Medicines & Healthcare products
Regulatory Agency

MHRA

PHASE I
ACCREDITATION SCHEME

Guidance Document

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Introduction

A proposal for the Medicines and Healthcare products Regulatory Agency (MHRA) Phase I accreditation scheme was published in November 2007. The scheme was fully implemented[1] in April 2008 and has been revised in October 2013, October 2015 and March 2021. This document serves to provide further guidance on aspects of the current scheme's requirements contained in Appendix 1 and the expectations of the MHRA when inspecting and awarding accreditation to Phase I units.

Reference should also be made to Chapter 12 of the MHRA Good Clinical Practice Guide[2].

The accreditation scheme remains voluntary and there is currently no intention to mandate the scheme in the UK.

Note: Where a sponsor selects a Phase I accredited unit, it will be because they have decided to have their trial conducted at a Phase I unit that surpasses basic regulatory requirements, as the accreditation scheme is concerned with the quality systems and operation of the unit. The sponsor must remember that it is the unit (i.e. the unit procedures and systems) that is inspected and receives accreditation. However some aspects relevant to the accreditation scheme are the responsibility of the sponsor (e.g. the collection, analysis and quality of the preclinical data) or may be retained by the sponsor (e.g. collection and analysis data for the decisions to continue the Phase I trial/dose escalate). Therefore, where the sponsor requires their trial(s) to be carried out in compliance with the accreditation scheme, the sponsor also needs to adhere to any requirements specified by the accredited unit and any activities they retain should be performed to a similar standard to that required by the accredited units procedures.

Clinical Trial Design and Set-up

Safety information availability (Appendix 1, point 1)

There should be formal agreements with the sponsor which clearly detail responsibilities for notifying the Principal Investigator (PI) immediately if/when the sponsor becomes aware of new safety/toxicology data. This aspect also needs to be considered in the following circumstances:

- where the Phase I unit sub-contracts another unit, the agreements should cover onward communication of safety information from the sponsor
- where the sponsor is not the owner of the Investigational Medicinal Product (IMP), for example, a non-commercial sponsor for a clinical trial with an unlicensed IMP

When reviewing safety information, the PI should be aware of the quality of the data, for example, that the data contained in the investigator's brochure (IB) is final data and that there is sufficient data for the PI to calculate the starting dose for a first in human (FIH) clinical trial and any dose increments (these calculation may form part of the risk assessment). If the PI requires additional safety information from the sponsor, this should be requested and provided.

Risk assessment/risk management/mitigation (Appendix 1, point 2)

Medical emergencies are rare in Phase I trials, however, as many of the products are unlicensed the potential risks of the particular IMP must be assessed and steps taken to mitigate these risks in accordance with the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'

(EMEA/CHMP/SWP/28367/07)[3]. In addition to this European Medicines Agency (EMA) guideline and the MHRA GCP guide[2], there is some useful information on the concept of general risk assessment available in the risk adaptive approach section of the MHRA Good Clinical Practice (GCP) forum.

Risk assessment is a continuous process throughout the life cycle of the trial. It begins as early as the proposal stage and will potentially change as the study is set-up and recruiting. The risk assessment can influence the development of the protocol, with its drafting and revision based on mitigations to identified risks. It is appreciated that most Phase I units have always performed risk assessments and contingency planning. However, for accreditation this should be a formalised process which is clearly documented. The resultant document, sometimes referred to a risk management plan or a contingency plan (here, the term 'risk assessment' will be used throughout), will be a living document and therefore should be reviewed regularly (e.g. when there are changes to the protocol or unit practices; or at regular intervals depending on the duration of the trial).

It should also be clear what data and documents have been used to perform the risk assessment (for example, the protocol, IB). The version and status of these documents (i.e. draft or final data) should be included as these documents may be updated throughout the course of the trial) and could potentially impact on and require a change to the risk assessment.

The procedure detailing the risk assessment should include the following aspects:

- who will perform and provide input into the risk assessment
- how the risk assessment will be documented
- who will review and approve the risk assessment
- circulation to relevant staff
- retention of the risk assessment
- maintenance of the risk assessment i.e. continual review and updating it as required.
- who has responsibility for ensuring compliance with the risk assessment, and for documentation of that compliance

When performing the risk assessment, units should ensure that all aspects of the trial and the associated risks are considered, that appropriate actions are put in place to mitigate those risks and that both the identified risks and actions are documented. (Note: It is expected that the risk assessment by the unit is done independently of any sponsor assessment and decisions that may already be in the protocol). Aspects that should be reviewed during the risk assessment process include (but are not limited to):

- whether the clinical trial requires Expert Advisory Group (EAG) review (the unit should make their own assessment and retain any discussions or possible disagreements with the sponsor)
- if it is a FIH trial and if so, confirmation/re-calculation of the starting dose and dose increments
- any dose escalation procedures
- relevance of study design (i.e. population, administration, assessments etc.)
- IMP (i.e. relevance of safety/toxicology information, mode of action, target, pharmacokinetic (PK)/pharmacodynamic (PD) information, etc.)
- any specific rescue medications/antidotes, supportive emergency facilities and staff, specific emergency scenarios etc

- extra staffing/resources (i.e. identifying specific training, expertise, facilities or specific location/wards in unit for conduct of certain trials etc.)

In addition, over the past decade, phase I trials have become much more complex, and a number of objectives that were previously the subject of separate trials are increasingly being integrated into one protocol. A single protocol may now include a single ascending dose (SAD), multiple ascending dose (MAD) and a patient cohort. Therefore, the risk assessment encompassing the FIH aspect of the first cohort of the protocol may be different from the risk assessment for the subsequent cohorts.

See below for some examples of risks and associated mitigation activities:

- due to the nature of the IMP, the risk assessment, protocol or MHRA/Research Ethics Committee (REC) condition of approval may require a medical doctor to be on the unit for a specific number of hours post dosing; evidence that this was done should be documented and retained (e.g. in the trial file or as per local practice requirements)
- the risk assessment may identify that as the unit has areas that are not routinely observed (e.g. single bedrooms), the dosing of FIH trials and subsequent post dose monitoring should be in an observed area for a specified time period (e.g. for 24h close observation after dosing in an observed ward). There should be documentation demonstrating that this has occurred
- the risk assessment may identify a particular medical emergency associated with the class of IMP that is not routinely covered by the unit; therefore, mitigation may include availability of specific equipment, specific staff training or trial specific emergency scenarios. Again, all these actions should be documented as evidence that the risk assessment was followed

Dose escalation (Appendix 1, point 2)

It is expected that the unit has a procedure in place to ensure that there are clear parameters for the dose escalation decision, that this is documented and that there is a system in place to prevent dose escalation with an inappropriate set of data. The MHRA expects the unit to ensure that the protocol, whether written by the sponsor or the unit itself, includes the number of subjects required to complete a cohort, details of the proposed data to be used for the decision and clear stopping rules. If this is not clear in the protocol, then this must be addressed in a separate document (agreed between the unit and the sponsor). There must be clear instructions not to proceed if dose escalation limits are violated, or until an appropriate substantial amendment receives regulatory and ethical approval.

Many clinical trials will be designed to incorporate dose leaders, i.e. dosing of subjects 24 hours apart, usually one placebo and one active. If the unit is involved in randomisation, then there must be a procedure in place to ensure that when using this approach dose leaders are not all randomised to placebo. Appropriate unblinded personnel (e.g. pharmacy staff or named individuals) should be identified to check the assessment of dose leaders prior to dosing and this should be documented.

The trial file must contain and clearly reflect the data reviewed and the decisions taken. It must also be clear what data will be reviewed and by whom, for example, the sponsor or representative may be reviewing unblinded data not available to the unit. It is expected that the decision to dose escalate is approved by the Sponsor and the PI and that this decision and the approvals are documented. The PI may delegate this task to another suitably qualified investigator involved in the clinical trial, but this delegation must be formally

authorised and documented before this individual performs the activity. The decision surrounding dose escalation must be clearly documented before any further subjects are dosed. It should be remembered that the outcome may not always be to escalate (e.g. doses could remain at the same level or be reduced), and these decisions are just as important and need to be documented in the same way.

It is imperative that the data used to make the decision are accurate. Therefore, **all data** used for the dose escalation decision must be subject to quality control procedures.

Where there are multiple sites recruiting in a dose escalation clinical trial and/or the data are being collated elsewhere (e.g. by the sponsor or third party vendor), it is expected that the unit satisfies themselves that all the data received from outside the unit are prepared to an equivalent standard as the unit's own procedures (i.e. those that have been assessed during the accreditation inspection by the MHRA). This may be via clarification with the sponsor or directly with the third party vendor. The sponsor and all PIs from each of the recruiting sites should be involved in the dose escalation decision. Therefore for a trial to be run to accreditation standards, the sponsor should ensure that the data they supply (either themselves or from a third party vendor) are also subject to quality control procedures.

Similar quality control procedures should also be considered for other important safety decisions, such as those made by a Data Monitoring Committee etc.

Medical Emergencies and Facilities

Emergency trolley (Appendix 1, point 4)

Based on the number of wards/beds and the layout of the unit, there must be enough emergency trolleys (or acceptable alternative, such as a grab bag) to ensure they are easily and rapidly accessible. The emergency trolley contents should reflect the current Resuscitation Council (UK) guidelines. Trolley contents may vary between units because they may be standardised throughout a specific hospital and thus staff in a given unit are unlikely to have been trained to use all items on the Resuscitation Council (UK) lists. Units may want to take the guidance of the hospital or contracted resuscitation officer to ensure that trolley content are appropriate. Where it is decided that there will be deviations from the Resuscitation Council (UK) guidance, this should be documented and retained for request upon inspection.

In some units the equipment or medicines that are not required to be readily available are held in alternative locations (e.g. ward drugs cupboard or pharmacy). Where this may be the case there should be clear consolidated oversight of where all Resuscitation Council contents are held or documented justification if not required. Also there should be documentation of any checks when there is a change to either the Resuscitation Council requirements or NHS policy.

Medical emergency rehearsal/periodic testing (Appendix 1, point 11)

Phase I unit personnel must be trained and prepared to identify when a subject is becoming unwell and to initiate treatment of a medical emergency if it arises. Drills or mock scenarios ensure that those who do not handle medical emergencies on a daily basis maintain their knowledge and skills; for this reason, such training is imperative. One method of doing this is to undertake scenarios that cover a variety of situations (e.g. cardiac arrest, anaphylaxis etc.) that allow staff to simulate what they would do in an emergency. Consideration should be given to when these scenarios are rehearsed in order to include the possibility of involving

night/agency/bank staff, busier times when volunteers are in the unit and the various locations around the unit. Some units have also incorporated testing of their unblinding procedures into the scenarios; this is recommended, but is not expected if there is separate testing of the unit's unblinding procedures.

These scenarios should be seen as learning opportunities and must be documented and distributed so that any learning points can be shared with all the clinical team, whether they attended the scenario or not. Any corrective and preventative actions following the scenario should be followed up and documented. Attendance at this training must be documented and tracked to ensure that all staff regularly take part. Although the number of training sessions will vary according to the size of the unit, it is expected that individual members of staff who are in contact with subjects should attend at least one session annually. The minimum frequency of training required for individual members of staff should be defined in the unit's procedures. It should also be noted that these scenarios are specific to the unit and types of trials they undertake etc. therefore are in addition to any scenarios conducted as part of a staff members life support certification (e.g. ALS/ILS/BLS or equivalent).

During an accreditation inspection the MHRA may ask for a demonstration of an emergency scenario, along with testing of a transfer to hospital. Some units have been able to utilise the local ambulance service and transfer the inspectors to hospital as part of the scenario, whereas others have driven to the hospital themselves. The inspectors will leave it up to the unit to decide how best to demonstrate this process.

Procedures should be in place to cover the transfer of a subject to hospital, and also to ensure that the treating physician has appropriate information about the IMP and the clinical trial, next of kin details and unblinding information where relevant. It is the accredited unit's responsibility to ensure the most likely method of transfer to hospital has been tested, or there is documentation supporting expected transfer times.

The nature and extent of the medical emergency procedures or medical emergency scenarios will vary depending on the type and location of the unit as this may involve the interaction with the hospital resuscitation team or paramedics during some of the scenarios. However, consideration should be given to providing a minimum level of scenario training for all staff who have direct contact with subjects to ensure they can identify and manage any emergencies within their remit; even if their role is only to open doors, make telephone calls or receive/direct the paramedics/resuscitation team etc.

Emergency scenarios specific to a trial may also be identified via the trial's risk assessment and these should be incorporated into trial specific training as necessary.

There should be a system to track emergency scenario training to ensure that it is being undertaken at the frequency required in the written procedures, that a variety of appropriate scenarios are taking place (e.g. different events, locations and times) and that relevant staff are sufficiently involved in the training.

Staff

Principal Investigator (PI) requirements (Appendix 1, point 12)

PI qualification, training and experience, including relevant post-graduate qualification for FIH trials

The expectation is that the unit has formal procedures in place that specify what investigators require in terms of qualifications, training and experience in relation to the types of trials for which they are "authorised" to act as a PI. Therefore, it is the units' responsibility to assign a suitably qualified PI; it is not the responsibility of the MHRA or REC to undertake this assessment when authorising/approving the clinical trial. However, a copy of the accreditation certificate of each unit is provided to the National Research Ethics Service (NRES) part of the Health Research Authority (HRA), to which RECs may refer. Where units have contracted medical doctors to act as a PI on FIH trials, they should be identified as key personnel and will thus be named on the accreditation certificate.

For FIH trials, the PI is required to hold a relevant clinical pharmacology post-graduate qualification; this is to provide assurance that 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.

Relevant accepted post-graduate qualifications include: **Diploma in Human Pharmacology, Completion of Speciality Training in Clinical Pharmacology and higher degrees in pharmacology such as MSc in Clinical Pharmacology.** Qualifications such as Member of the Royal College of Physicians (MRCP) and Completion of Specialty Training in Pharmaceutical Medicine (PMST) are highly desirable but are not considered to be sufficient. The Diploma in Pharmaceutical Medicine would only be considered acceptable where it is supported by experience in FIH trials (see section below on exemption process).

Investigators with a relevant Clinical Pharmacology Qualification

Investigators that hold relevant Clinical Pharmacology qualifications (as listed above) should still undergo training and assessment as per the Unit Standard Operating Procedures (SOPs). The unit must have a process to authorise the PI to act as a PI, once this is confirmed the PI for FIH trials should be added to the unit's accreditation certificate as key personnel, either during the initial application or as a variation.

Investigators without the relevant Clinical Pharmacology Qualification

Units with Investigators that do not hold the relevant Clinical Pharmacology Qualification but wish to undertake FIH trials within the accredited unit, the following routes are available:

1. for FIH trials in patients. If the proposed Investigator is directly employed by the Unit and has had the relevant training in the Phase I unit SOPs then one of the following routes could be taken:
    a. allocate Principal Investigator (PI) role to an Investigator that is already authorised as a FIH PI (due to meeting relevant qualifications or having received the exemption and is named on the Phase I accreditation certification) with the Investigator who does not hold the qualification being allocated as a Sub-Investigator
    b. allocate Investigator as Chief Investigator (if multi-site and CI is working in the Phase I unit as per the Phase I unit SOPs) with Principal Investigator role allocated to an Investigator that is already authorised as a FIH PI (due to

meeting relevant qualifications or having received the exemption and is named on the Phase I accreditation certification)

c. allocate Investigator as PI with Sub-Investigator role allocated to an Investigator that is already authorised as a FIH PI (due to meeting relevant qualifications or having received the exemption and is named on the Phase I accreditation certification). For a FIH trial in Patients it may be most appropriate for the expert in the therapeutic area to be the PI and a Sub-Investigator whom meets the criteria for FIH PI to be delegated responsibility for those tasks that require clinical pharmacology expertise, such as; contribution to and authorisation of the protocol, trial risk assessment, starting dose recalculations, review and authorisation of dose escalation data and decisions. This must be a formal delegation with clear allocation of responsibilities

2. oversight of a Phase I Review Committee (see relevant section below)
3. if the proposed Investigator does not have the relevant qualifications but does have extensive FIH experience, then a Faculty of Pharmaceutical Medicine (FPM) exemption could be sought (see relevant section)

Phase I Review Committee and Named Expert Advisor

It is acknowledged that in some trials units (mainly academic units), in addition to core staff such as nurses, technicians and possibly medical doctors who have the required qualifications, training and experience in conducting Phase I trials (including FIH), there will be other “visiting researchers” utilising the facilities for their own trials. These “visiting researchers” while being experts in their therapeutic area, and possibly later phase trials, may want to conduct their own Phase I trial, but may not meet all the requirements of the accreditation scheme for being the named PI (for example, they may not have the relevant post-graduate qualifications in pharmacology to be a PI for a FIH clinical trial). Funding applications, sponsor and/or publication requirements may mean that it is not appropriate for another medical doctor that is suitably qualified to be the named PI for the trial. In these circumstances, there should be a formal mechanism for the review of any requests to use the units’ facilities in order to identify those clinical trials that fall within the remit of the accreditation scheme. This mechanism should ensure that these trials are adequately assessed by relevant experts for suitability of the trial and the research staff, including the PI. Any gaps in the trial design/logistics and suitability of trial staff or PI should be captured and mitigations implemented, prior to agreement to support the trial at that facility.

To address this aspect, the unit should have in place a formal committee responsible for the review and risk assessment of Phase I clinical trials and the personnel involved in conducting the trial, with a particular emphasis on the suitability of the PI.

In order for a committee to be accepted under the terms of the accreditation scheme, a written procedure is required identifying the terms, remit and activities of the committee (this can be in the form of an SOP, terms of reference document, committee charter etc.) This written procedure would have to include:

- identifying relevant trials required to be submitted to the committee (i.e. Phase I trials)
- a minimum quorum of members. These members must have the relevant expertise to assess a Phase I trial (e.g. be able to review the IB, understand the preclinical data including calculating the starting dose/dose increments, assess the pharmacological aspects of the trial etc.) Members could thus be, for example, pharmacologists, toxicologists or a unit representative. In addition, in order to meet the accreditation

requirements, at least one member of the quorate committee should be a medical doctor experienced in Phase I clinical trials and who meets the requirements to act as a PI for FIH trials in their own right

- the minimum required experience/qualification of the committee members, plus provision to invite any experts/specialists if the committee do not have the relevant experience themselves in a particular therapeutic area or specialty (e.g. paediatrics, oncology etc.)
- a clear conflict of interest policy if the requesting researcher is a member of the committee (i.e. the requesting researcher/PI can participate in discussions; however, cannot influence the overall decision by the committee)
- a formalised mechanism for what documentation the committee requires for review, how these will be circulated and the provision of comments to the committee from non-attending members (or the allocation of a suitably qualified delegate). Documents may include (but will not be limited to): the protocol, IB/other safety information, regulatory/ethics documents, risk assessment, committee application form, CVs
- how the review of the proposed Phase I trial and the committee's decisions and recommendations will be documented. This will include the full risk assessment as per the accreditation scheme requirements (and as detailed earlier in this guidance document) and in addition include the review of the requesting researcher/PI and research team, detailing any identified gaps in expertise and their mitigation. The output of the committee may be the formal risk assessment or a supporting named document complementing the risk assessment
- the process for the committee's continued involvement throughout the lifecycle of the trial, including their oversight or input into amendments and ongoing safety updates, dose escalation decisions etc. This could also include any requirements for the submission and approvals of final or updated documents if the committee has made a decision based on draft pre-clinical data or a draft protocol
- the requirements for reviewing the requesting researcher's/PI's qualifications and experience in relation to a Phase I trial and in particular, a FIH trial. For example, if the requesting researcher/PI meets the accreditation scheme requirements for a FIH clinical trial, the committee could approve the investigator per se. However, should the requesting researcher/PI not meet the minimum requirements as detailed in the accreditation scheme, the committee must identify the gaps in the PI's expertise and assign a "named expert advisor" who will take responsibility to cover those gaps. The committee must clearly identify the remit and oversight of the "named expert advisor" and how this oversight will be documented. The committee itself may also decide to take a more active role in this type of trial to ensure there is appropriate oversight of key aspects such as dose escalation decisions, ongoing safety reviews etc. The requirement for a "named expert advisor" and any oversight activities should be documented within the committee's risk assessment report. Documentation to verify compliance with the identified mitigations throughout the course of the trial and the committee's role would also be required as evidence of compliance with the risk assessment

Where the committee has identified gaps/risks in certain areas of the trial and has recommended actions to mitigate them (for example, the committee may have identified the need for a "named expert advisor'' to provide advice to the PI or to make specific decisions), there must be clear documentation that the PI accepts those recommendations for the trial to go ahead and there must also be documentation that these conditions were met during the course of the trial.

It is acknowledged that in some specialist therapeutic areas (e.g. oncology) there are a number of PIs that, although they have no formal pharmacological post-graduate qualification, they have a significant amount of experience in phase I trials including FTIP and therefore should be exempt from the requirement to have a relevant pharmacology post-graduate qualification when undertaking these types of trials. In these cases, with the support of the Phase I committee, the PI can apply for the formal exemption via the FPM, as detailed in the guidance above.

However, there should be clear mechanisms for how the committee ensure that less experienced PIs do not use the committee process as an alternative to gaining an approved post-graduate qualification. For example, the ‘’named expert advisor’’ approach is only acceptable where the requesting researcher/PI is doing a ”one-off” or occasional Phase I trial. There should be a mechanism in place at the unit to allow for less experienced PIs intending to conduct subsequent or numerous FIH trials, to be formally mentored while working to gain their post-graduate qualification.

The PI would still retain their legal responsibility for the conduct of the trial as stated in the legislation, therefore, it is expected that the PI, the committee and the “named expert advisor” (where applicable) understand their obligations, accountability and responsibility, and this should be documented (e.g. in an agreement or the risk assessment etc.) Everyone should be aware of, identify and acknowledge their limitations in respect of the trial.

Note: The ‘Phase I Review Committee’ approach is required for units where there are researchers not contracted by the unit that request to undertake clinical trials including Phase I trials within the unit. Units that contract medical doctors that are appropriately authorised to act as PIs for Phase I trials (i.e. as part of their job description) and are allocated to trials do not require this committee. Units may wish to implement a committee of this type as routine to support the risk assessment process. However, this should not be used as a mechanism to allow a unit’s employed PIs who do not meet the accreditation requirements to act as PIs on FIH trials. It is also considered good practice (and is therefore recommended) that if units undertake clinical trials in specialist therapeutic areas, they implement a review committee for these types of trials and invite a therapeutic expert to address any identified gaps in experience.

Faculty of Pharmaceutical Medicine (FPM) exemption

It is recognised that there are a number of PIs that, although they do not hold the relevant post-graduate qualifications as listed above, have a significant amount of experience in pharmacology (and are often involved in teaching the post-graduate courses) and therefore could be exempt from the requirement to hold a post-graduate qualification. In these cases, PIs will have to demonstrate that they are sufficiently experienced and submit a rationale for their exemption to the Faculty of Pharmaceutical Medicine (FPM) for an independent peer review. There may be occasions where a PI may only be relevantly qualified in their field of expertise (e.g. vaccines, oncology etc) and as such only able to act as a PI for FIH trials in their field of expertise; again this will be submitted to the Faculty of Pharmaceutical Medicine for assessment and if approved would be listed as a condition and stated on the certificate. An exemption can also be requested for a PI who is a “visiting researcher”.

Where the PI is a “visiting researcher”, and thereby assessed by the unit, this exemption can also apply for those with a significant amount of experience in conducting FTIP trials. See the section “Phase I Review Committee/Named Expert Advisor” below for further details. In these

cases the “visiting researchers” will also be added to the accreditation certificate in addition to the units named representative.

A formal process for the submission of an exemption request can be found on the Phase I Accreditation Scheme page of the MHRA website[1].

EAG type trials - additional requirements for availability of medical doctors during and following dosing: requirement for ‘relevant and recent experience of handling medical emergencies’ (Appendix 1, point 13)

EAG type trials require medical doctors to have ‘relevant and recent experience of handling medical emergencies’. There are several ways that this can be met. A unit that is based in a hospital and can rely on calling the hospital’s resuscitation team in an emergency clearly meets this requirement. For those units not based in a hospital, this can be addressed in several other ways:

- the unit’s medical doctors also work part-time within clinical practice (for example, in the emergency department or Intensive Care Unit (ICU)). It is expected that a training log is maintained by these medical doctors to list their experiences within the clinical setting, with sufficient detail, to demonstrate that their experience remains relevant and recent. Honorary contracts with the hospital or other contractual arrangement for this should be in place
- phase I units have contracted in medical doctors with relevant and recent experience for the dosing days. The MHRA would expect the unit to have a contract in place with these medical doctors and the unit should have assessed their suitability for the role. In addition the unit must ensure that the contracted medics have received adequate training in GCP, the clinical trial and unit procedures
- phase I units have also employed medical doctors who have recently worked in relevant areas of clinical practice. Experience must remain recent therefore these medical doctors will be required to demonstrate how this is achieved

These medical doctors will not necessarily be PIs or investigators, although in some cases there will be overlap. The Accreditation Scheme requires that a medical doctor able to manage an acute emergency is present on dosing days for EAG type trials, but this does not have to be the PI.

Where there is a requirement to have a specialist medical doctor present (be this for a FIH, EAG type trial or with relevant expertise for the therapeutic indication etc, as specified in the protocol or risk assessment) in addition to the unit minimum staffing requirements, there should be documented evidence of when these specialists were present on the unit to verify they were present for the duration specified. For example, some units use a sign in/out register or the security tag date/time logs for their medical doctors to show their compliance with the risk assessment mitigation or minimum staffing requirements procedure.

Sufficient trained and experience staff availability (Appendix 1, point 14)

Acceptable minimum staff levels

Although the accreditation scheme requires Phase I units to have a procedure defining the minimum number of staff, the MHRA do not stipulate a specific number. The unit’s procedure must take into consideration the number of staff required to manage a medical emergency, should it arise. The procedure should also consider the levels of life support training and the use of agency/bank staff or, in the case of non-commercial units, visiting research teams. Staffing levels should also be modified in relation to the number of subjects on the unit, the

types of clinical trials being undertaken and the number of wards that are occupied. The unit should be able to provide evidence that the minimum staffing levels stipulated in their procedures or trial specific documents e.g. protocol or risk assessment have been complied with. The protocol or risk assessment may stipulate an increase in the staffing level above the minimum staffing levels stipulated in the unit procedures, but must not reduce them.

The procedure should encompass both nursing and medical staff and also give consideration to the flexibility for the range and types of trials that may be undertaken in the unit. However, it must be clear what the minimum requirements are and how they differ for FIH/EAG type trials and how increased or additional staffing will be identified (i.e. via the risk assessment).

Resourcing and allocation/delegation of staff

It is important that the unit has available trained and experienced staff (both medical doctors and nurses etc.) to undertake the trials they are conducting. Therefore, the resourcing and allocation of staff to the trials is an important aspect of the unit's day to day function. For units where there are visiting research staff (for example, in a non-commercial facility where researchers can undertake their trial in the unit), this must encompass the unit's review and assessment of not just the trial, but also all the visiting staff including the PI. This is important to ensure the PI is suitably qualified and that the allocation of resources from visiting staff meets the requirements of the accreditation scheme or is supplemented by core staff.

There should be formal procedures for the allocation and assignment of staff to key protocol tasks. This should encompass mechanisms to ensure that only staff that are trained and competent to perform that activity and have been formally delegated that activity are assigned. Therefore, the person(s) responsible for preparing the document assigning staff (this many be known by many names, for example, duty rota, procedure sheet, study allocation sheet etc.) should use all the available tools (i.e. both general training matrices, delegation logs or study specific training logs) to identify staff that are trained and competent before allocating them to the activities.

It is imperative that any documents used to record allocation of staff that are derived from the protocol (e.g. that contain the timings of trial tasks) are robust. Therefore, these tools must have a documented validation/QC to ensure they are in compliance with the relevant version of the protocol, otherwise it could lead to breach in protocol (legislation) and potential harm to subjects/trial integrity if safety measurements or assessments are missed.

Consideration should also be given to how the unit deals with unexpected absences. In addition the unit should ensure that it has sufficient resource, for example a 'spare' member of staff that is not allocated specific tasks, so they are able to support the team if there are problems, for example difficulties with a blood draw that may then lead to other blood draws becoming late unless someone else is able to step in and assist

As with any trial, it is expected that the PI only delegates tasks to suitably qualified personnel, therefore, personnel should only be listed on the delegation log if they are trained in GCP, competent in the specific task and trained in any study specific procedures (as documented in the various records, e.g. training records or the trial file).

Clinical staff requiring Immediate life Support (ILS) training (Appendix 1, point 15)

Immediate Life Support (ILS) training refers to the Resuscitation Council (UK) ILS Course or equivalent (including any paediatric life support for units conducting paediatric trials).

This should be updated annually, as staff working on healthy volunteer clinical trials are not faced with frequent medical emergencies it is important for frequent Life Support training. Some provision can be accommodated for in procedures to allow a short grace period in exceptional circumstances. If this is to occur, this should be documented, risk assessed and mitigations should be put in place such as additional assessment of competence and confidence of the individual in managing medical emergencies via in-house emergency scenarios or by removing the staff member from the minimal staffing.

Varying job titles and descriptions have caused confusion about the definition of clinical staff in relation to the accreditation scheme. Within the accreditation scheme, the meaning of "clinical staff" equates to at a minimum, the nurses, medical doctors and those staff that would be responsible for managing the subjects' care whilst they are in the unit, and therefore, the staff who would have a direct role in the management of medical emergencies. This may vary depending on the set-up of the unit, for example, it could encompass all the nurses and clinical technicians etc. especially where units are not located within a hospital or key staff who will be formally allocated responsibility for dealing with the medical emergencies (i.e. an allocated in-house resuscitation team that will manage the subject until the paramedics/hospital resuscitation team arrive). This should include any on-call or "bank" medical doctors or nurses that the unit employs that may have to cover medical emergencies.

Where there may be units that have core staff and also have trials that have a visiting research team, there must be a formal assessment of the research teams qualifications and training in relation to their life support training to ensure they either meet the minimum requirements for the unit, or the unit can ensure that core staff are resourced to the clinical trial to provide this aspect. This must be documented (e.g. as part of the risk assessment).

Subject Identification and Verification

Over-volunteering (Appendix 1, point 16)

The accreditation scheme requires a formal procedure to be in place to address how the unit will minimise the risk of over-volunteering for healthy volunteers and in some cases volunteer patients (e.g. diabetic or asthma studies). There is no single mechanism to combat this risk, but there are a variety of different activities that combined can reduce the risk of over-volunteering.

The unit should have a robust database that contains a comprehensive list of all the volunteers that have participated in any clinical trials the unit has undertaken, in order to identify the last time the unit has dosed the volunteer. The database should also identify any significant information relating to that volunteer, that may preclude them for use in particular trials. There should be procedures in place to manage the database which must comply with data protection regulations.

In addition, there are various physical examinations and safety assessments that can give indications to whether a volunteer has recently participated in a clinical trial at another unit. Also contacting the volunteers GP and asking about previous trial participation is routinely used.

In the UK there is a national volunteer database called The Over-volunteering Prevention Service (TOPS), which is managed and hosted by the Health Research Authority (HRA). It is

now a condition of the REC approval that units register subjects on TOPS for Phase I trials using healthy volunteers.

However, there are a number of other databases available, that units can choose to use in addition. For example:

- National Volunteer Register (NVR). This allows those units that have registered to view if a volunteer they intend to dose has participated in a clinical trial at one UK commercial Phase I unit
- Prefect Spider Search System (PSSS), a new European wide volunteer search engine
- VIP, however this tends to be used to register European and Japanese volunteer studies only

Patient trials are slightly more complicated. For the most part, where there is a set of comprehensive medical notes available providing their medical history (i.e. where the patient is identified in clinics or referred by their consultant), there would be no need to use TOPS. However, there are a group of "patient volunteers" (i.e. they are generally healthy, but may suffer from mild asthma, diabetes etc. and are responding to an advert) where there are no such suitable medical notes. For these types of subjects (i.e. the volunteer patient), there may be a justification to use TOPS. Any decision to use medical notes or TOPS should be documented (e.g. as part of the risk assessment).

When using TOPS it is expected that units document the checks performed and follow the TOPS guidance for entering subjects. This currently uses either the national insurance (NI) number for British nationals or passport number for non-British nationals. To ensure the correct information is registered and checked, when using the NI number, evidence should be requested for this to ensure it is the subject's own NI number that has been provided. Units should also consider how they check subjects with dual nationality to ensure they are not listed multiple times using different IDs.

Photographic identification (Appendix 1, point 17)

The accreditation scheme requires a formal procedure to be in place to address how subjects will be identified. This may vary depending on the type of trial being performed. For trials using healthy volunteers or patient volunteers (i.e. they are responding to an advert and not being recruited or referred by their treating medical doctor) then the unit has to be sure they can confirm who the subject is and are able to verify that it is the same person that attends all the trial visits. This must be done using a valid form of photographic ID (i.e. photo driving licence or passport). The unit should retain a copy in the subjects' records throughout the duration of the trial to check it is the same person at each visit, and should ideally retain it after completion for evidence of the subjects' existence, especially if there is no other mechanism to verify this. Some units utilise a digital photo which is saved in the subjects' records/volunteer database, this is acceptable to verify the subject at each visit. However, it is also recommended that a copy of the original photographic ID is retained as well (or at a minimum the unique details (i.e. passport or driving licence number.)

Confirmation of the subjects' past medical history (Appendix 1, point 18)

For all early phase trials using volunteers, it is good practice and therefore highly recommended to obtain confirmation of subjects' past medical history prior to dosing *via* the subjects' GP or other medical doctor (such as a hospital consultant for trials where they are not recruited by their own consultant, therefore have no access to the medical records for the patient) to provide assurance that the inclusion and exclusion criteria are met.

However, for FIH and EAG type trials using healthy volunteers, the unit is required to obtain verification and this should be in writing.

It is expected that the procedure for contacting the GP is formalised, clearly documenting how this will be performed, reviewed and documented, including the frequency. Consideration should be given to the various types of trials a unit undertakes and that their requirements are differentiated between (i.e. it is clear when a GP questionnaire is needed or not). Also, there may be occasions where a risk assessment for a particular trial identifies an increased need for vigilance (for example, a GP questionnaire is required in a trial that would not normally require it, or a new/up to date GP questionnaire is needed, or that the GP has access to a certain period of medical history, due to the eligibility criteria required).

Quality System

SOPs (Appendix 1, point 20)

It is appreciated that units will undertake a variety of studies, ranging from first in human (healthy volunteers and patients), EAG type trials to later phase clinical trials, Advanced Therapy IMPs (ATIMPs), other early phase trials using both healthy volunteers and volunteer patients etc. Therefore, consideration should be given to ensuring the formal procedures covering the unit's activities, are flexible enough to encompass the variety of trials, while making it clear what the minimum requirements are for meeting the accreditation scheme (i.e. where the requirements differ for Phase I trials, especially FIH and EAG type trials and those using healthy volunteers or patient volunteers).

Procedures need to ensure that the unit's own local requirements as well as the accreditation scheme requirements are encompassed and followed. Any emergency related procedure (for example, emergency unblinding, emergency alarm buttons, out of hours/emergency phone numbers etc.) should encompass routine testing, how this is documented, the frequency and any CAPA in the event of failures/issues.

The procedures should stipulate the minimum requirements, but also link into the risk assessment and how any additional or enhanced requirements will be documented for a specific trial.

Quality Control (Appendix 1, point 21)

Quality Control (QC) should be in built into procedures and include real-time review/checks of process and associated documentation. QC should be designed in relation to a process and the processes points of risk. Therefore the level and type of QC should depend on the process, risks to data integrity and subjects safety, for example emergency trolley checks are often conducted by two people, with the second person acting as a verifier, this is a method of real-time QC and we also see that this documentation is then subject to further completion checks prior to filing. However, we often see documentation that is required for demonstrating Phase I accreditation compliance that has never been subject to any QC and therefore errors/omissions exist throughout it as the process was conducted by a single person without any further QC of the documentation; for example, alarm call testing documentation, medical scenarios documentation, ALS/ILS trackers etc. Any issues identified by QC should be resolved as soon as possible. An escalation pathway should be in place if QC identifies trends in issues or significant issues are identified that require a more substantial action to be taken. The escalation pathway should link to a quality issue process which involves review of wider root cause and CAPA implementation where appropriate.

Quality Assurance (Appendix 1, point 22)

An effective internal audit and CAPA programme should be in place. The internal audit programme should incorporate the Phase I accreditation scheme and ensure it is audited routinely. This could be performed as a specific Phase I internal audit focusing on the scheme or the scheme could be audited against across a number of audits. Quality Assurance should be able to demonstrate how they have ensured compliance has been audited against the full Phase I scheme in the period of time between accreditation inspections. The frequency of audits should be risk based taking into account; previous inspection findings, internal audit findings and trends, Sponsor audit findings, quality incidents etc. Internal audits should be conducted by appropriately qualified and trained individuals (trained in audit and trained in Phase I accreditation requirements).

Miscellaneous

Location of units for accreditation

A unit does not need to be hospital based or based within a certain distance from a hospital to achieve accreditation. The procedure in place to deal with medical emergencies will be reviewed and expected to be commensurate with the unit's location. For example, where units are not located within a hospital, procedures and documentation should be reflective of dealing with paramedics, the local hospital and document times for commuting, especially at the busiest times. There are no UK regulations that require such units to be based on a hospital site.

Variations to units' accreditation

It is appreciated that during the period of accreditation, units will undergo changes, this may be to the personnel, the facilities and the procedures. Where these changes affect either:

- the key personnel (i.e. those listed on the accreditation certificate or providing key support under the terms of the accreditation scheme)
- the facilities (e.g. a change in the location or change of use/design/layout of the unit) or the equipment (e.g. emergency, telemetry, etc.)
- the formalised procedures for key activities described in the accreditation scheme (e.g. over-volunteering, volunteer databases, risk assessment, medical cover/provision, staffing levels, dose escalation etc.)

The unit should assess the changes and whether the MHRA should be notified of these changes, as they may affect their accreditation status and thus need to be reviewed for acceptability. Variations should be submitted to the MHRA phase I mailbox using the variation form available on the website. If there is uncertainty the unit should contact the GCP inspectorate for advice. All decisions and their rationale and/or contact with the MHRA should be documented and retained.

It is acknowledged that many changes will be acceptable based upon office review of the information, however, some may require a short inspection to ensure they are acceptable or may generate some queries and comments from the inspector before being accepted. It is acknowledged that where the changes are urgent (e.g. the addition of a new PI for FIH trials) the unit should contact the GCP inspectorate by telephone directly to arrange urgent action.

Inspection approach

From 2020 onwards a flexible hybrid approach may be taken to GCP and Phase I inspections; inspections may be necessitated to be conducted remotely with a reduced scope, they may be fully on-site or may involve both remote and on-site inspection days. The

approach for Phase I inspections would be risk proportionate and agreed with the Phase I unit to be inspected.

Common Findings

The most common findings from Phase I Accreditation Inspections are listed below:

- issues with the dose escalation process is by far the most common finding from these inspections, in particular:
  - decisions to escalate not documented, or approval documented post the next dose level
  - lack of clarity with respect to who took the escalation decision
  - data not provided with escalation decision documents
  - no quality control (QC) of data used to make escalation decisions
  - no clear procedure for handling dose escalation studies
- no formal procedure for risk assessment and risk management/mitigation
- failure to adequately document and demonstrate risk mitigation activities
- failure to update the risk assessment and mitigation based on new information (new IB, protocol amendments)
- emergency scenarios are inadequate i.e. too infrequent so that not all staff receive regular training, or only one medical emergency is rehearsed. Also a lack of follow-up and preventative action for any issues identified during the scenarios
- training records for agency/bank staff or consultant experts were incomplete or missing
- inadequate procedures for contacting medical doctors in an emergency outside of normal working hours, i.e. there were no regular documented tests of the system or during inspection the inspectors were unable to contact a medical doctor out of hours
- expired or missing items on the resuscitation trolley
- no formal procedure to address over-volunteering, or the steps taken to avoid over-volunteering have not been documented
- incorrect dosing of subjects, due to a lack of adequate procedures and resources
- inadequate documentation to verify that the staffing requirements defined in the risk assessment had been met or verification that the stated recruitments were not met.
- lack of robust procedures for the scheduling to ensure all protocol assessments were performed and that staff allocated were suitably trained and competent.

Relevant Websites:

Further guidance can be sourced from the following websites:

1. MHRA GCP – Phase I Accreditation Scheme Page: https://www.gov.uk/guidance/mhra-phase-i-accreditation-scheme
2. MHRA GCP Guide: For further information or to order a copy please visit the TSO website: http://www.tsoshop.co.uk/bookstore.asp?FO=1160007&DI=635071&trackid=000039
3. EMA Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07): https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational_en.pdf
4. MHRA GCP Forum and FAQs: http://forums.mhra.gov.uk/forumdisplay.php?1-Good-Clinical-Practice-(GCP)

Revisions:

Oct 2015: Update to sections:

- Emergency Trolley (Appendix 1, point 4)
- Medical Emergency Rehearsal/Periodic Testing (Appendix 1, point 11)
- Principal Investigator (PI) Requirements (Appendix 1, point 12)
  PI Qualification, training and experience, including relevant post-graduate qualification for FIH trials
- Clinical staff requiring Immediate life Support (ILS) training (Appendix 1, point 15).

April 2021: Update to sections:

- Staff, Principal Investigator (PI) Requirements (Appendix 1, point 12)
- Quality Control (Appendix 1, point 21)
- Quality Assurance (Appendix 1, point 22)
- Miscellaneous.

July 2022: Administrative updates only: MHRA branding, formatting and staff titles