Club Phase I & AGAH
3rd Joint Annual Meeting

Session 3:Managing the risk of Phase I trials
Accreditation of Phase I Units in the UK

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Lyon, 29 April 2009

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Changes to the regulatory environment for the conduct of clinical trials in the UK

- Historically one of the two least regulated countries in Western Europe
  - The Medicines for Human Use (Clinical Trials) Regulations 2004 - SI 2004/1031
  - The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 - SI 2006/1928

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Changes to the regulatory environment for the conduct of clinical trials in the UK

- Historically one of the two least regulated countries in Western Europe
  - Phase I studies in healthy subjects became regulated
  - GCP/GMP inspections became mandatory
  - Regulation of Ethics Committees
  - (formation of the NIHR Clinical Research Network)

22 Recommendations in Duff's Report

Three relate to the clinical environment for first-in-man studies

18. **Principal Investigators** who are responsible for the care of subjects in first-in-man trials should always be appropriately **qualified**, and satisfy themselves that they **know** enough **about the agent**, its target and mechanism of action to be in a position to make **informed clinical judgements**. The development of a national professional accreditation system for Principal Investigators conducting first-in-man clinical trials should be strongly encouraged.

19. In first-in-man studies where there is a predictable **risk** of certain types of severe adverse reaction, a treatment **strategy** should be considered beforehand. This should include the availability of specific antidotes where they exist and a clear plan of supportive treatment, including the pre-arranged **contingency** availability of ITU facilities.

20. First-in-man studies of higher risk medicines should always be conducted in an appropriate clinical **environment** supervised by staff with appropriate levels of training and expertise, with **immediate access to facilities for the treatment and stabilisation of individuals in an acute emergency**, and with pre-arranged contingency availability of **ITU facilities** in reasonable **proximity**.

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Phase I Accreditation Since April 2008

- Phase I accreditation scheme published 20 Nov 2007
- Inspections underway from February 2008
- Fully operational since April 2008
- Initially voluntary

Types of Accreditation

1. Standard – The required standard for all units
2. Supplementary – for those units also wishing to conduct studies requiring Expert Advisory Group (EAG) review.

Not levels – i.e. supplementary does not mean that units are more GCP compliant than those who achieve the standard accreditation.

UK Phase I Accreditation

Early Phase Units	Total*	Applied	Accredited
Industry	**5**	**1**	**0**
CRO	**27***	**16^**	**8/9**
CRC (NHS and academia)	**58**	**N/A**	**N/A**

* approximately
^ 14 Standard and Supplementary

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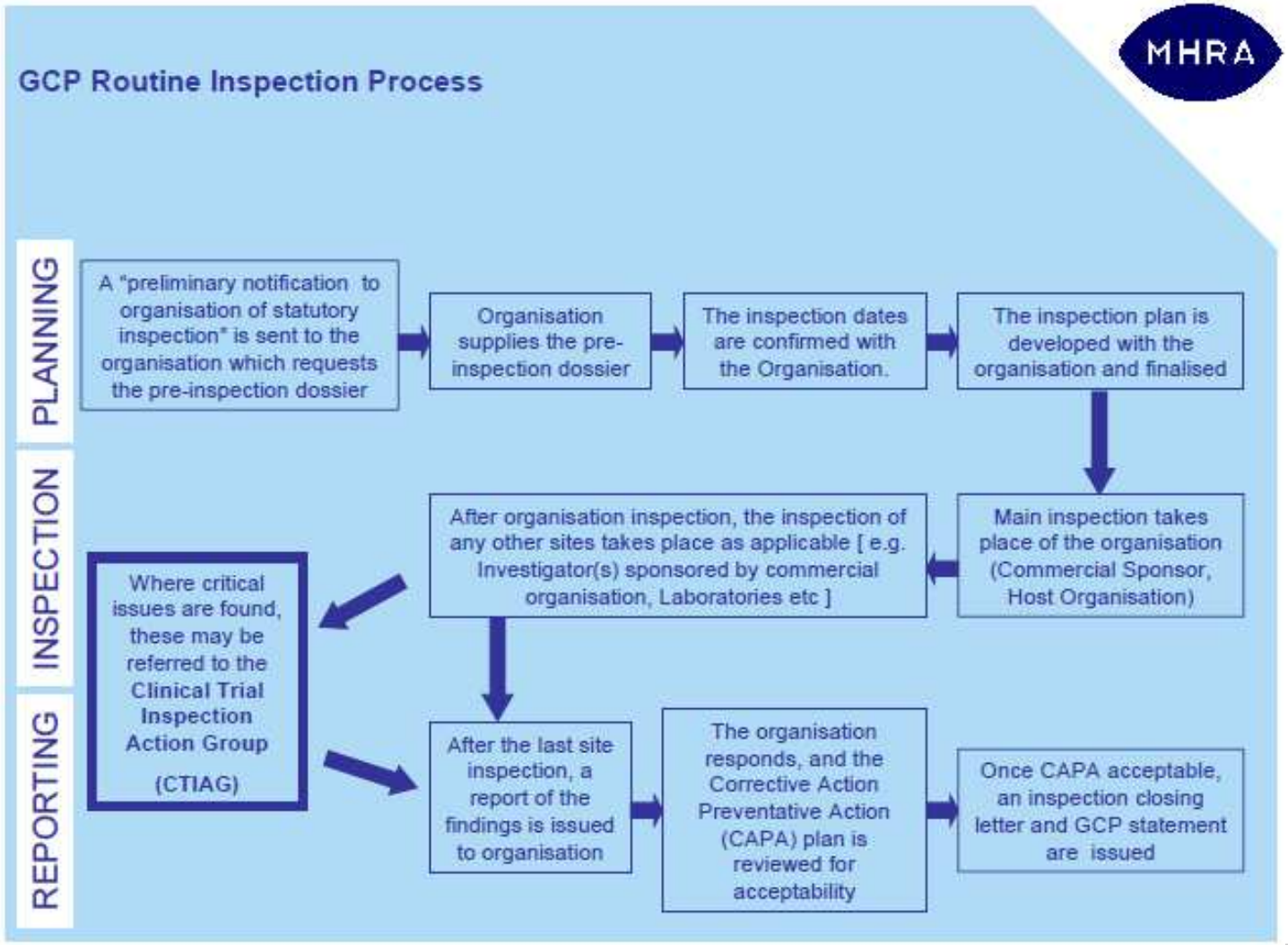

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Legal Background

- The GCP inspectorate of the MHRA is responsible for inspecting clinical trials for compliance with Good Clinical Practice.
- The Good Manufacturing Practice (GMP) Medicine Inspectorate inspects manufacturing facilities which may be part of a Phase I Unit
- They are one of the five medicines inspectorates at the MHRA. The other three being:
  - Pharmacovigilance (GPvP) Inspectorate
  - Good Distribution Practice (GDP) Medicine Inspectorate
  - Good Laboratory Practice (GLP) Monitoring Authority

What is inspected in a GCP Inspection

- Everything!
- In particular:
  - Dose Escalation Process
  - Rehearsal of medical emergencies
  - Risk management and contingency planning
  - Policy on minimum staffing levels

What is inspected (1)
Dose Escalation Process

- Procedure for dose escalation process
- Number of subject data sets required to escalate
- Stopping rules (with a clear statement that these must be followed)
- Randomisation of "dose leaders"
- Documentation of data review
- Escalation decision by Sponsor and PI
- QC procedures for data on which decision is based

What is inspected (2)
Rehearsal of medical emergencies

- Rehearsal of various emergency scenarios
- Documented learning scenarios
- Preventative and corrective actions must be documented and followed
- Demonstration of an emergency scenario (including transfer to a hospital if applicable)
- Informing of the hospital and next of kin
- Un-blinding process

List of Accredited Phase I Units

Name of Unit	Location	Type of Accreditation	Date of Accreditation
NHS hospital (<4 miles)			
Simbec Research Limited	Merthyr Tydfil	Standard and Supplementary	20-Jun-08
Charles River Clinical Services	Riccarton, Edinburgh	Standard and Supplementary	14-Jan-09
within private hospital			
LCG Bioscience	Bourn, Cambridge	Standard and Supplementary	09-Jun-08
InCROM	Stepney Green, London	Standard and Supplementary	25-Mar-09
adjacent to NHS hospital/NHS hospital (<0.5mile)			
GDRU (Quintiles)	Newcommen Street, London	Standard and Supplementary	18-Aug-08
Hammersmith Medicines Research	Cumberland Avenue, London	Standard and Supplementary	11-Feb-09
MDS Pharma Services	Lisburn Road, Belfast	Standard	25-Mar-09
within NHS hospital			
Richmond Pharmacology	Mayday Hospital, London	Standard and Supplementary	14-Oct-08
Richmond Pharmacology	St Georges Hospital, London	Standard and Supplementary	14-Oct-08

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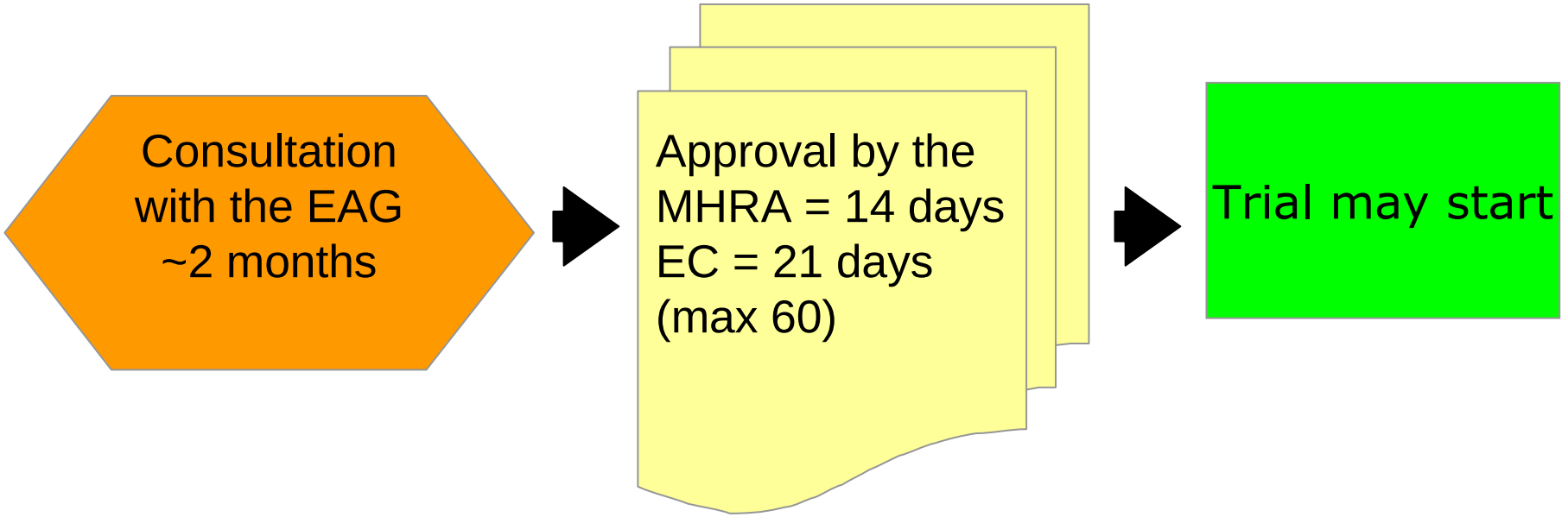
What is inspected (3)

Risk management and contingency planning

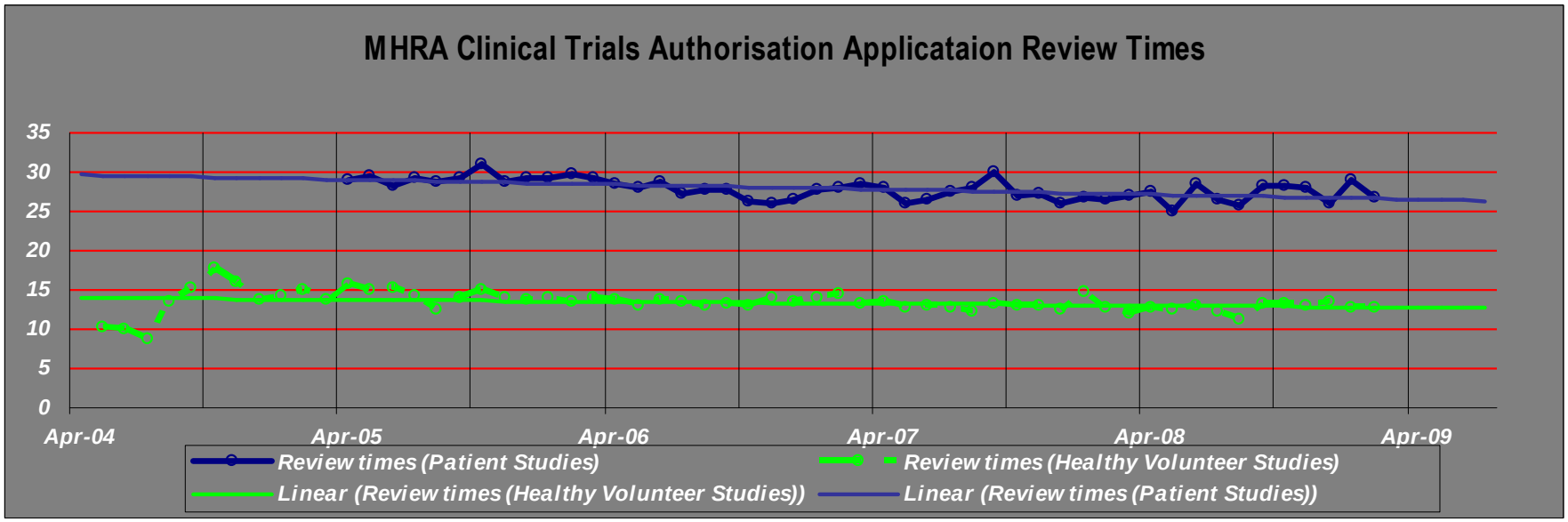
- Formal and documented risk assessments
- EMEA/CHMP/SWP/294648/2007 should be followed
- Documentation that a study does/not require EAG review

FTIM with "higher risk" IMP Application Process



Clinical Trial Authorisation Applications to the UK Competent Authority

April 2004 to February 2009



Data from www.mhra.gov.uk: the Medicines and Healthcare Regulatory Agency (MHRA), UK

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What is inspected (4)
Policy on minimum staffing levels

- No stipulation of specific numbers by the MHRA
- Adequate to respond adequately to an emergency
- Provision of evidence that the unit specific minimum staffing levels have been adhered to
- Provision of evidence that the protocol specific minimum staffing levels have been adhered to

Common Findings (1)

1. Issues with the dose escalation process is by far the most common finding from these inspections, in particular:
    - No clear procedure for handling dose escalation studies
    - 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 QC on data used to make escalation decisions

Common Findings (2)

2. No procedure for risk management
3. 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
4. Training records for agency or bank staff were incomplete or missing
5. 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.
6. Expired or missing items on the resuscitation trolley
7. No formal procedure to address overvolunteering, or the steps taken to avoid overvolunteering have not been documented.

Ethics Committees/Site Specific Approvals

- **Critical findings**: the REC is notified immediately, and NRES is also informed.
- **Major or Other findings**: The Inspection Information will be sent at the inspection close-out as one package to the local Ethics Committee
- **Inspection Information** is shared with the Ethics Committee:
  - Application Form
  - Inspection Report
  - Closing statement
  - Accreditation Certificate

What has the introduction of the accreditation achieved?

- Negative Aspects
  - Additional administrative burden
  - Additional cost

What has the introduction of the accreditation achieved?

- Opportunities
  - Changed the way in which we work
  - Establishing of minimum (best) practice across an entire UK based industry
  - Formal risk assessments prior to study start
  - Establishment of a risk mitigation processes
  - Clearer definition of the qualification and role of the Principal Investigator

It is a process!

Q & A

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