Standard Operating Procedure for Obtaining Health Research Authority Approval, Ethics Approval and Clinical Trial Authorisation for Clinical Trials of Investigational Medicinal Products

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JBRU/SPON/S29/01	12/03/11	To amalgamate the Guidance for Trial approvals Version 4 dated 07.07.2009 with the CTC SOP for permission and approvals for Clinical trials into an SOP for JBRU	Anne Marie Downey
JRO/SPON/S29/02	12/03/14	Add references to MHRA notification scheme, update references to GTAC, remove international procedures, clarify site specific approvals	Gemma Jones & Anne Marie Downey
JRO/SPON/S29/03	22/07/16	Integrating the HRA process and CESP systems for clinical trial applications. Decommissioning of CSP system	Nimrita Verma & Shriram Velamuri

ACRONYMS:	
ATIMPS	Advanced Therapy Medicinal Product
ARSAC	Administration of Radioactive Substances Advisory Committee
CA	Competent Authority
CESP	Common European Submission Platform
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
COA	Compliance Oversight Advisor
CSP	The NIHR Coordinated System for gaining NHS Permission
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Products
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMO	Genetically Modified Organism
GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
HSC	Health and Social Care
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomized Controlled Trial Number
JRO	Joint Research Office
MHRA	Medicines and Healthcare Products Regulatory Agency
NHS	National Health Service
NIHR CSPRN	National Institute for Health Research Coordinated System for gaining NHS Permission Clinical Research Network
NIMP	Non Investigational Medicinal Product
PI	Principal Investigator
PAF	Portfolio Adoption Form
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RM(ATIMPS)	Regulatory Manager for ATIMPS
RM(P)	Regulatory Manager (Pharmaceuticals)
SI	Statutory Instrument
SOP	Standard Operating Procedure
SRA	Sponsor Regulatory Advisor
TMF	Trial Master File
UCL	University College London

SOP for Obtaining REC, CTA and Site Specific Approvals for CTIMPs

1. PURPOSE

This Standard Operating Procedure (SOP) describes the process for obtaining Health Research Authority (HRA), Competent Authority and Site Specific Approvals for Clinical Trials of Investigational Products (CTIMPS) that are sponsored by University College London (UCL) and managed within the Joint Research Office (JRO).

2. JOINT RESEARCH OFFICE POLICY

All SOPs produced by the JRO must be used in conjunction with local NHS Trust and UCL policies and procedures.

The JRO acts as the representative of the Sponsor and will be the official name used on all SOPs.

3. BACKGROUND

All SOPs are written in accordance with applicable GCP requirements as outlined in Directives 2001/20/EC and 2005/20/EC (in the UK, these Directives were transposed into UK law by SI 2004/1031, SI 2006/1928) and subsequent amendments and when applicable Regulation 536/2014 and subsequent relevant SIs. Where applicable it incorporates elements of ICH GCP tripartite guidelines (E6).

According to Directive 2001/20/EC ('The Clinical Trials Directive'), it is the Sponsors' responsibility to ensure that clinical trials of investigational medicinal products in human subjects have a clinical trial authorisation (CTA) from the competent authority (MHRA in the UK) and approval from Health Research Authority in place, prior to the start of the study.

As per the 'Risk-adapted approaches to the management of clinical trials of investigational medicinal products' a **Notification to the MHRA** may be made in place of a full CTA application. Notifications can only be made for 'Type A' trials. These are trials involving medicinal products licensed in any EU Member State if:

- they relate to the licensed range of indications, dosage and form
- or, they involve off-label use (such as in paediatrics and oncology, etc.) if this off-label use is established practice and supported by **sufficient published evidence** and/or guidelines.

HRA will review applications for research within the NHS including CTIMPs.

GTAC is responsible for the oversight of clinical trials of Gene therapy medicinal products as defined in Part IV **of Directive 2003/63/EC** (amending Directive 2001/83/EC). GTAC is the UK national REC for gene therapy clinical research according to regulation 14(5) of The Medicines for Human Use (Clinical Trials) Regulations 2004.

All research that involves NHS patients or resources must gain the HRA approval.

Depending on the type of trial, approval from other bodies may also be required such as

- Ministry of Justice (National Offender Management Service)
- NHS / HSC research offices
- NRES/ NHS / HSC Research Ethics Committees
- National Information Governance Board (NIGB)
- Social Care Research Ethics Committee
- Trials with genetically modified organisms: Health and Safety Executive (Contained use of genetically modified organisms (GMOs)

- Deliberate release activities: Department for Environment, Food and Rural Affairs (Defra)
- Radioactive substances: Administration of Radioactive Substances Advisory Committee (ARSAC). If research involves exposures to radioactive substances in addition to normal clinical care, an ARSAC (Administration of Radioactive Substances Advisory Committee) research certificate is required at each site.
- Trials involving medical devices: MHRA Clinical trials for medical devices section.

IRAS is a single system for applying for the permissions and approvals for health and social care / community care research in the UK including clinical trials. It enables researchers to enter information about their project once instead of duplicating information in separate application forms. It applies filters to ensure that the data collected and collated is appropriate to the type of trial, and consequently the permissions and approvals required.

4. SCOPE OF THIS SOP

All clinical trials sponsored by UCL and managed by the JRO.

This SOP outlines the procedure for obtaining HRA, CA and Site specific approvals in the UK.

Where another unit (e.g. CTU/ CRO) is delegated to manage HRA, CA and site specific approvals, the specific roles and responsibilities will be outlined in an agreement between the parties. Applicable parts of this SOP will apply if it is agreed that the JRO is responsible for oversight of HRA, CA or site specific approval processes.

This SOP applies to the trial with sites in England. Management of non-England sites will have to be done in conjunction with HRA, the review boards of the respective countries, and the local R&D.

Management of non UK sites is delegated in an agreement to appropriate organisations (e.g. CTU/CRO) that the JRO has assessed as suitable for the management of non-UK sites. Section 6.8 outlines JRO responsibilities for international sites.

The procedures for obtaining other types of approvals which may also be required fall outside the scope of this SOP.

5. RESPONSIBLE PERSONNEL

The SRA/ RM (ATIMPS) together with the Chief Investigator (CI) are responsible for ensuring that appropriate ethical and regulatory approvals are obtained prior to initiating a trial.

The CI is responsible for drafting the relevant applications.

The SRA/ RM (ATIMPS)/ RM(P) is responsible for the review and approval of the contents of the applications.

The CI and PI where applicable are responsible for submitting the documents to HRA.

The SRA/ RM (ATIMPS) is responsible for submitting the CA application.

6. PROCEDURE

The Three key stages of setting up clinical research trial are:

1. Regulatory and Portfolio Submissions

2. Other Submission

3. Site Setup. This process will also be applicable for trials where UCL is the Legal Representative.

Stage 1: Regulatory and Portfolio Submissions

A. HRA Submission

	Procedure	Responsibility
6.1 IRAS application form	**IRAS application form** Complete the IRAS form (the IRAS form is a combined REC and R& D form) Transfer the Form* to the SRA / RM (ATIMPS) for review and approval. *Transfer the form to the sponsor's IRAS account for this purpose by selecting the button '**Transfer'** on the Navigation Page of IRAS, and entering the following email address: CTIMPs@ucl.ac.uk. Alternatively a pdf copy can be emailed.	CI
6.2 Associated Documents	ATIMPs Complete the combined IRAS form and upload all generic documents** specified in the combined checklist of the IRAS application form. NB Patient specific documents (Information Sheet, Consent form, and GP Letters) must have the IRAS ID on them. *(Refer to the appendix of HRA Submission pack checklist*)	CI
6.3	**Application Review** The SRA/ RM (ATIMPS) will review the IRAS form and supporting documents and will provide comments. MHRA form (Part B) is reviewed by the Regulatory Manager-Pharmaceuticals, the information from this section is populated in the IRAS form. Sections 6.3- 6. may be repeated until final versions are agreed between the CI and the SRA/ RM (ATIMPS)	SRA/ RM (ATIMPS)
6.4	Finalise the IRAS application form and transfer back to CI.	SRA/ RM (ATIMPS)
6.5	CI to lock and sign form and transfer back to CTIMPs@ucl.ac.uk	CI
6.6	Complete **Sponsor authorisation** of the locked IRAS form and return to the CI	SRA/RM (ATIMPS)
6.7	IRAS application to be made through Central Booking Service and submitted to HRA	CI

	(further guidance on the Central Booking Service- refer to the HRA website)	
6.8	File a signed copy of the signed IRAS form and supporting documents in the TMF and forward copies to the SRA/ RM (ATIMPS).	CI
Portfolio Application		
6.9	To submit an application for adoption, question 5b in the IRAS project filter "Do you want your application to be processed through the NIHR Coordinated System for gaining NHS Permission?" should be answered 'Yes'. Complete **CSP Application Form** generated in IRAS and submit to the lead CRN as per the instructions.https://www.crn.nihr.ac.uk/can-help/funders-academics/nihrcrn-portfolio/	CI

	HRA Assessment/ Response	
6.11	HRA issues outcome of the Initial Assessment via letter to CI. CI to forward Initial assessment letter to Sponsor.	CI
6.12	If possible, the CI should attend the REC meeting at which the relevant REC will consider their application. The application will be assessed and discussed at the REC meeting and the applicant will be sent a letter informing them of: • Favourable opinion with standard conditions • Favourable opinion with standard and additional conditions • Provisional opinion with request for further information, clarification or revision • Provisional opinion pending consultation with a referee – a written request for information may be made following receipt of the referee's advice • Unfavourable opinion Assessment, response and timelines are set out in the NRES SOPs. Inform with the SRA/ RM (ATIMPS) of the opinion. Address all the conditions and remarks ***in liaison with the SRA/ RM (ATIMPS)*** and submit response to the REC for final opinion. Ensure all documentation submitted to the REC and all correspondence received from the REC are forwarded to the SRA/ RM (ATIMPS). File copies of these documents in the TMF.	CI
6.13	HRA Final Approval HRA will issue final approval, once all approvals are in place. Forward the approval to the Sponsor.	CI

B. MHRA submission and approvals

It is recommended that applications are made using the IRAS online application form which can be accessed at www.myresearchproject.org.uk. Application forms to the CA must be made via CESP, but specifics on this application will not be covered in this SOP.

Section No.	Procedure	Responsibility
6.14.1	Complete the CTA application in IRAS Transfer the Form* to the SRA/ RM (ATIMPS) for review and approval. *Transfer the form to the sponsor's IRAS account for this purpose by selecting the button '**Transfer'** on the Navigation Page of IRAS, and entering the following email address: CTIMPs@ucl.ac.uk. Alternatively a pdf copy can be sent by email.	CI
6.14.2	**Supporting documents** CTA applications and Notifications to the MHRA require submission of specific supporting documentation alongside a completed application form as per the MHRA website. Draft/ obtain the required supporting documents in liaison with the SRA/ RM (ATIMPS) and RM (P). Selected supporting documents will be identified as per Sponsor's SOP S24 Standard Operating Procedure for Sourcing Investigational Medicinal Product for UCL Sponsored Trial The IMP label template will be prepared as per the Sponsor's SOP 09 IMP labelling*. The Investigator's Brochure will be prepared as per the Sponsor's SOP 03 for creating and maintaining an IB where applicable*. Forward all supporting documents to the SRA/ RM (ATIMPS) for review and approval.	CI *where applicable SRA/ RM (ATIMPS)/ RM (P)
6.14.3	Ensure the SRA/ RM (ATIMPS) and RM (P) have reviewed the CTA application form and supporting documents.	SRA/ RM (ATIMPS) / RM (P)
***Sections 6.12.1- 6.12.3 may be repeated until final versions are agreed between the CI and the SRA/ RM (ATIMPS)/ RM (P)*		
6.14.4	Once approved, the CI will submit the form via IRAS and transfer or send pdf submitted form to the SRA/ RM (ATIMPS) for signatures and authorisation on behalf of the sponsor.	CI/SRA/ RM (ATIMPS)
6.14.5	Pay the applicable MHRA fee. Instructions on how to pay the fee can be found on the MHRA website. Send proof of payment to the SRA/ RM (ATIMPS).	CI

6.14.6	Complete authorisation on behalf of the sponsor, format and submit the CTA application or Notification as per MHRA requirements on the MHRA website. All submission to MHRA must be done through the CESP systems. Forward relevant signed paper copies of the application form and supporting documents to the CI. Retain copies in the Sponsor file.	SRA/ RM (ATIMPS)
6.14.7	**MHRA Assessment/ Response** Forward the MHRA acknowledgement of a valid application to the CI on receipt and retain a copy for the Sponsor file. If the submission is not valid then a new application will need to be submitted with missing elements. **For Notification trials only** The notification will be acknowledged by the MHRA with a letter to say that the trial may go ahead after 14 days from receipt of notification, if the MHRA has not raised any objections. *Forward the MHRA acknowledgement of a valid application to the CI on receipt and retain a copy for the Sponsor file.* For these trials therefore the acknowledgement letter will act as the authorisation. If the MHRA raises objections to the notification, then the submission will be assessed as for a standard request for authorization. When the CTA application has been assessed by the MHRA the applicant will be sent a letter informing them of: • Acceptance of the request for a clinical trial authorisation OR • Acceptance of the request for a clinical trial authorisation subject to conditions, OR • Grounds for non-acceptance of the request for a clinical trial authorisation. Forward the response letter to the CI once received. MHRA will send a copy of this letter to HRA. If conditions or remarks are listed address all the conditions and remarks ***in liaison with the CI and RM (P)*** and submit an amended request to the MHRA. An amended request for a clinical trial authorisation to the MHRA must be made within the timelines set out in SI 2004 1031, unless otherwise agreed with the MHRA. On receipt forward the Acceptance/ Grounds for non acceptance of the request to the CI and retain a copy for the Sponsor file. Ensure that all conditions/remarks on the CTA letter are addressed and **all related documentation to evidence that conditions/remarks have been met retained in the TMF and sponsor file.**	SRA/ RM (ATIMPS)/ RM (P)

6.14.8	**Withdrawals** Unexpected events or additional information may require the JRO to withdraw a request for authorisation before the CA has reached its decision on authorisation*. The SRA/ RM (ATIMPS) should inform the CA that they wish to withdraw the application by following the instructions on the MHRA website. To resubmit the application it must be identified in as a resubmission in the cover letter (resubmission letter) and in the dedicated field of the clinical trial application form. The initial EudraCT number must be used with a letter after the number sequence A for the first resubmission, B for the second etc. * It is not possible to withdraw an application once grounds for non-acceptance have been issued.	SRA/ RM (ATIMPS)

C. Other Submissions (Gene therapy, ARSAC)

For Gene therapy and other approvals, follow the usual procedure of submissions in IRAS. If your application is for REC approval for a gene therapy trial you must apply to the Gene Therapy Advisory Committee.

Preliminary Research Application (PRA)

For research involving administration of radioactive materials, a Preliminary Research Application (PRA) must be completed and submitted to the Administration of Radioactive Substance Advisory Committee (ARSAC). The fully signed PRA must be emailed along with the Patient Information Sheet (PIS) to the ARSAC support unit. The PRA should be submitted at the same time as the regulatory submission (REC and MHRA). If there are no comments raised, then ARSAC will issue an ARSAC approval.

Once the ARSAC approval is secured, study sites can apply for site specific ARSAC approval. Further information can be obtained from the ARSAC website.
NB: HRA will not issue an HRA approval for the study, until ARSAC approves the study.

Stage 3: Site Setup

6.15 NHS sites

The Sponsor to send the Initial assessment letter from HRA (along with local Information pack) to the site team, who will confirm the sites's capability and capacity. Following the confirmation, the site and CI team to exchange contracts and then site can be initiated and activated.

6.15.1	Upon receiving the Initial Assessment letter, CI to email Local Information Pack (LIP) + HRA Initial assessment letter to the Local R and D and Site team.	CI/SRA/RM (ATIMPs)
6.15.2	Confirmation of capacity and capability for conducting the study	Site team+ Local R and D
6.15.3	Send the Final HRA approval to the local R and D and Site team.	CI
6.15.4	Contract signed off (fully executed site agreements in place)	SRA/RM (ATIMPs)
6.15.5	Schedule a SIV and Site activation (no site specific site approval will be issued)	SRA/RM (ATIMPs)

Follow the pathway in Appendix 1

6.16 For NHS Sites outside England

HRA shares applications information with appropriate review boards in Wales, Scotland and Ireland. The local site team does the governance checks and completes the site specific information (SSIFs) and then issues the R and D approval. At this stage the CI is responsible for getting the signatures on the agreements and then the site initiation visit can be planned.

6.16.1	Send the local information pack and HRA initial assessment to local R and D and Site team.	CI
6.16.2	Completion of site specific information (SSIF)	Site team
6.16.3	Local governance checks	Site R and D
6.16.4	Send the Final HRA approval to the Local R and D team and site team	CI
6.16.5	Site R and D Approval	Site R and D
6.16.6	Contracts signatures.	CI/ Site R and D

6.17 Non-NHS sites (e.g. University or Private practice)

Site Specific Information Forms (SSIF) completed in IRAS and required documentation for Site Specific Assessment for non-NHS sites will be submitted to the REC responsible for reviewing the trial as a whole. The CI in liaison with the local PI (where applicable) will be responsible for the application and will ensure the correct version of the SSIF applicable to non-NHS sites is selected.

Where possible SSA applications will be submitted to the REC on confirmation that the main application is valid, SSA(s) will be undertaken at the same time as the main ethical review. The outcome of the SSA(s) will then be included in the notification of ethical opinion given by the REC.

6.18 Non-NHS sites in Phase I trials

Applications will be made as above for non-NHS sites.
Where the research site/unit holds Standard and Supplementary Accreditation from the MHRA, SSA will be carried out by the main REC in parallel with the ethical review of the full application.

Where the research site / unit are not accredited the REC may approach the local REC and ask for their advice on the issue.

7. REFERENCES

The Medicines for Human Use (Clinical Trials) Regulations 2004
http://www.legislation.gov.uk/uksi/2004/1031/contents/made

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006
http://www.legislation.gov.uk/uksi/2006/1928/made

The Clinical Trials Directive (2001/20/EC)
http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.
http://ec.europa.eu/health/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf

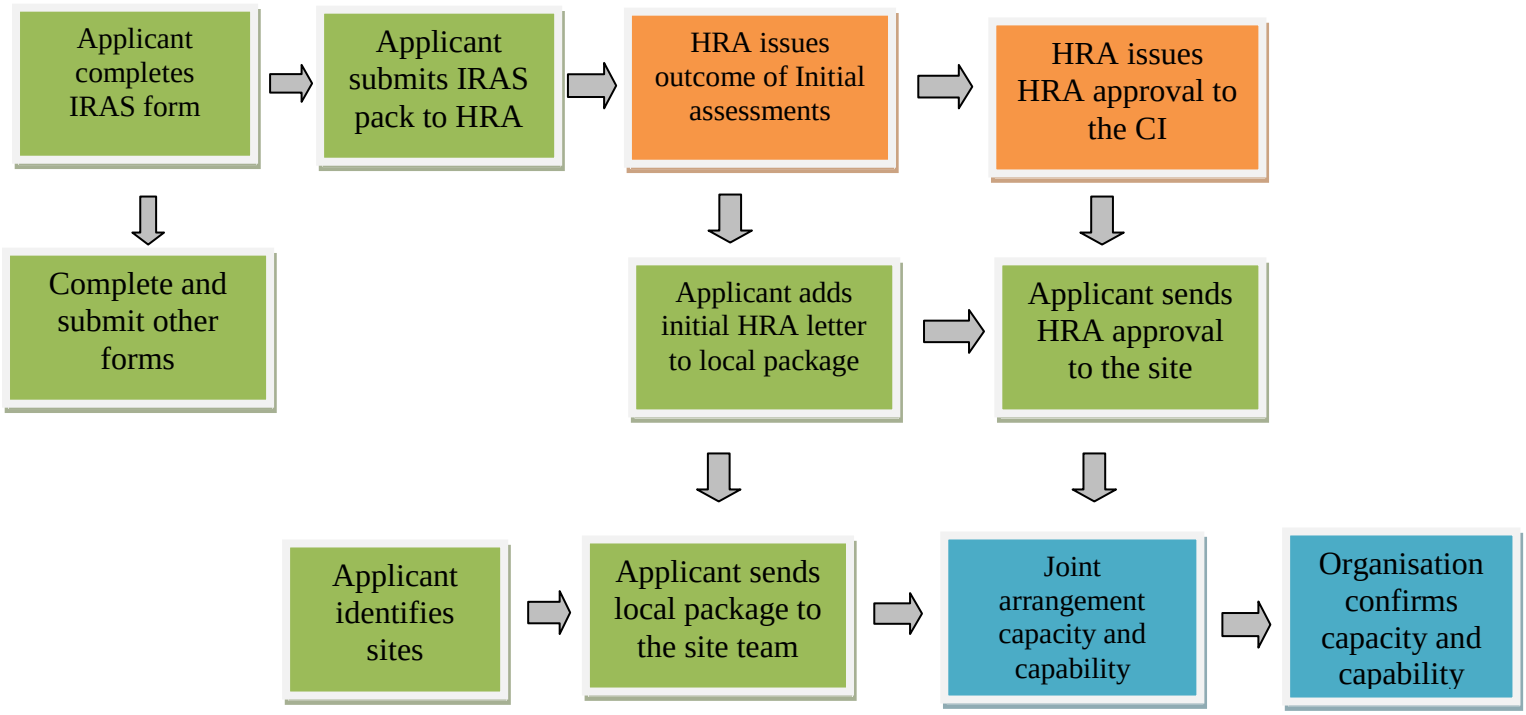
Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of a substantial amendment and declaration of the end of the trial, Revision 2 October 2005
http://eudract.emea.europa.eu/docs/Detailed%20guidance%20CTA.pdf

JRO SOPS and Working document templates:
http://www.ucl.ac.uk/jro/standingoperatingprocedures

Health Research Authority (HRA)
http://www.hra.nhs.uk/

8. APPENDICES

Appendix 1: Overall HRA approval pathway



9. TEMPLATES/LOGS ASSOCIATED TO THIS SOP

1	JRO SPON S07 Standard Operating Procedure for granting UCL sponsorship for Clinical Trials of Investigational Medicinal Products (CTIMPs)
2	JRO_SPON_S09: Standard Operating Procedure for Investigational Medicinal Product Labelling
3	JRO SPON S28: SOP for Insuring all Clinical Studies Sponsored or managed by UCL
4	JRO SOP S03 Standard Operating Procedure for creating and maintaining an Investigator's Brochure (IB) for UCL Developed Products
5	JRO SOP S24 Standard Operating Procedure for Sourcing Investigational Medicinal Product for UCL Sponsored Trial
6	SOP training log (Section 12 of SOP), http://www.ucl.ac.uk/joint-rd-unit/clinical_trials_unit/SOPs
7	Individual Staff SOP and courses log, http://www.ucl.ac.uk/joint-rd-unit/clinical_trials_unit/SOPs
8	Process map on setting up a CTIMP with UCL JRO

Resources

For guidance on using IRAS, please refer to the following link:
https://www.myresearchproject.org.uk/ELearning/IRAS_E_learning.htm

For guidance on HRA, please refer to the following link:
http://www.hra.nhs.uk/

For additional information on completing REC applications, go to:
http://www.hra.nhs.uk/resources/For additional information on completing applications to the MHRA, go to:
http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/index.htm

CLRNs go to: http://www.crncc.nihr.ac.uk/index/clinical/csp.html.

Please refer to the following link for review timelines:

http://www.hra.nhs.uk/resources/after-you-apply/knowledgebase-nhs-rec-review-outcomes/nres_sops_v5-1_2012-03-14-2/

http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Applyingforaclinicaltrialauthorisation/Generalinformation/#l5

10. SOP DISSEMINATION AND TRAINING

SOPs will be distributed to the concerned staff. Staff concerned by the SOP will sign the SOP training log (12. SOP TRAINING LOG) which is part of each SOP. The training for this version of the SOP will constitute of the person reading the SOP and being provided with the opportunity to ask specific questions to the author of the SOP.

SOPs relevant to "JRO staff and investigators" or investigators only will be provided to the investigators at the time of the trial initiation. The investigator will sign section 12 of the SOP, the "SOP training log".

The SOPs and relevant templates and logs will be available on the JRO website shortly after having been released.

11. SIGNATURE PAGE

Author and Job Title:	Nimrita Verma, Sponsor Regulatory Advisor Shriram Velamuri, Sponsor Regulatory Advisor
Signatures:	
Date:	22/06/16
Authorised by: **Name and Job Title**	Helen Cadiou, Head of QA
Signature:	
Date:	22/06/16

12. SOP TRAINING LOG

	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	I confirm that I understand & agree to work to this SOP **SIGNATURE**	**Name of Trainer (**if training required)	**Signature**	**Date**
1							
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	I confirm that I understand & agree to work to this SOP **SIGNATURE**	**Name of Trainer (**if training required)	**Signature**	**Date**
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	Name of Staff (Capital letters)	**Job Title:** **Department:**	**Training Date**	I confirm that I understand & agree to work to this SOP **SIGNATURE**	**Name of Trainer (**if training required)	**Signature**	**Date**
15							
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