## Title: ICRF Application Standard Operating Procedure

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| Related SOPs and Policies: | ICRF-POL02 Operational Policy<br>ICRF-OR05 Induction SOP |

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## Document version numbering

| Version | Date | Updated by | Reason for change |
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| 1 | Jan 2015 | Karen Mosley | New SOP (information previously included in the Application Policy and PRB guidance) |
| 2 | March 2015 | Karen Mosley | Minor revisions to reflect changes to PRB process |
| 2.1 | May 2015 | Karen Mosley | Minor revisions to reflect changes to PRB approval process |
| 2.2 | Dec 2016 | Karen Mosley | Minor revisions to reflect changes to PRB approval process |
| 3 | Feb 18 | Karen Mosley | Minor revisions to reflect changes to PRB approval process and CRF name |

## 1.0 Background

The NIHR Imperial CRF (ICRF) supports a broad range of clinical research studies involving both patients and healthy volunteers. The ICRF Protocol Review Board (PRB) reviews all studies applying to use the ICRF to ensure that only those studies that are in line with the overall strategy and objectives of the ICRF, i.e. early phase clinical trials and experimental medicine studies are approved.

## 2.0 Purpose

The purpose of this SOP is to describe the processes surrounding application to the ICRF PRB from investigators wishing to run their study in the ICRF, other PRB responsibilities, and procedures relating to booking participants.

## 3.0 Scope

All applications to the ICRF PRB.

## 4.0 Responsibilities

### 4.1 Principal Investigator (PI)

The PI is responsible for the conduct of the study in the CRF. They are responsible for ensuring that all information included in the PRB application is valid so that the PRB decision is based on the correct information. The PI is also responsible for ensuring that all staff working on the study, once approved, have the required training.

### 4.2 PRB members

The PRB are responsible for reviewing, approving or rejecting all new studies submitted to the ICRF, and for providing continuous oversight of studies once initiated.

### 4.3 ICRF General Manager

The ICRF General Manager is responsible for acting as the main point of contact for all new studies. They are responsible for receiving, recording and distributing all study documentation prior to the PRB meeting, updating the post-PRB documents and conveying the outcome of the PRB meeting to the applicants.

### 4.4 ICRF Lead Nurse

The ICRF Lead Nurse is responsible for approving all study visits

### 4.5 ICRF Management Team

The ICRF Management Team is responsible for ensuring that the PRB receive all information requiring their review e.g. serious breaches. Team also referred to as the PRB sub-committee for final approval of studies

### 4.6 ICRF Administrator

The ICRF Administrators are responsible for booking all subject visits once the study has been approved.

### 4.7 ICRF PA

The ICRF PA will be responsible for creating the PRB agenda and inviting researchers to attend the meeting. If the ICRF PA is unavailable the General Manager may delegate another member of the ICRF staff.

## 5.0 Glossary

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| ICRF | NIHR Imperial Clinical Research Facility |
| PRB / PIPRB | Protocol Review Board / Phase I Protocol Review Board |
| CRAMP | Clinical Risk Assessment and Management Plan |
| CTIMP | Clinical Trial of an Investigational Medicinal Product (drug) |
| FIH | First in Human CTIMP study i.e. first use of a drug in human volunteers |
| ICRF Management Team | Team consisting of the Head of Clinical Studies, Lead Nurse and General Manager. |
| PRB Sub-committee | Name used for ICRF Management Team when undertaking final PRB review of studies |
| ICRF GM | ICRF General Manager |
| ICRF PA | CRF personal assistant and administrator |

## 6.0 Procedure

### 6.1 PRB procedures

#### 6.1.1 PRB meetings schedule

There are two types of PRB meeting: standard (PRB; all studies other than Phase I CTIMP) and Phase I (PIPRB; Phase I CTIMPs only).

The standard meetings are held twice monthly, on the second and fourth Thursday of the month. Phase I meetings are held on the fourth Thursday of the month. If no studies are submitted the meeting may be cancelled.

#### 6.1.2 Application documents

Current ICRF Users or new researchers will apply to the standard PRB by submitting a copy of the PRB application form, protocol and PI CV. A Clinical Risk Assessment and Management Plan (CRAMP) must be submitted for all CTIMP and CT-Device studies. If the study is Phase I, they will also submit a copy of the Investigators Brochure. This must be sent to the ICRF General Manager (ICRF GM) at least one week prior to the PRB meeting.

The ICRF GM will create a new study folder on the ICRF shared drive (electronic study folder), save the submitted documents to the relevant sub-folders, and enter the study onto the Research Database. The key details and documents will then be circulated to the core PRB/PIPRB, and ad hoc members as required, at least 3 working days prior to the meeting. The ICRF PA will invite the study team to the meeting and will create the agenda.

#### 6.1.3 PRB/PIPRB review

The PRB/PIPRB will review the documents prior to the meeting with the following considerations:

- To prioritise studies in line with the overall strategy and objectives of the ICRF i.e. early phase clinical trials and experimental medicine studies
- To offer scientific advice to Investigators where appropriate
- To consider resource implications and approve their use
- To review and revise the submitted documents to ensure that studies are safe for the subjects involved
- To establish if studies can be effectively implemented and delivered time efficiently

- To advise on the type and duration of medical cover for first and subsequent administrations of an IMP
- Where appropriate, to seek expert opinion from leaders in the specific field of the study being reviewed
- To review and approve treatment regimens
- To determine whether the PI/researchers have the appropriate experience/knowledge to conduct a CTIMP study
- For First-In-Human (FIH) trials, PIPRB members with expertise/qualifications in Clinical Pharmacology, Pre-Clinical Toxicology and Medical Statistics, may recalculate the starting dose, subject to review of the sponsor experience.

#### 6.1.4 Phase I/FIH Study Team

The PI will provide details of their qualifications and clinical research experience. The PIPRB will assess each investigator's background and training to determine whether or not they are suitable to act as PI for a Phase I / FIH study.

For FIH studies:

- The PI's previous experience of FIH studies and clinical pharmacology will be reviewed to determine whether the PI is able to review pre-clinical data, assess the pharmacology and subsequent aspects such as the proposed starting dose, dose escalation proposal/stopping criteria etc. They will thus be able to ensure that they have all the relevant information from the sponsor and be able to interpret it before dosing subjects.

The PIPRB may approve a PI for a non-FIH study who does not fulfil the above criteria but who is known to the committee and considered to be a sufficiently experienced clinical researcher.

If the PI does not meet the requirements for a FIH study, the PIPRB may approve the PI subject to the following conditions:

- The study does not involve a high risk compound that requires approval from the Expert Advisory Group (EAG) to the Committee on Human Medicines (CHM)
- A named Expert Advisor is assigned to support the PI if considered necessary based on the review. Advisors will have formal clinical pharmacology training and/or be a senior clinical researcher with experience of conducting Phase I or FIH studies and personal experience as a PI on FIH studies.
- Advisors will provide supervision to the novice PI through e.g. scheduled meetings, oversight of dosing decisions and regular contact throughout the lifecycle of the study. The name of the Advisor and specific requirements will be detailed in the CRAMP.

#### 6.1.5 PRB meeting

- The study team will attend the meeting where possible to give a brief overview, outline their ICRF requirements, and answer any questions. Attendance is compulsory for phase I studies. Once the study team have left the room the PRB will discuss any issues raised, and reach a decision as to whether the study should be approved, deferred or rejected. A CRAMP may be requested for non-CTIMP studies with potential risks
- **Approved to Enter Green Light Process**. Study will initially be granted conditional approval. The study will enter the green light period and will be approved once all conditions have been met, and all necessary study-specific requirements are in place. Approval for a period of 12 months to

commence from the date of the PRB sub-committee meeting at which the study was granted full approval (see 6.2 notification of outcome).

- **Deferred**. The committee is unable to make a decision from the information submitted. Additional information will be requested and/or the investigator invited to attend a subsequent PRB meeting to discuss the project further. If a study is deferred awaiting further information, and the PRB committee agrees, the study may be approved by Chair's action in consultation with the Board Committee.
- **Rejected**. The study is not approved to go ahead in the ICRF. The reason(s) for non-acceptance will be notified. The study may go ahead elsewhere in the Trust in line with standard R&D and Research Ethics approvals.

### 6.2 Notification of outcome

**Conditional Approval:** After the PRB, the ICRF GM or delegate will amend and update the application form to reflect all changes required as an outcome of PRB review. Key outstanding requirements will be detailed in the PRB comments section and the relevant meeting minutes added. The application form will be saved to the electronic study folder on the shared drive and marked as 'post-PRB draft'. The PI will be sent an email informing them of the committee's decision within 5 working days. The PI must sign and return a copy of the post-PRB application form to demonstrate their agreement with these changes, and provide evidence that all conditions have been met. The post PRB application form will be countersigned by the Chair or delegate (a member of the PRB sub-committee), scanned, and saved to the shared drive.

**Approval**: The PI must inform the PRB sub-committee (ICRF Management Team) of the planned first patient first visit date at least three working days prior to the proposed date. The sub-committee will review all outstanding actions. If these have been met the PRB approval letter will be issued and the study may start. If not the PI will have to resolve these issues before approval is granted. Until final approval has been issued, participant bookings may not be made.

**Deferred Approval:** The PI will be sent an email informing them of the committee's decision within 5 working days. This will detail the reasons for deferral. Once the PI has addressed these issues the study may be resubmitted to the PRB

**Rejected:** The PI will be sent an email informing them of the committee's decision within 5 working days with the reasons for rejection detailed.

#### 6.2.1 Appeals

The applicants have the right to appeal the decision. Initially the applicants should put their concerns in writing to the ICRF Director. The ICRF Director will consider the appeal. If the ICRF Director accepts the grounds for appeal, it will be re-presented to the PRB. The PRB will then decide whether to approve or reject the study

#### 6.2.2 Amendments and changes

The PRB must review all CTIMP substantial amendments. The amendment details will be submitted by the PI, the PI's delegate or the ICRF study contact. Wherever possible this should be prior to or at the same time as ethics/HRA/regulatory submission (as applicable). The PRB will consider whether they accept the planned changes. If accepted the PI will be notified by email by the ICRF GM or delegate on behalf of the PRB. Once the amendment has full approval a copy of the amendment checklist should be submitted to the PRB sub-committee for reference. Any change to the risk assessment will be indicated on the checklist and a revised CRAMP should be completed to include these changes before the amendment is implemented.

For any significant changes to the PRB approved conditions for any study, not relating to a CTIMP substantial amendment, (e.g. request for nursing support) a Change to PRB Agreement Form must be completed and submitted to the PRB for approval.

#### 6.2.3 SUSARs, SAEs, clinical incidents and protocol violations

SUSARs, significant SAEs, clinical incidents or other significant breaches will be reported to the PRB by the ICRF Management Team. This will comprise an overview of the incident, the implications of the events, any action points required to minimise the risk of a similar occurrence within the ICRF, a review of relevant policies/procedures and whether these have addressed any issues identified. The PRB will discuss whether any further action is required. If so the member who raised the issue will notify the involved parties post meeting.

If the incident requires immediate action, a member of the ICRF Management Team must be contacted. In most cases they will identify the action to be taken without referral to the PRB, but if the action would have a significant impact on the study, e.g. stopping recruitment, the PRB Chair (or delegate if unavailable) must be contacted to ratify the decision.

#### 6.2.4 Annual Renewals

All studies must be reviewed on an annual basis. A renewal request will be sent to the PI/researcher two months before the due date. This must be completed in full and returned before the end date of the original approval. The renewal request will be sent to the PRB for review and if successful a renewal letter will be issued. The study team's training records will be reviewed at this point and renewals will only be issued if these are all in date. For CTIMPs, ICRF will check the records and will only issue a renewal if these are up to date. For non-CTIMPs the PI will take on this responsibility.

#### 6.2.5 Study Completion

An ICRF End of Study Notification form must be submitted to the ICRF once the study has ended in the ICRF. This will be notified to the PRB. Investigators are expected to acknowledge the CRF in publications, and inform the ICRF of all publications that relate to work facilitated by the ICRF, either physically or intellectually.

#### 6.2.6 Removal of CRF access

The PRB has the right to revoke a PI's (or any member of their study team's) access and use of the ICRF if it is felt that this is an appropriate course of action. This decision would not be taken without exhausting other options and would be fully documented.

### 6.3 Study Initiation and Green Light Process

Studies may not start until the following have been completed

- Researchers requiring access to the ICRF have completed ICRF induction (see SOP ICRF-OR05)
- Copies of all study and training documents have been received and evidence of ICRF SOP reading obtained. Substantive or honorary contracts with the Trust must be in place
- Clear contact details for all the research team and representatives of the sponsor e.g. monitoring team, emergency and out of hours contact details have been received
- Signed copy of the Post-PRB application form has been received
- The Clinical Risk Assessment and Management Plan has been agreed and signed off for all CTIMP/CT-device studies, or where the PRB decide one is required

- All PRB-identified actions have been satisfactorily addressed and all study-specific requirements are in place including a lab manual where applicable

Each PRB approved study will be allocated to an ICRF named person who works as a Study Contact. Researchers will liaise with their Study Contact to ensure that the above conditions are met and to keep the ICRF informed of study progress. A study initiation visit (SIV) must be arranged for all CTIMP studies prior to study start. The SIV cannot go ahead until the signed CRAMP has been received, as this will be used as a training document

Once the above criteria have been met, the PRB sub-committee (at least two of the ICRF Senior Management Team) will review the study and agree whether it may start. This decision will take up to three working days. Once agreed the final approval letter will be sent, the study will receive a green tick on CRF Manager and the study team may begin booking

### 6.4 Booking requests

Requests for bookings will only be accepted if they are presented to the ICRF either electronically (via NHS email only), or by hand on the current version of the booking form. The forms are available on the ICRF website or on request. Forms will only be accepted if they are completed in full. Failure to provide appropriate information may mean that the booking cannot be processed and forms will be returned. Forms must be received at least 2 working days in advance of the visit.

Upon receipt of the request form, reception will record the date and time of receipt on the form and enter the visit onto CRF Manager. Requests are managed on a first-come-first-served basis. The request will be reviewed to confirm that an appropriate bed space and the appropriate skill mix of staff is available to facilitate the admission. If it is not possible to accommodate the visit, the ICRF User will be contacted and another date/time arranged. ICRF staff cannot be guaranteed for all visits. If staff are not available the ICRF User will be informed.

If the volunteer is not registered with the Trust, the Administrator will arrange registration so the volunteer will have a hospital number and medical notes.

Research volunteers requiring transport to the Trust will require this to be booked either by the research team or, if agreed at study set up, via the study's taxi account. Unless otherwise stated any travel expenses will be charged to the study's expenditure code.

## 7.0 Related Documents and References:

### 7.1 ICRF Documents

- ICRF-POL02 Operational Policy
- ICRF-OR05 Induction SOP

### 7.2 Relevant Forms

- ICRF-OR09 Form 1 PRB Application Form
- ICRF-OR09 Form 3 Clinical Risk Assessment and Management Plan (including guidance notes)
- ICRF-OR09 Form 4 Phase 1 Additional Information Form
- ICRF-OR09 Form 5 PRB Change Form
- ICRF-OR09 Form 6 Booking request single visit
- ICRF-OR09 Form 7 Booking request multiple visits
- ICRF-OR05 Form 1 Amendment checklist