A multidisciplinary approach to Complex Clinical Trials

SESSION 3: TRIALS DESIGN - BASKET OR UMBRELLA FOR OPTIMAL PROGRESS

CDDF Multi-Stakeholder Workshop

Presented by Theodor Framke on 15 November 2022
Data Analytics and Methods Taskforce

Disclaimer

The presenter does not have any conflict of interests.

Agenda

1. ACT EU
2. What are complex innovative designs and why are they relevant?
3. CCT - Question and Answers
4. Outlook & Summary

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EMA drafting group for the Q&A

Caroline Pothet and Ralf Herold (slides)

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

Facilitate **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

ACT EU Priority actions and domains 2022-2023

Governance & Integration

1. Develop a **governance rationalisation strategy** (aligning different expert groups and working parties)

7. Reinforce the **coordination** between **scientific advice on CT approval and CT design** and link to the methodologies working party domain.

9. Successfully establish **CT safety monitoring** and bridge to the EU4Health Joint Action and start its integration into a pre- and post-marketing safety monitoring framework.

Engagement

3. Establish a **multi-stakeholder platform**, including patients, after stakeholder analysis.

6. Plan and launch a targeted **communication campaign** to engage all enablers.

10. Deliver a clinical trials **training curriculum** on drug development and regulatory science with links to SMEs & academia.

Methods & Practice

4. Implementing the **GCP modernisation** informed by the development of guidance at ICH.

8. Develop and publish key **methodologies guidance** e.g. on AI/ML impacted CTs, complex trials, decentralised CTs and IVDR/CTR interface (to strengthen links between innovation and scientific advice fora).

Impact

2. The successful and timely **implementation of the CTR** and its implementing acts.

- **KPIs** to track performance of the European CT environment.
- **Promote larger, multinational trials** specifically in academia

5. **Analyse data about clinical trials** leveraging academic, non-profit, European, and international initiatives, improving the impact of policymaking and funding to support evidence-based decision making.

Introduction

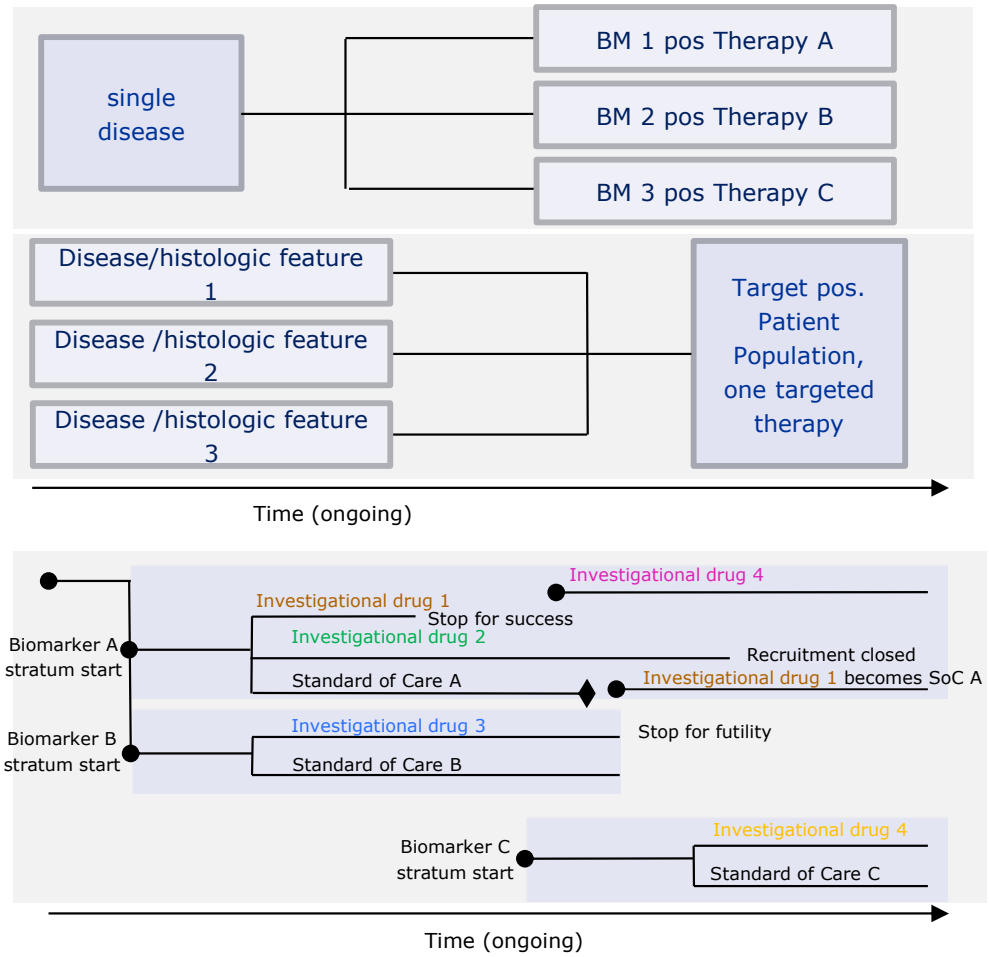
Examples:

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
- Not yet much experience, few examples available, topic increasingly being picked up
- Q&A document published in May, joint work of EMA, EC, CTCG

- Recent publications: Review Paper from Woodcock & LaVange (2017), Howard et al. (2018), Collignon et al. (2020), Parker and Weir (2020), Bretz and Koenig (2020), Berry (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 since 2018

Why is this relevant?

- Motivation for Platform trials quite heterogeneous. Some reasons:
  - Standardised framework/platform, mainly organisational
  - 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

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

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

Selected highlights from the Questions

- Focus on clear and precise hypotheses and pre-specification
- Co-sponsorship
- Re-assessment of benefit/risk
- Aspects that would benefit from Scientific Advice: adaptive/seamless aspects, Bayesian approaches, submission approach, biomarkers, novel methodologies

- Graphical visualisation encouraged
- Bayesian Statistics
- Additional considerations (i.e. trial integrity)
- Considerations on controls (list of attributes)
- Substudies may not be independent (i.e. safety, cross-referencing)

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 to be published soon; work on Reflection Paper will start subsequently

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Summary

- 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
- New elements have been introduced to accommodate complex settings
- Parts are of high relevance for statisticians
- Will affect innovation: clarifications; large, multinational trials; efficiency gains

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Thank you for your attention

Further information

Contact me at theodor.framke@ema.europa.eu

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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