AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

Initiation and Conduct of Complex Clinical Trials from the regulatory point of view

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28/09/2020

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Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	☐	☐	☐	X optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	☐	☐	☐	X optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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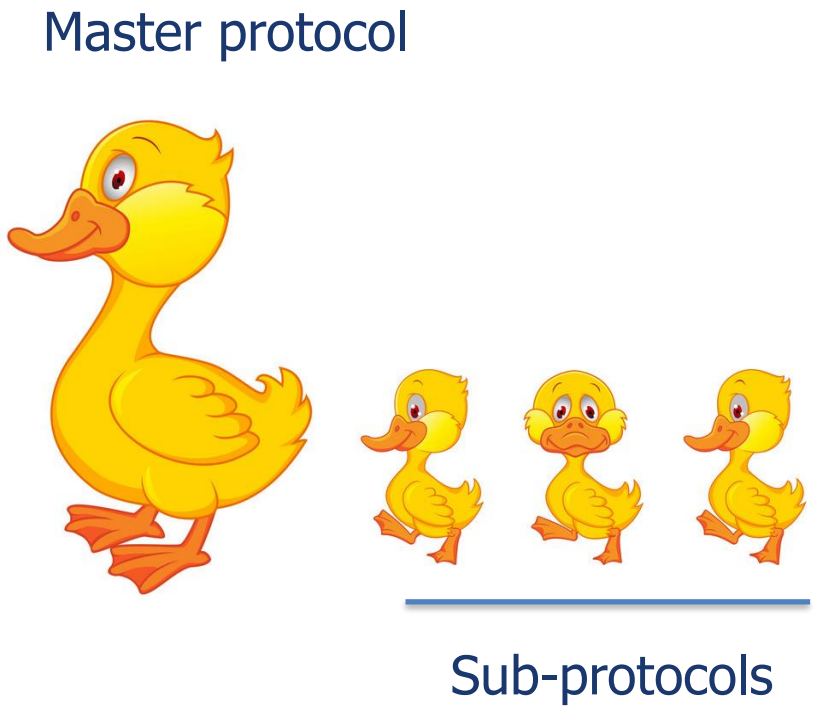
N.B. I am not receiving any compensation

What is a clinical trial with complex design?

A clinical trial is considered to have a complex clinical trial design if it has separate parts that could constitute individual clinical trials and/or is characterised by extensive prospective adaptations such as planned additions of new Investigational Medicinal Products (IMPs) or new target populations.



Clinical Trials with complex design
Main characteristics

- Common operational framework that increases efficiency (optimization of operational resources and allocation of trial subjects to the most suitable sub-protocol or arm).
- Common screening platform ensuring operational efficiency and facilitating patient recruitment.
- Organization in master protocol and sub-protocols
- Extensive adaptations in course of the trial (that should be described at the beginning)

Example of Clinical Trials with complex design

Umbrella

Umbrella trials investigate the safety/efficacy of several IMPs in a single population.

Basket

Basket trials generally investigate the safety/efficacy of an IMP or combination of IMPs across a variety of populations.

Platform

Platform trials may test several IMPs in one or multiple populations in a highly dynamic design.

Extensive adaptive features

Complex clinical trial designs often include prospective adaptations

- Addition of new IMPs and/or populations by new sub-protocols or arms during the course of the trial
- Closure of sub-protocols based on futility or safety analyses thus potentially making sub-protocol-specific results available during the course of the trial.

Master Protocol

- Should describe the overall clinical trial design including components and operational aspects applicable to all related sub-protocols (i.e. clinical trial rationale, objectives, endpoints, benefit-risk assessment, safety monitoring and reporting, main eligibility and/or treatment allocation.)

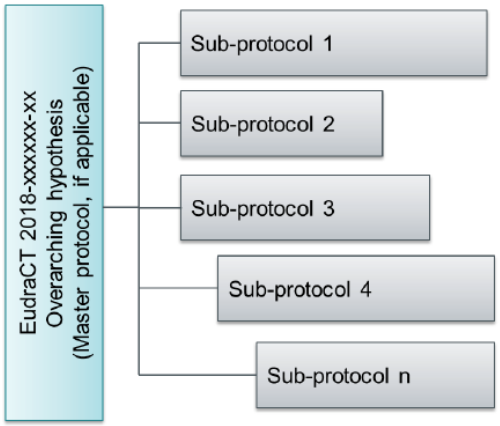
- Should clearly describe how trial subjects are allocated to the individual sub-protocols or arms

- Should describe decision criteria for opening and closing of sub-protocols/arms as well as for re-allocating trial subjects from one sub-protocol to another, if applicable.

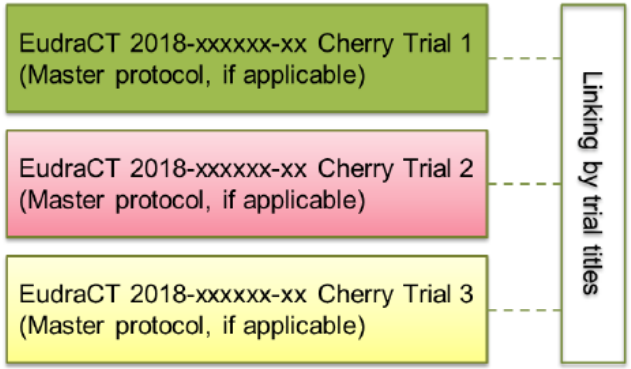
Structure of complex trial designs

The typical structure of complex trial designs is the presence of either several sub-protocols or arms sharing a common control arm
Complex clinical trials with sub-protocols can be submitted either as one single complex clinical trial or as separate clinical trials.

One single complex clinical trial



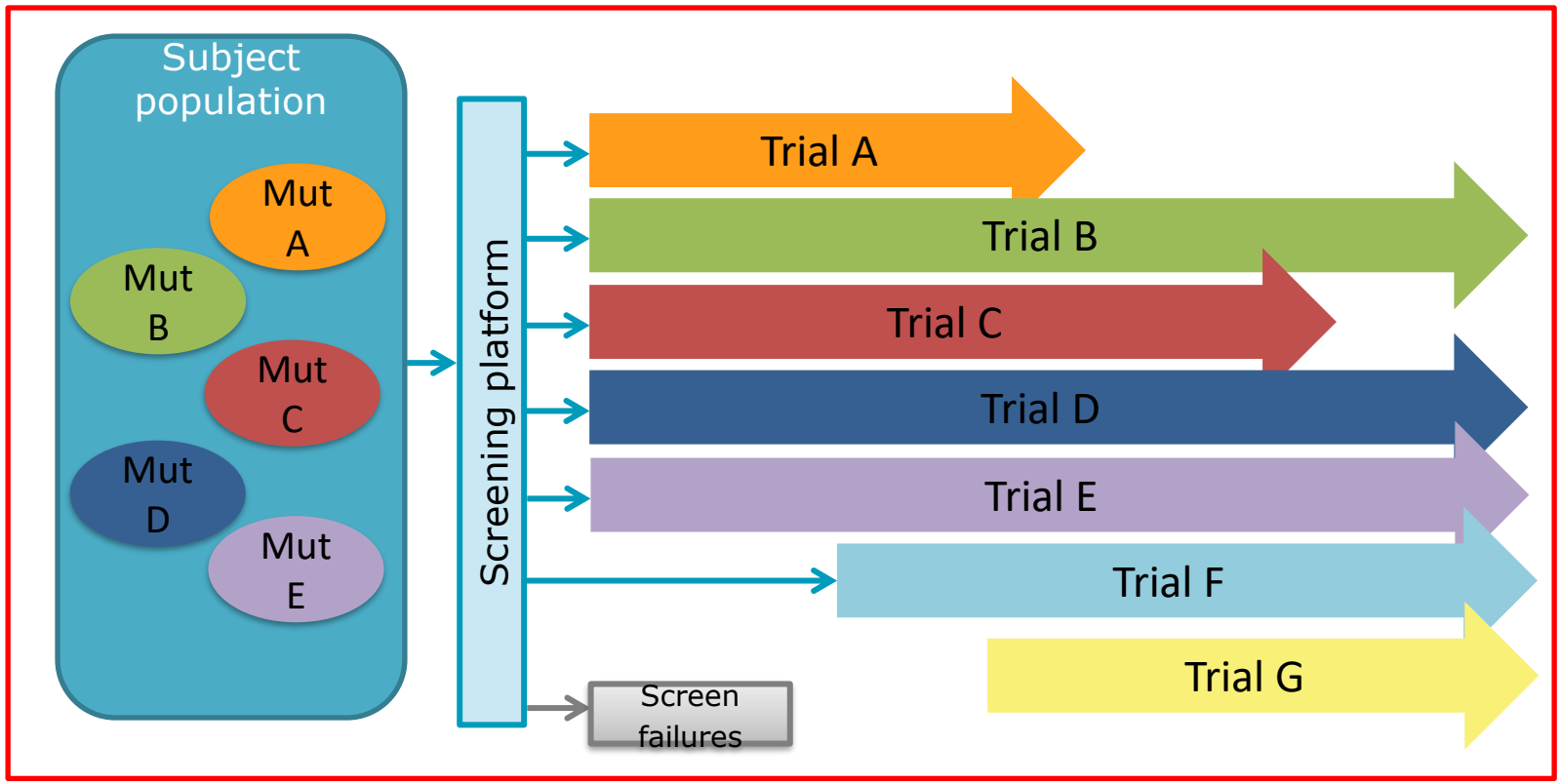
Separate clinical trials



If the clinical trials have a master protocol and are submitted as separate clinical trials, the master protocol should be submitted with each clinical trial application

Challenge – Changes during life cycle of CT*

New sub-protocols are added by substantial amendments → Platform Trial



*In addition to predefined ones in the protocol

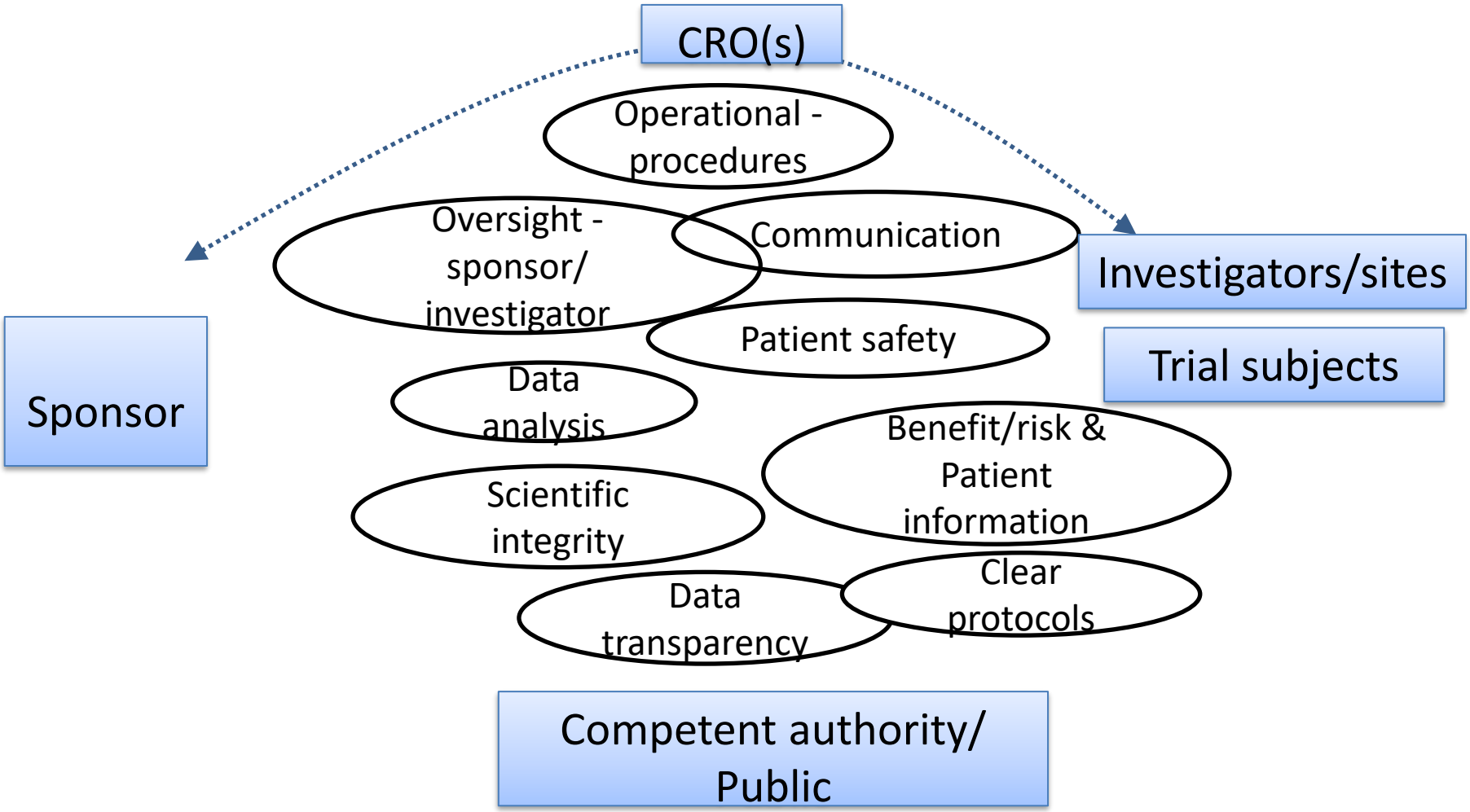
Challenge: Key review point in CTA authorisation

Clinical trial application (CTA) assessed and approved per trial/protocol (EudraCT number) within EU regulatory frame
→ evaluation of each trial "case-by-case":

Relevant aspects

- scientifically sound – what is a trial?
- clear detailed protocol
- subject safety prevails over all other interests
- robust data – operational complexity
- positive benefit-risk assessment

Challenge: Complexity reflected on CT conduct



CTFG recommendations*

→ To facilitate complex trials
ensuring patient safety and data integrity

→ Provide transparency on concerns of competent authorities expected to be address by CT submission

*Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials, CTFG, 12 February 2019, www.hma.eu/ctfg

Initiating and conducting a complex CT design
Key Recommedations

1. Clearly describe and justify design
2. Maintain scientific integrity
3. Ensure quality of trial conduct and optimise clinical feasibility
4. Ensure safety of trial subjects
5. Maintain data integrity
6. Reassess benefit-risk balance at critical steps throughout clinical trial
7. Validate companion diagnostics
8. Consider data transparency

Regulatory concerns and issues

- Complicated and large protocols for review with all in one and cross-reference to annexes with information on sub-trials
  → We could miss something, high work load –short timeline
- Adaptations: addition of new sub-protocol by amendments where procedures are not "fit for purpose" and our concept of one EudraCT number per protocol is challenged (US: IND, may not have the same challenge).
- May be challenging to understand scope of trial, also for ethical committees.
- Describe trial design thoroughly
- Justify submission as one EudraCT trial and maintain scientific integrity or consider separate EudraCT No for sub-trials (especially in platform designs)

Conclusion: Take home message

- Voluntary Harmonized Procedure (VHP) – joint assessment before national submission of multinational clinical trial applications - highly recommended for complex trial applications with master protocols.
- Recommendations on clear communication and relevant issues for consideration in substantial amendment applications with new IMPs/populations (recommendation paper, section 5).
- Principles valid for new CT designs

Challenging the CTFG recommendations?

→ Seek advice from
relevant EU member states…

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