Health Research Authority
London - Chelsea Research Ethics Committee
Research Ethics Committee (REC) Bristol Centre
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Lewins Mead
Bristol
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Telephone: 0207 1048055

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

19 May 2017

Dr Isabel Syndikus
Consultant Clinical Oncologist
Clatterbridge Cancer Centre
Bebbington
Wirral
Merseyside
CH63 4JY

Dear Dr Syndikus

Study title:	**A phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost**
REC reference:	**17/LO/0731**
Protocol number:	**ICR-CTSU/2016/10062**
IRAS project ID:	**219463**

The Research Ethics Committee reviewed the above application at the meeting held on 08 May 2017. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Decision: Favourable Opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

The Chair welcomed you and Ms Hassan to the meeting.

- **<u>Social or scientific value; scientific design and conduct of the study</u>**

The Committee stated that it found the Participant Information Sheet very good for such a complex study. The Committee asked for some clarification as it noted in one place C2 was described as involving IMRT and in other place it was described as involving HDR.

You suggested that was correct and that it didn't matter how the boost treatment was delivered, it would have the same end effect. Not all sites in the UK had HDR as it was expensive and had resource implications. You told the Committee that The Royal Marsden Foundation Trust used IMRT whilst Leeds used HDR. You commented that many centres might only be able to deliver two arms. In your experience the outlook after one year was similar for both delivery methods. You indicated that there were some co-morbidities that precluded HDR from being chosen.

The Committee asked why the applicants planned to use 24 sites?

You suggested that you needed to prove it was feasible to recruit to each of the treatment arms as part of the trial funding milestones.

The Committee questioned what percentage of the sites could offer all the treatment arms?

You indicated that only 9 of the sites had HDR. You said that they would look at the patient's MRI and characteristics and decide which arms they might be suitable for.

The Committee sought clarification on whether participants would only get the PIS for the treatment arms they could be offered at their site.

You confirmed the situation, remarking that it made no sense to offer participants information about study arms that the site could not deliver.

The Committee accepted these responses.

- **Informed consent process and the adequacy and completeness of participant information**

The Committee noted the studies interest in toxicity and asked the applicants what the side effects were and the study team would tell the participant about them.

You suggested you had been sceptical at first. After treating 150 patients with IMT boost, you had observed it being well tolerated after five years. You had completed a pilot in 2010 and then applied for funding for an applied randomised controlled trial in 2012. The RCT had not been funded due to a lack of experience. Since then you had observed no significant increase in toxicity which was also supported by trials in the Netherlands.

The Committee sought clarification on whether the participants would have a conversation about the possibility of their cancer spreading before they got the Participant Information Sheet (PIS), as spread was described as a risk on the PIS.

You stated that the staging scans would show any risk of spread and they would have already had conversations with the clinical team about possible spread before being approached to participate in the study. You suggested that almost 10 years' experience had shown that the risk categories may not be accurate and that sometimes patients with good risk scores got bad outcomes. You indicated that the translational aspects needed more research and that was why they were proposing a separate sub study requiring consent to access tumour block samples and perform analysis in the future to identify who might do well and also who might need the boost.

The Committee accepted this response.

The researchers left the meeting.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Covering letter on headed paper [PIVOTALboost Ethics Cover letter]		10 April 2017
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [ICR Clinical Trial Insurance 2016_2017]	n/a	15 July 2016
GP/consultant information sheets or letters [PIVOTALboost GP letter]	1.0	28 March 2017
IRAS Application Form [IRAS_Form_10042017]		10 April 2017
IRAS Application Form XML file [IRAS_Form_10042017]		10 April 2017
IRAS Checklist XML [Checklist_10042017]		10 April 2017
Letter from funder [PIVOTALboost Funder approval]	1	08 August 2016
Letter from sponsor [PIVOTALboost Sponsor permission for submission]	1	30 March 2017
Non-validated questionnaire [PIVOTALboost baseline QL booklet]	1.0	28 March 2017
Non-validated questionnaire [PIVOTALboost IPSS booklet]	1.0	28 March 2017
Non-validated questionnaire [PIVOTALboost Week 18 QL booklet]	1.0	28 March 2017

Non-validated questionnaire [PIVOTALboost QL fup booklet]	1.0	28 March 2017
Other [PIVOTALboost QL baseline letter]	1.0	28 March 2017
Other [PIVOTALboost QL booklet cover letter]	1.0	28 March 2017
Other [PIVOTALboost QL booklet reminder letter]	1.0	28 March 2017
Other [PIVOTALboost QL off study form]	1.0	28 March 2017
Participant consent form [PIVOTALboost Consent Form]	1	28 March 2017
Participant information sheet (PIS) [PIVOTALboost PIS AvsB]	1	28 March 2017
Participant information sheet (PIS) [PIVOTALboost PIS ABC1D1 HDR]	1	28 March 2017
Participant information sheet (PIS) [PIVOTALboost PIS ABC2D2 HDR]	1	28 March 2017
Participant information sheet (PIS) [PIVOTALboost PIS ABC2D2 IMRT]	1	28 March 2017
Referee's report or other scientific critique report [PIVOTALboost CRUK peer review]	n/a	06 July 2016
Research protocol or project proposal [PIVOTALboost protocol]	1	27 March 2017
Summary CV for Chief Investigator (CI) [CV Isabel Syndikus]	1	03 April 2017

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

No declarations of interest were made.

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

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

17/LO/0731	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

P.P.
Dr Michael Schachter
Chair

E-mail: nrescommittee.london-chelsea@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Ms Clare Cruickshank, The Institute of Cancer Research*
Ms Julie Curtis, The Institute of Cancer Research/The Royal Marsden NHS Trust

London - Chelsea Research Ethics Committee

Attendance at Committee meeting on 08 May 2017

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Roger A'Hern	Medical Statistician	Yes	
Dr Judy Allfrey	Retired Civil Servant	Yes	
Dr. Sonya Babu-Narayan	Clinical Senior Lecturer and Consultant Cardiologist	Yes	
Mrs Christine Gratus	Retired Brand & Communication Consultant	Yes	
Ms Karen Lipworth	Lead Medical Writer	Yes	
Mr Serge Miodragovic	Ophthalmology Clinical Research Coordinator	Yes	
Mrs Patricia Pank	Retired University Lecturer	Yes	
Mrs Paula Rogers	Cardiology Research Nurse	Yes	
Ms Cate Savidge	CT Scanning Superintendent	Yes	
Dr Michael Schachter	Clinical Pharmacologist	Yes	Meeting Chair
Dr Mary Taj	Consultant Paediatric Oncologist	No	
Miss Isobel Vass	Magistrate	Yes	
Ms Mary Watkinson	Teacher	Yes	
Mr Fraser Wilson	Retired Civil Servant	No	

Also in attendance:

Name	*Position (or reason for attending)*
Dr Sarah Graves	REC Manager