European Academy of Hospital Pharmacy Biotechnology Educational Summit

Clinical trials

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(Acknowledgment Mark Howells)

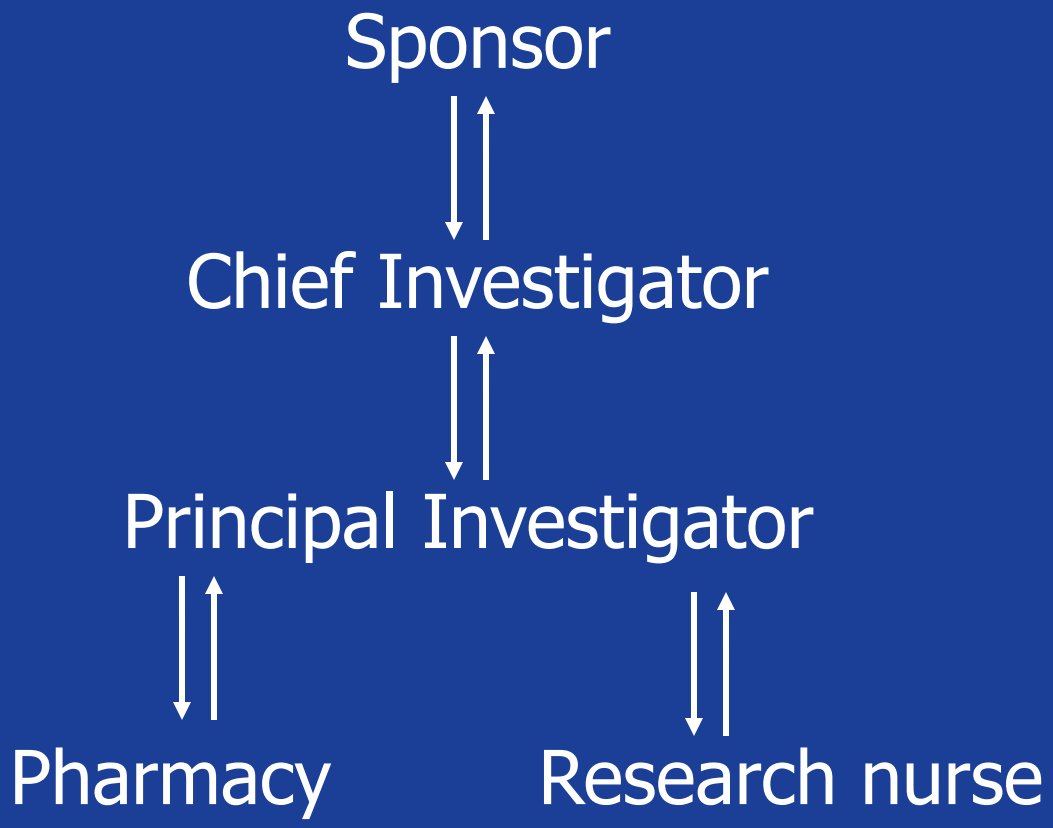
Objectives

- Have an appreciation and overview of clinical trials
- Understand potential roles for Hospital Pharmacy in supporting clinical trials
- Understand clinical trials in relation to biopharmaceuticals
- To determine mechanisms for dissemination of the knowledge and understanding gained

Scope

- Who is the research team?
- Who is responsible for what?
- How does Pharmacy fit into the picture?

The research team hierarchy



Sponsor

- An individual, company, institution or organisation that takes responsibility for the initiation, management and/or financing of a clinical trial

Sponsor’s responsibilities

- Quality assurance and control
- Trial design
- Management, data handling and records
- Investigator selection
- Notification/submission to regulatory authorities
- Investigational products
- Monitoring

Adverse Drug Reactions and Suspected (ADRs)

Chief Investigator (CI)

- The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the Chief Investigator

Principal Investigator (PI)

- The investigator responsible for the research site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of a single-site study, the CI and the PI will normally be the same person

Investigator's responsibilities

- Qualifications
- Openness
- Adequate resources
- Medical care
- Communication with REC/IRB
- Records and reporting
- Compliance with protocol (Adherence to guidelines)
- Investigational product
- Randomisation procedures
- ADR reporting

REC, research ethics committee; IRB, Institutional review board

Delegation of tasks

- Must document when tasks are delegated
- Those persons to whom tasks are delegated must be capable, by training and experience, to carry out the tasks

The research nurse

- Should be qualified and experienced
- Patient selection
- Usually the one doing the work

Eligibility

Data recording

Informed consent

Lots of regulations

- Medicines Act 1968
- EU Directive 2001/20/EC (CT Directive)
- EU Directive 2005/28/EC (GCP Directive)
- The Medicines for Human Use (Clinical Trials) Regulations 2004
- Good Manufacturing Practice (GMP)
- Duthie report
- Trust policies
- Standard Operating Procedures
- Just the start – its BIG!

What is an IMP?

"A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use."

ICH-GCP definition

ICH-GCP, International conference on harmonisation-Good Clinical Practice

So what is an IMP?

- An IMP is an Investigational Medicinal Product

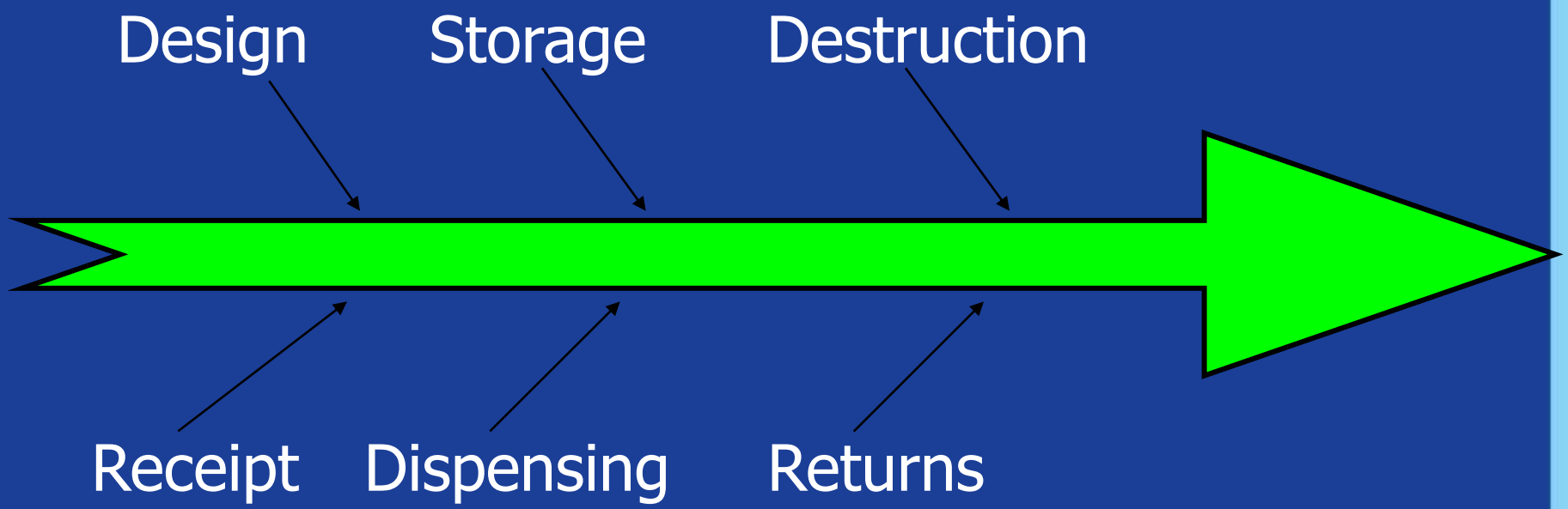
Pharmacy's role

What do the guidelines say?

- The investigator may/should delegate some or all of the investigator's/institution's duties for IMP accountability to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution

  ICH-GCP: 4.6.2

The Pharmacy role



The Pharmacy team

- Pharmacists
- Technicians
- Stores staff
- Assistants
- Clerical staff

What do people think we do?

- Store medicines for trials
- Dispense medicines for trials
- Hold up research

What can we do?

- Advise on protocol design
- Design study specific documentation
- Assist with the packaging of IMPs
- Environmental monitoring
- Staff training
- Dispensing
- Stock accountability
- Storage etc

Pharmacy ‘responsibilities’

- To safeguard trial subjects, staff and the Trust
- To ensure IMPs are used as per protocol
- To ensure our procedures comply with current guidelines and regulations

Staff

- Education and training
  - GCP
  - EU (Clinical Trials) Directive
  - Research Governance Framework
- All staff

Experience

Facilities

- Adequate storage for IMPs and returns
- Environment monitoring
- Storage and management of study files and prescriptions

Resources

- Fees for work
- Part of the clinical trial agreement between sponsor and Trust
- R&D approval
- Quality systems

Communication

- Internal
  - Research team
  - R&D
  - Pharmacy
- External
  - Sponsors
  - Monitors and auditors

Learning objectives

Do we….

- Have an appreciation and overview of clinical trials?
- Understand potential roles for Hospital Pharmacy in supporting clinical trials?

Yes (?)

No (?)

OK, now the hard part!

- Understand clinical trials in relation to Biopharmaceuticals

  ONLY NINE (9) points

1. All clinical trials of investigational medicinal products (IMP) come under the EU Clinical Trials Directive (http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.html)
   A massive statutory instrument document in legalise. This came into being as UK law on the 1st May 2004 as Directive 2001/20/EC or what we know as The Clinical Trials Directive (http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf)

   Fundamentally ALL clinical trials of medicinal products come under this directive with no exceptions.

2. For 'biopharmaceutical' read IMP – the legislation does not differentiate. If the product being tested has a pharmacological action in man then it is within the EU directive. (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/clinical_trial_qa_april_2006.pdf) for an algorithm that is used to decide if a product is within the scope of the directive.

3. All trials must be conducted according to Good Clinical Practice guidance – general considerations can be found at http://www.emea.europa.eu/pdfs/human/ich/029195en.pdf

   Basically this is a collection of documents that dictate what is considered to be good practice in trials or IMPs. It has been agreed that if these guidelines are followed then the resulting data will be accepted as valid for consideration for a licence application in the US, the EU and Japan.

4. Biopharmaceuticals are not different. They are still IMPs and have no special exceptions to my knolwledge - except that gene therapies must be passed by a GTAC gene therapy advisory committee which is a sort of ethics committee for gene therapies (http://www.advisorybodies.doh.gov.uk/genetics/gtac/).

5. In the UK before any trial of an IMP takes place it must have ethics approval (www.nres.npsa.nhs.uk) , MHRA approval (www.mhra.gov.uk) and R&D approval which is the final sign off by the Trust taking part (www.rdforum.nhs.uk). There will/may be similar requirements in your member state and YOU need to know what it is!

6. There are lots of examples of Biopharmaceuticals in trials – especially in cancer studies – and they area all treated like any other study of an IMP.

7. An excellent source of information is the Clinical Trial toolkit at www.ct-toolkit.ac.uk where you will find links to all sorts of documents.

8. From the pharmacy perspective this means that all trials of IMPs must be dealt with according to the principles of ICH GCP (can be found at www.ich.org) The underlying document of which is E6 (http://www.ich.org/LOB/media/MEDIA482.pdf). Pharmacists should also be aware of the good manufacturing guidelines (GMP) of which annex 13 is specifically for IMPs (http://www.ct-toolkit.ac.uk/_db/_documents/Annex_13.pdf)

   The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

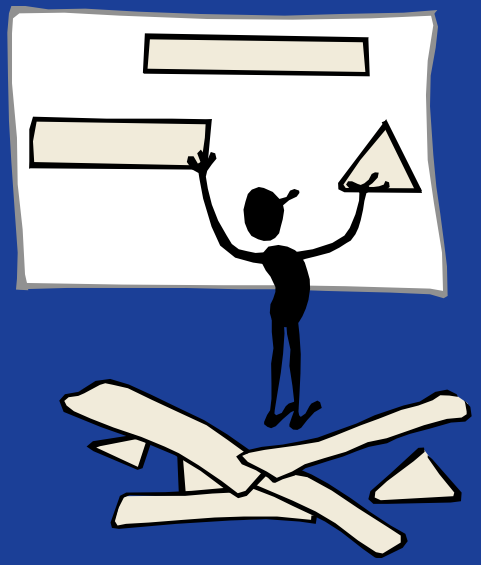
9. Finally a 104 page document detailing what could go wrong and how to prevent it – the TGN1412. Expert Scientific Group report on the Northwick park incident. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117

OK, now the really hard part!

- Understand clinical trials in relation to Biopharmaceuticals

…its the same as for any IMP rest, but add

point 4 – gene therapies
point 9 – everyone is looking!



Final objective

- How do we transfer the understanding?
- Do we need to?
- Should we warn our colleagues?
- Should we keep quiet (TGN1412)