European Federation of Pharmaceutical Industries and Associations

Delivering on innovative trials: an industry's perspective

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CDDF meeting

Agenda

1. The future of clinical trials
2. Why complex clinical trials are important?
3. Different clinical designs features
4. Current and future complex clinical trial environment
5. Conclusions

Future of clinical trials

Increase collaboration, flexibility, mutual recognition and reliance among regulators and other stakeholders

- Equity in access and awareness
  - Improve access and build trust
  - Improve awareness of CTs
- Innovation, efficiency and speed
  - Parallel processing at risk
  - Sponsor's knowledge sharing
  - Collaboration amongst sponsors
- Adaptive and flexible approach
  - Using RWE/RWD
  - Large pragmatic trials
- Efficiency and convenience
  - Improved clinical operations
  - Decentralised clinical trials
  - Embrace digital tools

EFPIA 5-Year Clinical Trial Strategy: Vision and Actions

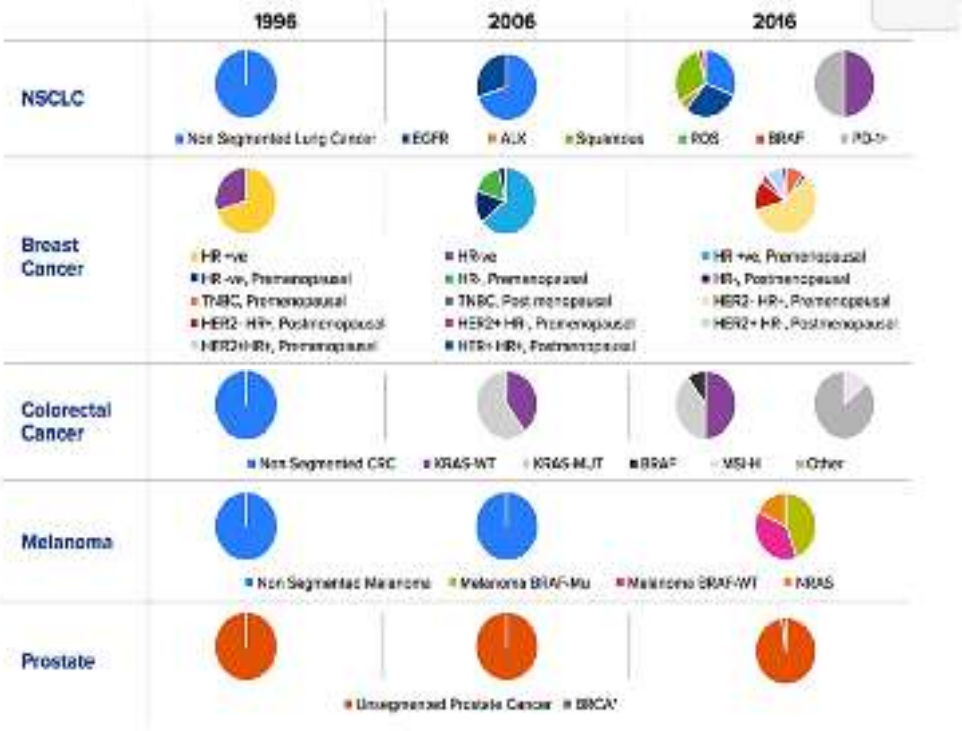
Europe can take a leading role in optimising clinical development by enhancing the patient's experience of clinical trials with the overall aim of accelerating the development of innovative medicines

- Societal support and trust
- Patient empowerment
- Patient-centric innovation by design

Why are complex clinical trials important? (1/2)

Complex clinical trials are needed more than ever to accelerate drug development and bring innovative medicines to patients

- Example: Oncology
  - Recent discoveries in immuno-oncology led to an expansion of new cancer therapies entering clinical development
  - Traditional drug development pathway is slow with novel agents taking an average of 12 years to reach clinical practice
  - Leads to a constriction of agents and combinations awaiting clinical evaluation



Source: Global Oncology Trends 2017: Advances, Complexity, and Cost. QuintilesIMS Institute. June 2017

Why are complex clinical trials important? (2/2)

- **combine multiple clinical questions within a single trial**
  - more efficient, informative and ethical
  - more flexible by utilising results accumulating in the trial to modify the trial's course
  - make better use of resources (⏳ and €) and might require fewer participants
  - Example: SARS-Cov-2 (Covid-19)
    - Overcoming barriers to starting up sites
    - Increasing participants at existing sites
    - Using the COVID experience to inform our preparedness for future pandemics

I-SPY Covid

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Solidarity Trial Vaccines & Solidarity Therapeutics Trial (WHO)

REMAP-CAP

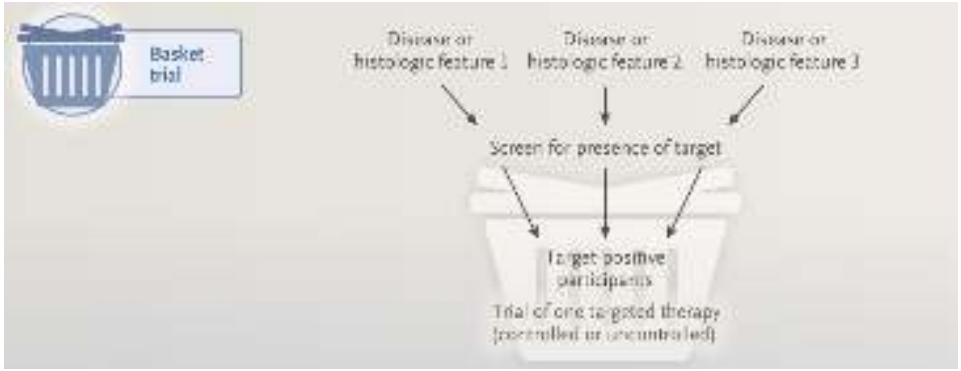
Adaptive COVID-19 Treatment Trial (ACTT)

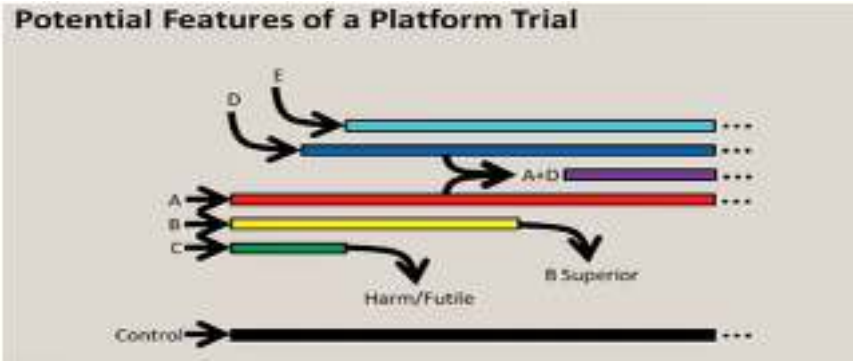
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) NIH

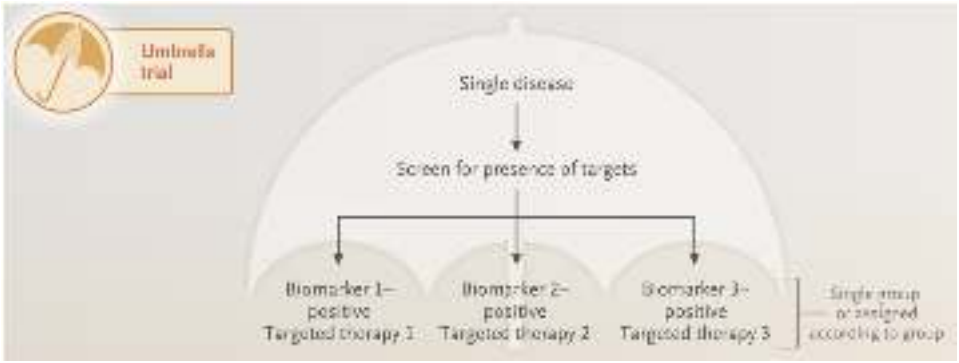
EFFECT OF DEXAMETHASONE IN PATIENTS WITH ARDS AND COVID-19 (REMED)

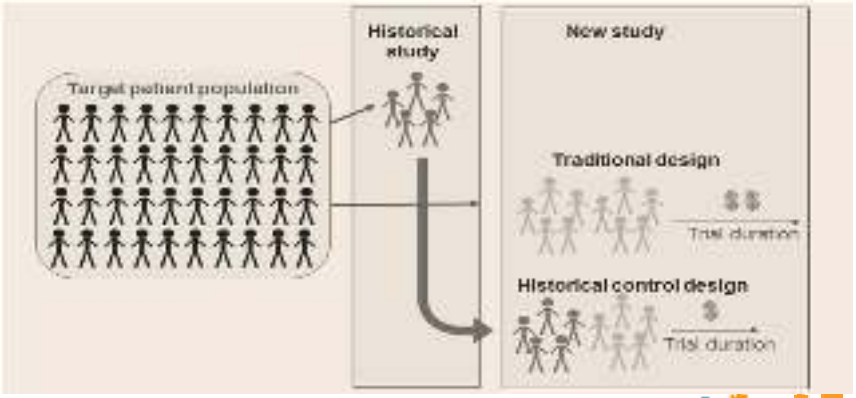
PRINCIPLE
Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses

Range of innovative clinical trial designs



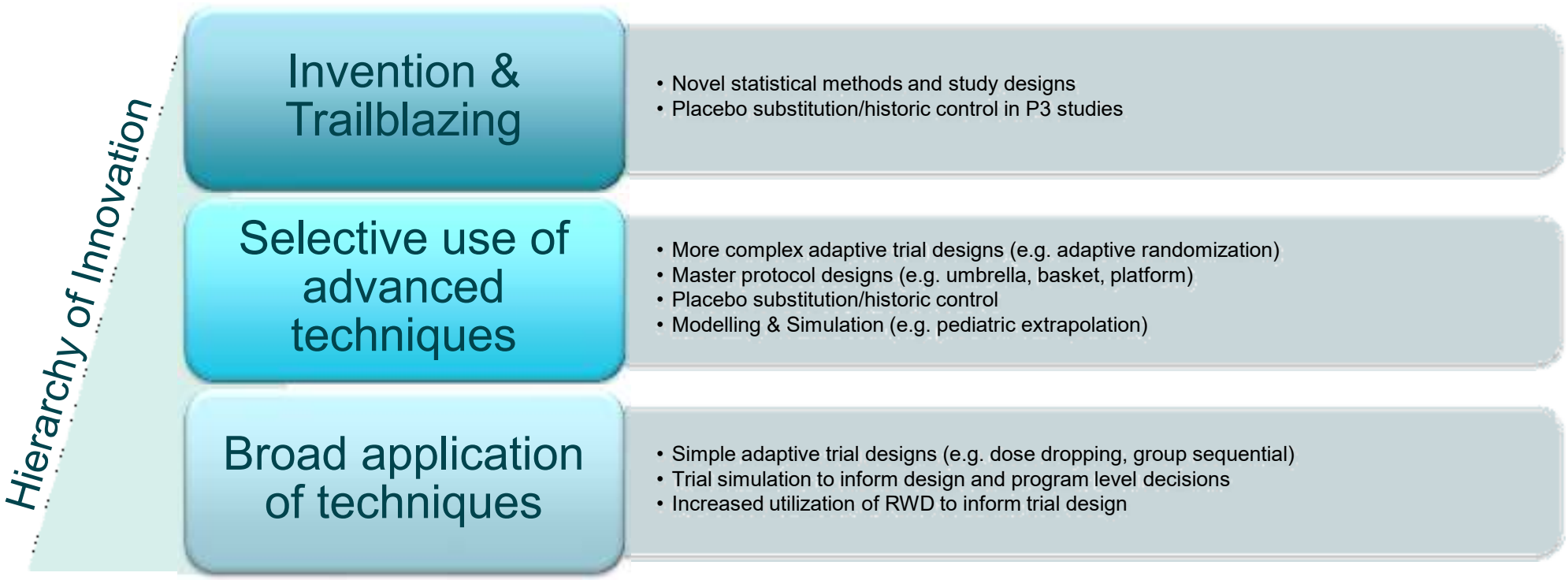






Source: Woodcock & LaVange NEJM 2017

Variable innovative trial designs experience



Adaptive design types and their benefit

Adaptive randomization	• Patients randomized to treatments which are more likely to be effective, may result with reduced sample size
Adaptive dose-finding	• Better understanding of treatment doses to improve probability treatment is successful in phase 3
Group sequential design	• Stopping trials early for futility or efficacy, patients don't continue to receive an ineffective treatment
Sample size re-estimation	• Checking assumptions still hold and trial retains sufficient power to assess trial objectives
Seamless P2/3 design	• Faster decision making and progressing promising treatments quicker for patients
Adaptive enrichment design	• Targeting patients most likely to benefit from the treatment, reducing variability to treatment

Small populations: Umbrella trial – EPOCH 1/2/3/4
Ilaris® (Canakinumab)

- CACZ885N2301 Ph III pivotal study in Periodic Fever Syndromes (crFMF, TRAPS, HIDS)

TNF receptor-associated periodic syndrome

TRAPS

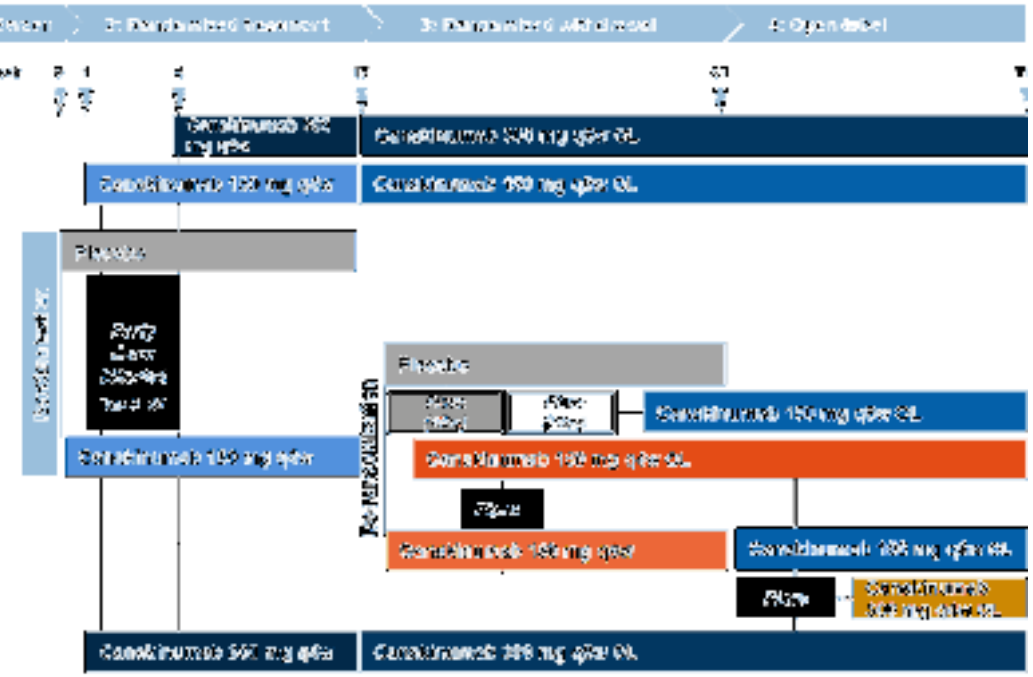
colchicine-resistant Familial Mediterranean fever

crFMF

Hyper-IgD syndrome

HIDS

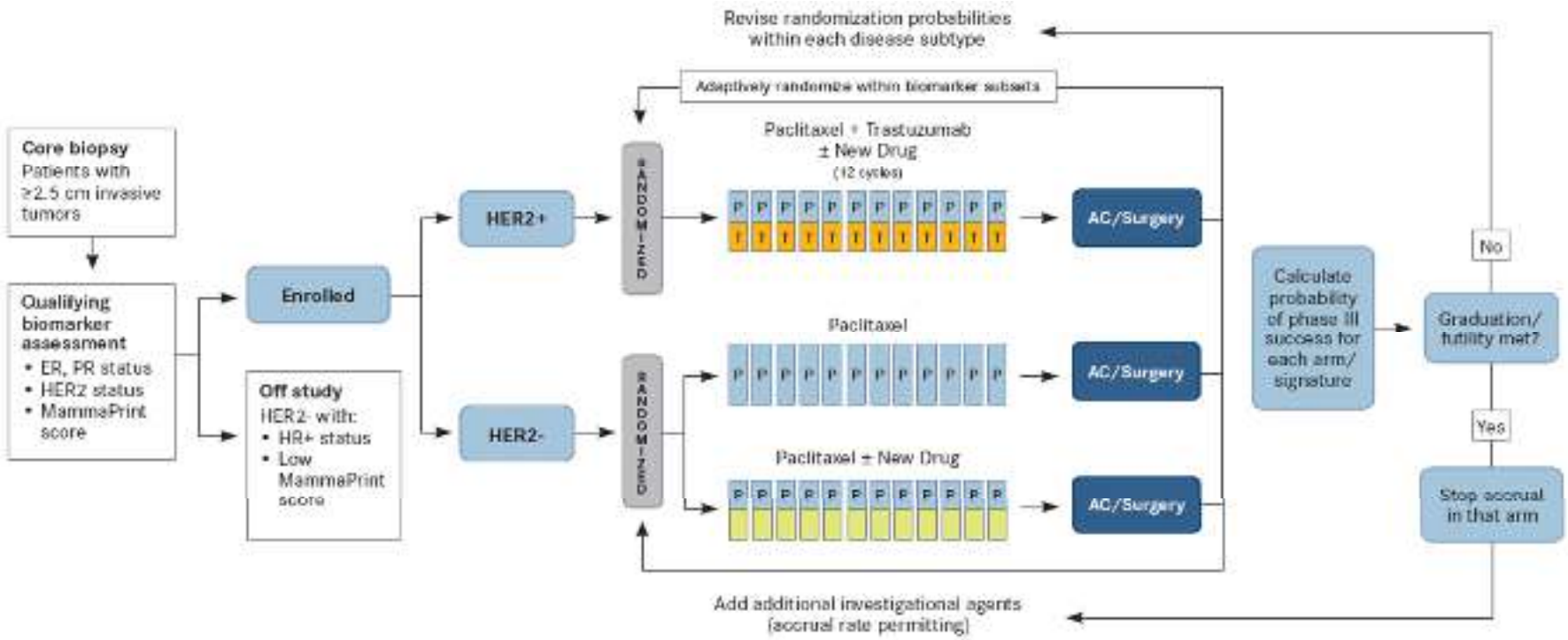
Identical for all 3 cohorts



- Primary objective: to demonstrate > of canakinumab 150 mg q4w VS placebo in reducing disease activity by resolving flare by D15 and inhibiting new flares over 16w of treatment

Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes | NEJM

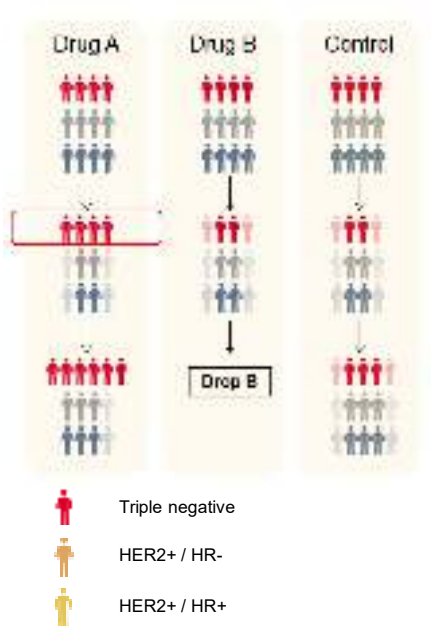
Large population: platform trial – I-SPY 2
Bayesian predictive probability of success



HER2: human epidermal growth factor receptor 2

https://www.ispytrials.org/

Large population: Platform trial – I-SPY 2
Response-adaptive randomisation



HER2: human epidermal growth factor receptor 2 – HR: hormone receptor

https://www.ispytrials.org/

Benefits of CCTs

- Increased and earlier patient access to targeted therapies
- Identify promising or ineffective medicine earlier, reduction of failure rate in PhIII and reduction of patient exposure to ineffective drug
- Efficiently study multiple compounds / multiple targets in one operational set-up
- Flexible design to adapt to data being collected and change in treatment landscape
- Operational and resource efficiency (common control arm, infrastructures, shorter start-up time for new sites...)
- Central molecular screening: faster accrual and increased likelihood of patient eligibility for at least one of the cohorts
- Accelerated drug development and approval

From challenges to solutions

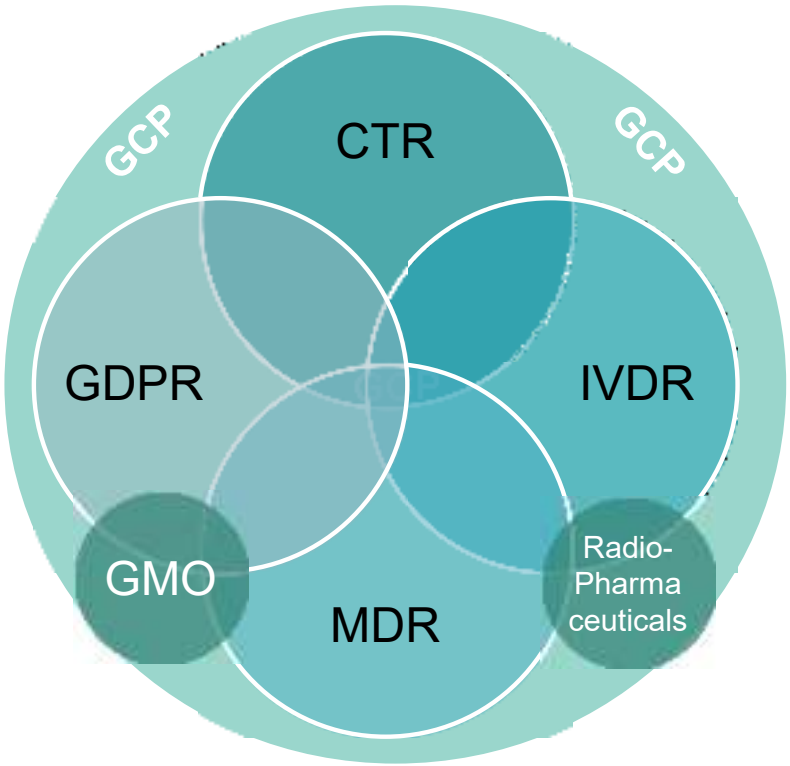
- **Ensure sufficient technical capability/capacity**
- **Increase regulator and stakeholder collaboration**
- **Provide timely advice and engagement**
- **Facilitate global approaches to innovative trials**

- Regulators strongly encouraged sponsors to:
  - Communicate early
  - Take account of available guidance
  - Plan effectively
  - Ensure that all elements of the trial design reflect the overarching scientific concept
  - Be ready to fully justify the selection of a CCT approach rather than more classical/standard trials.
- Without more alignment across regulators there is a risk of duplication or contradiction of advice
- There is a need for a collaborative multistakeholder platform to facilitate interaction and learning amongst regulators

Practical issues for implementing CCTs

- **Seeking opportunities to discuss innovative designs prior to submission via scientific advice**
- **Impact of the EU Clinical Trial Regulation**
  - Adaptation of endpoints during trials requires new CTA or amendment
  - Seamless adaptive designs (Ph I-II) and implementation of FIH guideline requires submission to authority between phases
  - For trials running over a very long period, some regulators are requesting interim reports to be submitted
  - Challenging to convince all stakeholders of the patient benefits using innovative designs
  - Role of Data Monitoring Committees and interactions with regulatory agencies
- **Divergence of regulatory requirements across different regions**
- **Risk of Europe not being able to participate in trials due to competitive environment**

Conclusion: Innovation in clinical research is a priority!



- **Pandemic showed us that innovation in clinical research should be a priority**
- **EU clinical research space is alreally incredibly complex**
- **Need for a paradigm change for patients, sponsors, regulators and payers**
  - Prioritise education activities
  - New Clinical Trial Regulation could impact approval
  - More discussion needed with all stakeholders
  - Regulators, HTAs and payers acceptability is key for success
- **EFPIA welcomes the ACT-EU initiative**
- **Benefiting patients by efficiently generating robust evidence for regulatory and payer decision making**

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Thank you