CTFG perspective:
New EU recommendations on Complex Clinical Trials

7th Conference on Clinical Trials in the Nordic Countries, Oslo 2019

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Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

Clinical Trials Facilitation and Coordination Group (HMA)

Published: 12 February 2019

Published on CTFG webpage (under 'Key documents list', 'Guidance'): www.hma.eu/ctfg

→ Consolidated view of EU competent authorities in relation to authorization of clinical trials

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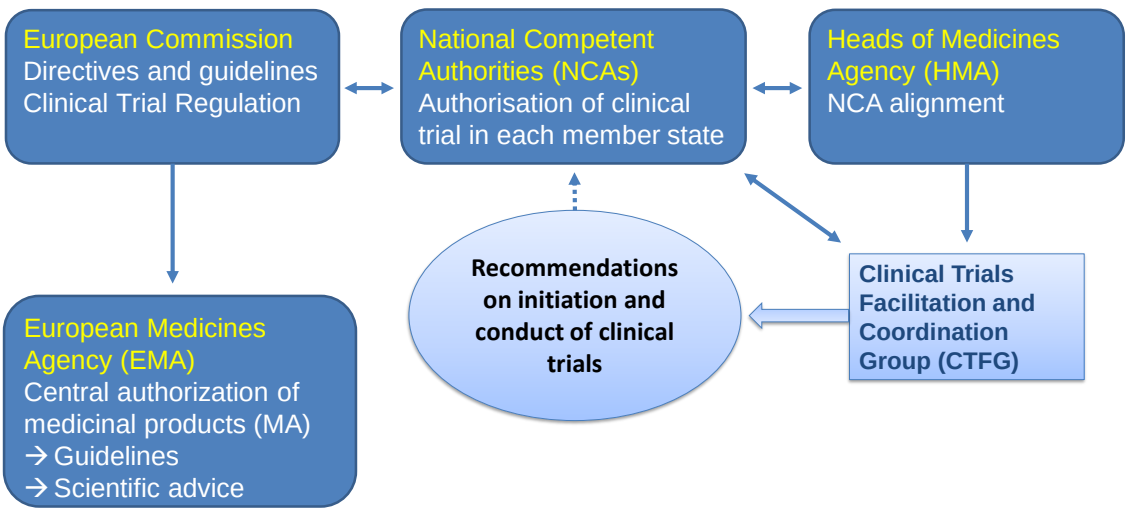
EU governance on Clinical Trials – CTFG ensures aligment



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Outline

- Terminology – which trials are we talking about?
- EU CA challenges on complex trials
  - Challenging the EudraCT system
  - Concerns for compromised transparency
- Regulatory advice – how to use the recommendation paper

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Terminology: Complex Trials & Master Protocols

Platform?

See protocols with combined trials and screening platforms without use of 'master protocol'

→ CTFG use 'complex trials' as overarching term to avoid narrowing scope of paper

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Complex Trials &/or Master Protocols

- US Master Protocol:
  - 'One overarching protocol designed to answer multiple questions' (Janet Woodcock and Lisa M. LaVange).
  - 'An over-arching protocol or trial mechanism comprised of several parallel sub-trials differing by molecular features' (Lindsay A. Renfro)

- CTFG Complex Trial: 'Separate parts (sub-protocols) that could constitute individual clinical trials'.

  → EU: Sub-study is a detailed investigation into a research question not addressed by the principal trial in sub-population → we used 'sub-protocol'

Same trials - Terminology not yet aligned

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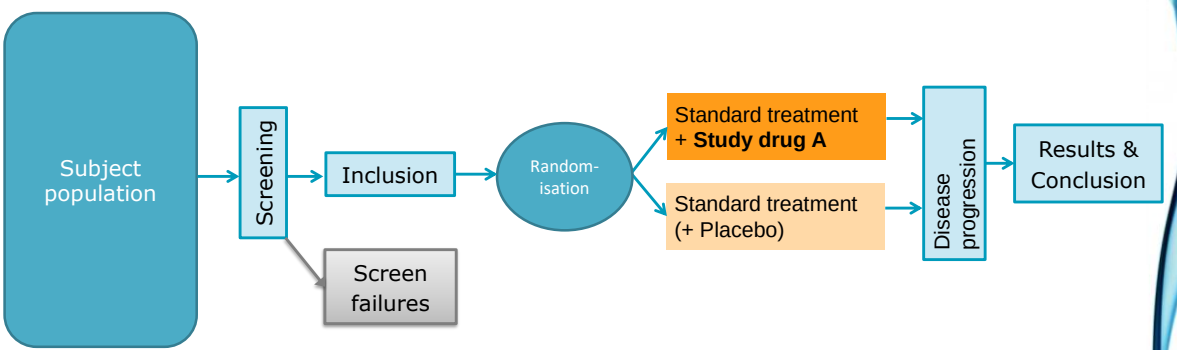
Optimization of infrastructure and patient recruitment

Conventional clinical trial:



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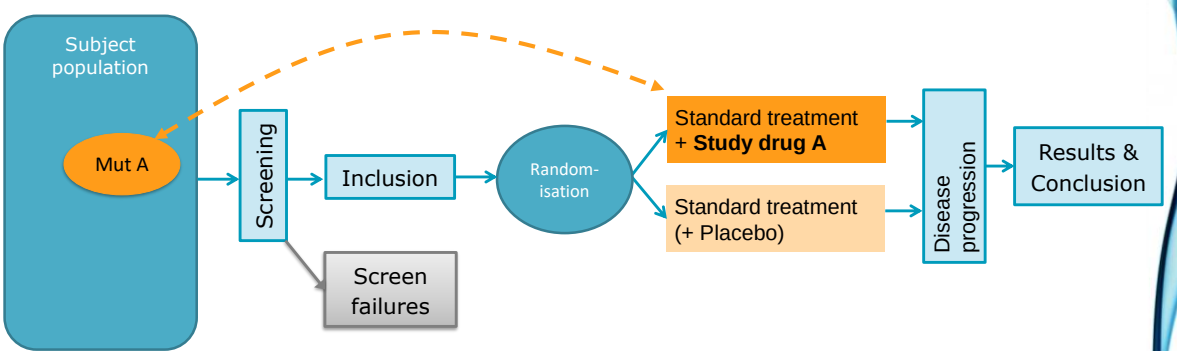
Personalised medicine: drugs targeted toward patient biology e.g. mutation or protein level ~ "enrichment" trial → smaller trials with fewer patients



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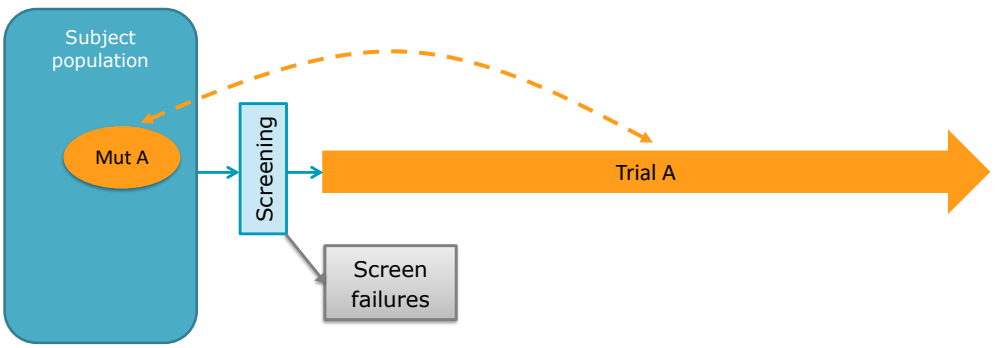

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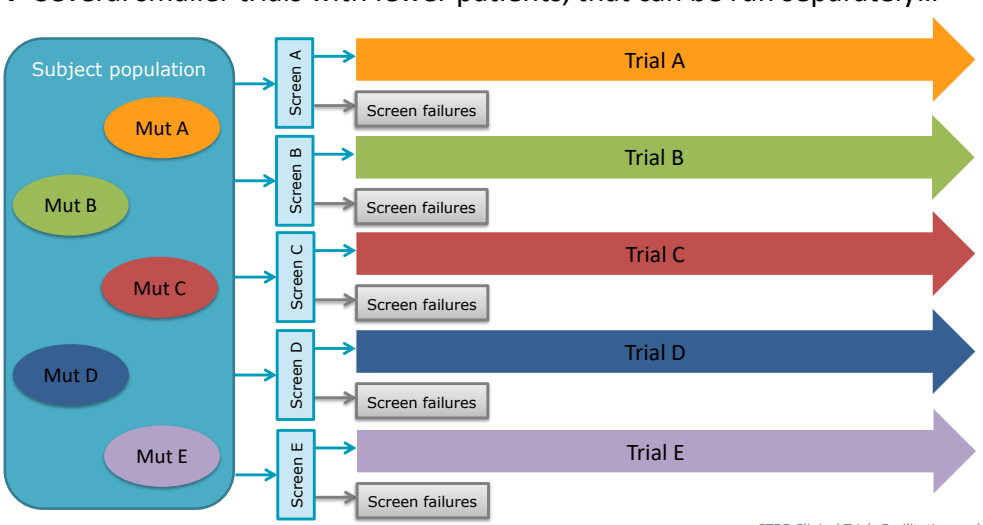
Current development:

→ Several smaller trials with fewer patients, that can be run separately…



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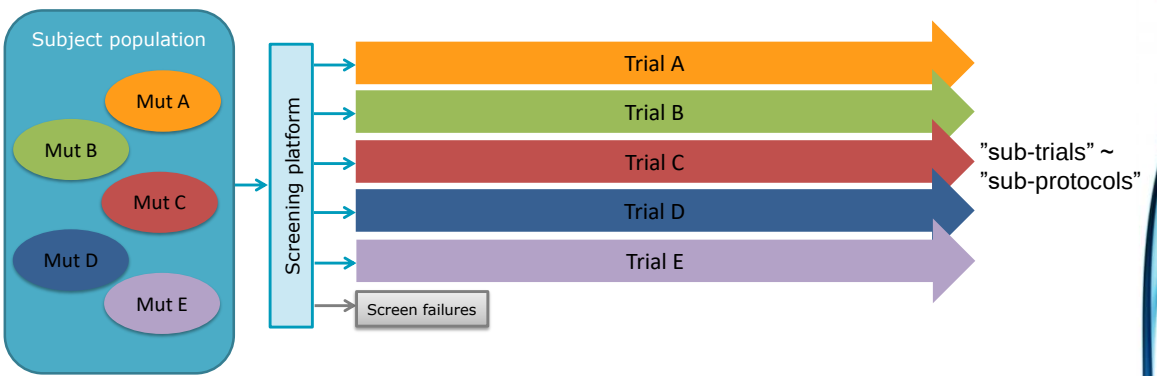
Complex clinical trial: several trials in one protocol

…or one complex umbrella trial with shared operational infrastructure and optimization of subject allocation: fewer screen failures and one screening platform



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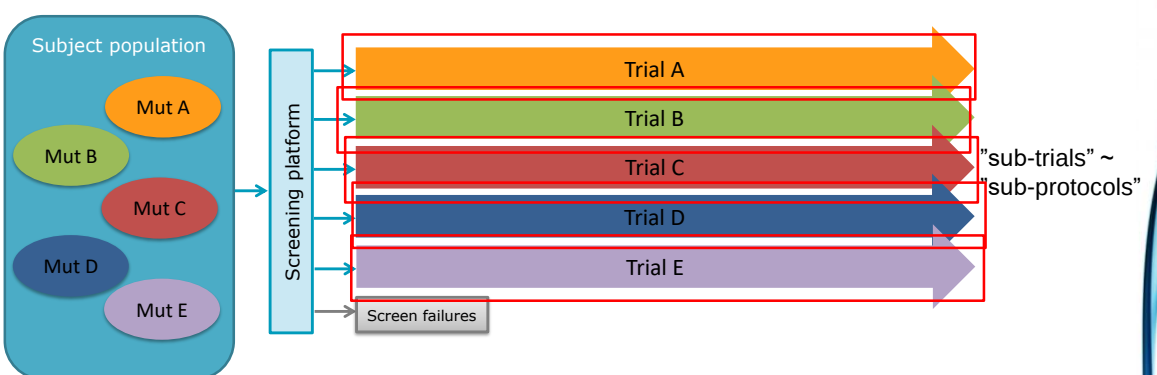
CTFG challenge: ‘Combined trials’

Sub-trials/sub-protocols would usually have had separate EudraCT numbers → often combined under one EudraCT number



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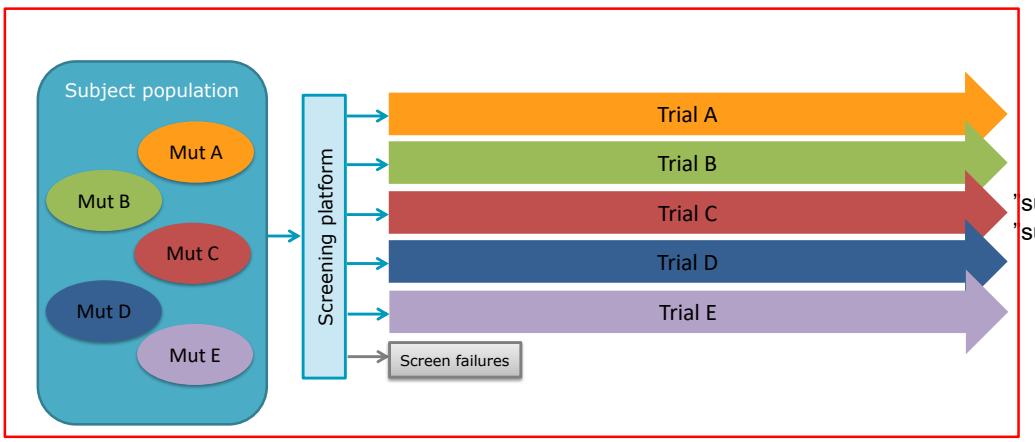

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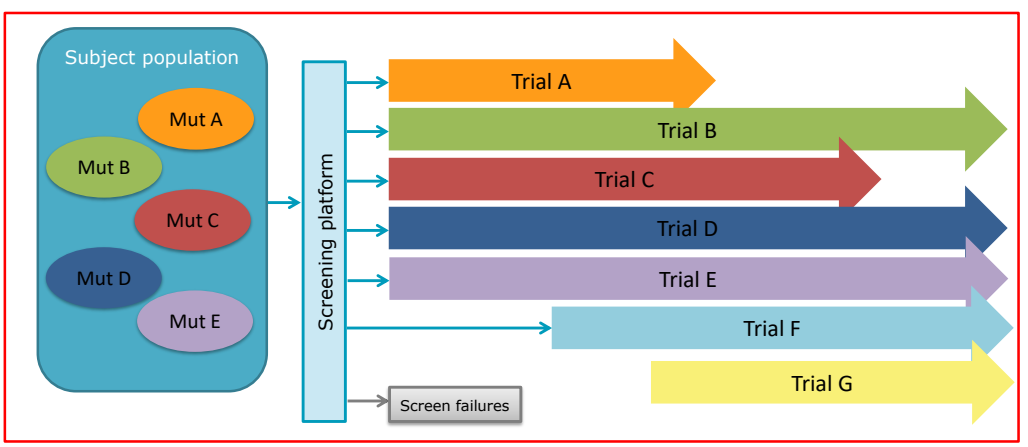
CTFG challenge: 'Combined trials'

New sub-protocols are added by substantial amendments ~ platform study



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Complex trials challenge key review point in CTA authorisation

EU: clinical trial application (CTA) – per trial/protocol (EudraCT number)
→ evaluation of each trial "case-by-case"

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

EU Directive 2001/20/EU & ICH E6 (R2) (GCP)

CTFG recommendations to facilitate trials ensuring patient safety and data integrity:

Provide transparency on concerns with tools to address them with aligned EU CTA perspective

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Compromised transparency throughout clinical trial by registering complex trial as one EudraCT number

1) Authorization of trial:
   - Complicated and large protocols for review with 'all in one and cross-reference to annexes with information on sub-trials → We could miss something..
   - Adaptations: addition of new sub-trials by amendments where procedures are not "fit for purpose" and our concept of one EudraCT No per protocol is challenged (US: IND, may not have the same challenge).
   - May be challenging to understand scope of trial, also for ethical committees.

→ Read CTFG recommendations. Describe trial design thoroughly (R1)
→ Justify submission as one EudraCT trial and maintain scientific integrity (R2)
→Consider separate EudraCT No for sub-trials, especially in platform designs

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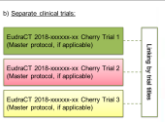
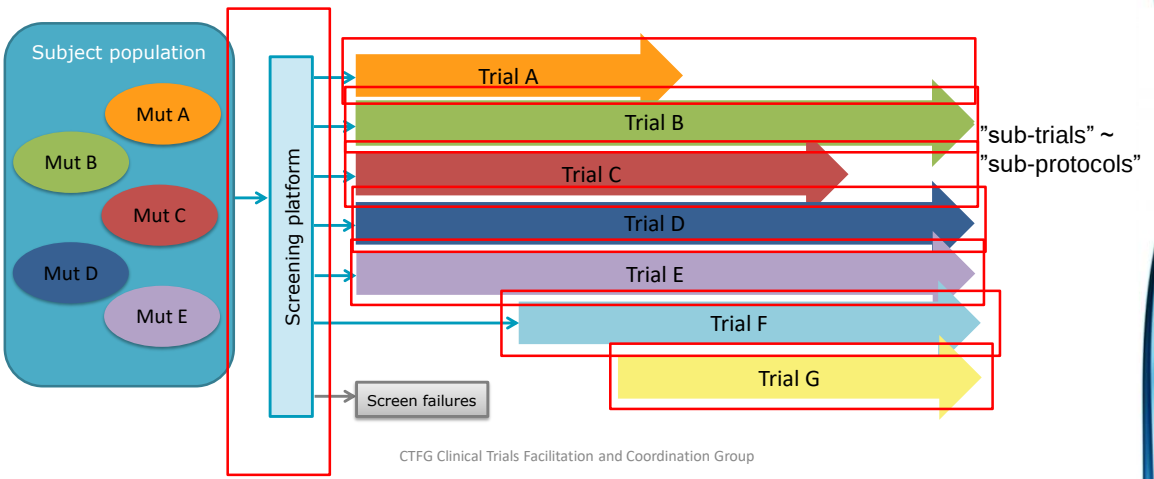
Consider separate EudraCT numbers



Describe screening platform, allocation to sub-protocols and overall operational framework in master protocol – and submit with each EudraCT study



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Compromised transparency throughout clinical trial by registering master protocol as one EudraCT number in Europe

2) Trial conduct:

- **Main purpose of protocol is to facilitate trial conduct at investigator sites.**
  Recommendation No 3-5: feasibility at study sites, subject safety, trial integrity

→ Have you asked investigator sites whether putting all into one protocol optimizes trial conduct?? Relevant for cover letter to justify design.

→Ensure us that safety and risk-mitigations are tailed to each drug and population

→Ensure us that you are in control of the operational complexity (at sponsor site, CROs, study sites). Multi partner studies: One sponsor to take responsibility for screening platform and overall operational framework.

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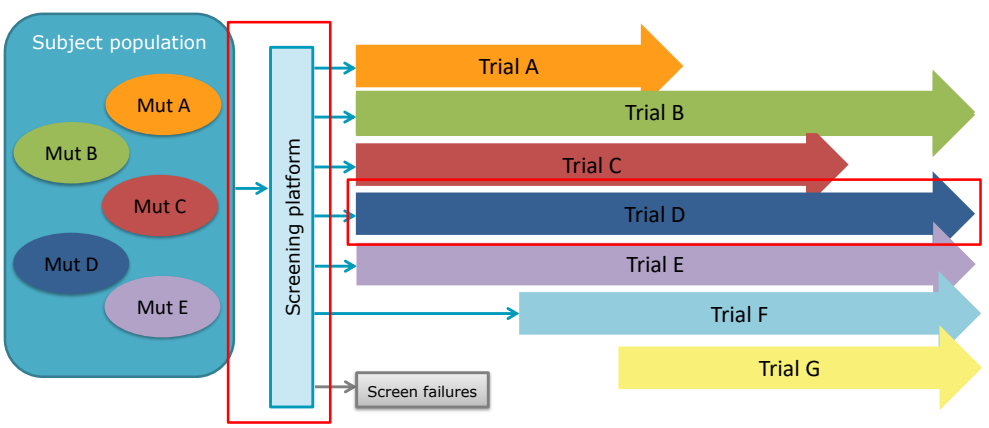
Compromised transparency throughout clinical trial by registering master protocol as one EudraCT number in Europe

2) Trial conduct:
   - How to provide clear information to trial subjects? *(recom No 6)*

→ Re-evaluate benefit-risk balance at critical steps and consider update of subject information and re-consent (ICF).

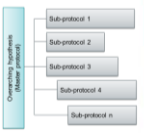
→ Focus on providing clear and only relevant information to trial subjects e.g. by staged consent for screening platforms.

Clear information to trial subjects by staged consent?



→ Note that this is new for EU ethical committees. Make sure to explain procedure well and consent trial subjects after each step. Explain benefit to patient.

Compromised transparency throughout clinical trial by registering all as one EudraCT number



3) End of trial: Data are published in EudraCT database within 1 year.
   - "Never ending" trials with many new sub-trials will prevent timely publishing of data from closed sub-trials.
   - "Data drowning"….more difficult to find the data you are looking for when data from many sub-trials are published under same EudraCT number.
     → *CTFG R8: data transparency:* describe publication policy in protocol e.g. journals, press-release, study reports, indexed data…
     (CTR may provide option for publication of interim data – not solve all issues.)

   - *Premature EOT notification: authority safety alert compromised in complex trials.*

   → *CTFG suggests urgent safety measure. Describe if you suggest alternative.*

Regulatory advice – how to use the paper

- 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).
- Challenging the CTFG recommendations?
  → Seek advice from relevant EU member states.

CTFG recommendations: meant to facilitate complex trials by providing transparency on concerns with tools to address them with an aligned EU CTA perspective

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