First in Human Clinical Trials of medicines

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Topics

- MHRA Clinical Trials Unit
- Clinical Trials Legislation
- Assessment of a clinical trial and FIH considerations
  - Pharmaceutical
  - Non-clinical (pharmaco-toxicological)
  - Clinical
- Higher Risk FIH trials
- Guidance
MHRA Clinical Trials Unit

• The Clinical Trials Unit is a stand-alone Unit of the MHRA Licensing Division
  – Product Life-Cycle Assessment Teams (PLATs)
  – Biologicals Unit
  – Clinical Trials Unit (CTU)
  – Product Licensing – Parallel Imports Unit (PLPI)
  – Statistics Unit
  – Expert Committee Support and Service Management (ECSSM)
Role of MHRA Clinical Trials Unit

- We assess all applications to conduct interventional clinical trials with investigational medicinal products in the UK
  - Phase I-IV, including FTIH, Chemical, Biotech, ATMPs
- We assess the initial application to conduct a trial and any subsequent substantial amendments to the protocol and product
- We review the emerging safety profile of the product and take action where necessary
- We provide scientific and regulatory advice to stakeholders
- We liaise with other MHRA Units:
  - Licensing colleagues
  - GxP Inspectors
- We input to UK and European policy and guidelines
Drug Development Process

On average, it takes over 12 years and costs over £1 billion to develop new medicines.
CT legislation

• Currently CTs regulated by Directive 2001/20 EC → transposed into national law (in UK by SI 2004 No1031)
  - Inconsistent implementation across Member States
  - Increased costs and time to start a trial
  - Trial numbers decreased 2007-11 (but now increasing)

• New CT Regulation 536/2014 published May 2014. Streamlined approval procedure:
  - Single EU portal and database
  - Joint assessment of multi-state applications
  - Risk proportionate: ‘low-intervention trials’
  - Increased transparency
National Roles in CT authorisation

According to the current legislation, clinical trials of medicinal products in human subjects require:

1. Authorisation by the competent authority (MHRA in the UK);

2. Favourable opinion by an ethics committee, including any local site approvals (eg NHS in UK)

These roles are independent but complimentary. Possible to get MHRA approval but unfavourable ethics opinion (or vice versa).

Note in future, under the new Regulation a single member state decision will be provided to sponsors rather than separate competent authority and ethics approvals
MHRA Assessment

• An assessor from each scientific discipline is allocated to the application

• Each assessor reviews the data and prepares an assessment report

• Independent assessment with collaboration when required

• First in Human and First in UK trials are presented and discussed at a weekly multidisciplinary meeting

• Higher risk First in Human studies also receive external independent expert advice
Assessment process – General Principles

Decisions made based on **safety** considerations (Benefit vs. Risk)

‘*Do the data supplied support the use of this product, administered in this way, in the proposed dose for the proposed duration, to this ‘type’ of participant?*’

**There is risk associated with all trials**

The degree of acceptable risk depends on a number of factors

**Risk:Benefit in a healthy volunteer FIH trial may be very different from a Phase 3 cancer study**
MHRA Assessment

• Will ensure that:
  - The benefit risk ratio is favourable for trial subjects
  - The trial design protects the scientific integrity of data accrued

• Does not evaluate the suitability of the trial in the context of overarching drug development

• We will not:
  - Optimise protocols
  - Advise on formulation development
  - Etc.

If you want development advice → Scientific Advice Meeting
Pharmaceutical Assessment

• Safety in respect of the quality of the drug substance and drug product.

• Substance:
  - Route of synthesis, proof of structure, impurity profile, specification/batch analysis, stability.

• Product:
  - Composition, method of manufacture, specification/batch analysis, stability.

• Adventitious Agents
  - Viral
  - Non-viral
Pharmaceutical Assessment

Phase 1/ FIH considerations:

• Is the product fit for purpose given the stage of development?
  – Powder in bottle/capsule $\rightarrow$ formulated product

• Dosing accuracy for small doses? (adsorption, dilution)

• Has it been manufactured in the same way as the pre-clinical material?
  – Impurity profile supported?
  – Is there a reference to define biological activity?
Non-clinical Assessment

- Safety of the product from the perspective of the non-clinical testing and the protocol design.
- Basic PK ($T_{max}$, $t_{1/2}$, bioavailability, % protein binding, elimination routes)
- Evidence of efficacy (inc. dose rationale)
- Safety pharmacology (cardiac, renal, liver, CNS)
- Appropriateness of test species used
- Acute/chronic toxicity studies
- Genotoxicity studies
- Reproduction studies (if women can be included in trials)
Non-clinical Assessment

**Phase 1/FIH considerations**
- Estimation of safe starting dose for clinical trials
- Dose response relations
- Identification of potential target organs
- Identification of parameters for clinical monitoring
- Characterisation of toxic effects with respect to target organs
- Relationship to duration and extent of systemic exposure
- Potential reversibility of toxic effects
Clinical Assessment

• Looking at the safety of the trial from the perspective of the protocol design, human data (if any available!) and the pre-clinical data.

• dose, duration, dose escalation,
• potential efficacy
• trial subjects
• potential hazards, risk mitigation measures
• safety monitoring and reporting
Clinical Assessment

Phase 1/FIH considerations

Is the trial design appropriate based on available data?
- Study population, safety monitoring
- Starting dose, dose escalation, sentinel dosing, transition to next cohort, withdrawal criteria
- Trial stopping criteria

What are the target organs (as predicted by animal data) and are there any ‘off target’ signals?

Are there appropriate risk mitigation strategies in place?

If it is multi-centre: is there a communication plan in place?
Outcome of Assessment

• The result of the assessment is either:
  - acceptance (with or without conditions), or;
  - request for further information (‘Grounds for Non-Acceptance’ (GNA)).

  **THIS IS NOT A REJECTION OF THE APPLICATION!**

• Where further information is requested, this should be submitted for assessment.
• In almost all cases, this additional information allows the application to be authorised.
• Where the information is not acceptable (or no response is submitted) the application is rejected.
Advisory Committees

MHRA can request expert advice from CHM/CTBVEAG
- Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBV-EAG) and Commission for Human Medicines (CHM)

First-in-human clinical trials involving novel compounds with certain characteristics making them higher risk, for example:
- Acts via a cascade system where there may be an amplification effect
- Where animal data are unlikely to be predictive of activity in humans
- Target connected to multiple signaling pathways
- Acts via the immune system with a target or mechanism of action which is novel
- Others as necessary

Consideration by MHRA assessors, then EAG +/- CHM, then feedback to applicant, then ‘formal’ application
The safety of FIH trials is very good...

However....
2006 - TGN 1412 (UK)
2015 - BIA 10-2474 (France)
FIH Guidance

• Following the TGN 1412 incident in March 2006, a Guideline on strategies to identify and mitigate risks for first-in-human with investigational medicinal products was adopted by the CHMP with an effective date of 1 September 2007.

• This was largely based on the findings from the independent UK report into the incident chaired by Sir Gordon Duff.

• This document provides guidance on the identification of risk and strategies to mitigate such risk.
  
Revision to the FIH Guidance

• In the 10 years since the guidance has been published more innovative trials designs are being used and many FIH trials are now performed with integrated protocols potentially combining different study parts.

• Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

• Two MHRA assessors (non-clinical, clinical) involved in the update
Updated guideline published 15\textsuperscript{th} November 2016

- **Nov-Feb**: Consultation
- **March**: Workshop
- **May**: Final version presented to the European Commission
- **July**: Adoption

Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

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<tr>
<th>Event Description</th>
<th>Date</th>
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<tr>
<td>Adopted by CHMP for release for consultation</td>
<td>10 November 2016</td>
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<tr>
<td>Start of public consultation</td>
<td>15 November 2016</td>
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<tr>
<td>End of consultation (deadline for comments)</td>
<td>28 February 2017</td>
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<tr>
<td>Adopted by CHMP</td>
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Some Key points

• integrated protocols potentially combining a number of different study parts, e.g. single and multiple ascending doses (SAD and MAD), food interaction, different age groups and early proof of concept or early proof of principle parts.
  • extension of the remit of the guidance beyond single ascending dose FIH trials to incorporate other early phase trials and designs
• clarification on the choice of trial subjects
• overall dose/exposure range and scheme including stopping rules
• rolling review of emerging human data during the study
• More emphasis on a risk-based approach
A note on “guidelines”

- The updated guidance should not be seen as a barrier to innovation
  - Flexibility is allowed
  - It is not a recipe for these trials
  - Nor is it legislation – it is a scientific guideline

- If there are any issues – ASK!
- Don’t let anyone tell you “the regulator will never accept that”!
  - We are open to innovative approaches eg
    - Protocol design
    - Design space for manufacture
Sources of advice from MHRA CTU

• Scientific / Regulatory / Innovation office advice
  • 75-100 per year
  • Usually early phase (join with colleagues if MA advice needed)
  • Exceptionally: ‘house calls’!

• Dedicated Clinical Trial Helpline
  • Approx. 3500 emails + 5000 phone calls per year
    – 14 day target response (currently ~3.5 days)
  • Protocol review on whether research is CTIMP
    – response time of approx. 7 days

• Direct access to assessors – telephone number and /or email address on assessment outcome letters to sponsors
Summary

- All clinical trials are assessed on a benefit versus risk basis.
- All trials carry risk! Identification and mitigation of risk is key.
- In UK FIH studies are peer reviewed by the CTU team and higher risk trials receive independent external expert advice.
  - We assess about 80 per year
- A new guideline on FIH (and ‘early’ trials) trials will be published very soon
- MHRA Clinical Trials Unit has a range of opportunities for innovators to seek advice.
  - If you want to explore innovative approaches come and see us – we are receptive to new ideas!

- Thank you – any questions?