MHRA

PHASE I
ACCREDITATION SCHEME

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1. Background

The TGN1412 incident, in March 2006, where six trial subjects became seriously ill and were admitted to intensive care, has raised the profile of phase I clinical trials in general and 'First in human' (FIH) trials in particular.

It is recognised that the recommendations from the Expert Scientific Group on Phase I Clinical Trials (ESG) include procedural changes for the conduct of FIH studies and that European guidance on First in Human studies on Investigational Medicinal Products (IMPs) has been published. The MHRA will also seek the opinion of the Clinical Trials Expert Advisory Group of the Commission on Human Medicines (CTEAG) for those FIH studies with risk factors that would require review before a clinical trial may be authorised. To maximise subject safety and to create additional public confidence in the regulatory oversight of such trials, it is proposed that a voluntary accreditation scheme be established for units conducting phase I trials in the UK.

The aim would be to formalise routine inspections and to increase the scope and depth of inspections in order to provide MHRA and Ethics Committees with more information about the units seeking to conduct these trials, so that approval decisions are made even more robust.

The scheme would give assurance that units within the scheme meet satisfactory standards for avoiding harm to trial subjects and for handling medical emergencies should they arise.

The MHRA GCP Inspectorate already carries out GCP inspections of units conducting phase I trials in the UK and, at the beginning of 2006, moved to a cyclical programme of inspections of these units.

2. Scope

It is proposed that a voluntary accreditation scheme is created 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 (Statutory Instrument 2004/1031[1]). . The scheme would have a classification system based on facilities, training and experience of personnel and ability to manage trials with certain risk factors that would require review by the CTEAG. Further information on these risk factors can be found on the MHRA website[2] and in the 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 will initially be for units conducting non-therapeutic Phase I studies, including those units conducting early phase studies in 'patient volunteer' populations e.g. asthma sufferers. The proposal is not initially intended for Phase I studies in severely ill patients which are conducted in a hospital setting. The accreditation scheme is also not intended to apply to units who only conduct non-drug trials, i.e. those that do not require a Clinical Trial Authorisation (CTA). The Scheme will be reviewed post-implementation and the MHRA intends to work with those conducting Phase I studies in patients in order to achieve an appropriate accreditation scheme for these units.

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 studies have adequate staff and facilities for dealing with any such emergencies.

This accreditation scheme is concerned with the operation of Phase I units. Sponsors have additional responsibilities with respect to the design of the study and the collection and analysis of preclinical data. It is essential that sponsors are aware of potential risks and take steps to mitigate these risks[3].

Statutory GCP Inspections have been in place since May 2004. Those Units that are part of the voluntary 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 who are not accredited are not precluded from conducting clinical trials, since the scheme is voluntary. However, ethics committees will take the absence of accreditation into account when considering the trial site and may consider conducting their own site inspection.

3. Classification of Units

From a review of completed accreditation application forms submitted by participating units to the MHRA GCP Inspectorate, units conducting early phase trials will be assessed and accredited. There will be two types of accreditation.

Standard Accreditation

Standard units will be accredited to carry out all phase I trials other than FIH trials with risk factors that would require CTEAG review. Examples of trials where expert advice may be sought can be found on the MHRA website[2] This will be the standard applied for all UK Phase I Units.

Supplementary Accreditation

Units who wish to be accredited to carry out clinical trials with compounds at all levels of risk, including those that require review of risk factors by the CTEAG may apply for Supplementary accreditation.. The unit must demonstrate that appropriately trained and experienced staff are available on dosing days. It is not a requirement that these units are physically located within a hospital, providing that the unit is able to demonstrate that experienced personnel and facilities are immediately available to manage medical emergencies.

The MHRA Clinical Trials Unit may make a recommendation when issuing a CTA that it is expected that the study is to be carried out in a Clinical Trial Unit with personnel and facilities appropriate to the perceived level of risk.

4. Intended operation of the accreditation scheme

The scheme will be operated on a voluntary basis. Standard accreditation inspections equate to the current GCP Inspections. Supplementary accreditation inspections would be wider in scope and more detailed than the current GCP inspections.

Units will complete a detailed application form and apply for either Standard or Supplementary accreditation and the inspection will be carried out accordingly, with an appropriate fee. Fees will be consistent with current inspection fees, and these are subject to a separate consultation document (MLX 334, published on the MHRA website[2]). In addition, there will be an initial set-up fee, plus a small fee each time a new certificate is issued. A request to re-classify from Standard to Supplementary at a later date will require a further fee, as an inspection will be required to assess criteria not previously reviewed.

Once inspected, the unit would be accredited accordingly, and an accreditation certificate issued. The certificate will be valid for 2 years, and a re-inspection will be performed prior to renewal of the certificate. Units are required to submit to the MHRA GCP Inspectorate any significant changes within this 2-year period. Significant changes are those that affect the basis upon which the accreditation was based as outlined in Appendix I, for example:

- Relocation of the Unit, or addition of facilities (e.g. extension of existing unit, the permanent use of facilities at another location)
- 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, these will be the Physicians, including the Medical Director (or the physician who has overall responsibility for medical aspects), 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) and the Pharmacist or individual responsible for the emergency drugs.
- Significant contractual changes in agreements with local hospitals.

If changes at the unit result in any of the accreditation criteria no longer being met, the MHRA GCP Inspectorate must be informed immediately. If substantial changes occur during a clinical trial, then the Ethics Committee and MHRA CTU need to be informed where appropriate and in accordance with the legislation.

Inspection reports and accreditation certificates, noting the classification, will be sent to appropriate ethics committees/NRES to assist them with their responsibility to carry out site-specific assessments of these units. Local ethics committees/hospital trusts, retain the responsibility for site-specific review, in accordance with current procedures. The accreditation grading will help to inform this assessment. Ethics Committees may request further information to assist with the site specific assessment, whether or not the unit participates in the accreditation scheme.

5. Reporting Accreditation Inspections

Following routine accreditation inspections, which have not resulted in critical findings, an inspection report will usually be produced within 30 working days. Any major findings in the area of subject safety (e.g. eligibility, medical cover, subject identification etc.) will need to be resolved prior to accreditation.

If critical findings are made during the inspection, the lead inspector will promptly inform the relevant NHS Trust, NRES, MHRA Clinical Trials Unit, as appropriate, and in accordance with the memorandum of understanding between MHRA and NRES. An accreditation certificate will not be issued unless and until critical findings have been adequately resolved.

6. References

1. The Medicines for Human Use (Clinical Trials) regulations 1994 (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 (EMEA/CHMP/SWP/28367/07)

Appendix 1

Criteria for Classification

In addition to there being no unresolved critical findings and no unresolved major findings in the area of subject safety (e.g. eligibility, medical cover, subject identification etc.) at the site the following will need to be in place for all units conducting phase I trials, who wish to participate in the voluntary scheme:

Standard accreditation

Units will be accredited to carry out trials other than FIH trials with risk factors that require CTEAG review

All units participating in the scheme are required to have the following;

1. It is expected that the unit have either an existing agreement with the hospital for supporting emergencies arising from their clinical trials or is able to demonstrate communication and notification of trial information (e.g. dosing times) with the hospitals emergency teams. The hospital emergency response team and the ITU must be aware of the Research Unit, the nature of the research (e.g. First in Human, Biologicals etc.), and that they could be referred patients from the unit at any time.
2. The Unit must have robust (and tested) arrangements for immediate maintenance of life support (i.e. resuscitation and stabilisation) and onward transfer of subjects to hospital, where necessary. Periodic all staff testing of emergency scenarios should occur within the unit and be documented.
3. There must be documentation that demonstrates that physicians are authorised to act as principal investigator in first in human studies – as described by their job description, and supported by a *curriculum vitae* and training record It is expected that Principal Investigators have relevant clinical experience, plus a post graduate qualification, such as a Diploma in Pharmaceutical medicine, Diploma in Human Pharmacology, MSc in Clinical Pharmacology or equivalent.
4. The unit must have appropriate numbers of staff with adequate training to handle medical emergencies.
5. Contracts and agreements with sponsors (or internal memorandum of understanding for in-house units) must detail procedures and responsibilities for notifying the investigator immediately if/when new safety/toxicology data come to light.
6. There must be a procedure in place to address 'overvolunteering'.
7. There must be written Standard Operating Procedures (SOPs) for every aspect of the study process. Specifically these SOPs must include:
    a. Transfer of subjects to hospital; to include the provision of all relevant medical information regarding the trial and the subject(s) in question to the hospital
    b. Medical emergencies to include stabilising subjects in an acute emergency
    c. Out-of-hours medical cover and contact with sponsor or IMP responsible person(s)
    d. Training and refresher training in emergency resuscitation procedures
    e. Procedures for handling common medical emergencies e.g. syncope, hypotension, anaphylaxis, cardiac arrest
    f. Unblinding in an emergency.
    g. Dose escalation

8. The unit must be able to demonstrate that there are sufficient numbers of trained staff employed by or contracted to the unit. 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
9. Clinical staff must be appropriately and currently trained to initiate 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 Training and annual updates.
10. An emergency trolley should be available that is easily and rapidly accessible. There should be a trolley in each main area, that can be moved quickly to where it is needed. The emergency trolley should be stocked as per the current resuscitation council guidelines and should carry as a minimum:
    a. Oxygen and delivery apparatus
    b. Equipment for procedures such as cannulation and suitable fluids for IV infusion
    c. Laryngeal Mask Airways or other supraglottic airway devices
    d. Self-inflating bag, or equivalent, for assisted ventilation
    e. Suction equipment
    f. Defibrillator – this should be an AED defibrillator with a manual override
    g. Instruments for intubation and emergency cricothyroidotomy should be carried on the trolley for use by appropriately experienced personnel or a responding emergency team only.
11. Continuous monitoring equipment must be available to include ECG, pulse oximetry, vital signs such as blood pressure, heart rate and temperature.
12. The contents of the trolley should be checked weekly, and the checks documented. Expiry dates for medication on the trolley should be checked regularly and documented. If the trolley or the emergency drug box is sealed then the tamper proof seal should be checked weekly.
13. Subjects must be provided with 24-hour emergency contact numbers for while they are outside the unit. The Unit must also hold the contact numbers for volunteers to ensure that they are able to be contacted outside the unit should the need arise.
14. Beds (where used for dosing days) must be able to be tilted and adjusted for height.
15. There must be alarm points in areas where the subjects will be e.g. showers, toilets, in the ward and recreational area. Staff must be able to open bathroom doors from the outside in an emergency.
16. There must be a robust procedure in place to accurately identify subjects, utilising photographic identification, thereby ensuring that the person screened is the person dosed.

Supplementary accreditation

The following are additional to the requirements for Standard accreditation:

1. It is essential that the unit demonstrates that appropriately trained and experienced staff are available on dosing days. Clinical Research Physicians in these units must be trained to Advanced Life Support (ALS) standards and experienced in handling medical emergencies. In addition to theoretical knowledge, the Clinical Research Physicians must have relevant and recent experience of handling medical emergencies. Units may approach this in a number of ways, for example:

    - Clinical Research Physicians may participate on an ongoing basis in periodic clinical attachments involving periodic participation in a hospital resuscitation team rota to ensure continued exposure to identifying and handling real medical emergencies.

    And/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.

    And/or

    - Phase I units 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.

    Research physicians employed by Phase I units seeking supplementary accreditation must be able to demonstrate appropriate training and experience in handing medical emergencies. A procedure must be in place to address the assessment of continuing competency in this area and may be achieved by peer review, audit or other means. This continuing assessment must be documented and countersigned by the assessors. A training record must be kept and a log maintained to document exposure to medical emergencies in order to demonstrate that they remain experienced and competent to handle such emergencies.

2. There must be a procedure in place for contingency planning. This must include consideration of availability of specific antidotes/emergency treatments and predictable reactions based on the pharmacology of the IMP.
3. It is a requirement that confirmation of subjects' past medical history for these trials is received *via* the subjects' GP, or other medic such as hospital consultant for patient studies, to provide assurance that inclusion and exclusion criteria are met.