MHRA
Regulating Medicines and Medical Devices

Adaptive study design in early phase research: The regulatory perspective

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Medicines and Healthcare Products Regulatory Agency

MHRA Family

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CPRD NIBSC MHRA

Medicines & Healthcare products Regulatory Agency (MHRA): Regulatory overview

- **Regulation of medicines**
  - Clinical trials authorisations
  - Marketing authorisations
  - Post marketing safety monitoring
  - Inspections
  - Enforcement and prosecution

- **Regulation of medical devices**
  - Clinical trial authorisations
  - Overseeing notified bodies
  - Post market surveillance/inspection
  - Enforcement and prosecution

- **Blood safety and quality**
  - Adverse event reports
  - Inspections

Strategic priorities

- Influencing the shape of future EU regulatory framework with a focus on safety surveillance and falsified medicines

- Supporting research, innovation and regulation:
  - simplifying and reducing regulatory burden
  - supporting strategies that promote life sciences in the UK

- Merger with NIBSC

- Creating an organisation fit for the future: supporting opportunities arising from the newly expanded organisation.

MHRA Clinical Trials Unit

– The Clinical Trials Unit is part 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)

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
- We assess substantial amendments to the protocol and product
- We review safety reports
- We liaise with other MHRA Units:
  - Licensing colleagues
  - GxP Inspectors
  - Committee Support

MHRA CTU experience with adaptive study designs

What do we mean by “adaptive study design”?

- Adaptive protocol Vs ‘umbrella/bundle’ protocol?
- EMA: A study design is called “adaptive” if statistical methodology allows the modification of a design element (e.g. sample-size, randomisation ratio, number of treatment arms) at an interim analysis with full control of the type I error.
- FDA: a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypothesis based on analysis of (interim) data from subjects in the study
- Other: any design which uses accumulating data to decide how to modify aspects of the study without undermining the *validity* and *integrity* of the trial.
    - Uses prospective decisions – adaptations are ‘by design’ not ‘ad hoc’

Does the MHRA accept adaptive protocol design?

Yes! Supporting research and innovation is one of our key strategic priorities.

- We are open to suggestions
- The onus is on the sponsor to provide clear and justified risk mitigation proposals in the protocol.

- Note: MHRA CTU assesses the protocol in terms of **safety** of the proposed trial and may not have insight on proposed development of the product for MA (i.e. the merits of the individual trial are assessed) → scientific advice is available for questions on the development plan.

At which stage?

- Exploratory?
  - Probably most common at this stage
  - Mainly ‘umbrella’ protocols

- Seamless’ Phase II / III combinations?
  - Not as common
  - Depends on the study
  - E.g. ‘dropping’ arms
  - will a ‘proper’ PIII be needed for MA??

Are adaptive designs common?

- Concept has been around for a long time!

- MHRA CTU see mostly ‘umbrella / bundle’ types (“true” adaptive design protocols are relatively rare)

- Time of licensing – still not common to support MA

How far can you go?

- When is an amendment required?
  - In a lot of respects this is up to the sponsor
  - single dose → multiple dose?
- Scientific advice meeting – NCA / EMA?
  - Not normally required by MHRA. If the sponsor wants specific advice in terms of development or if the design is very novel then it is a good idea to speak to the regulators.
- EAG / CHM review?
  - The protocol design in itself would not lead to the need for independent expert review. This would be a down to risk factors associated with the IMP.

Are adaptive designs easier or harder to review from a MHRA perspective?

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- There is *more* to assess in the same timeframe as a single part protocol
  - But we have no prejudice against them!

- Are they harder or easier to write and perform?!

What issues can you face?

If the protocol is not written explicitly:

- There is the potential for an increased number of grounds for non-acceptance
    - advantages are that if the GNAs are answered satisfactorily you are good to go and it will always be quicker than submitting separate submissions.
    - if GNAs are not answered satisfactorily → rejection (resubmission)

- Might be required to submit amendments

- Regulatory risks depend on the regulatory role of the study – will it be used for basis of MA approval?
- Scientific risk – if there is no regulatory risk the sponsor will bear the scientific risk

- Logistical issues: e.g accountability/return of IMP from a dropped arm

What could applicants do better?

- Be clear and explicit in the protocol (define and justify!)
- We cannot assume or give benefit of the doubt

In general: if an assessor can read the protocol and know what will happen to subjects from the start to the finish of the study then there's a good chance there will be few issues

(this doesn't imply that it will approved!)

Are there any guidance documents?

Just one EU document to date:

- **REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN** CHMP/EWP/2459/02 (Adopted 2007)

This is referenced in many recent guidance documents

FDA Draft Guidance:

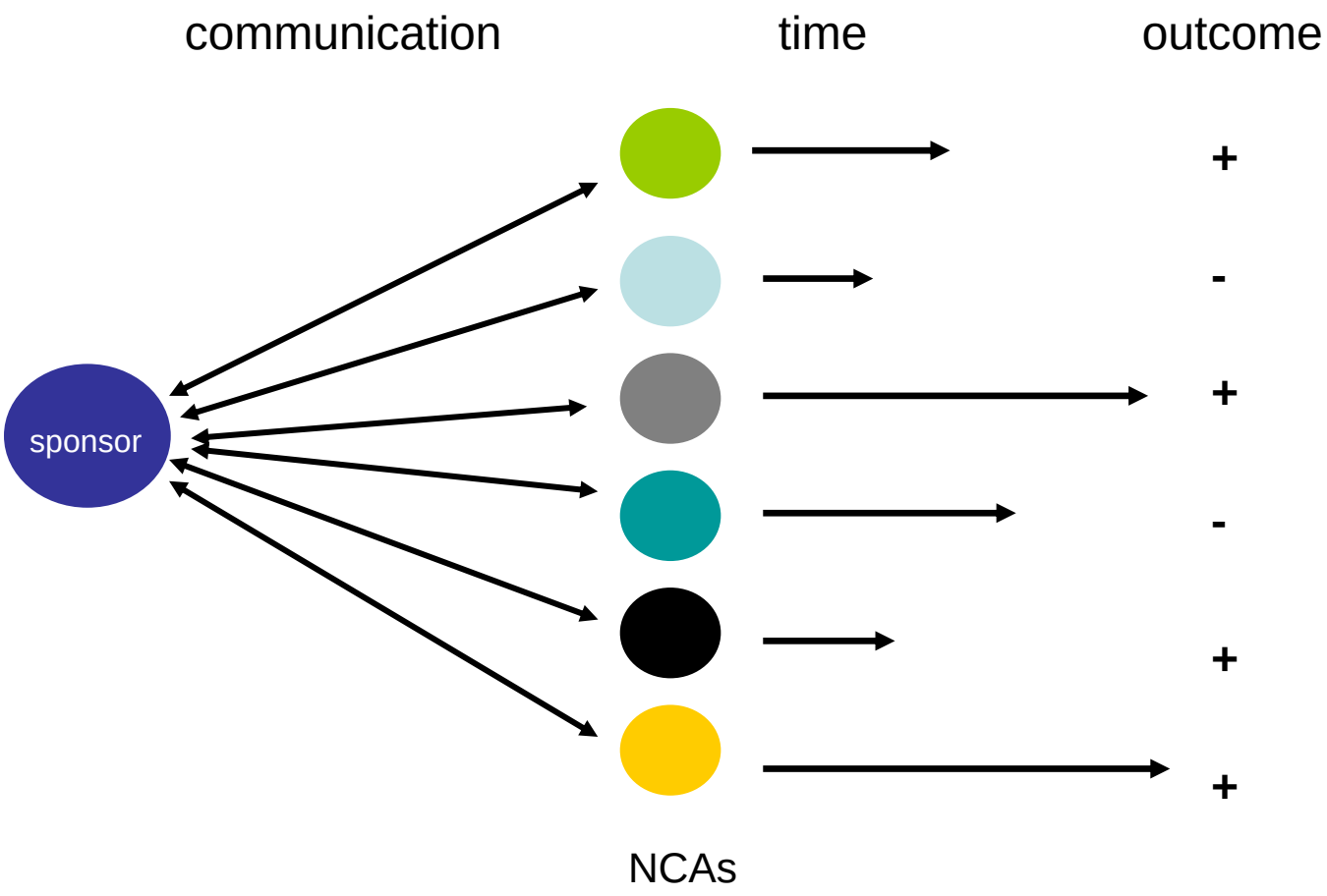
- Guidance for Industry. Adaptive Design Clinical Trials for Drugs and Biologics (February 2010)

Are there differences in approach in different EU MS (or in USA)?

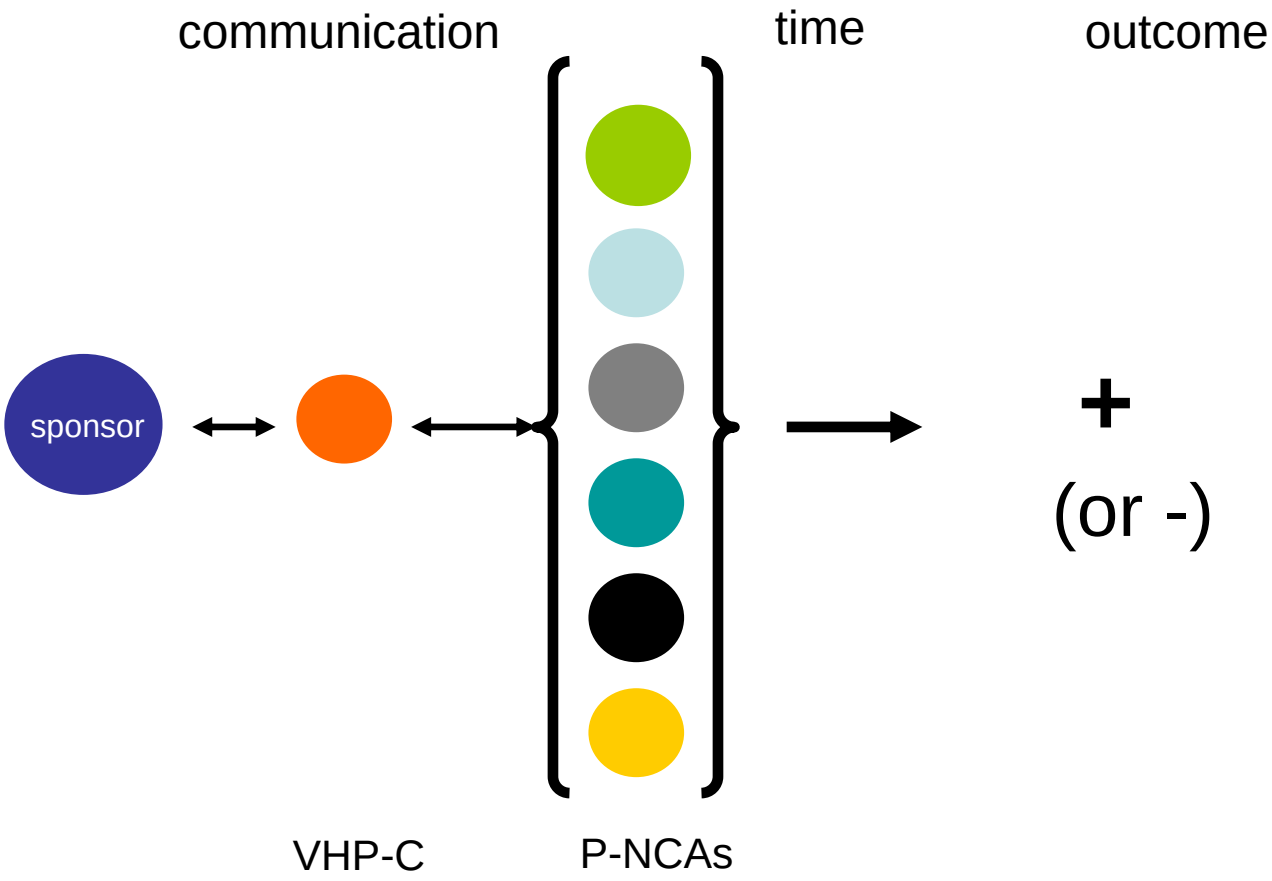
- Clinical trials authorisations are a National Competence

- There are initiatives to harmonise decisions across EU: e.g. You might consider the Voluntary Harmonisation Procedure (VHP)

EU Multi-national clinical trials: current situation



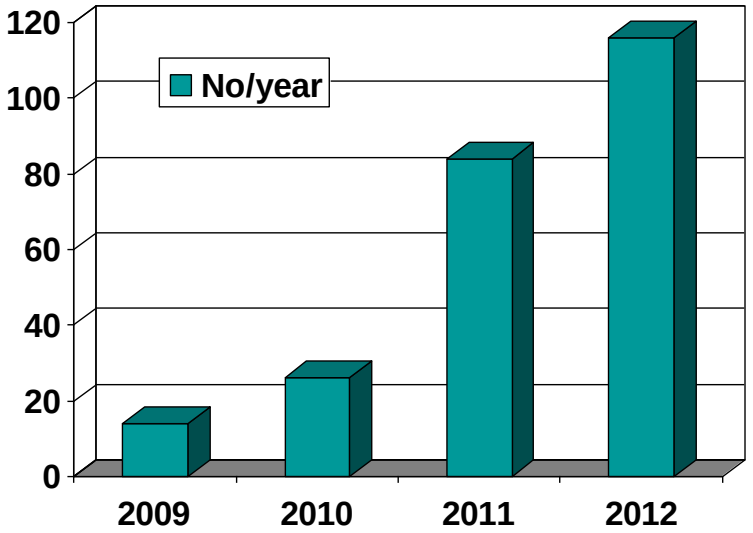
EU Multi-national clinical trials: VHP



VHP

- **Three Phases:**

1. Request/validation
2. VHP Assessment
3. National CTA application submission



VHP Advantages

- Single application
  - One set of core documentation
  - No MS-specific requirements
  - Fixed timelines
- Single, consolidated set of questions
  - GNAs reduced by up to average of 50%
- Harmonised scientific discussion in the Member States concerned

- Addresses many criticisms of Clinical Trials Directive
  - Don’t need to wait for new legislation

Summary – tips for submitting an adaptive protocol design

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- Golden rule: The protocol should be written such that the assessor has a clear understanding of what data will be used to make the adaptations proposed in the study.

- Sometimes things “need said” (don’t rely on the assessor to make the judgement for you)

- If you are considering an EU MN-CT the VHP route may be worthwhile

- If the protocol design is truly novel, consider seeking scientific advice from MHRA CTU ± Licensing colleagues