EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Regulatory view on complex innovative designs

A multi-disciplinary approach to progress Complex Clinical Trials

7th EFSPI Regulatory Statistics Workshop
Basel, Switzerland

Presented by Theodor Framke on 15 September 2022
Data Analytics and Methods Task Force

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# Agenda

1. Overview – What are complex innovative designs, why are they relevant?
2. CCT - Question and Answers
3. Challenges and Outlook

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EMA drafting group

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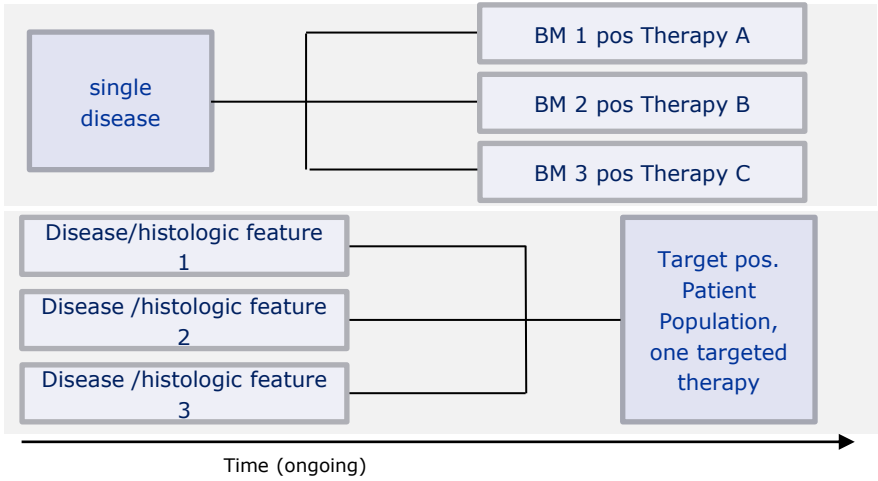
# Introduction

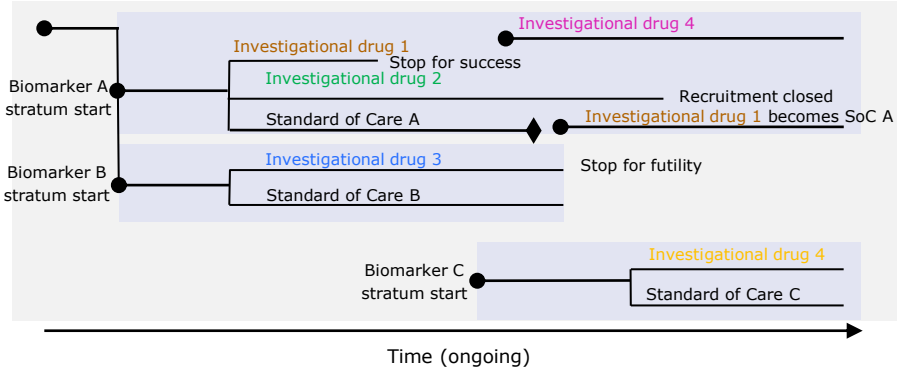
**Umbrella trial**: single disease/target population, multiple therapies

**Basket trial**: single therapy, multiple disease/target populations

**Platform trial**: combination of the above or more complex…

Note that this classification does not preclude a specific trial design




Woodcock & LaVange: Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both, *N Engl J Med* 2017;377:62-70, DOI: 10.1056/NEJMra1510062

# Background & work on master protocols

- Attempt to facilitate efficient development (sometimes for only administrative reasons, operational advantages)
- Not linked to a specific phase or design
- Limited experience, few examples available, topic increasingly picked up
- Q&A document published in May, joint work of EMA, EC, CTCG
- Clinical Trials Regulation now provides a single entry point for all CT applications with one set of documents for all MSs, supported by CTIS

- Publications: Review Paper from Woodcock & LaVange (2017), Howard et al. (2018), Collignon et al. (2020), Parker and Weir (2020), Bretz and Koenig (2020), Sridhara et al. (2021)
- Approaches to master protocols: EU PEARL, CTFG recommendations (2019), …
- Other terminology used by FDA is Complex Innovative trial designs, CID Pilot Meeting Program until 2022

# Why is this relevant?

- Motivation for Platform trials quite heterogeneous. Some reasons:
  - Standardised framework/platform, mainly logistical
  - Collaboration, reduced costs/efforts
  - Wish for relaxed Type I error control
- Provides an additional opportunity for a controlled trial
- Controls may not be concurrent

- Multitude of potential comparisons and adaptions
- Various practical issues in the conduct of a platform trial
- Platform trials played a role during the COVID-19 pandemic
- Proposals often seen in Scientific Advice, not yet at Marketing Authorisation Application stage

# Accelerating Clinical Trials in the EU (ACT EU)

ACT EU is an initiative to **transform the EU clinical research environment** in support of medical innovation and better patient outcomes.

- **Builds on the momentum** of the Clinical Trials Regulation and CTIS
- **Driven by** the Network Strategy to 2025 and the EU Pharmaceutical Strategy
- Launched 13 January 2022
- Read the press release and paper

# ACT EU objectives

Support the conduct of **large, multinational trials** with specific support for:

- SME, academia and Health Technology Assessment bodies (HTAs); and
- Trials which address unmet needs, rare diseases & medicines for public health crises
- One of the priority actions is on **methodologies**

Faciilitate **coordinated scientific advice** to support trial authorisation, marketing authorisation & the medicine lifecycle

Ensure **a unified European approach** for trial processes and strategic matters at the international level

**Engage all stakeholders** to deliver inclusive patient-oriented medicines development and delivery across populations

# Regulatory Background

- CTFG: Recommendation on Initiation and Conduct of Complex Clinical Trials (Feb 2019)
- European medicines agencies network strategy: EMA RSS: Foster innovation in trials – Work with stakeholders, EMRN and EC to promote and facilitate the conduct of complex clinical trials and other innovative clinical trial designs
- Outcome published under the Accelerating Clinical Trials in the EU (ACT EU) initiative
- Call from Industry, e.g. trade organisations' analysis of barriers and limitations to use and acceptance of complex trials (Nov 2020, LINK), workshop (5-6 Oct 21)
- DG SANTE B4 convened CTEG subgroup on complex trials (11/2020):
  EFPIA, ACRO, The Guild, EuropaBIO, EUCOPE, EORTC, and CFTG chairs, EMA
  - Jan 2021: Each stakeholder identified issues in case studies of complex trials (quick exercise, several EMA colleagues involved)
  - Started March 2021: Questions-and-answers document, jointly by **DG SANTE**, **CTFG**, **EMA**

# Questions, Questions, Questions…

1. Important considerations for the **planning** and **conduct** of complex clinical trials
2. Which **additional considerations** are needed for the design and conduct of master protocol studies?
3. How to describe and explain **Bayesian** approaches in complex clinical trials?
4. What are the considerations for planning, collection and use of **control data** from within a complex clinical trial for regulatory purposes?
5. Which principles apply, and which regulatory pathways should be considered when using **biomarkers** and biomarker assays in complex clinical trials and consequently applying for marketing authorisations?
6. **Safety, rights** and **well-being** of participants
7. **Transparency** (balance with integrity) and **communication** between regulators, sponsors and investigators

23 May 2022
EMA/298712/2022

Complex clinical trials – Questions and answers
Version 2022-05-23

| | |
|---|---|
| Draft agreed by Drafting Group experts (from EMA scientific committees, EMA working parties, EMA staff and Clinical Trials Coordination Group) | May 2022 |
| Draft agreed by Clinical Trials Coordination Group | May 2022 |
| Draft agreed by Clinical Trials Expert Group | May 2022 |
| Adopted by ACT EU Steering Group | 23 May 2022 |

| | |
|---|---|
| Keywords | Clinical trial; complex clinical trial; clinical trial authorisation application; marketing authorisation application; trial design; trial analysis; Clinical Trials Regulation; master protocol; platform trial; biomarker; adaptive design; modifications; Bayes; control data; transparency |

For questions related to this document, please write to ACTEU@ema.europa.eu.

# Q1: Important considerations for the planning and conduct

- ICH E8(R1): ask important questions and answer them with appropriate studies -> need to understand what the CCT addresses
- Focus on clear and precise hypotheses and pre-specification
- Submission as separate or multiple trials under Clinical Trial Regulation
- Co-sponsorship
- Re-assessment of benefit/risk
- Aspects that would benefit from Scientific Advice: adaptive/seamless aspects, Bayesian approaches, submission approach, biomarkers, novel methodologies

# Q2: Additional considerations

**List of issues (non-exhaustive):**

- Rules/criteria behind treatment allocations
- Sponsorship and confidentiality agreements and contractual responsibilities
- Access to data and means to maintain data and trial integrity
- Documents that describe the role of different relevant governance and/or oversight committees
- Safety management and overview
- Process of giving informed consent

**Further points**

- Sound study planning, trial integrity
- clear understanding of the regulatory purposes
- Graphical visualisation depicting all closed, current and future planned sub-protocols is encouraged in the cover letter
- Master protocol part plus at least one sub-protocols at the time of the initial CTA
- Cross-referencing
- Where to include additional information

# Q4: Considerations for control data

- Restriction to controls within platform trial
- Initial proposal did not find agreement, need for revision
- Focus on **attributes** for a trial: concurrency, treatment allocation, similarity of disease, study population, sample, investigators/personnel, Standard of Care, blinding, sites, protocol
- Q&A addresses neither scientific questions, nor the regulatory acceptance of no controls
- Multiplicity issues not covered, no consensus yet.

# Plans for the future

- The Question and Answer document may be **updated** in the future.
- Not all topics of biostatistical relevance could be covered
- Need for additional guidance document identified (-> statistical design, multiplicity)
- Will complement other documents, not replace them
- Concept Paper on Platform Trials to be published soon; work on Reflection Paper will start subsequently

Source: https://pixabay.com/photos/sunset-dusk-evening-atmosphere-2827738/

# Summary

- Need for interdisciplinary discussion and multi-stakeholder involvement -> Collaborative approach useful for a multidisciplinary guidance document
- It is a *first* step and many others will follow
- Q&A longer than initially anticipated, the outcome covers a variety of relevant topics
- Parts of it are of high relevance for statisticians

Questions for (panel) discussion:

- Which aspects of Complex Clinical Trials are of high importance for industry?
- Concepts and definitions as in "ordinary" trials – are we using the same ones?

# References


- Berry S (2020): Potential Statistical Issues Between Designers and Regulators in Confirmatory Basket, Umbrella, and Platform Trials, *Clinical Pharmacology & Therapeutics*, 108 (3), 444-446. doi:10.1002/cpt.1908
- Burger U et al. (2021): The Use of External Controls: To What Extent Can It Currently Be Recommended? *Pharmaceutical Statistics*, 20(6), 1002-1016. DOI: 10.1002/pst.2120
- Clinical Trials Facilitation and Coordination Group (2019): Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials, Link, accessed 24/08/2022
- Collignon O et al. (2020): Current Statistical Considerations and Regulatory Perspectives on the Planning of Confirmatory Basket, Umbrella, and Platform Trials, *Clinical Pharmacology & Therapeutics*, 107(5), 1059-1067, doi:10.1002/cpt.1804
- EC, EMA, HMA (2022): Complex clinical trials – Questions and answers, Link, accessed 24/08/2022
- Howard DR et al. 2018, Recommendations on multiple testing adjustment in multi-arm trials with a shared control group, *Statistical Methods in Medical Research*, Vol. 27(5), 1513–1530 DOI: 10.1177/0962280216664759
- Parker, R., & Weir, C. (2020). Non-adjustment for multiple testing in multi-arm trials of distinct treatments: rationale and justification. *Clinical Trials*, 1740774520941419. doi: 10.1177/1740774520941419
- Sridhara R et al. (2022): Type I Error Considerations in Master Protocols With Common Control in Oncology Trials: Report of an American Statistical Association Biopharmaceutical Section Open Forum Discussion, *Statistics in Biopharmaceutical Statistics*, 14(3), 349-352, doi 10.1080/19466315.2021.190673
- Woodcock J, LaVange LM (2017): Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both, *N Engl J Med*, 377:62-70, DOI: 10.1056/NEJMra1510062

# Any questions?

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