



Medicines & Healthcare products
Regulatory Agency



MHRA

PHASE I

ACCREDITATION SCHEME

REQUIREMENTS

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1. Background

As detailed in the original implementation of the accreditation scheme in April 2008, one of the recommendations from the Expert Scientific Group on Phase I Clinical Trials (ESG) following the TGN1412 incident in March 2006, was that a voluntary accreditation scheme be established for units conducting Phase I trials, in particular for those conducting first in human (FIH) trials and for those trials with risk factors that would require review by the Clinical Trials, Biologicals and Vaccines Expert Advisory Group of the Commission on Human Medicines (EAG) before it may be authorised.

The MHRA GCP Inspectorate has routinely inspected units conducting Phase I trials in the UK in a cyclical programme since 2006. However, the MHRA only inspects within the scope of the clinical trial regulations and therefore many aspects relating to how these units performed Phase I trials at that time could only be made as recommendations.

The original aim of the MHRA Phase I accreditation scheme was to increase the scope and depth of inspections in order to provide the MHRA and Research Ethics Committees (REC) with more information about the units seeking to conduct these trials, so that approval decisions could be made even more robust.

The scheme was designed to give assurance that units within the scheme not only met but surpassed the basic regulatory GCP aspects by having additional “best practice” procedures that encompassed the highest standards for avoiding harm to trial subjects and for handling medical emergencies should they arise. Thus also assuring sponsors that accredited units make significant contributions to enhancing the safety of volunteers and are considered to be centres of excellence for Phase I research.

The original accreditation scheme was formally implemented in April 2008 and the initial scope was for units conducting non-therapeutic Phase I trials, including those units conducting early phase trials in the ‘patient volunteer’ populations e.g. asthma sufferers. It was not intended to cover Phase I trials in severely ill patients conducted in a hospital setting (including first time in patient trials (FTIP) such as in oncology), non-interventional drug trials, i.e. those that do not require a Clinical Trial Authorisation (CTA) or non-drug trials.

The scheme originally allowed for the classification of units into two types; standard accreditation (accredited to carry out all Phase I trials other than FIH trials with risk factors that would require EAG review) and supplementary accreditation (accredited to carry out clinical trials with compounds at all levels of risk, including those that require review of risk factors by the EAG).

The accreditation scheme was revised in October 2013 after 5 years to:

- Accommodate a single classification system.
- Expand the scope to include units that function differently to the traditional commercial Phase I unit, for example, those units in an academic setting.
- Include more types of trials that can be covered by the scheme, for example, FTIP and patient volunteer (PV) trials that may be performed in the accredited unit.

This revision makes a change to the certification period, amends the acceptable post-graduate qualifications for FIH Principal Investigators for consistency with the guidance document, and provides some clarification on the life support training and medical emergency scenarios.

2. Scope

The scheme continues to be voluntary for units (commercial and non-commercial) conducting Phase I trials - i.e. clinical trials to study the pharmacology of an investigational medical product when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial (UK Statutory Instrument 2004/1031¹).

The scheme has a single classification system which is based on the unit's procedures and facilities, plus the training and experience of the unit's personnel; thus assessing the ability of the unit to manage trials, including those with certain risk factors (such as those for FIH trials or trials that would require review by the EAG). Further information on these risk factors can be found on the MHRA website² and in the Committee for Medicinal Products for Human Use (CHMP) 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products'³.

The scope of the scheme encompasses both stand alone facilities and named units within a hospital or academic setting (i.e. either a commercial organisations wards/areas or a pre-defined non-commercial clinical research facility/unit, including their named or core staff). The accreditation does not cover the entire hospital and all the wards and staff, or trials performed outside the named unit.

The scheme covers Phase I and other "early phase" trials in healthy volunteers (HV), patient volunteer (PV) and patient populations (see definitions in section 7). It is not intended to cover non-interventional drug trials, i.e. those that do not require a Clinical Trial Authorisation (CTA), non-drug trials or later phase trials (i.e. Phase II to IV).

Serious Adverse Drug Reactions may occur in any trial, regardless of the perceived 'higher risk' of certain compounds and molecules. There are also risks associated with trial procedures (for example, inhalation studies, bronchoscopy etc.) and the possibility of reactions to marketed drugs used as comparators and non-IMPs used as challenge agents. It is therefore vital that all units conducting Phase I trials have adequate staff and facilities for dealing with any such emergencies.

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. Also, sponsors should already be aware of all the potential risks in the clinical trial and take steps to mitigate these risks³.

MHRA statutory GCP Inspections have been in place since May 2004. Those units that are part of the voluntary Phase I accreditation scheme will not receive additional routine statutory GCP systems inspections. However, the MHRA reserves the right to perform a triggered inspection of the unit if concerns arise or if important information comes to light that requires investigation. Units may also be inspected by other regulatory authorities or as part

of European Medicines Agency (EMA) inspections (i.e. inspections requested by the CHMP) or as an investigator site as part of a sponsor inspection.

Units that are not accredited are not excluded from conducting Phase I clinical trials, since the scheme is voluntary. However, RECs/R&D Departments (where applicable) will take the absence of accreditation into account when considering the trial site and may consider conducting their own site inspection.

3. Accreditation of Units

Potential applicants will submit a completed application form (available from the MHRA website²) and any associated documents to the MHRA GCP inspectorate. This will be assessed and on completion of a successful inspection verifying that all the requirements have been met, the unit will be recommended for accreditation.

A unit must be able to demonstrate that it is able to carry out clinical trials with compounds at all levels of risk, including those that have never been tested in man (FIH) and those that require review of risk factors by the EAG. This means they must have formal procedures in place and appropriately trained and experienced staff available to cover all the requirements stated in Appendix 1.

4. Operation of the Accreditation Scheme

The scheme is operated on a voluntary basis. The inspections conducted for the accreditation scheme encompass a wider scope than standard GCP inspections and includes a detailed review of the unit's systems and procedures relevant to the accreditation scheme requirements.

When units apply for accreditation, an inspection will be carried out accordingly with an appropriate fee. Fees are consistent with current inspection fees. In addition, there will be an initial set-up fee, plus a small fee for issue of the certificate. Any variations to the certification requested at a later date may require a further inspection and therefore an additional fee as an inspection may be required to assess the criteria or facilities not previously reviewed.

Once an inspection has demonstrated that the requirements of the scheme are met, the unit will be accredited accordingly, and an accreditation certificate issued. The certificate will be valid for up to 3 years, and a re-inspection performed prior to renewal of the certificate. Units are required to submit to the MHRA GCP Inspectorate any significant changes or variations within this 3-year period. Significant changes or variations are those that affect the basis upon which the accreditation is granted as outlined in Appendix I. For example, these may include:

- Relocation of the unit or change to facilities (e.g. extension of an existing unit or the permanent use of facilities at another location).
- Significant changes to procedures that impact on key aspects of the accreditation scheme (e.g. changes to procedures relating to medical emergencies, subject recruitment, resourcing and staffing, minimum staffing requirements and the risk assessment)
- Changes in key personnel - titles used for key personnel will differ between organisations and units will need to review the requirements in the accreditation scheme and determine which personnel are key to attaining and maintaining those requirements. However, in general, key personnel will be the medical doctors

(including the Medical Director or the medical doctor who has overall responsibility for medical aspects), any PIs authorised for FIH trials (or the person responsible for assessing the PI for a clinical trial), Senior Nurses, Clinic Manager (i.e. the person who has overall responsibility for the day to day running of the clinic and the clinic equipment, e.g. emergency trolley), the Pharmacist (or individual responsible for the emergency drugs) and also the person responsible for maintaining the unit's quality system.

- Significant contractual changes in agreements with local hospitals.

The inspectorate will assess the changes and decide if an inspection is warranted or if the changes can be accepted based on the documentation provided. The inspector will issue a variation approval or a new certificate, as applicable once the changes have been approved. If changes at the unit result in any of the accreditation criteria no longer being met, the MHRA GCP Inspectorate must be informed immediately, and could result in a suspension of the accreditation (refer to section 6 for further details). If substantial changes occur during a clinical trial, then the Research Ethics Committee (REC) and MHRA CTU need to be informed where appropriate and in accordance with the legislation.

MHRA keeps the National Research Ethics Service (NRES), part of the Health Research Authority (HRA) informed of the status of units, including forwarding of relevant documents (e.g. Inspection reports and accreditation certificates, or any information on the suspension or termination of the units accreditation status) in order to assist the REC with their responsibility to carry out site-specific assessments of these units. The REC will assess non-NHS units, while the R&D department on behalf of the hospital Trust will be responsible for NHS units. However, RECs may request further information to assist with the site specific assessment, whether or not the unit participates in the accreditation scheme.

The MHRA GCP Inspectorate will maintain a list of accredited units; this list will be posted on the MHRA website².

5. Reporting Accreditation Inspections

Following initial accreditation and routine re-accreditation inspections, which have not resulted in critical findings, an inspection report will usually be produced within the standard timeframe for routine GCP inspections (this is currently 25 working days). Any major findings, particularly in the area of subject safety (e.g. eligibility, medical cover and subject identification) will need to be resolved prior to accreditation or re-accreditation. Responses will be required as per the standard format for routine GCP inspections; however, for any findings related to the key requirements of the accreditation scheme, evidence will need to be submitted along with the responses (e.g. the relevant updated SOP or examples of the new/completed forms).

If critical findings are identified during the inspection, the lead inspector will promptly inform the MHRA CTU and NRES, as appropriate. Also the legal entity which the unit forms part of (e.g. the NHS Trust or University for academic units) will be notified. Critical findings are reviewed by the MHRA Inspection Action Group (IAG) according to standard MHRA procedures and a decision will be taken as to what action should be taken, this could include suspension or revocation of the unit's accreditation (refer to section 6).

Upon adequate resolution of all findings, the inspection will be closed as per the standard format for GCP inspections and an accreditation certificate (including re-accreditation) will be issued.

6. Suspension/Revocation of Accreditation

Once accredited, units must continue to demonstrate compliance with the requirements of the scheme in order to maintain their accreditation. However, should serious issues be identified at the unit, either by themselves or as a result of information received by the MHRA (e.g. through inspection, a complaint, serious breach report or information from HRA), this may then lead to a temporary suspension of the unit's accreditation status or, ultimately, removal of their accreditation status.

When a unit is suspended or removed from the accreditation scheme, this does not prevent them from continuing to recruit and treat subjects; however they will be required to inform the sponsors as well as associated RECs/R&D departments of any current and upcoming trials they are conducting of their suspension or removal.

7. Definitions

Definitions	
Phase I (according to Statutory Instrument)	A clinical trial to study the pharmacology of an investigational medical product (IMP) when administered to humans, where the sponsor and investigator have no knowledge of any evidence that the product has effects likely to be beneficial to the subjects of the trial. Note: It is recognised that this definition is too restrictive to apply to all Phase I trials, for example, in oncology, anaesthesia, genetic disorders, immunological.
Early Phase	All types of Phase I trials using either healthy volunteers, volunteer patients and/or patients, including FIH, FTIP.
First in human (FIH)	IMP is administered to a human for the first time.
First time in patient (FTIP)	This is a subset of FIH, where it would be unethical or not possible to administer the IMP to a healthy volunteer. Therefore, the IMP is administered to a patient. It does not refer to a Phase II trial where the IMP was previously given to a health volunteer.
Healthy volunteer (HV)	A well (generally healthy, not sick) person who agrees to participate in a clinical trial for reason other than medical purposes and receives no direct health benefit from participating.
Patient volunteer (PV)	A person who has a specific medical condition (e.g. asthma or diabetes etc.) relevant to the clinical trial that agrees to participate in a clinical trial for reason other than medical purposes and is unlikely to receive a direct health benefit from participating. [Usually recruited via advertising or units may hold a panel of volunteers.]
Patient	A person being treated for a specific medical condition who has been invited or referred by the GP/consultant to participate in a clinical trial. Patients may receive a therapeutic benefit from the trial.
Clinical Trials,	The Commissions on Human Medicines (CHMP) group of

Biologicals and Vaccines Expert Advisory Group (EAG)	experts available to regulatory authorities to seek an opinion for those trials with risk factors that would require review before it is authorised.
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8. References

1. The Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031), as amended.
2. www.mhra.gov.uk
3. Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMA/CHMP/SWP/28367/07)
4. MHRA Phase I Accreditation Scheme Guidance Document

9. Revisions

Sept 2015:

- Section 4: increase in the scheme certification to a 3 year period, in line with the risk based inspection programme, unless there is justification for a reduced certificate period.
- Appendix 1, point 11: clarification that scenarios are in addition to those undertaken for life support certification.
- Appendix 1 point 12: Clarification regarding Diploma in Pharmaceutical Medicine (for consistency with the Accreditation Scheme Guidance Document, version 2)
- Appendix 1 point 15: clarification that this includes any paediatric life support training.

Appendix 1: Requirements

In addition to there being no unresolved critical and major findings in GCP at the unit, particular in the area of subject safety (e.g. eligibility, medical cover, subject identification etc.), the following **must** be in place for all units that wish to be accredited to carry out clinical trials with compounds at **all levels of risk**, including those that have never been tested in man (i.e. FIH) and those that require review of risk factors by the EAG:

Clinical Trial Design and Set-up

1. An agreement with sponsors (or internal memorandum of understanding for in-house units) detailing procedures and responsibilities for notifying the investigator immediately if/when new safety/toxicology data come to light.
2. A formal risk assessment and risk management/mitigation strategy. This must be able to demonstrate that the unit (independently of the sponsor) continuously verifies and assesses all aspects of the trial, including any pre-clinical data and pharmacology. For example (but not limited to), trial design, starting dose calculations, dose escalation proposals, stopping criteria, exposure, predictable reactions/adverse events, availability of any specific antidotes or emergency treatments and any additional and/or specialist staffing and/or training.

Medical Emergencies and Facilities

3. An agreement with the hospital for supporting emergencies arising from the clinical trials performed by the unit *or* the ability to demonstrate communication and notification of trial information (e.g. dosing times) with the hospital's emergency teams. The hospital resuscitation committee, emergency response team and the Intensive Care Unit (ICU) staff (as applicable) must be aware of the accredited unit, the nature of the research (e.g. FIH, Biologicals etc.), and that they could be referred patients from the unit at any time.
4. An emergency trolley must be available that is easily and rapidly accessible. There must be a trolley in each main area, which can be moved quickly to where it is needed. The emergency trolley must be stocked as per the current resuscitation council guidelines and carry as a minimum:
 - a. Oxygen and delivery apparatus
 - b. Equipment for procedures such as cannulation and suitable fluids for IV infusion
 - c. Supraglottic airway devices (e.g. laryngeal mask airway, i-gel)
 - d. Self-inflating bag, or equivalent, for assisted ventilation
 - e. Suction equipment
 - f. Defibrillator – this should be an automated external defibrillator (AED) defibrillator with a manual override
 - g. Equipment for tracheal intubation and emergency cricothyroidotomy should be available for use by appropriately experienced personnel or a responding emergency team only.
5. There must be a documented weekly check of the contents of the emergency trolley, including regular checks of the expiry dates for medication and equipment. If the emergency trolley or the emergency drug box is sealed then the tamper proof seal should be checked weekly.
6. Continuous monitoring equipment must be available to include ECG, pulse oximetry, vital signs such as blood pressure, heart rate and temperature.
7. Beds used for dosing days must be able to be tilted and adjusted for height.

8. Alarms must be placed in any areas likely to be occupied by subjects (e.g. showers, toilets, ward(s) and recreational areas(s)) and these must be regularly tested (and the testing documented).
9. Staff must be able to open the toilet/bathroom doors from the outside in an emergency.
10. A robust (and tested) arrangement for immediate maintenance of life support (i.e. resuscitation and stabilisation of subjects in an acute emergency) and onward transfer of subjects to hospital, where necessary
11. All staff must undergo periodic testing of emergency scenarios within the unit. This testing must be documented. For those staff in contact with subjects, they must attend at least one scenario a year in addition to any scenarios conducted as part of a staff members life support certification (e.g. ALS/ILS/BLS or equivalent)..

Staff

12. Documentation that demonstrates that medical doctors are authorised to act as principal investigator – for example, as described by their job description (or other formal documentation approved by appropriately appointed personnel, such as the risk assessment, an authorisation statement, etc.), and supported by a *curriculum vitae* and training record. It is expected that Principal Investigators have relevant qualifications, training and clinical experience.

For medical doctors that wish to undertake first in human trials (FIH), in addition to the above it is expected that Principal Investigators for FIH trials have relevant clinical experience in running Phase I trials, plus a post-graduate qualification, such as a Diploma in Human Pharmacology, MSc in Clinical Pharmacology or equivalent. The Diploma in Pharmaceutical Medicine would only be considered acceptable where it is supported by experience in FIH trials.

Where the unit does not directly employ the PI, there must be a mechanism for the unit to assess the trial and the suitability of the PI, plus their research team (as applicable) and ensure there is responsibility formally assigned that meets the above qualifications, training and experience where gaps are identified (e.g. use of a Phase I review committee and expert advisor, information is available on expectation in the associated guidance⁴).

13. Documentation that demonstrates that appropriately trained and experienced staff are available on dosing days. During the conduct of EAG type trials, medical doctors trained to Advanced Life Support (ALS) standards and experienced in handling medical emergencies must be present during and following dosing for a defined period. In addition to theoretical knowledge, the medical doctors must have relevant and recent experience of handling medical emergencies. Units may approach this in a number of ways, for example:

- The units employed (or core staff) Clinical Research Physicians (CRP) are ALS trained^A and may participate on an ongoing basis in periodic clinical attachments involving participation in a hospital resuscitation team rota to ensure continued exposure to identifying and handling real medical emergencies^B.

Or

- Appropriately trained clinicians with up-to-date emergency medicine experience may be brought in to the unit on a contract basis during dosing days. These contract staff must also be trained in ALS, the study protocol, unit procedures and GCP. The contractor would not be expected to take on the role of the Principal Investigator and must be appropriately supervised whilst in the unit. Indemnity

arrangements made by the Sponsor and/or unit must also apply to the contract medic.

Or

- Phase I unit may be located within a hospital; with critical care facilities. The unit will have 24-hour access to the hospital emergency response team, who can arrive at the unit within minutes of an emergency.

^A *For paediatric Phase I trials an equivalent paediatric life support training (for example, Advanced Paediatric Life Support (APLS) or European Paediatric Life Support (EPLS)).*

^B *Where the unit uses its employed (or core) CRPs to provide cover in a medical emergency, the CRPs must be able to demonstrate appropriate training and experience in handling medical emergencies. A procedure must be in place to address the assessment of continuing competency in this area (e.g. it may be achieved by peer review, audit or other means). This continuing assessment must be documented and countersigned by the assessors. Evidence must be kept to document exposure to medical emergencies in order to demonstrate that they remain experienced and competent to handle such emergencies.*

14. Documentation to demonstrate that there are sufficient numbers of trained and experienced staff employed by or contracted to the unit for all activities conducted by the unit (including appropriate numbers of staff with adequate training to handle medical emergencies). There must be sufficient cover for dosing days and overnight stays. The unit must have in place a policy or SOP that stipulates the minimum staffing levels during clinical conduct of the study.
15. Staff that are appropriately and currently trained and assessed as competent to perform the activities that they are assigned to undertake. In addition, for clinical staff this must include initiating resuscitation (i.e. basic airway management and ventilation, i.v. cannulation and fluid therapy, giving adrenaline, CPR and use of an automated external defibrillator (AED)). Annual updates are required. At a minimum clinical staff should receive Immediate Life Support (ILS) Training and annual updates (or equivalent paediatric life support training (e.g. PILs) for units that undertake paediatric trials).

Subject Identification

16. A procedure to address 'over-volunteering'.
17. A robust procedure to accurately identify subjects. For volunteers this must include utilising photographic identification, thereby verifying the persons identify/existence and ensuring that the person screened is the person dosed.
18. For FIH and EAG type trials, unit is required to confirm the subjects' past medical history. For volunteers, this should be received *via* the subjects' GP, or other medical doctor (such as hospital consultant for patient 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 inclusion and exclusion criteria are met.
19. The unit must also hold the contact numbers for subjects to ensure that they are able to be contacted outside the unit should the need arise. Subjects must also be provided with 24-hour emergency contact numbers for while they are outside the unit.

Quality System

20. Written Standard Operating Procedures (SOPs) for every aspect of the unit's activities including all the accreditation requirements. These SOPs must specifically include (but are not limited to):
- a. Procedures for handling common medical emergencies e.g. syncope, hypotension, anaphylaxis, cardiac arrest
 - b. Out-of-hours medical cover and contact with sponsor or IMP responsible person(s)
 - c. Procedures for handling immediate maintenance of life support (i.e. resuscitation and stabilisation of subjects in an acute emergency)
 - d. Transfer of subjects to hospital, including the provision of all relevant medical information regarding the trial and the subject(s) in question to the hospital
 - e. Training and refresher training, including competency assessments for all key activities, including emergency resuscitation procedures
 - f. Unblinding in an emergency
 - g. Risk assessment and mitigation
 - h. Dose escalation
 - i. Staffing level/resourcing
 - j. Expectation for minimum qualifications, training and experience for key roles and responsibilities (e.g. PIs, nurses, Phase I review committees etc).
 - k. Minimum staffing requirements
 - l. Subject recruitment, including identification, medical history and over-volunteering.

[Note: This is not an exhaustive list, and units should ensure all activities are formalised adequately, especially where these impact on accreditation requirements.]