Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Anthony Gordon
UK Chief Investigator
Imperial College London
11th floor Intensive Care Unit
Charing Cross Hospital
Fulham Palace Road
w6 8rf

Email: hra.approval@nhs.net

23 July 2018

Dear Professor Gordon

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia**
IRAS project ID:	**237150**
EudraCT number:	**2015-002340-14**
REC reference:	**18/LO/0660**
Sponsor	**University Medical Centre Utrecht**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales*, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

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

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Dr Farah Al-Beidh

Tel: 02033110211

Email: farah.al-beidh@icnarc.org

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **237150**. Please quote this on all correspondence.

Yours sincerely

Juliana Araujo
Assessor
Email: hra.approval@nhs.net

Copy to: *Sponsor Representative: Dr Farah Al-Beidh, ICNARC*
Lead NHS R&D Office Representative: Mrs Gisela M Pereira Barreto, Imperial College London Healthcare Trust

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template		
Contract/Study Agreement template		
Contract/Study Agreement template		20 March 2018
Contract/Study Agreement template		20 March 2018
Contract/Study Agreement template [REMAP-CAP clinical Trial: Summary of changes to the model agreement]		
Copies of advertisement materials for research participants	VERSION 1	21 December 2017
Copies of advertisement materials for research participants	VERSION 1	21 December 2017
Covering letter on headed paper [REC covering letter from CI]		20 March 2018
Covering letter on headed paper [REMAP CAP Substantial amendment AM01 18.06.2018 Cover letter si]		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		16 January 2018
HRA Schedule of Events [HRA Schedule of Events Validated]	Version 1	07 February 2018
HRA Statement of Activities [HRA Statement of Actives Validated]	Version 1	19 March 2018
IRAS Application Form [IRAS_Form_23032018]		23 March 2018
Letter from funder [Evidence of funding document]		23 May 2018
Letter from sponsor		13 March 2018
Notice of Substantial Amendment (CTIMP) [REMAP CAP Substantial amend AM01 IRAS 2018.07.04]	1	21 June 2018
Other [CTAAcceptanceofAmendedRequest]		01 June 2018
Other [CTANoticeofNon-Acceptance]		11 May 2018
Other [REMAP-CAP European Region-Specific Appendix V2 20171214]	2	14 December 2017
Other [REMAP-CAP European Region-Specific Appendix V2.1 20180524_clean]	2.1	24 May 2018
Other [REMAP-CAP European Region-Specific Appendix V2.1 20180524_clean]	2.1	24 May 2018
Other [REMAP-CAP European Region-Specific Appendix V2.1 20180524_TC]	2.1	24 May 2018
Other [REMAP-CAP European Region-Specific Appendix]	version 2	14 December 2017
Other [REMAP-CAP Macrolide Duration Domain-Specific Appendix]	version 2	12 December 2017
Other [REMAP-CAP Protocol Amendment Summary]	version 2	13 December 2017
Other [REMAP-CAP Statistical Analysis Appendix]	version 2	12 December 2017
Other [REMAP-CAP Synopsis]	version 2	15 January 2018
Other [REMAP-CAP Antibiotic Domain-Specific Appendix]	version 2	12 December 2017
Other [REMAP-CAP Corticosteroid Domain-Specific	version 2	12 December

Appendix]		2017
Other [Levofloaxacin SPC]	version 1	14 February 2018
Other [Moxifloxacin SPC]	version 1	14 February 2018
Other [Pip-tazo SPC]	version 1	14 February 2018
Other [Azithromycin SPC]	version 1	14 February 2018
Other [Ceftaroline SPC]	version 1	14 February 2018
Other [Ceftriaxone SPC]	version 1	14 February 2018
Other [Clarithromycin SPC]	version 1	14 February 2018
Other [Co_amoxi_clav SPC]	version 1	14 February 2018
Participant information sheet (PIS) [UK REMAP-CAP Information for participants and Consent Form]	2.0	19 April 2018
Participant information sheet (PIS) [UK REMAP-CAP Retrospective Information for participants and Consent Form]	2.0	19 April 2018
Participant information sheet (PIS) [UK REMAP-CAP Information for PerLR and Consent Form]	2.0	19 April 2018
Participant information sheet (PIS) [ProLR ICF]	version 1	07 March 2018
Research protocol or project proposal [Core Protocol]	version 2	12 December 2017
Response to Additional Conditions Met		30 April 2018
Summary CV for Chief Investigator (CI) [Prof Gordon CV]		01 February 2018
Summary of product characteristics (SmPC) [Hydrocortisone SMPC]		14 February 2018
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Protocol summary]	version 2	15 January 2018
18-LO-0660 237150 Application_valid_requires_SSA 2018.04.04.pdf		04 April 2018
18-LO-0660 237150 Favourable_opinion_at_first_review-2018.04.26.pdf		26 April 2018
Acknowledgement_for_documentation_received_following_a_FO_FIFO_30.04.30.pdf		30 April 2018
18 Lo 0660 - Letter of valid amendment - 06.07.18.pdf		06 July 2018
237150, 18/LO/0660, SE39 (Approval) REC Confirmation of FO for NOSA .eml		19 July 2018

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards?	Comments
1.1	IRAS application completed correctly	Yes	Multiple NHS organisations will be involved in this study. The following organisations have confirmed participation: Blackpool Teaching Hospitals NHS Foundation Trust Bradford Teaching Hospitals NHS Foundation Trust Central Manchester University Hospitals NHS Foundation Trust Derby Teaching Hospitals NHS Foundation Trust Imperial College Healthcare NHS Trust Leeds Teaching Hospitals NHS Trust Morriston Hospital North Bristol NHS Trust Nottingham University Hospitals NHS Trust Poole Hospital NHS Foundation Trust Royal Cornwall Hospitals NHS Trust St Helens and Knowsley Teaching Hospitals NHS Trust Taunton and Somerset NHS

Section	Assessment Criteria	Compliant with Standards?	Comments
			Foundation Trust University Hospitals Coventry and Warwickshire NHS Trust
2.1	Participant information/consent documents and consent process	Yes	Consent will be sought for access to access data held by Case MixProgramme run by the CNARC or by NHS Digital. Consent will also be sought for sharing participants' name, postcode, date of birth and NHS number with NHS digital for data linkage purposes.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The Statement of Activities and the Schedule of Events were submitted. The sponsor proposes the use of a modified model agreement. A Summary of Changes document was submitted highlighting the changes to be made to the following sections: • Study Governance • Obligations of the parties • Liabilities and Indemnity • Publication • Intellectual Property Rights (IPR) • Financial and supplies arrangements • Suspension or Early Termination • Dispute resolution
4.2	Insurance/indemnity arrangements assessed	Yes	No comments
4.3	Financial arrangements assessed	Yes	The sponsor secured from funding from the University Medical Center Utrecht..

Section	Assessment Criteria	Compliant with Standards?	Comments
			Evidence of funding was provided on the PREPARE Amendment 3 – Amendment Justification document, dated 23/05/2018. Schedule 1 of the Statement of Activities outlines the funds and resources to be allocated to the research sites.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Yes	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	NHS Research Ethics Committee favourable opinion was confirmed by the London - Surrey Borders Research Ethics Committee on 30 April 2018.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Yes	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a multi-site study undertaking the same research activities; there is therefore one research type. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
As per the Statement of Activities provided a Principal Investigator will be in place at each participating NHS organisation. No assistance to identify potential Principal Investigators is required from the participating NHS organisations. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
It is unlikely that letters of access or honorary research contracts will be applicable, except where local network staff employed by another Trust (or University) are involved (and then it is likely that arrangements are already in place). Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in A18 or A19 of the IRAS form, would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.