties acknowledge and agree that BAYER shall not be held responsible or liable for the planning, performance and/or conduct of the STUDY or study-related obligations or claims arising from or in relation thereto, except to the extent that BAYER has specifically assumed the responsibility of certain STUDY related functions under this Agreement and its Appendices. If BAYER has provided BAYER PRODUCT to CONTRACT PARTNERS for the purpose of the STUDY, BAYER shall be responsible for any deviations from the BAYER PRODUCT'S agreed upon specifications.
- 11.2 CONTRACT PARTNERS represent and warrant that they will hold adequate insurance as required by the local requirements. BAYER is not responsible and/or liable for the insurance premium, nor for any other costs or claims in relation to the insurance.
- 11.3 During and after the period of this Agreement CONTRACT PARTNERS will defend, indemnify and hold harmless BAYER, its AFFILIATES and their respective directors, officers, employees, agents, successors, and assigns from and against any and all liabilities, claims, suits, damages, costs and expenses, including reasonable legal fees, (hereinafter "Loss") resulting from the conduct of the STUDY, which result from the performance of the STUDY save to the extent that such Loss is caused by the negligent or willful breach of contract or statutory duties by BAYER.
- 11.4 BAYER shall defend, indemnify and hold harmless INSTITUTION and its directors, officers, employees, agents, successors, and assigns from and against any and all Loss resulting from (i) the fact that the supplied BAYER PRODUCT does not meet the agreed specification/quality, or (ii) the breach of any covenant, representation or warranty made by BAYER under this Agreement; or (iii) any negligent act or omission, breach of contract or statutory duty on the part of its servants, agents or employees, in all cases excluding liability for consequential losses or loss of business.

§ 12 – Term of the Agreement

This Agreement is effective upon signature of the Parties hereunder and ends upon the later of (a) completion of the STUDY, or (b) receipt by BAYER of all data and reports pursuant to Section 6 above from the CONTRACT PARTNERS, or (c) the payment of the last installment by BAYER.

§ 13 – Termination, Termination effects

- 13.1 Notwithstanding any other termination right set forth herein, BAYER reserves the right to terminate this Agreement at any time by written notice to the other Parties.
- 13.2 Either Party may terminate this Agreement by giving written notice to the other:
- if that other commits any material or repeated breach of this Agreement which, if capable of remedy, has not been remedied within 30 days after receipt of a written notice identifying the breach and requiring it to be remedied; or
 - if that other becomes bankrupt; goes into liquidation; suffers a meeting of its creditors; has any sort of trustee, receiver, administrator, administrative receiver or similar officer appointed in respect of any of its assets; is unable to pay its debts; ceases or threatens to cease to carry on business; suffers any judgment or execution which remains unsatisfied for 10 days; or anything similar or analogous to any of the foregoing in any relevant jurisdiction; or
 - if the STUDY is not approved by the relevant ethics committee/s and/or the relevant regulatory authorities or such approval is fully or partially revoked, if applicable.
- 13.3 If BAYER terminates this Agreement pursuant to the termination right set forth in Section 2.3, the CONTRACT PARTNERS will (a) pay back to BAYER any payment received under this Agreement, and (b) return any BAYER PRODUCT supplied by BAYER under this Agreement. The Parties agree that BAYER will not lose the termination right pursuant to 2.3 due to delayed assertion, especially if BAYER had inquired regularly about the progress of the STUDY before.
- 13.4 Other than in cases of termination for breach of this Agreement by CONTRACT PARTNERS or PRINCIPAL INVESTIGATOR, BAYER shall make all payments due hereunder which have accrued up to the date such termination notice is received. Should INSTITUTION have received higher payments than the payments due according to the work already performed, INSTITUTION shall reimburse the balance to BAYER. In cases of termination for breach of this Agreement by CONTRACT PARTNERS or PRINCIPAL INVESTIGATOR, no further payments shall be due.
- 13.5 In case of any early termination CONTRACT PARTNERS will provide a report of the previously gained knowledge and RESULTS. BAYER PRODUCT and other materials, documentation or CONFIDENTIAL INFORMATION made available by or on behalf of BAYER or any of its AFFILIATES are to be returned to BAYER or, on BAYER's request, destroyed according to the instructions to be provided by BAYER after completion or termination of the STUDY, such destruction to be confirmed in writing to BAYER, with the exception of documentation which must be retained with the CONTRACT PARTNERS to fulfil the STUDY documentation retention requirements of Good Clinical Practice.
- 13.6 The rights and obligations of BAYER and the CONTRACT PARTNERS, which by intent or meaning have validity beyond such termination (including without limitation rights with respect to ownership, patents, confidentiality, liability and indemnification) shall survive the early termination or expiration of this Agreement.

§ 14 – Miscellaneous

- 14.1 The Parties acknowledge that this Agreement is not conditioned on any pre-existing or future business relationship between BAYER and the CONTRACT PARTNERS. It is also not conditioned on any business or other decisions the CONTRACT PARTNERS have made or may make relating to BAYER or its products or any AFFILIATES and their products and BAYER neither seeks nor expects the CONTRACT PARTNERS or those with whom they practice to prescribe, supply, administer, recommend, buy or sell any BAYER product as a result of this Agreement.
- 14.2 Each Party to this Agreement shall act as an independent contractor and shall not be construed for any purpose as the partner, agent, employee or representative to the other Party.
- 14.3 BAYER shall have the right to assign this Agreement to any of its AFFILIATES upon prior written notice to the CONTRACT PARTNERS. Notwithstanding the foregoing, neither Party

- shall assign its rights or duties under this Agreement to another without prior written consent of the other Party.
- 14.4 The invalidity of a particular provision of this Agreement shall not affect the validity of the remaining provisions. The Parties shall replace the invalid provision with a valid provision that comes closest to effectuating the intent of the Parties at the time of the Agreement's execution.
- 14.5 The waiver or acquiescence by any Party or the failure of any Party to claim a breach of any provision of this Agreement will not be deemed to constitute a waiver with respect to any subsequent breach of any provisions hereof.
- 14.6 Amendments and extensions to this Agreement shall not be effective unless in written form and signed by all Parties.
- 14.7 This Agreement is subject to the laws of England and Wales. Each party hereby submits to the exclusive jurisdiction of the English courts.



date 08.02.2013

Dr Owen Collins
on behalf of Bayer Plc



date 12/2/13

SIGNATURE

INSTITUTION: Professor Alan Sinclair



date 10/02/2013

SIGNATURE

PRINCIPAL INVESTIGATOR: Professor Geoffrey Hackett

Appendix 1 Assessment Form
Appendix 2 Responsibility Matrix