

## **GCP INSPECTORATE**

# **RESPONSES TO PUBLIC CONSULTATION OF THE PHASE I ACCREDITATION SCHEME October 2007**

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## **1. Introduction**

This document serves to summarise the responses received from the public following the production of the proposal for the UK Phase I Accreditation Scheme, published on 30<sup>th</sup> August 2007. The consultation ended on 12<sup>th</sup> October 2007 and a total of 53 responses were received from concerned parties. Responses were received from a variety of sources including Sponsors, Phase I Units, NHS representatives, Ethics Committees and the Commission on Human Medicines and the Expert Advisory Group. A list of responders can be found in Appendix 1; this list does not include those responders who wished their name or response to remain confidential.

## **2. 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' trials in particular. To create additional public confidence in the regulatory oversight of such trials, it was proposed that an accreditation scheme be established for units conducting phase I trials, thus extending the recommendations of the Expert Scientific Group (ESG) to include all Phase I studies, not only those of 'higher risk' molecules conducted for the first time in man.

The aim is 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 facilities seeking to conduct these trials, so that approval decisions are made even more robust. The scheme would give assurance that facilities within the scheme meet satisfactory standards for avoiding harm to trial subjects and for handling medical emergencies if they arose. The MHRA GCP Inspectorate already carries out GCP inspections of units conducting phase I trials and, at the beginning of 2006, moved to a cyclical programme of inspections of these units.

## **3. Responses to Proposal**

### **3.1 Overview**

Overall the majority of responders welcomed the proposed scheme and supported the consideration and evaluation of potential risks and measures to be taken to minimise these risks. The accreditation scheme is widely seen as an important step in maximising volunteer safety. However, two of the 53 responses did not support the proposed scheme and raised concerns that the scheme would be burdensome and may damage the Phase I industry in the UK.

### **3.2 Specific**

#### **3.2.1. Voluntary Scheme**

The majority of responders stated that the scheme should be mandatory and not voluntary and questioned the value of the scheme if it was not mandatory. Others stated that although the scheme is intended to be run as voluntary, it will essentially become mandatory as Sponsors are unlikely to place studies with those Units that do not have accreditation (please also refer to 3.3.1).

### **3.2.2 Training of Clinical Research Staff**

There were concerns in relation to the requirement to ensure that Clinical Research Physicians must have recent experience in handling medical emergencies that goes beyond theoretical knowledge. The Phase I accreditation proposal made suggestions as to how this could be achieved. The suggestions were to either bring in, on contract, experienced physicians for dosing days or ensure existing physicians received the appropriate training. Concerns were raised over perceived difficulties in finding appropriate placements in the NHS for Phase I Physicians. There were also concerns raised over indemnity issues, the need for an honorary contract and also a perceived lack of co-operation within NHS Trusts. It was also felt by a number of responders that the focus on resuscitation and cardiac arrest may be inappropriate for Phase I units as this is a rare scenario in healthy volunteer studies.

### **3.2.3 Standard and Supplementary Accreditation**

Several responders questioned the need for two levels of accreditation, specifying that all units should meet the requirements as severe adverse reactions may also occur with well established drugs. Clarification was sought regarding the levels of accreditation, as there was concern raised over the perception that the Standard accreditation offers a lower level of protection to volunteers.

## **3.3 Questions Raised**

### **3.3.1 Why is the scheme voluntary and not mandatory?**

To introduce a mandatory scheme would exceed the MHRA's powers under the Clinical Trials Directive. The Clinical Trials Directive comprehensively sets out the compulsory requirements for a trial and the relevant considerations; at present, there is no scope for the UK to add further requirements.

### **3.3.2 If a unit does not obtain voluntary accreditation, will it be able to conduct Phase I clinical trials?**

There will be no consequence if the Unit does not have accreditation simply because they do not wish to apply. Units who are not accredited are not precluded from conducting clinical trials, since the scheme is voluntary. If the Unit does not attain a satisfactory standard, this would indicate serious non-compliance with GCP and further action would be taken; this would be the case whether the Unit was part of the accreditation scheme or not. However, National Research Ethics Service (NRES) will take the absence of accreditation in to account when considering the trial site and may consider conducting their own site inspection. The MHRA Clinical Trials Unit may make a recommendation with regards to facilities for those studies reviewed by the EAG, but not with regards to the accreditation status of the unit.

### **3.3.3 Are there any transitional arrangements? Following application, a delay in inspection may result in a delay in accreditation. Those accredited first may have a commercial advantage.**

It is the intention of the MHRA to issue accreditation in April 2008. Before the end of 2007, Units will be invited to apply for accreditation. Inspection will follow where necessary. It may be possible to grant standard accreditation without an immediate inspection, where a recent statutory GCP inspection has taken place.

### **3.3.4 If the MHRA Clinical Trials Unit make a recommendation with respect to site facilities, what action will be taken if the Sponsor chooses not to follow the recommendation?**

MHRA will not take any action, as this would be a recommendation and not a condition of approval. However, the Ethics Committee may choose to consider whether a site inspection

is required and may take into account the recommendations of the MHRA before granting approval.

**3.3.5 Are these accreditation inspections in addition to the statutory inspections?**

No. Those Units that are part of the voluntary scheme will not receive additional routine statutory GCP systems inspections. However, the MHRA reserve the right to perform a triggered inspection of the Unit if concerns arise or if important information comes to light that requires investigation.

**3.3.6 Will an accreditation certificate be issued if there are critical findings?**

No. If there are critical findings from the inspection a certificate of accreditation will not be issued, as the unit will not have fulfilled the requirements for accreditation. Critical issues would need to be resolved prior to accreditation, and a follow-up inspection may be required.

**3.3.7 Will the requirement for supplementary accreditation include all FIH studies or just those deemed to be 'higher risk'?**

The supplementary accreditation is intended for those studies that are referred to the EAG for the review of risk factors, for example First in Human trials with novel compounds.

**3.3.8 Is this accreditation scheme likely to be adopted in the rest of the EU and if so when?**

Phase I studies have been extensively discussed in the European arena and the CHMP have produced a guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMA/CHMP/SWP/294648/2007)

There are likely to be changes in guidance and legislation at the European level, however these are still under discussion.

**3.3.9 Is it the intention to announce a set time for the consideration stage between application, inspection and decision?**

It is not our intention to impose time constraints at this time, however we will abide by the current procedure of issuing inspection reports, and therefore accreditation certificates within 30 days of the inspection.

**3.3.10 Will the MHRA consider the Diploma in Human Pharmacology currently being proposed by the Faculty of Pharmaceutical Medicine together with relevant clinical experience appropriate authorisation for PIs?**

The MHRA supports the implementation of the Diploma. Appropriate authorisation will include relevant experience in addition to postgraduate qualifications, which may include the Diploma or other relevant qualification.

**3.3.11 Will the MHRA meet with the DoH with regards to physicians from CROs attending and actively participating with emergency response teams?**

The MHRA would support such an initiative.

**3.3.12 Will an Regulatory Impact Assessment be made?**

As this is a voluntary scheme, the regulatory impact is assessed to be minimal. However, the fees MLX 334 published on 17<sup>th</sup> October 2007 and currently undergoing public consultation, includes the provision for the accreditation scheme, and includes a regulatory impact assessment.

**3.3.13 What is the definition of '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.

For those commercial Phase I units based within a hospital it is not expected that NHS Trust personnel (e.g. those in the hospital emergency response team) are listed as key personnel for the purposes of accreditation, unless there is a contract in place with individuals who provide locum services.

**3.3.14 What information is required to be sent to the local hospital?**

It is not intended that the Units forward the protocols for each study; not only would this not serve any purpose for the local Trust, but it would also breach Sponsor confidentiality. The local hospital must be aware of the Unit, the types of studies undertaken e.g. FIH, biologicals etc. and it is also recommended that they are informed of first dosing days.

**3.3.15 Would the MHRA consider requiring an annual update report, in order that Phase I units are prompted to inform the MHRA of any changes that may impact on the accreditation?**

The accreditation proposal stipulates that units must inform the Inspectorate of any significant changes that affect the basis upon which accreditation was granted. The completion of an annual update will add to the burden of administration of the scheme both to the Phase I Unit and to the MHRA, therefore it is not the intention of the Inspectorate to implement a requirement for an annual update.

**3.3.16 What is the definition of ‘non-therapeutic’ study, as some oncology trials will collect efficacy data?**

A Phase I trial is defined in the legislation as a clinical trial 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 (SI 2004/1031). An oncology trial where the investigator is collecting efficacy data will still fulfil the criteria of Phase I (and non-therapeutic) where there is no evidence of therapeutic benefit.

**3.3.17 If supplementary accreditation has been applied for and the unit fails to meet it but meets the standard accreditation level, will that be given?**

Standard accreditation will be granted, providing all relevant criteria have been met.

**3.3.18 Will the MHRA be taking any liability for incidents which occur in a site they have accredited?**

The MHRA will not be taking any liability for such incidents. Clinical trials remain the responsibility of the Sponsor and the legislation clearly lays out responsibilities of both the Sponsor and Investigator. Participation in an accreditation scheme does not exempt Sponsors and Investigators from these responsibilities.

**3.3.19 Will Inspection reports also be sent the Sponsors?**

Accreditation inspection reports will be sent to Ethics Committees, but will not routinely be sent to Sponsors. GCP Inspections routinely review several studies during a systems inspection. Therefore, inspection reports may contain references to several studies, with several different sponsors, and it would therefore be a breach of confidentiality if these reports were distributed widely. It is the intention of the GCP Inspectorate to publish a list of accredited Units on the MHRA website.

**3.3.20 There is no mention of Quality Assurance in the scheme – would it be a sound recommendation to emphasise the importance of QA in improving quality and reducing risk?**

The accreditation proposal focuses on the key areas required to ensure patient safety and as such does not provide an exhaustive list of each area reviewed by the Inspectors. GCP Inspections routinely include review of quality assurance procedures, and this area will continue to be reviewed and assessed during an inspection for accreditation.

**4. Summary**

The MHRA would like to thank all those who contributed to the consultation of the proposed scheme and is grateful for the many helpful and constructive comments received. We are also grateful to the members of the Phase I Accreditation Consultative Committee who have engaged in discussion with the Inspectorate and added their expertise to the proposal. The proposal will be amended taking into consideration these responses and the final scheme will be published. The GCP Inspectorate will reconvene the Consultative Committee to review the scheme following implementation.

## **Appendix 1 – List of Responders**

Commission on Human Medicines and the Expert Advisory Group (CHM/EAG)  
Kyowa Hakko UK Ltd  
GlaxoSmithKline  
Royal College of Radiologists  
Clinical Contract Research Organisation (CCRA)  
BioIndustry Association (BIA)  
AstraZeneca  
Institute of Clinical Research (ICR)  
Faculty of Pharmaceutical Medicine, Royal College of Physicians  
Hammersmith Medicines Research  
Cancer Research UK (CRUK)  
Richmond Pharmacology  
Royal College of Nursing  
Wellcome Trust  
Association of Human Pharmacology in the Pharmaceutical Industry (AHPPI)  
Covance  
Royal College of Physicians of Edinburgh  
Chief Pharmacists Group  
Leander Edmunds (“Healthy Volunteer”)  
NHS  
UK Resuscitation Council  
Liverpool REC  
British Association of Research Quality Assurance (BARQA)