Is there a need for a uniform European accreditation system for Phase 1 units?

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Questions

• Do we need Phase 1 Accreditation systems?
  – Would a Phase 1 accreditation system be able to prevent an incident similar to TGN1412?

• Do we need a uniform European system?
  – What would be the advantages?
  – What would be the challenges?
Overview

1. Current Phase 1 Accreditation status in Europe
2. Does the accreditation system in the UK serve its purpose?
3. Advantages, Disadvantages and Challenges of Phase 1 accreditation systems
4. A European system, what are the potential benefits and challenges?
Current status

Germany and Belgium do not currently have accreditation systems.

France and the UK do have authorisation/accreditation systems.
Current status in other EU countries

Existing systems are not necessarily managed by the competent authority and they are not necessarily an accreditation for GCP:

- Romania – have a certificate for all clinical trial sites, including Phase I
- Hungary – have an accreditation system for Phase I, which is valid for 3 years (there are less than 5 such units in Hungary)
- Italy – accreditation exists for Phase I private clinics only. This is administered by local authorities, and is not a GCP inspection.
- There is interest in the UK system from outside the UK
- Some units outside the UK have adopted key points from the UK scheme
- Other EU member states are considering an Accreditation Scheme
# Current status in France and UK

<table>
<thead>
<tr>
<th>Features</th>
<th>France</th>
<th>UK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
<td>Mandatory authorisation</td>
<td>Mandatory GCP/GMP authorisation</td>
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<tr>
<td></td>
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<td>Voluntary P 1 Accreditation</td>
</tr>
<tr>
<td><strong>Introduction and revisions</strong></td>
<td>1988 (I), 2006 (R), 2010 (R)</td>
<td>GCP/GMP 2004 (I)</td>
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<td></td>
<td></td>
<td>GCP/GMP 2006(R) cyclical, P1 Accreditation 2008 (I)</td>
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<tr>
<td><strong>Levels</strong></td>
<td>One level</td>
<td>GCP/GMP authorisation</td>
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<tr>
<td></td>
<td></td>
<td>Standard/Supplementary Accreditation</td>
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<tr>
<td><strong>Valid Period</strong></td>
<td>5 years</td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Units concerned</strong></td>
<td>Conducting biomedical research</td>
<td>Conducting non-therapeutic CT (IMP), Commercial and non-commercial</td>
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## Current status in France and UK

<table>
<thead>
<tr>
<th>Features</th>
<th>France</th>
<th>UK</th>
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<tbody>
<tr>
<td>Administered by</td>
<td>Local Health Authority</td>
<td>National RA (MHRA)</td>
</tr>
<tr>
<td>Inspections conducted by</td>
<td>One doctor &amp; pharmacist</td>
<td>Two to three MHRA GCP inspectors</td>
</tr>
<tr>
<td>Latest key requirements</td>
<td>Decree 2010: •Staff training</td>
<td>Phase 1 Accreditation proposal 2007 &amp; FAQ 2009:</td>
</tr>
<tr>
<td></td>
<td>•Standard Operating procedures</td>
<td>Facility and key-staff specific</td>
</tr>
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<td></td>
<td>•Participation in national volunteer register</td>
<td></td>
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<tr>
<td></td>
<td>•Medical Emergency arrangements</td>
<td></td>
</tr>
<tr>
<td></td>
<td>•Collaboration with competent Investigator and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pharmacologist</td>
<td></td>
</tr>
<tr>
<td></td>
<td>•Pharmacy requirements</td>
<td></td>
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<td></td>
<td>•Allocation of responsibility to the person in</td>
<td></td>
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<tr>
<td></td>
<td>charge of the research unit</td>
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Current status in the UK

- **Green Light Sign Off**
- **Contingency Planning and Risk Assessment conducted by the PI**
- **PI postgraduate qualifications**
- **Confirmation of medical and study history of participants**
- **Dose escalation procedures including minimum data requirements**
- **Quality control of dose escalation data**
- **Stopping rules and decision making**
- **Randomisation procedures for dose leaders**
- **Resuscitation and medical emergency arrangements, including rehearsals and hospital transfers**

A unit can pass the (mandatory) MHRA GCP inspections but fail the (voluntary) Phase 1 Accreditation inspection if the key requirements are not met.

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Using the UK Phase 1 accreditation as an example, would it avoid an incident comparable to TGN?
An experienced PI who seeks expert advice in areas outside their competence would:

- Question if the animal model and calculation of first dose is relevant
- Realise from the information available that the physiological activity of the compound is relatively novel and the intensity of effects could be extensive, non-linear and dangerous
- A small group of subjects would be dosed at any one time (likely no more than one)
- Intensive monitoring by physicians experienced in dealing with emergencies would be in place at all times
The test

Contingency Planning and Risk Assessment conducted by the PI

Green Light Sign Off

PI postgraduate qualifications

PI qualifications considered relevant by the MHRA

• PI should be able to calculate the proposed starting dose
• Should be able to review pre-clinical data
• Should question the sponsor to ensure they have all relevant information and should be able to interpret it
• Relevant postgraduate qualifications such as Dip Pharm Med, Diploma in Human Pharmacology, Specialist Accreditation in Clinical Pharmacology, higher degree in Pharmacology
• Exemption from postgraduate qualifications is possible if the PI has significant amount of experience

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The test

Contingency Planning and Risk Assessment conducted by the PI

PI postgraduate qualifications

Confirmation of medical and study history of participants

Green Light Sign Off

Medical History of Participants

• Can as part of the scheme make an important contribution to avoiding serious incidents

Resuscitation and medical emergency arrangements, including rehearsals and hospital transfers

Randomisation procedures for dose leaders

Stopping rules and decision making

Quality control of dose escalation data

Dose escalation procedures including minimum data requirements

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Dose escalation and stopping rules

- Are not applicable for managing the risk of the first dose
- Can as part of the scheme help to prevent incidents from occurring at consecutive dose levels (when the pharmacological effects may become more apparent)
- Require quick and appropriate data interpretation
The test

Contingency Planning and Risk Assessment conducted by the PI

PI postgraduate qualifications

Confirmation

Resuscitation and medical emergency arrangements, including rehearsals and hospital transfers

Green Light Sign Off

Confirmation

Dose leaders help to manage risks

Randomisation procedures for dose leaders

Stopping rules and decision making

Quality control of dose escalation data

Dose escalation procedures including minimum data requirements

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Resuscitation and emergency procedures

- Can only avoid an incident if the focus is on early recognition and treatment of acute medical conditions and critical illness
- Research unit and PI need to recognize the limits of their competency dealing with acutely ill patients
- Study specific planned and rehearsed emergency procedures can avoid delay in specialist medical care
The test

- Ensures that all approvals, contracts and indemnities are in place
- Would not by itself prevent a serious incident but assists
## Advantages and Disadvantages

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<tr>
<th>Party concerned</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Public</strong></td>
<td>• Contribution to the prevention of critical medical incidents</td>
<td>• Sense of false security once all boxes are ticked</td>
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<td></td>
<td>• Public confidence</td>
<td></td>
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<td></td>
<td>• Introduction of minimum standards</td>
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<td></td>
<td>• Could encourage more collaboration between academic and commercial units</td>
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<tr>
<td><strong>Sponsor</strong></td>
<td>• Quality mark</td>
<td>• Cost</td>
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<tr>
<td></td>
<td>• Confidence in choice</td>
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<td>• Supports the use of adaptive study designs</td>
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## Advantages and Disadvantages

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</tr>
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</table>
| Investigator    | • Investigator back-up and protection  
• Supports the conduct of complex early phase clinical trials | • Significant administrative effort  
• May impact on international competitiveness due to increased costs |
To introduce *gold* rather than *minimum* standards under appropriate stewardship

Fluid changes in inspector *expectations* which may not always be evidence based and or laid down in any guidelines

 Unless a medical doctor with significant Phase 1 experience is included in the inspection team, inspectors may lack *expertise to assess the clinical environment*

*PI qualifications* do need higher relevance and appropriate assessment

*Academic units* lag behind and may have difficulties complying

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A European System

What could it add to the national systems?

- Provide a platform for European knowledge transfer
- Provide clear European guidance
- Make Europe a ‘Continent of Excellence’ for complex early Phase Clinical Research

What would be the challenges?

- In order to be uniform would the accreditation be national according to European Guidelines or would there be an international inspection team/agency?
- The two main current European systems in France and the UK are quite different, with regards to content, conduct and legal basis, how would local differences be dealt with, in particular if more countries would get involved?
- What would be the legal basis (the UK system is currently voluntary)?
Thank you

- Ms Gail Francis, MHRA UK, who provided an update on the current status of the UK Phase 1 Accreditation system
- Dr Alain Patat, Biotrial France, who provided information on the French system
- Dr David Sciberras, Amgen UK, who provided a summary of the ABPI feedback on the UK system to the MHRA
Is there a need for a uniform European accreditation system for Phase 1 units?

Are there any additional potential benefits and challenges?
Would the challenges and efforts outweigh the benefits?
Rather than needing a European system would it be nice to have?

Are national or no accreditation systems preferable?
Do we need something different or something additional (such as a European training programme for Principal Investigators?)