Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Regulatory perspective of early phase I/II designs, including basket, umbrella and platform designs

Presented by Khadija Rantell

Disclaimer

The views expressed in this presentation are those of the speaker and not necessarily those of the MHRA.

Abbreviations

B/R: Benefit/Risk
CHMP:Committee for Medicinal Products for Human Use
CTA: Clinical Trial Authorisation
CTFG: Clinical Trials Facilitating Group
DD: Drug Development
D-E-R: Does-Exposure-Response
ICH E9: Statistical Principles for Clinical Trials
ICH E4: Dose-Response Information to Support Drug Registration
ICH E8: General Considerations for Clinical Trials
EAG: Expert Advisory Group
EMA: European Medicine Agency
MAA: Marketing Authorisation Application
MSWP: Modelling and Simulation Working Party
NCA: National Competent Authority
PDCO: EU Paediatric Committee
PK: Pharmacokinetics
SA: Scientific Advice (National and European)
SAWP: Scientific Advice Working Party

Marketing Authorisation

European Directive 2001/83/EC

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- **Legislation** requires that marketing authorisation for a medicinal product shall be **refused** if:

(a) the **risk-benefit** balance is not considered to be favourable; or

(b) its **therapeutic efficacy** is insufficiently substantiated by the applicant; or

(c) its qualitative and quantitative composition is not as declared.

- **"therapeutic efficacy"** is considered in terms of the clinical relevance as well as statistical significance

Plan

There are **two parts** to this talk

- **Part I:** Early Phase I/II
- **Part II:** Novel study designs (adaptive designs, master protocols: basket, umbrella, platform, matrix designs)

Phase I trials- Key questions

Is the drug **safe** and at **which dose**?

Which patient population? and

Which drug/regimen to prioritise?

ICH E8 – Early Phase trials

- **Phase I** studies typically involve one or a combination of the following aspects:
  a) *Estimation of Initial Safety and Tolerability*
  b) *Pharmacokinetics*
  c) *Assessment of Pharmacodynamics*
  d) *Early Measurement of Drug Activity*
- **Phase II** studies seek to explore therapeutic efficacy and involves the following aspects:
  a) *Determine the dose(s) and regimen for the Phase III*
  b) *Evaluation of potential endpoints, therapeutic regimen, and target population*

Current recommendations under ICH E4

- **D-E-R** is an integral part of drug development.
- **PK** information can be used to choose a wide range of doses.
- Trials should be well-controlled using appropriate approaches to minimise bias e.g. randomisation and blinding.
- Pros and Cons of different study designs are discussed.
- Focus should be on the dose-response function, not individual pairwise comparisons.

- **No loss of time and minimal extra effort is needed compared to DD plans that ignore dose-response**

Motivation

- **During regulatory assessment lack of information related to E-R will increase uncertainties, may delay approval, and create additional regulatory requirements in terms of post approval commitments.**

- Doses are rarely formally optimised in Phase II studies, selecting the right dose based on robust Phase I and II dose-finding studies is paramount.

- Good **dose finding** and **D-E-R** can:
  - serve as evidence of efficacy (unmet medical need)
  - support a single pivotal study
  - provide a strong database to support extrapolation to other groups e.g. paediatrics
  - be used to address **limitations** of data and **uncertainties** at the stage of MAA

Source: Sacks et al, JAMA. 2014; Cross et al, Pharmacoepidemiology and Drug Safety. 2002; Ehmman et al, Expert Opinion on Pharmacology. 2015.

Regulatory expectations

- **DR** relationship should examined in all stages of the **DD.**
- **ER** analysis is the method of choice for finding the proper dosing regimen for new medicine and for optimising the dosing regimen in new populations and indications.
- The dose finding strategy should be tailored to the specific development needs.
- **All methods are acceptable if fit for purpose**.
- **Regulators are open to new innovative methods for drug development. Early dialogue with regulators is recommended.**

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Qualification of novel methodologies (2009)

- This is a voluntary scientific pathway to facilitate communication between the scientific community and regulators and to address challenges in **DD**. The qualification process lead to either:

  (i) CHMP **Qualification Opinion** on the acceptability of a specific use of the proposed method, based on the assessment of submitted data (**public, e.g. MCP-Mod**)

  (ii) CHMP **Qualification Advice** on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted (**confidential**).

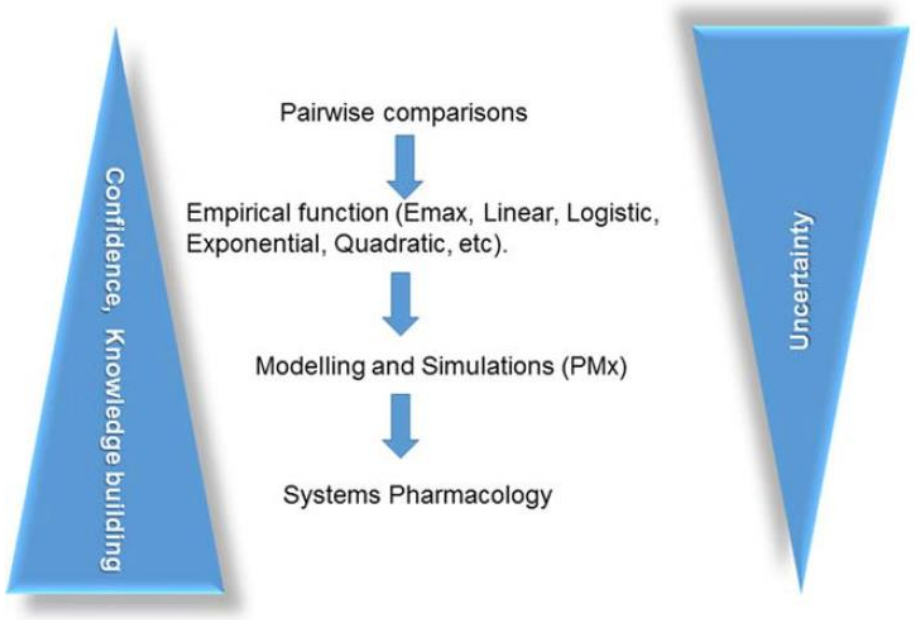
- Guidance to applicant documents available at EMA website.

MSWG (2013)

- The **MSWG** was established in January 2013 to provide specialist scientific support to the **SAWP**, **PDCO** and **CHMP**.
- The **MSWG** responsibilities include assessment of modeling methodology.
- The **MHRA** are members of the **MSWG.**
- Examples of use of modelling and simulation include:
  - Paediatric Dose Finding/Extrapolation
  - Dose Selection
  - Inform SmPC (label)
- Publications on MS are available at the EMA website

EMA report from dose-finding workshop (2014)

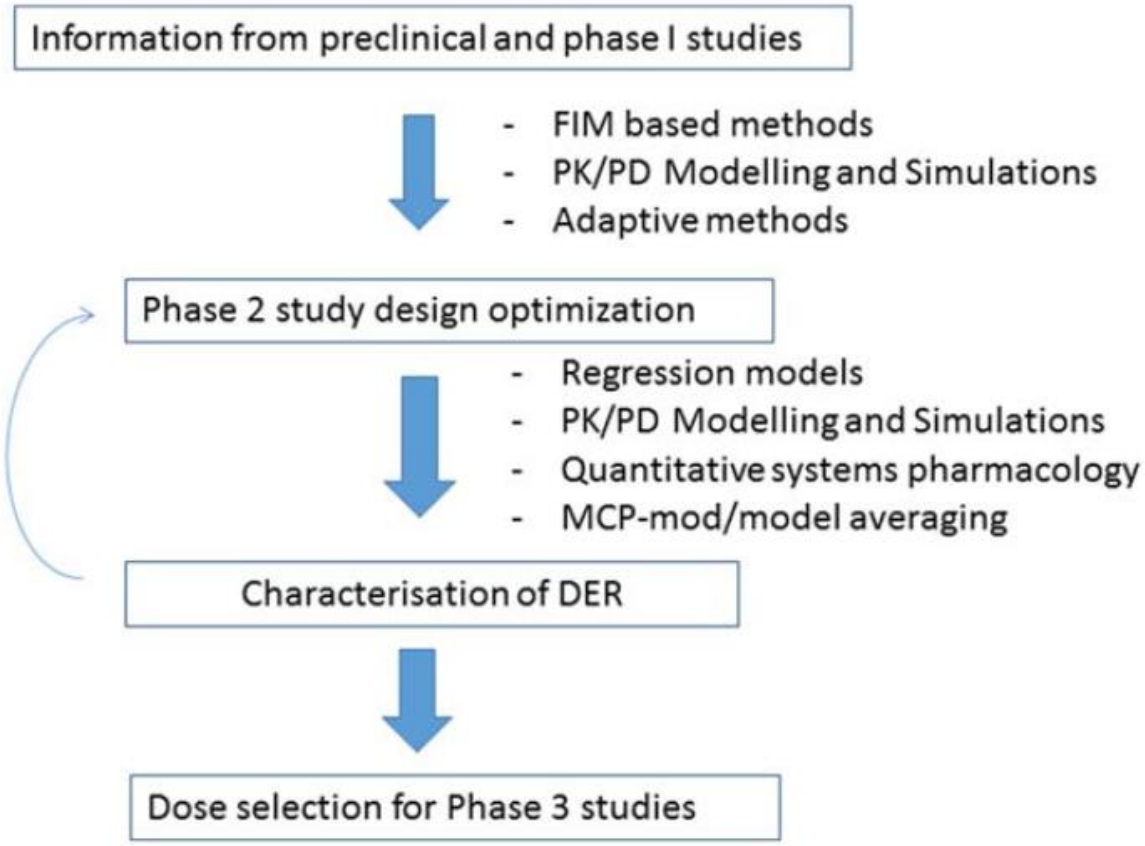
- **Misperception** that exploratory development and dose finding is the company's risk.
- For **B/R evaluation**, dose-selection should be based on the totality of data



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5529745/pdf/PSP4-6-418.pdf

EMA report from dose-finding workshop (2014)

Different methods for data analysis/and or study designs are summarised



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5529745/pdf/PSP4-6-418.pdf

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MHRA experience: based on assessment + SA

- **Phase I** designs have become complicated and yet algorithm based designs (e.g. **A+B designs**) are still the design of choice.
- Sponsors lack expertise on **model-based** methods and are not involving the external expert.
- Complex designs but without link to simple decision making rules.
- Weak early phase trials with limited data on **D-E-R** characterisation.
- Continued use of sub-optimal method e.g. pairwise comparison for dose(s) selection.

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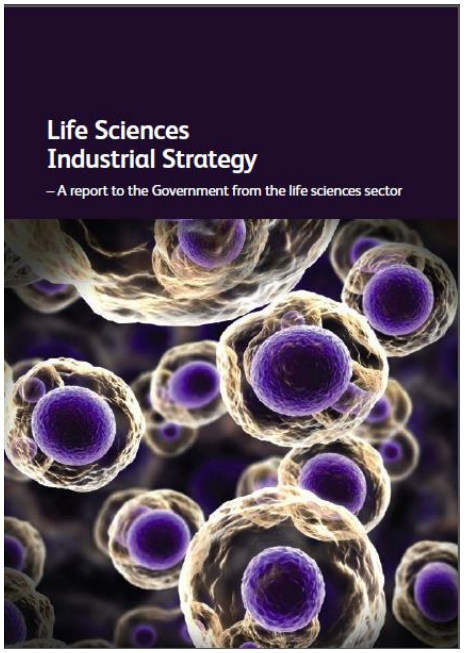
Part II: Innovative trial designs

Life Sciences Industrial Strategy 2017 report to the UK Government:

Our goal



"As the UK seeks to do more **complex and innovative trials**, MHRA needs to continue engaging with sponsors to **assist with innovative protocol designs** and should facilitate efficient approval of complex trials and amendments to such trials, for example, to add new arms.

The **UK should attempt to lead the innovation** in clinical trial methodology, such as basket trials, and should also attempt to embed routine genomic analysis to make trials more targeted, smaller and more likely to deliver high efficacy."

Master protocols are new approaches to clinical trials driven by the need for enhanced efficiency (patients and resources).

Clinical trials- standard vs complex designs

- A clinical trial is a clinical investigation with a **pre-defined objective** aimed at addressing **a precise hypothesis**.
- **A complex clinical trial** (investigating several IMPs/ and or populations) submitted as one trial is expected to have an '**overarching** hypothesis' defining the scientific objective(s) of **the whole trial**.
- **Prospective planning** of adaptations is crucial to avoid biases.
- The **B/R** balance should be positive both for the entire trial and for each sub-protocol.

What will be covered

- How MHRA support innovative designs
- Current regulatory approaches
- Challenges
- Top tips!

Supporting innovative designs

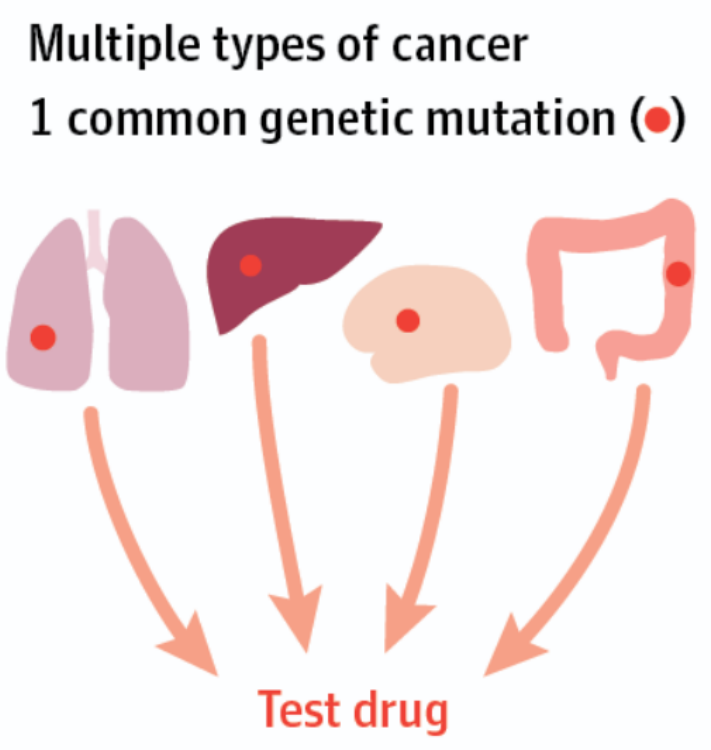
- In the **UK**, the Experimental Cancer Medicine Centre (**ECMC**) Network is at the forefront of developing and delivering innovative trials.
- The **MHRA** welcomes and supports safe innovative approaches to clinical trials.
- The **MHRA** has also a representative at the Clinical Trial Facilitation Group (**CTFG**) of the Heads of Medicinal Agencies (**HMA**) whose responsibilities included promoting harmonisation of clinical trials assessment decisions and the administrative process across the **NCA (e.g. MHRA)**.
- The **MHRA** provide input to the MRC/NIHR funding group by highlighting gaps in clinical trials methodologies as identified by the regulators.
- At the European level , a **policy position paper on umbrella and basket trials** has been drafted by the Biostatistics Working Party (**BSWP**)**.**
- The **CTFG** has published a paper which represents European view regarding authorisation and conduct of clinical trials with complex trial designs.

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf

Innovative trials designs

- The first hurdle in innovative trials is lack of common terminology.
- Assessment should be based on **trial design elements** rather than terminology used to describe the study.
- Adaptations can be acceptable if safe and scientifically justified.
- Future adaptations must **be pre-specified** as much as possible.
- Standard s**tatistical principles** are also applicable to innovative trial designs e.g. implication of interim analyses on the overall integrity of the trial and Type I error control.

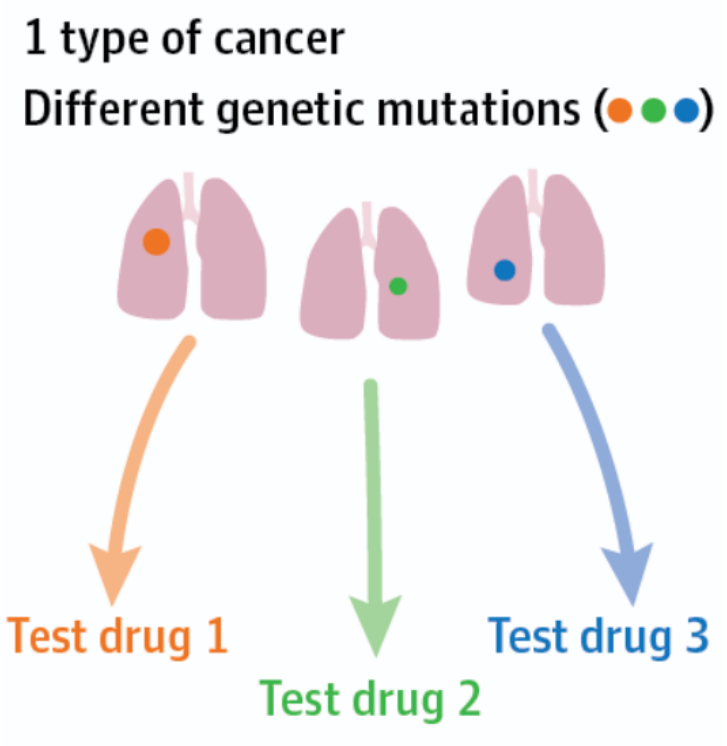
Innovative designs: Basket trials



JAMA Oncol. 2017;3(3):423. doi:10.1001/jamaoncol.2016.5299

Note: Use of a common control is not always suitable but may help to put the results into perspectives

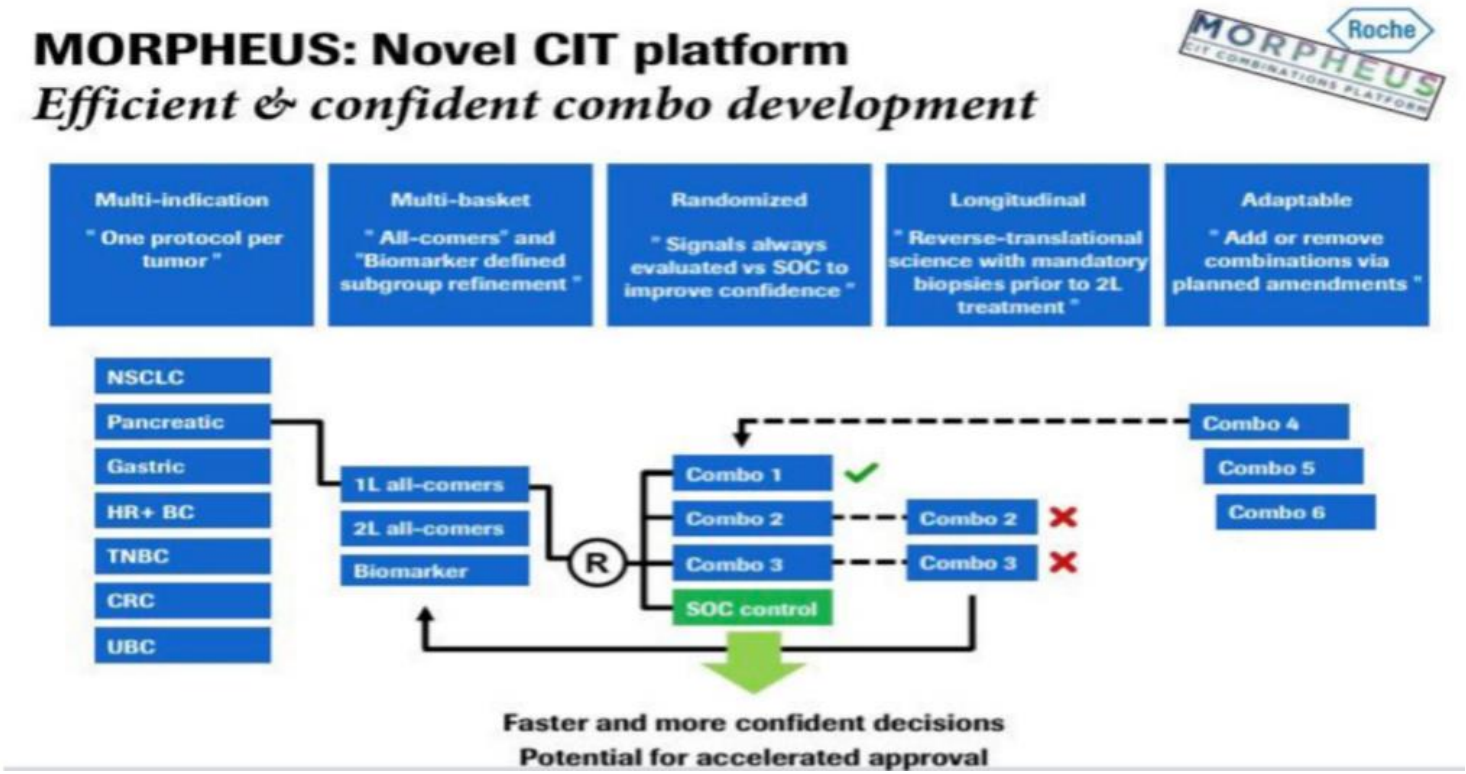
Innovative designs: Umbrella trials



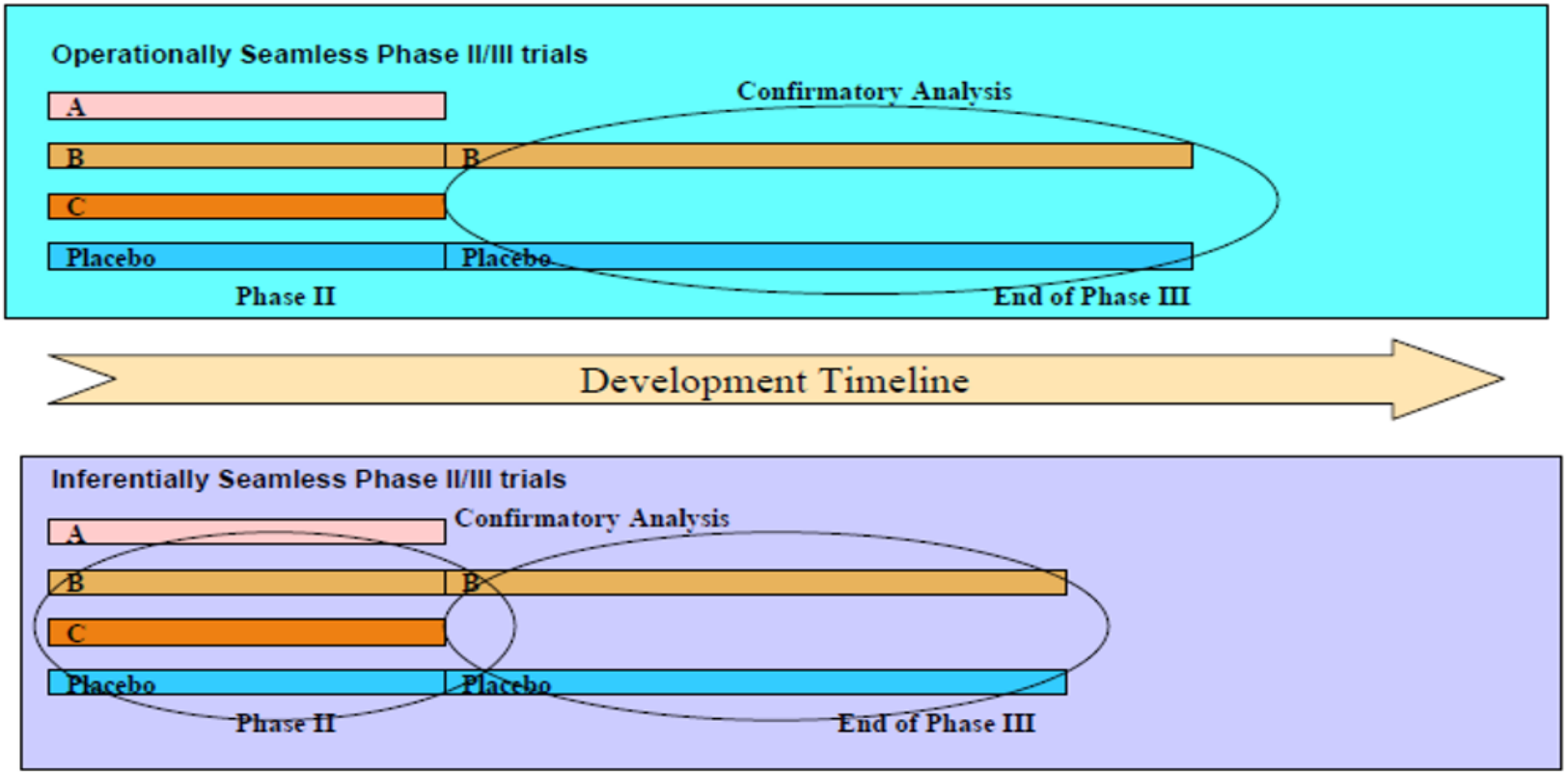
JAMA Oncol. 2017;3(3):423. doi:10.1001/jamaoncol.2016.5299

Note: Design may be randomised or use external controls depending on the disease.

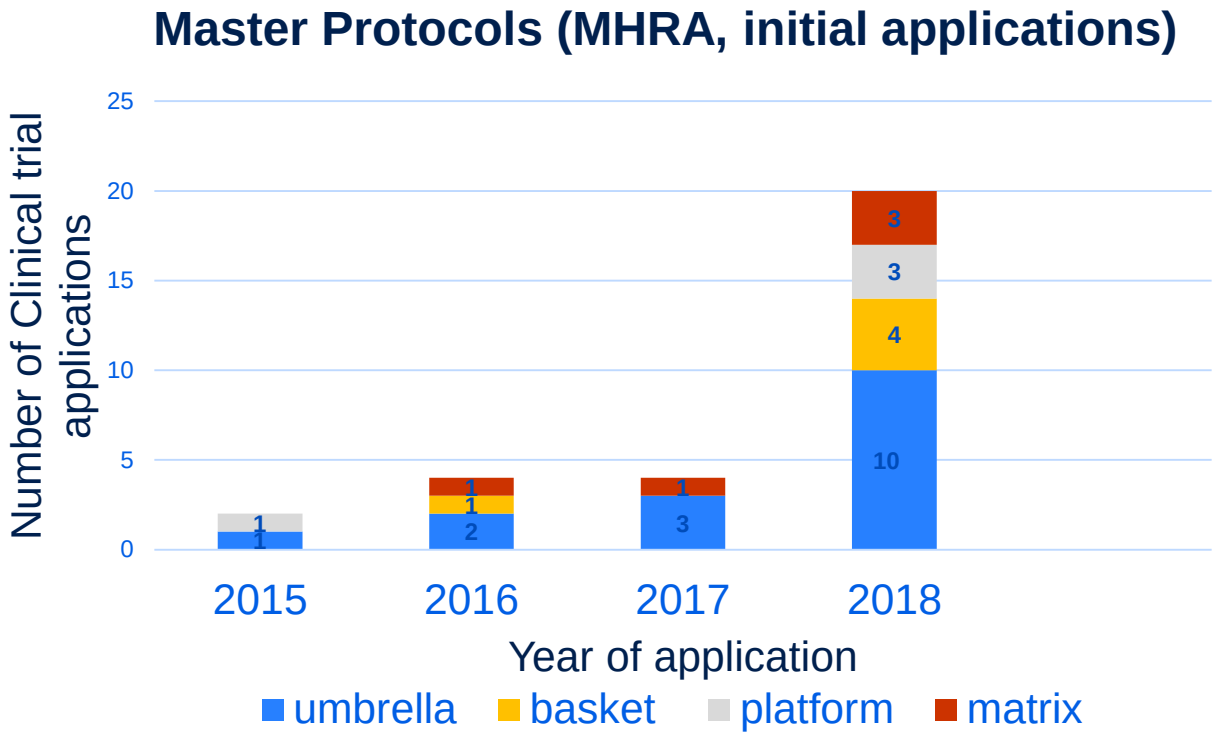
Innovative designs: Platform



Innovative designs: Seamless phase



MHRA experience



Common issues

- Adaptations can be acceptable if safe and scientifically justified.
- Allocation of single **EudraCT** number to a complex trial is challenging but acceptable if the trial is safe and scientifically sound.
- Approval is based on safety considerations, scientific rationale and whether the Sponsor is be able to justify:
  - the choice of a complex trial design and explain why it is superior to a simpler, traditional design.
  - that future adaptations are consistent with the original trial hypothesis and should be stated up front as much as possible.
  - the statistical considerations (stopping criteria, Type I error control, bias, data pooling,…) are in place.
  - the trial has a beginning and an end. Never ending trials may be acceptable but the judgment is made on case by case basis.
- **Subjects should only be included in comparisons for which they would have been eligible at randomisation**

Characteristics of innovative trials (MHRA CTA)

- **2-3/90 CTA** per month have innovative designs.
- All trials with innovative designs were conducted in oncology patients (CHMP guideline anti-cancer treatment updated).
- All were Phase I/II studies.
- Majority of CTA are approved or pending approval.

Innovative designs statistical challenges

- Master protocols have raised a number of challenging regulatory and statistical questions, especially as regards the control of the **Type I error rate.**

- **Type I error control** is not an issue for regulators in early/exploratory phase trials. However, it should be born in mind to avoid taking forward too many ineffective treatments to later phases.

Innovative designs statistical challenges

- In a **confirmatory setting**, the following should be considered:
  - Independence of sub-studies (umbrella, basket, and platform)
  - Use of shared control (umbrella)
  - Randomisation to sub-studies (umbrella)
  - Overlapping populations (basket)
  - Pooling (basket)
  - Differences in subgroup analyses (basket)
  - Adding, removing treatment arms, adaptive designs (platform)
  - Structural changes to patients population (platform)

- Two relevant publications are expected from the BSWG (EMA) and ECMC, which will include statistical considerations of innovative designs and recommendation on complex trials, respectively.

Summary

- The **MHRA** are tracking and gaining more experience in innovative designs
- The biggest barrier from our perspective for any clinical trial related issue/concern is not coming to **ask our advice early enough** (or at all!).
- **We can offer:**

- Scientific advice
  - https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra
- Broader scope meetings
- Regulatory advice
- Innovation office meetings
  - https://www.gov.uk/government/groups/mhra-innovation-office
  - innovationoffice@mhra.gov.uk
- SCOPE meetings – is it a CTIMP or not?
- Email advice – clintrialhelpline@mhra.gov.uk
- Telephone assistance – 020 3080 6456

Thank you for your attention

Acknowledgment

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References

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- Recommendation paper on the initiation and conduct of complex trials

http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2019_02_CTFG_Recommendation_paper_on_Complex_Clinical_Trials.pdf

- New clinical trial designs in the era of precision medicines: An overview of definitions, strengths and weaknesses, and current use in oncology

https://www.sciencedirect.com/science/article/pii/S030573721830201 9?via%3Dihub

- Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. New England Journal of Medicine. 2017;377(1):62-70

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