Multi-stakeholder workshop

# Accelerating Adoption of Complex Clinical Trials in Europe and beyond

## 5 - 6 October 2021

#CCTWorkshop2021

Multi-stakeholder workshop

5 - 6 October 2021

14:00

# Welcome & Introduction

Sini Eskola (EFPIA) &
Jan Geissler (Patvocates)

Day 1
5 October
2021

# Welcome & Introduction

Moderator of the day:
Christine Fletcher (GSK, EFPIA)

# Multi-stakeholder workshop 5 - 6 October 2021

## Day 1: 5 october 2021

**14:00**

**Welcome & Introduction**
Sini Eskola (EFPIA)
Jan Geissler (Patvocates)

**14:10**

**SESSION 1**
**Setting the scene & Sharing experience – CTA approval**
Anja Schiel (EMA SAWP, NoMA)

- 5' **Introduction**
  Anja Schiel (EMA SAWP, NoMA)
- 15' **CTFG experience of CCTs**
  Elke Stahl (CTFG, BfArM)
- 15' **US pilot feedback - FDA's experience so far**
  Dionne Price (FDA)
- 15' **CTTI, European initiatives, IMI EU Pearl**
  Solange Corriol-Rohou (AstraZeneca, EFPIA)

**15:00**

**SESSION 2**
**Stakeholders' priorities & expectations**
Claas Röhl (NF Patients United)

- 10' **Patients**
  Dominique Hamerlijnck (EUPATI)
- 10' **Regulators - EU & beyond**
  Anthony Humphreys (EMA)
- 10' **Ethics Committees**
  Martin Brunner (Ethics Committee, AT)
- 10' **HTA bodies**
  Niklas Hedberg (TLV SE, EUnetHTA)
- 10' **Industry Perspective**
  Lucia D'Apote (Amgen, EFPIA)
- 10' **Investigators**
  Birgit Geoerger (Gustave Roussy Institute, FR)
- 25' **Panel discussion**

16:25 Coffee break

**16:45**

**Breakout Sessions**

1. **Design of Master Protocols**
   Christine Fletcher (GSK, EFPIA)
   Lada Leyens (Roche, EFPIA)
2. **Regulatory processes and system**
   Anja Schiel (EMA SAWP, NoMA)
   Lucia D'Apote (Amgen, EFPIA)
3. **Patient involvement**
   Claas Röhl (NF Patients United, AT)
   Solange Corriol-Rohou(AZ, EFPIA)

**18:45**

**Concluding remarks**
Christine Fletcher (GSK, EFPIA)
Mireille Muller (Novartis, EFPIA)
Anja Schiel (EMA SAWP, NoMA)

19:00 End of Day 1

## Day 2: 6 october 2021

**14:00**

**Introduction to Day 2**
Sini Eskola (EFPIA)
Peter Arlett (EMA)

**14:10**

**SESSION 1**
**Feedback from Day 1 Breakout Sessions**
Breakout Sessions Chairs

**14:40**

**SESSION 2 - Breakout Sessions**

4. **Trials incorporating historical controls or with adaptative features**
   Christine Fletcher (GSK, EFPIA)
   Frank Bretz (Novartis, EFPIA)
5. **Operation & implementation**
   Olga Kholmanskikh (CTFG, FAMHP)
   Josse R. Thomas (Ethics Committee, BE)
6. **Education & Training**
   Begonya Nafria Escalera (eYPAGnet, ES)
   Mireille Muller (Novartis, EFPIA)

16:40 Coffee break

**16:50**

**Feedback from Day 2 Breakout Sessions**
Breakout Sessions Chairs

**17:20**

**Panel session to discuss main outputs & propose next steps/action plan**
Anja Schiel (EMA SAWP, NoMA)
Nick Sykes (Pfizer, EFPIA)

**EU Commission**
Kristof Bonnarens
(EC DG SANTE)

**FDA**
Dionne Price (FDA)

**CTFG**
Elke Stahl
(CTFG Co-Chair, BfArM)

**Ethics Committees**
Josse R. Thomas
(Ethics Committee, BE)

**Patient representatives**
Rita Magenheim (GENTURIS)

**HTA bodies**
Niklas Hedberg
(SE TUV, EunetHTA)

**Industry**
Christine Fletcher
(GSK, EFPIA)

**NGO**
Stephane Lejeune
(EORTC)

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18:30 End of Day 1

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# List of speakers

- **Peter Arlett**
  Head of Data Analytics and Methods Task Force, EMA
- **Kristof Bonnarens**
  European Commission, DG SANTE
- **Frank Bretz**
  Novartis - EFPIA
- **Martine Brunner**
  Ethics Committee, AT
- **Solange Corriol-Rohou**
  AstraZeneca - EFPIA
- **Lucia D'Apote**
  Amgen - EFPIA
- **Sini Eskola**
  EFPIA secretariat
- **Christine Fletcher**
  GSK -EFPIA
- **Jan Geissler**
  Patvocates
- **Birgit Geoerger**
  Gustave Roussy Institute, France
- **Dominique Hamerlijnck**
  EUPATI
- **Niklas Hedberg**
  SE TUV, EunetHTA
- **Antony Humphreys**
  Head Regulatory Science Strategy Task Force, EMA
- **Olga Kholmanskikh**
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- **Begonya Nafria Escalera**
  eYPAGnet, SE
- **Dionne Price**
  Director, Division of Biometrics IV, CDER, FDA
- **Claas Röhl**
  NF Patients United, AT
- **Anja Schiel**
  Chair EMA SAWP, NoMA
- **Elke Stahl**
  CTFG Co-Chair - BfArM
- **Nick Sykes**
  Pfizer-EFPIA
- **Josse R. Thomas**
  Ethics Committee, BE

Join our **Q&A** at

# Slido.com
# #867 213

Direct link to our Q&A:
**https://app.sli.do/event/htnou5aw**

You can scan the QR-code with your mobile device
for direct access to the Q&A

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# CTFG experience of CCT

**Elke Stahl**

Session1 – Setting the scene & Sharing experiences – CTA approval


NF Patients United
efpia European Federation of Pharmaceutical Industries and Associations
BARC
PPD
Norwegian Medicines Agency

# European Regulatory Frame

Clinical trials are assessed and decided **per clinical trial** / protocol
**per member states -** NCA (approval) and Ethics Committee (pos. opinion)

Key review point of a CT application
→ **evaluation of each trial "case-by-case"**:

- scientifically sound – 'ONE trial'
- clear detailed protocol
- subject safety prevails over all other interests – risk mitigations
- robust data – operational complexity
- positive benefit-risk assessment

CTFG = ClinicalTrials Facilitation and Coordination Group

# Terminology : ‘Complex Clinical Trials’

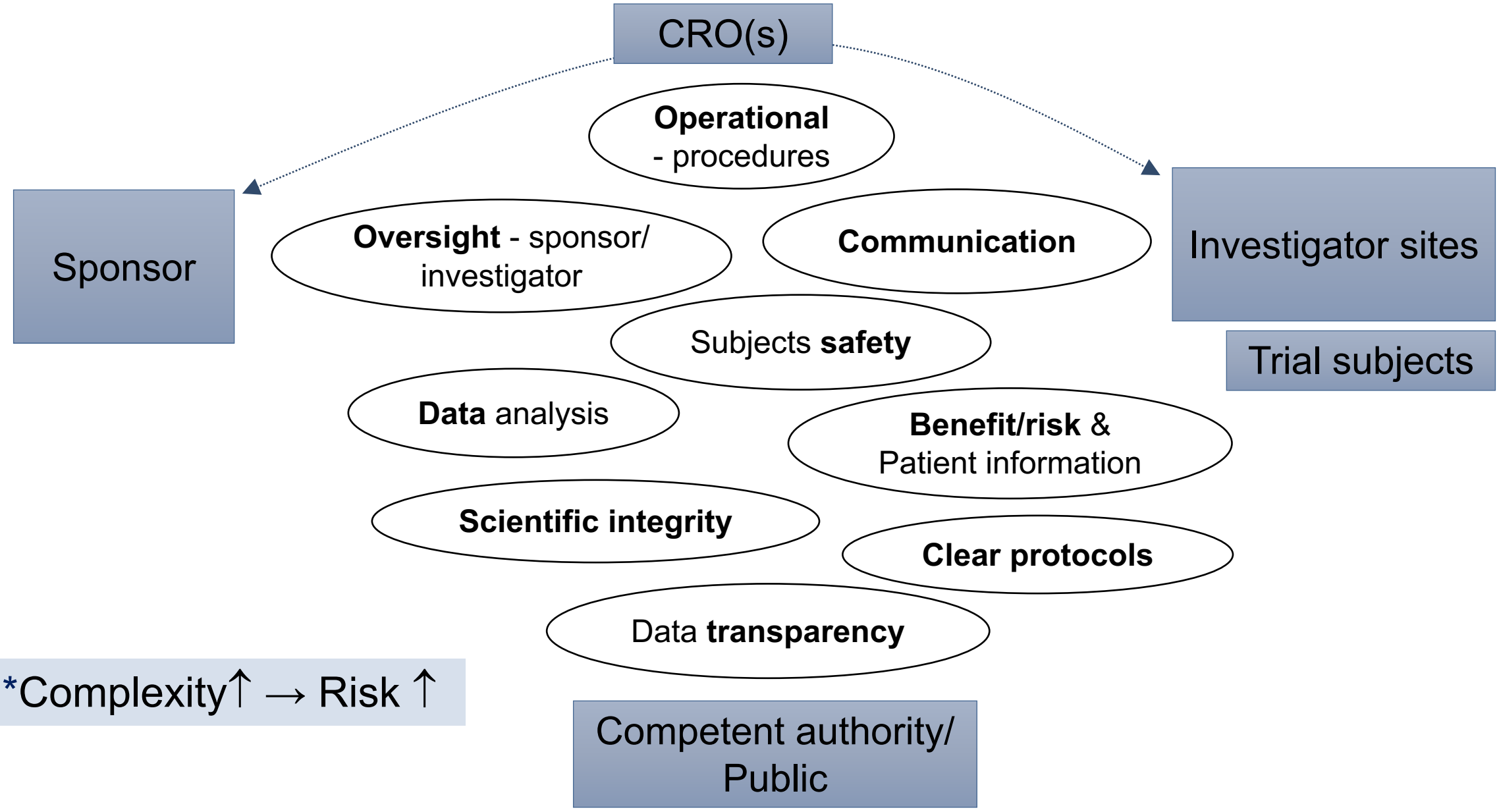
Platform?

Protocols with complex/combined CTs and screening platforms with/-out use of ‘master protocol’

→ CTFG use ‘complex clinical trials’ as **overarching term**
Principles apply to **wide coverage of new** *innovative* **CT design**
→ allow for ‘**evolution**’ in CT design

→ Note: Terminology EU and US differs, however cover same type of trials

# Challenges & Opportunities



# CTFG key recommendations for initiation and conduct of complex clinical trials*

→ **Consolidated view of EU competent authorities**

→ To facilitate complex trials and ensuring subjects safety + data integrity

→ Provide transparency of competent authorities expectations to be address by CTA submission :

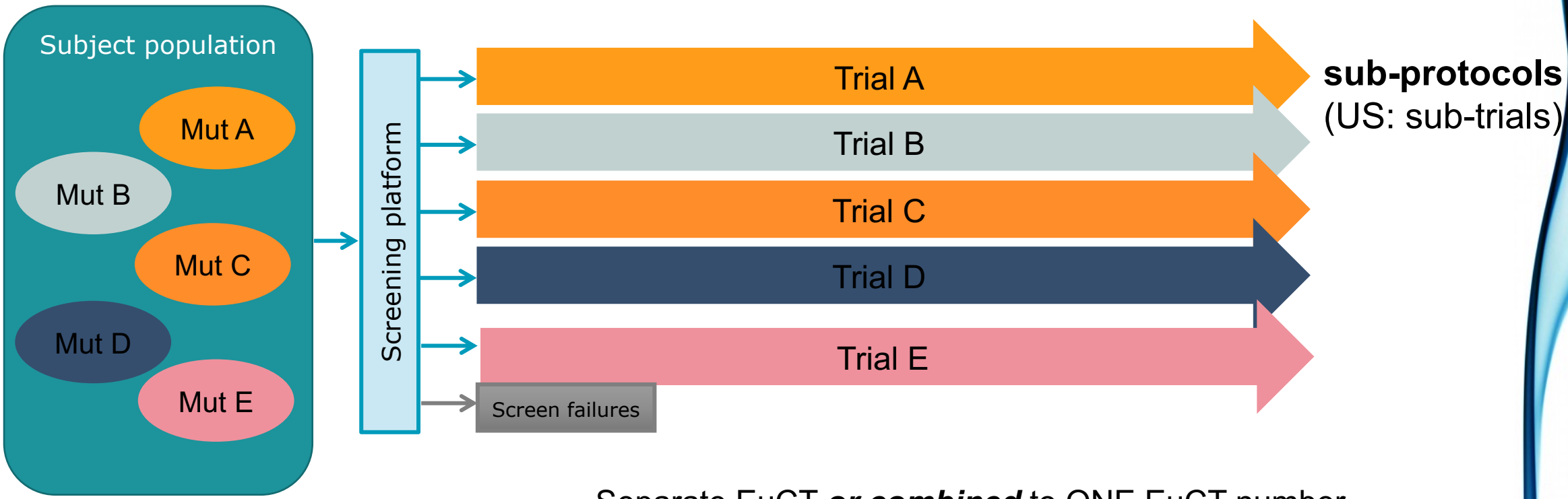
1. Clearly describe and justify design
2. Maintain scientific integrity
3. Ensure quality of trial conduct and optimise clinical feasibility
4. Ensure safety of trial subjects
5. Maintain data integrity
6. Reassess benefit-risk balance at critical steps throughout CT
7. Validate companion diagnostics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

*February 2019, www.hma.eu/ctfg

# Complex clinical trial: several trials in one protocol

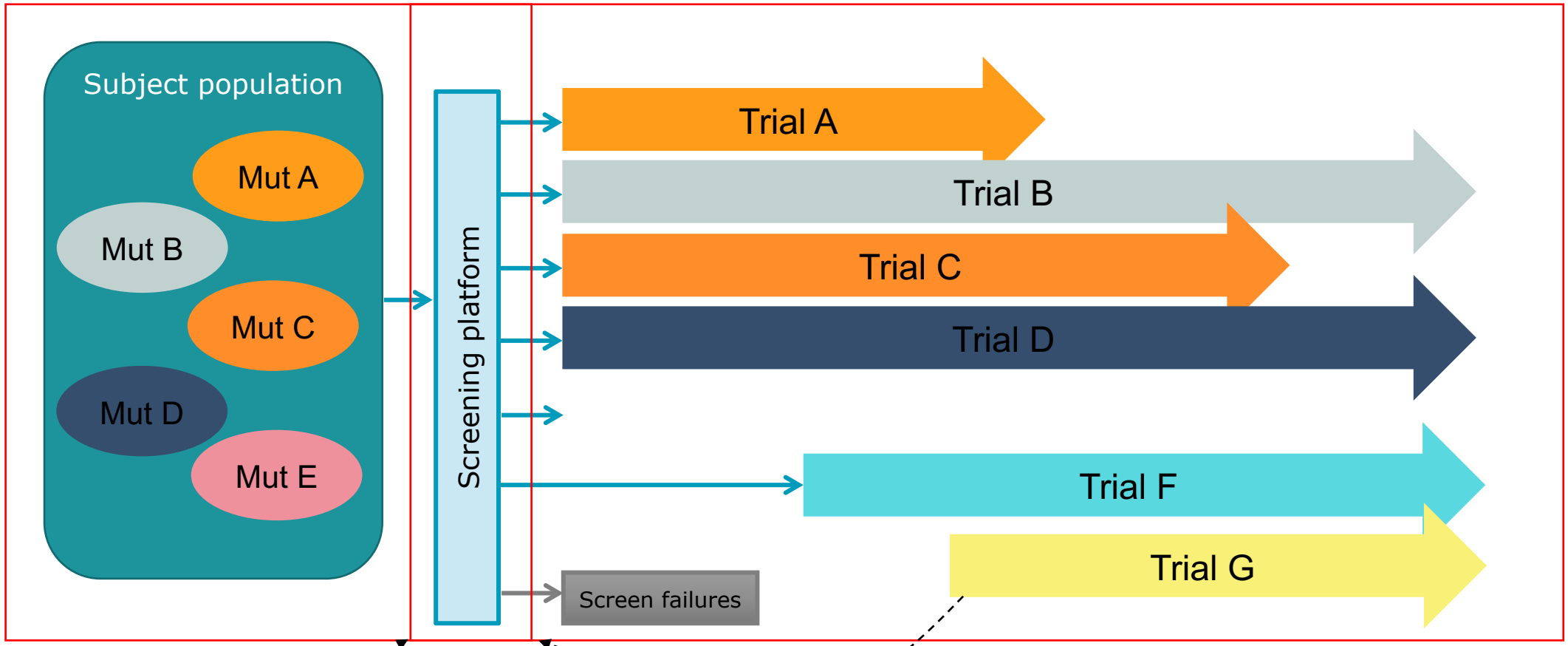
…or one complex trial with **shared operational infrastructure** and **optimization of subject allocation**

→ fewer screen failures and **one screening platform**




Separate EuCT ***or combined*** to ONE EuCT number

# Scientific integrity for single CT trial



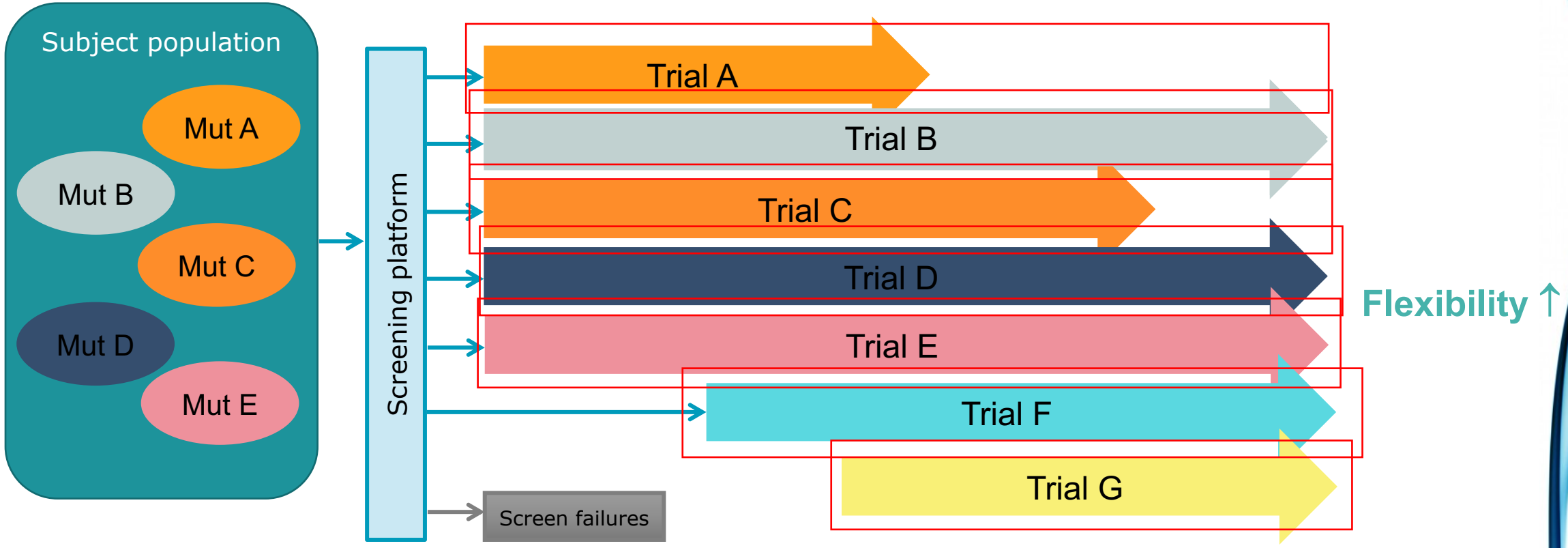

Overarching hypothesis/objective for trial at initiation

Sub-protocols added must fit the initial trial objective
Benefit Risk remains positive for all sub-protocols :
**Substantial Amendments add new IMP in sub-protocols improved ☺**

CTFG

# Consider separate EuCT numbers

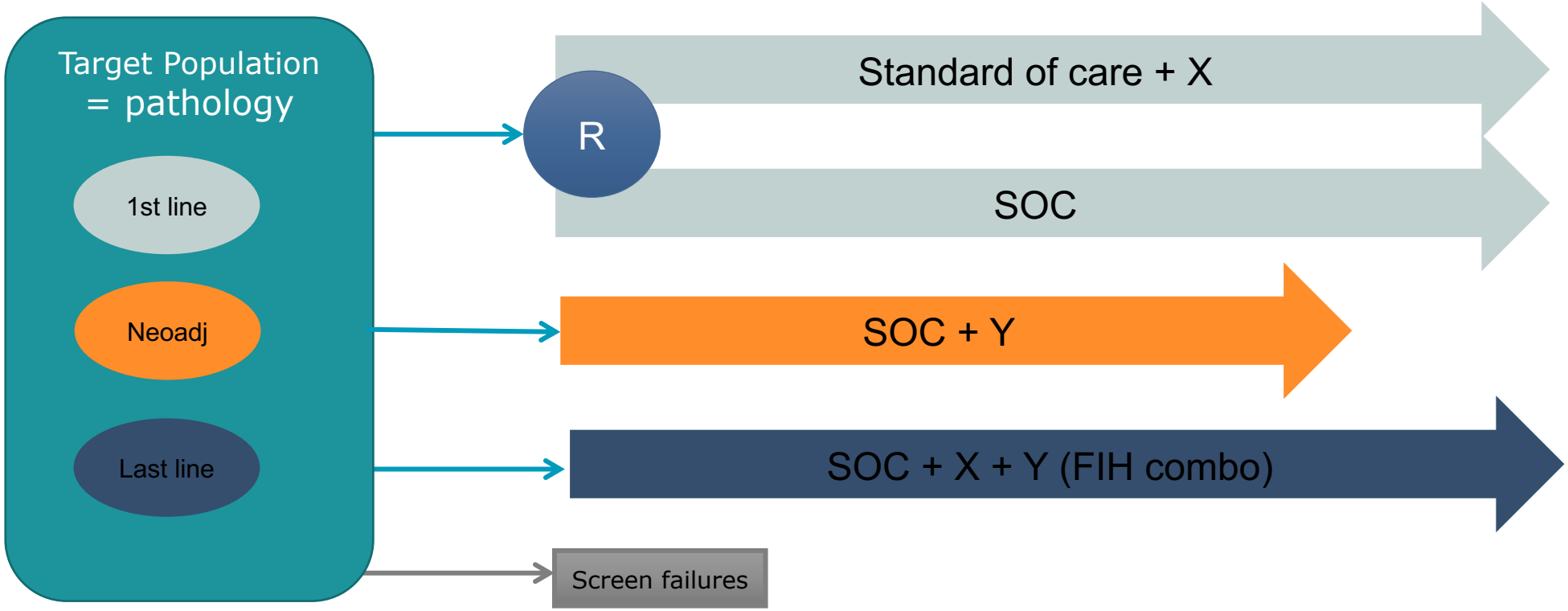
Describe screening platform, allocation to sub-protocols and overall operational framework in **master protocol** – and **submit with each EuCT**




**Substantial Amendments are challenging and a limiting factor @ CTR !**

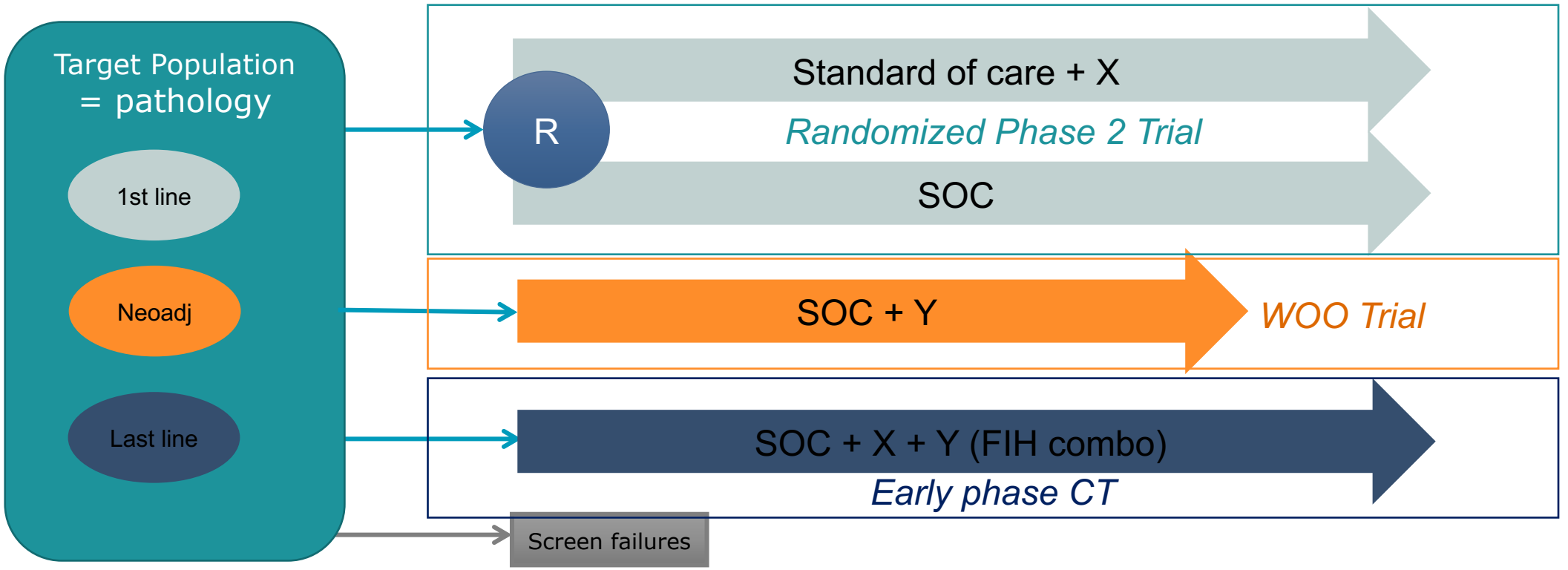
# Example in renal cancer setting (I)

Can we consider that the same pathology defines ONE overaching scientific hypothesis/objective?




Unique population?

# Example in renal cancer setting (II)




➢ 3 separate clinical trials

# Trial Conduct

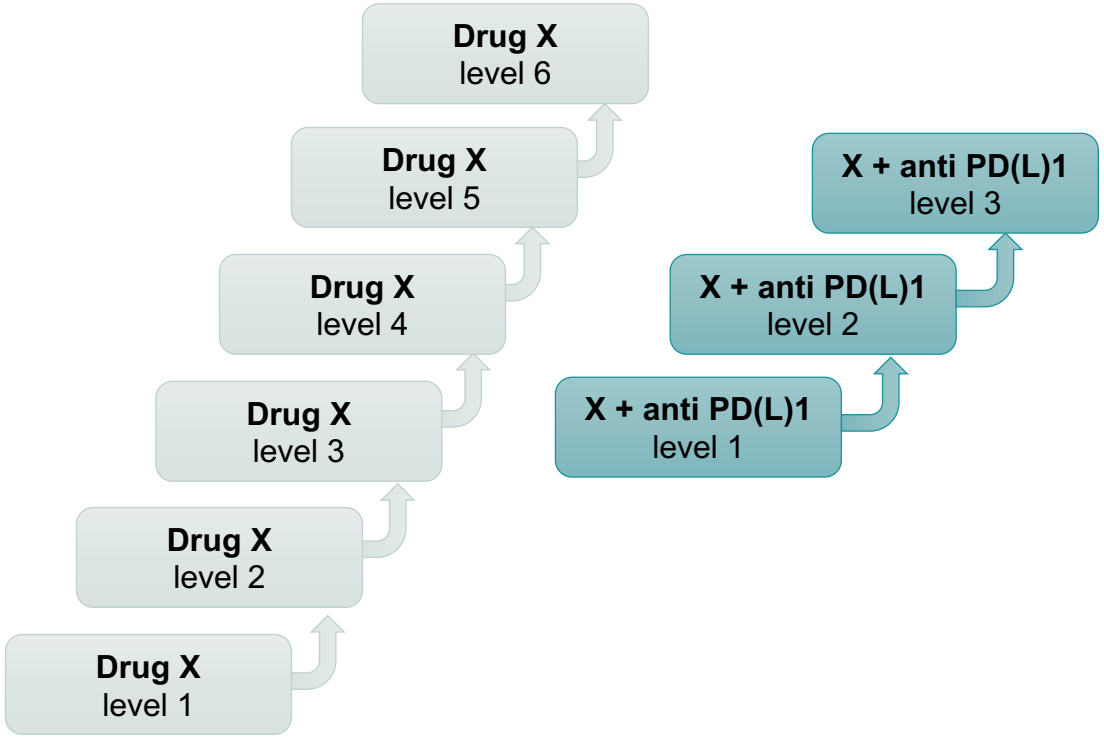
- **Protocol to facilitate trial conduct at investigator sites**:
  Is one protocol optimizes the trial conduct?
  Feasibility at study sites, subject safety, trial integrity and quality?
- **Safety and risk-mitigations are tailed to each drug and population**:
  Complexity↑ if different surveillance needed than specified in the one Master Protocol - define in sub-protocol

➢ Ensure **you have trial oversight** and **in control** of the operational complexity (at sponsor's, CRO's and study sites) and across all sub-protocols.
Multi-partner studies: <u>One</u> sponsor to take responsibility for overall operational frame

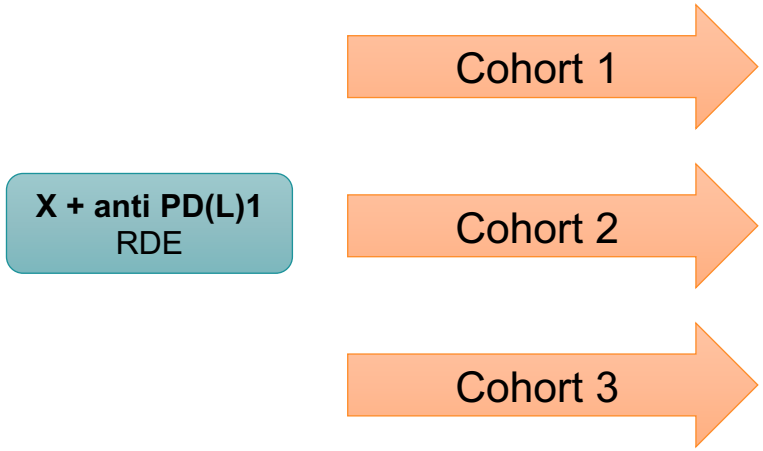
- **Benefit risk update at critical steps** to master protocol and sub-protocols
  Substantial changes to master protocol not expected, modifications should not affect the master protocol. However, if needed : amendment to all trials with this master protocol or may consider new CT; Changes to sub-protocols more likely and easier

# CCT and Independent DMC

**Complex Early Phase CT** : dose escalation vs expansion cohorts




Safety Monitoring Board (SMB)




Safety Monitoring Board (SMB)
&
**Independent** Data Monitoring Committee (IDMC)

CTFG

# CCT Trial Duration - Purpose

- **End of Clinical Trial to be defined, not endless**
  Evolution over time e.g. treatment, population, control, benefit-risk…
  Transparency of interim results : one vs multiple trials, trial integrity
  single CT versus multiple ?

- **Support postive Benefit Risk**
  Fulfil positive benefit risk balance for **CT application** :
  ensure safety/well being/rights of participants and robustness/integrity of data !
  Positive benefit risk for **marketing authorisation application** :
  evidence for efficacy and tolerability/safety !

# Overall

- **Scope of CCT is wide** and allows for evolution in CT
- Increasing complexity is increasing risk → **risk mitigation**
- Take care of the **key aspects** which might be affected
- **Strategic** planning of submission as **one or multiple** clinical trials for operational/regulatory flexibility (one Master Protocol + sub-protocol/s)
- Overarching hypothesis - **Oversight across all sub protocols** :
  CCT with continous **positive benefit risk**

➢ **CCT topics in discussion**

Follow up to CTFG's recommendation paper planned :
QnA jointly by CTFG + EMA + COM, work in progress

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## Complex Innovative Designs

# PDUFA VI CID Pilot Program

Dionne L. Price, Ph.D.

October 5, 2021

U.S. FOOD & DRUG ADMINISTRATION

# Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views and policies.

# CID Goal : Bring safe and effective products to patients

https://www.cdc.gov/ncbddd/musculardystrophy/index.html

# Federal Register Notice

44274 Federal Register / Vol. 83, No. 169 / Thursday, August 30, 2018 / Notices

such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov*.

• If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a

in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf*.

*Docket:* For access to the docket to

comment period allows adequate time for interested persons to submit comments to ensure that the Agency can consider the comments on this draft guidance before it begins work on the final version of the guidance.

**II. Electronic Access**

Persons with access to the internet may obtain the draft guidance at either *https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm* or *https://www.regulations.gov*.

Dated: August 23, 2018.

**Leslie Kux,**

*Associate Commissioner for Policy.*

[FR Doc. 2018–18775 Filed 8–29–18; 8:45 am]

BILLING CODE 4164–01–P

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA–2018–N–0049]**

**Complex Innovative Designs Pilot Meeting Program**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The sixth iteration of the Prescription Drug User Fee Act (PDUFA VI), incorporated as part of the FDA Reauthorization Act of 2017 (FDARA), highlights the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs. The Food and Drug Administration (FDA or Agency) is announcing a pilot meeting program that affords sponsors who are selected the opportunity to meet with Agency staff to discuss the use of complex innovative trial design (CID) approaches in medical product development.

label to assist that office in processing your requests. See the **SUPPLEMENTARY**

access to the draft

**FOR FURTHER INFORMATION CONTACT:** Lubna Merchant, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 4418, Silver Spring, MD 20993–0002, 301–796–5162, email: *Lubna.Merchant@fda.hhs.gov;* or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903

…highlights the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In connection with the sixth iteration of PDUFA, FDA committed to conduct a pilot program for highly innovative trial designs for which analytically derived properties (*e.g.,* Type I error) may not be feasible, and simulations are necessary to determine trial operating characteristics. The Agency also committed to issue a **Federal Register**

Notice announcing the pilot program, clarifying pilot program eligibility, and describing the proposal submission and selection process (see PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, section I.J.4.b. (*https://www.fda.gov/downloads/ForIndustry/*

*UserFees/PrescriptionDrugUserFee/UCM511438.pdf*))

.

# CID includes….

- Complex Adaptive Designs (frequentist or Bayesian)
  - Seamless designs
    - For example, combining dose-finding and hypothesis confirmation in a trial
  - Adaptations to multiple design features such as treatment arm selection, patient allocation, or endpoint selection
- Formal incorporation of “prior” information
  - Placebo augmentation using external controls or other data sources (e.g. real world data)
  - Leveraging or borrowing strength from information internal or external to the trial

# CID includes….

- Use of a posterior probability to determine trial success criteria
- Master protocols (platform, umbrella, and basket designs)
- Sequentially Multiple Assignment Randomized Trial (SMART) designs

# CID Pilot Meeting Program

- Joint effort of the Center for Drug Evaluation and Research and Center for Biologic  Evaluation and Research
- Sponsors
  - submit designs
  - have the opportunity to engage with **regulatory team** on designs via two meetings
- Agency
  - will select up to 2 submissions per quarter
  - uses the design as a case study for continuing education and information sharing
- Meetings led by statistical units with participation from all relevant disciplines
- Five year duration

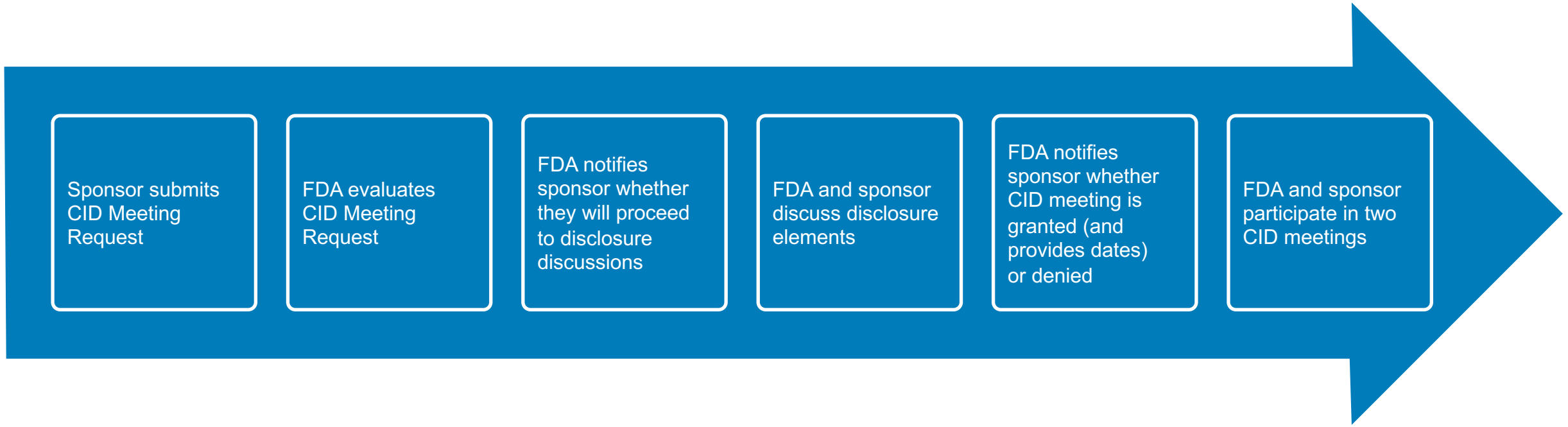
# Eligibility Criteria

- The sponsor must have a pre-IND or IND number for the medical product(s) included in the CID proposal with the intent of implementing the CID in the pilot program application.
- The proposed CID is intended to provide substantial evidence of effectiveness to support regulatory approval of the medical product.
- The trial is not a first in human study, and there is sufficient clinical information available to inform the proposed CID.
- **The sponsor and FDA are able to reach agreement on the trial design information to be publicly disclosed.**

# FDA Evaluation of Meeting Request

- Need for simulations to assess trial design operating characteristics
- Therapeutic need
- Trial design appropriateness for CID Pilot Meeting Program
- Level of innovation of the trial design
- Value proposition of the CID

# CID Pilot Meeting Process



# Progress to date

- 5 accepted submissions span several therapeutic areas
  - Neurology
  - Analgesia
  - Rheumatology
  - Oncology
- Designs incorporated
  - Bayesian hierarchical modeling
  - Use of formal priors
  - Formulation of a master protocol

# Rationale for denied meeting requests

- Lack of clarity on an appropriate endpoint
- Additional interactions would add little value to the extensive advice already received
- Low level of innovation – revision to a primary endpoint in an ongoing trial

** Sponsors may continue via other regulatory routes

# Case Example 1

- **Summary:**
  - Randomized, double-blind, placebo-controlled, phase 2/3 trial
  - Population: Duchenne muscular dystrophy
  - Bayesian adaptive design with the following potential adaptations:
    - Stop the trial for efficacy or safety
    - Modify the sample size
    - Drop an arm
    - Pool doses
    - Change randomization ratio
  - Also proposed to explore placebo augmentation with historical controls

# Case Example 2

- **Summary:**
  - Randomized, double-blind, group sequential, non-inferiority trial
  - Population: pediatric multiple sclerosis
  - Bayesian framework utilizing meta-analytic predictive priors to leverage information from external adult and pediatric studies

# Case Example 3

- **Summary:**
  - Randomized, double-blind, placebo-controlled, master protocol to evaluate multiple interventions across multiple pain conditions
  - Possible adaptations
    - Stop for futility
    - Modify sample size
    - Add or remove arms
  - Bayesian hierarchical model to leverage placebo and treatment effect information

# Case Example 4

- **Summary:**
  - Randomized, double-blind, Bayesian adaptive design
  - Population: Systemic lupus erythematosus
  - Features
    - Response adaptive randomization
    - Bayesian hierarchical model for dose selection
    - Interim analyses for futility and to inform dose and endpoint selection for future studies

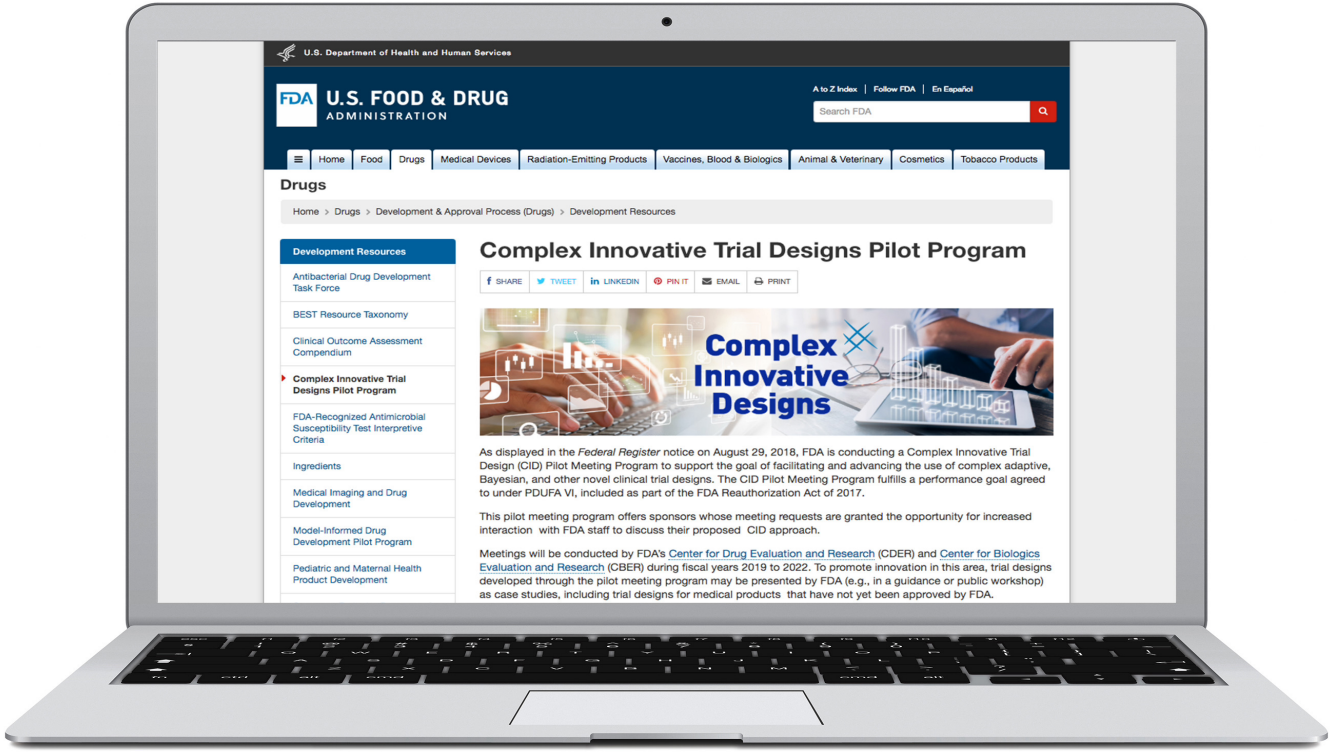
# Case Example 5

- **Summary:**
  - Randomized, open-label, controlled trial
  - Population: Diffuse large B-cell lymphoma
  - Incorporation of external controls using a Bayesian dynamic borrowing approach

# Summary

- CIDs may aid in addressing challenges
  - Value-added
- The pilot program is a multi-disciplinary effort
  - Importance of relevant disciplines
- The simulation process is iterative
  - Importance of simulation plan and simulation report
- The pilot program promotes collaborative learning
  - Disclosure

# Website




**https://www.fda.gov/CIDpilot**

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# CTTI, European initiatives, IMI EU Pearl EU…

**Solange Corriol-Rohou, MD**
**Sr Global Policy Director, AstraZeneca**

## Session 1 - Setting the scene & Sharing experience


EFPIA European Federation of Pharmaceutical Industries and Associations
PPD
Norwegian Medicines Agency

# Current initiatives to optimise drugs development


EU-funded projects


Public-Private Partnerships




# Some EU-funded projects

- **FP7 ASTERIX** project - Advances in Small Trials dEsign for Regulatory Innovation and eXcellence - focused on the development of more efficient and effective research designs to study new drugs and treatments for rare diseases. The overall aim was to achieve more reliable and cost-efficient clinical development of treatments for rare diseases and to stimulate the search for treatments for these devastating and largely ignored diseases.
  - Develop design and analysis methods for single trials and series of trials in small populations.
  - Include patient-level information and perspectives in design and decision making throughout the clinical trial process.
  - Validate new methods and propose improvements for regulatory purposes

  ➔ Final report on the EC website: https://cordis.europa.eu/project/id/603160/reporting

- **H2020-funded PERMIT project**: Development of methodological recommendations for robust and reproducible personalised medicine research.

- **H2020 funded EU-Response** allows the European expansion of the **DisCoVeRy** study, a Phase III, open-label, adaptive, randomised, controlled, multicentre clinical trial designed to evaluate the safety and efficacy of medicinal products in hospitalised adult patients diagnosed with COVID-19.
  - **EU-RESPONSE** has built a new multinational EU Adaptive Platform Trial, EU-SolidAct, for emerging infectious diseases, to improve EU's responsiveness to pandemic crisis.
  - EU-SolidAct is a flexible platform, providing a modular trial network enabling EU hospitals' participation. Data collection ranges from clinical assessment parameters to PROMs and advanced biobanking.

- **The 9th Framework Programme, also known as Horizon Europe**, has replaced the framework programme Horizon 2020 (H2020), as of January 2021.

# Complex clinical trials & IMI

- **COMBACTE-NET** project is dedicated to building strong clinical, laboratory and research networks across Europe to enable more efficient clinical testing of novel antimicrobial drugs
  - HONEST-PREPS observational study for a subsequent platform trial to set up an infrastructure to prospectively enrol patients at risks of **HAP/VAP in ICU.**

- **EPAD** is pioneering a novel, more flexible approach to clinical trials of drugs designed to prevent Alzheimer's dementia - Proof of Concept platform developed to run Phase II trials involving participants with **preclinical and prodromal Alzheimer's disease**, and with biomarker evidence of Alzheimer's disease pathology using a consistent set of outcomes.

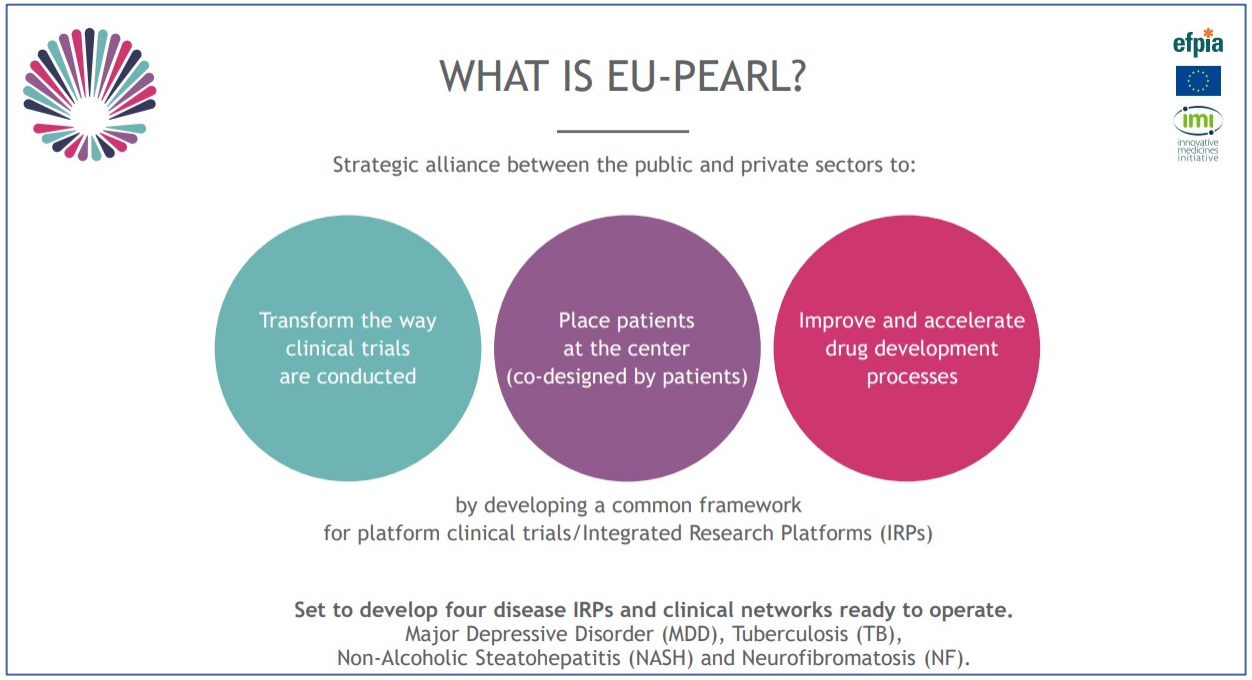
- **INNODIA** - Clinical trial master protocol specifically designed for Phase 2 clinical trials of people who have just been diagnosed with **type 1 diabetes** allowing for adaptive trials to test different drugs in parallel.

- **NECESSITY** - to identify and evaluate discriminative biomarkers for stratification of **primary Sjögren's Syndrome (pSS)** patients predictive of organ involvement and disease progression, and to set up an innovative "multi-arm multi-stage platform trial" able to include all the different types of patients with pSS in different arms, with different types of drugs and with different methodology.

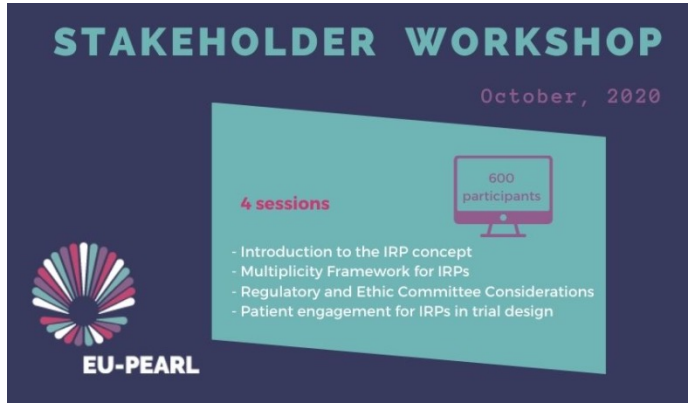
- **UNITE4TB** – The project aims to develop a new approach to trialing TB drugs in Phase 2 clinical trials.
  - Simulation tools will be first used to identify the optimal doses for each drug, prior to running a multi-arm, adaptive clinical trial of the best candidate regimens.

*HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia: TB: tuberculosis*

# The initiative ‘EU Patient centric clinical trial platforms’




- A strategic partnership between the public and private sectors to shape the future of clinical trials – Nov. 2019 - April 2023.
- Aims to create a framework for patient-centric IRP trials, through which novel techniques and treatments developed by multiple companies and organizations are tested in a platform trial.
- Stakeholder Workshop in Oct. 2020 brought together around 600 experts to foster the debate on platform trials.

# Build Better, Faster Clinical Trials

- There is a need for agile clinical trials that foster collaboration to address major public health threats and ongoing research challenges.

- Working with stakeholders across the clinical trials ecosystem, CTTI developed a robust set of resources - including a Master Protocol Design & Implementation Guide, Value Proposition Guide, and FDA Engagement Tool - that guide the appropriate use of master protocols.

- Additionally, specific to the pandemic, CTTI led a panel discussion in Jan. 2021 on *The Fastest Path to Effective COVID-19 Treatments: Using Master Protocol Studies*, highlighting results from an analysis of data from ClinicalTrials.gov, as well as best practices and insights from those involved in COVID-19 treatment master protocols.

# ICH & CCTs – work in progress

## Building on EMA and FDA guidelines, on experience, shared learnings and best practices and on EMA-EFPIA Workshops

- **Adaptive CTs – ICH E20** – to provide a transparent and harmonised set of principles for the regulatory review of these studies in a global drug development program, i.e., design, conduct, analysis, and interpretation

  ➔ Expected guideline finalisation by 2023

- **Paediatric Extrapolation – ICH E11A** – to provide information on study designs and statistical analysis methods used when incorporating paediatric extrapolation into a paediatric drug development plan

  ➔ Expected guideline finalisation by 2022



**Public-Private Partnerships**

efpia
European Federation of Pharmaceutical Industries and Associations

**EU-funded projects**




# To conclude:

Several initiatives focusing on innovative designs are currently ongoing

Collaborations, share learnings, patients' involvement, training & education, and best practices are key

With the today workshop, we want to build/link with existing initiatives and identify issue solving proposals and best practices

# Thank you!

Multi-stakeholder workshop

5 - 6 October 2021

Day 1
5 October 2021

15:00

# SESSION 2
# Stakeholders' priorities & expectations

## Claas Röhl (NF Patients United)

- 10' **Patients**
  Dominique Hamerlijnck (EUPATI)
- 10' **Regulators - EU & beyond**
  Anthony Humphreys (EMA)
- 10' **Ethics Committees**
  Martin Brunner
  (Ethics Committee, AT)
- 10' **HTA bodies**
  Niklas Hedberg
  (TLV SE, EUnetHTA)
- 10' **Sponsors: Industry, Academia & non-profit organisations**
  Lucia D'Apote
  (Amgen, EFPIA)
- 10' **Investigators**
  Birgit Geoerger
  (Gustave Roussy Institute, FR)
- 25' **Panel discussion**

# Chair: Claas Röhl, Obmann NF Kinder / Obmann NF Patients United / Obmann EUPATI Austria

## Session 2 – Stakeholders' priorities & expectations


NF Patients United | efpia European Federation of Pharmaceutical Industries and Associations | BARC | PPD | Norwegian Medicines Agency

# Our objective

- To understand the perspectives of the different stakeholders
- To learn about the challenges but also about the opportunities
- To identify possible low hanging fruits for multi-stakeholder-collaboration

# Panelists

| | |
|---|---|
| Patients | Dominique Hamerlijnck (EUPATI) |
| Regulators - EU & beyond | Anthony Humphreys (EMA) |
| Ethics Committees | Martin Brunner (Ethics Committee, AT) |
| HTA bodies | Niklas Hedberg (TLV SE, EUnetHTA) |
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# Patients' perspective on complex clinical trials

**Dominique Hamerlijnck, MPhil, MBA, EUPATI fellow**

Stakeholders' priorities & expectations


EFPIA European Federation of Pharmaceutical Industries and Associations · PPD · Norwegian Medicines Agency

# Conflict of interest and affiliations

- Patient expert and patient
- Co-chair clinical research consortium working with a patient registry
- Engaged as a patient expert in all stages of medicine R&D
- Advisor for pharma companies on patient engagement and as a patient expert
- Advising in the EU and Netherlands on research applications

Affiliations: EUPATI, European Lung Foundation, Dutch Lung Foundation, HTAi, ISPOR

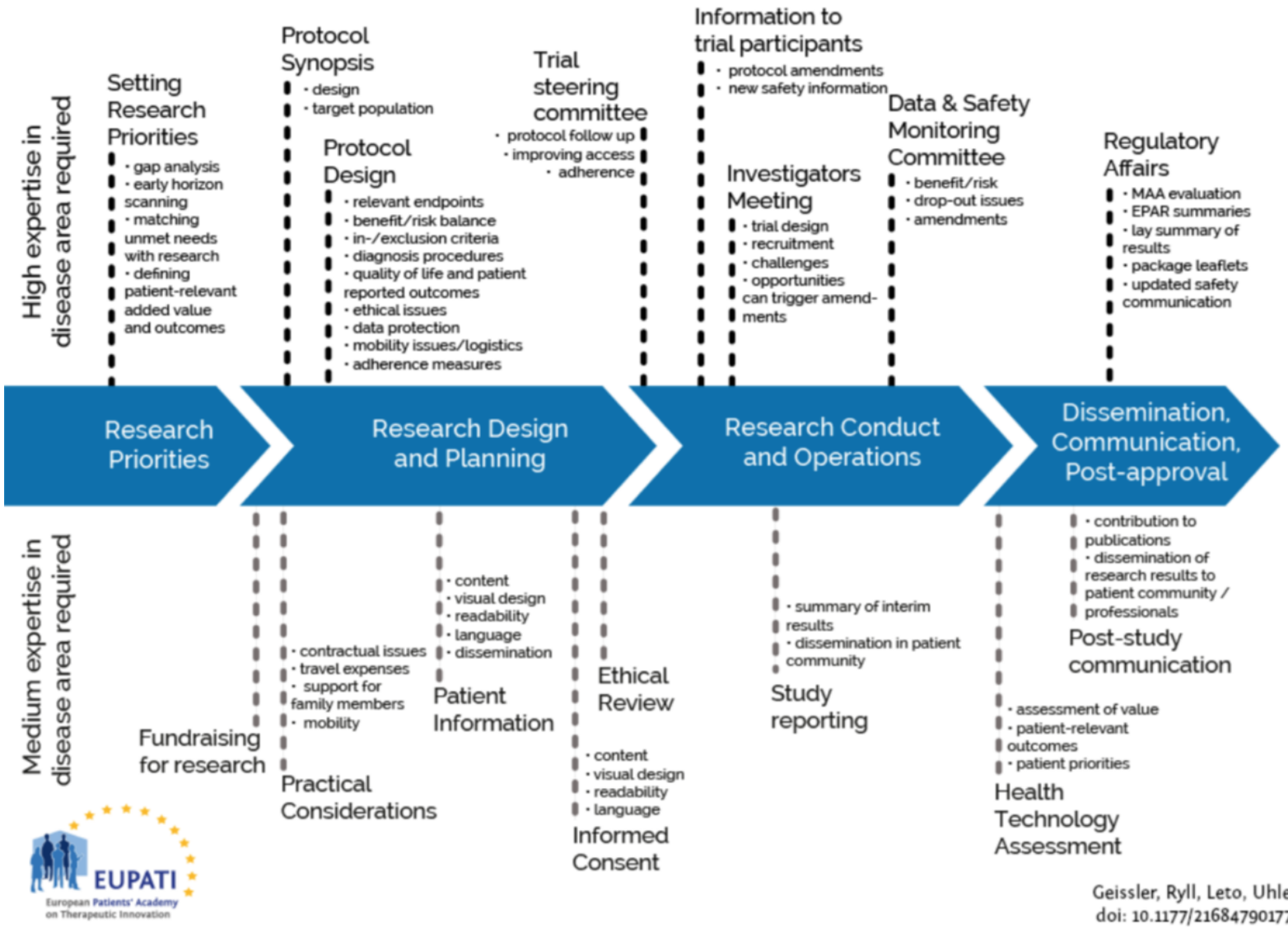
# The need for patient expertise

- EUPATI, EURORDIS, PARADIGM have developed guidances for engaging patients in all phases of clinical research. EUPATI not only train patients, but stakeholders in patient engagement
- As IMI recently wrote in the introduction to an event on October 7th:

  “For many years, patient involvement in research was restricted to participating in clinical studies and trials as research subjects. Today, it is widely recognised that **patients can and should be much more involved in all aspects of research, including agenda setting, study design, communication, and ethics**. At the same time, many researchers are now well aware that **patients bring unique knowledge and skills to projects which can help to improve the quality of research**. However, there are still too many projects and initiatives where patients are either not involved at all, or where their involvement comes too late to allow them to really influence the project's direction and outcomes”

  IMI Impact on patient involvement https://www.imi.europa.eu/news-events/newsroom/imi-impact-patient-involvement

# Patient involvement in medicines R&D




Geissler, Ryll, Leto, Uhlenhopp
doi: 10.1177/2168479017706405

# Advantages of complex clinical trials from a patient perspective

- Addressing multiple clinical questions in 1 trial
- Earlier access to a novel treatment for the patients
- Accelerate drug development
- Adverse Outcome Pathways (AOP) and Beneficial Outcome Pathways (BOP)
- Value for patients

# Challenges in complex clinical trials a patient perspective

- Choosing the relevant set of Clinical Outcome Assessments Symptoms and signs relevant for the people with the disease.
- Trial design
- Inclusion and informed consent
- Increased barriers for participation
- Ethics

# Evaluation of medecines and medical devices

| Risks | Other non-health factors | Benefit |
| --- | --- | --- |
| Adverse events<br>Side effects<br>Costs | Ease of use<br>Method of administration<br>Design<br>Information | Efficacy |

# References


- EUPATI https://www.eupati.eu/
- FDA CDER Patient-Focused Drug Development(PFDD) https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development
- FDA Draft Guidance Benefit-Risk Assessment for New Drug and Biological Products September 2021 https://www.fda.gov/media/152544/download
- IMI Impact on patient involvement https://www.imi.europa.eu/news-events/newsroom/imi-impact-patient-involvement

# Thank you

- If you are looking for a patient expert: https://collaborate.eupati.eu/

- If you are looking for training in patient engagement https://eupati.eu/training/

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Regulators - EU & beyond

Accelerating Adoption of Complex Clinical Trials in Europe and beyond

EFPIA multi-stakeholder workshop


Presented by Tony Humphreys on 5 October 2021
Head of Regulatory Science and Innovation Task Force

# Opportunities for a better EU environment for innovative clinical trials

EUROPEAN MEDICINES AGENCY

The Clinical Trials (CT) Regulation in 2022 and the new Clinical Trials Information Service (CTIS) launch

The mandate for CT innovation in the EMAN Strategy to 2025

The EC Pharmaceutical Strategy

The creation of HERA and the EMA extended mandate

The EU's Beating Cancer Plan with cancer therapeutics driving innovation in clinical trial design and data sources

Improving interfaces with European research funding in enabling more meaningful trials for regulatory purposes

Modernisation of the Global Good Clinical Practice standards (through ICH E6 and E8)

The establishment of the CTAG and the transformation of the CTFG mandate

The launch of the EC Joint Action to support cooperation on safety assessment

The evolution of the INNO platform

Working parties: The establishment of the methodology domain

Potential data interface within CTIS/EudraCT and EV databases to strengthen advice

# EMAN Strategy to 2025 - Foster collaborative evidence generation

EUROPEAN MEDICINES AGENCY

Supporting innovation and digitalisation in clinical trials by strengthening the Network's expertise in handling more complex designs, including the use of data analytics and real-world data.

- ✓ Foster innovation in clinical trials and develop the regulatory framework for emerging clinical data generation
- ✓ Develop further the collaboration of various groups involved with scientific advice and/or regulatory guidance

# Driving collaborative evidence generation
# Improving the scientific quality of evaluations

EUROPEAN MEDICINES AGENCY

**Foster innovation in clinical trials**

- **Establish a multi-stakeholder, neutral, platform, to enable new approaches to clinical studies and to position the EU as a preferred location for innovative clinical research;**
- Drive development and adoption of novel practices that facilitate clinical trial authorisation, GCP and HTA acceptance at EU and international level;
- **Work with stakeholders, the EU Medicines Regulatory Network and the European Commission to promote and facilitate the conduct of complex clinical trials and other innovative clinical trial designs;**
- **Promote increased information sharing on clinical trial design, conduct, results and best practices. Build on this information and the multi-stakeholder platforms to enable further education, training and sharing of best practice in order to accelerate innovative change;**
- Critically assess the clinical value of new and emerging endpoints and their role in facilitating patients' access to new medicines;
- Promote the inclusion of neglected populations such as pregnant women, the elderly and those of diverse ethnicity in clinical trials.

# Driving collaborative evidence generation
# Improving the scientific quality of evaluations

EUROPEAN MEDICINES AGENCY

**Foster innovation in clinical trials**

- Establish a multi-stakeholder, neutral, platform, to enable new approaches to clinical studies and to position the EU as a preferred location for innovative clinical research;
  - Outline Framework, Mandate and Objectives established and published.
  - Two workshops to initiate platform focused on GCP Renovation, complex trials and launch of CT Regulation.
- Work with stakeholders, the EU Medicines Regulatory Network and the European Commission to promote and facilitate the conduct of complex clinical trials and other innovative clinical trial designs;
  - Action and workstreams for complex clinical trials established.
- Promote increased information sharing on clinical trial design, conduct, results and best practices. Build on this information and the multi-stakeholder platforms to enable further education, training and sharing of best practice in order to accelerate innovative change;
  - Publish paper on availability and methods for use of public information on clinical trials

# Any questions?

## Further information

Anthony.Humphreys@ema.europa.eu

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Telephone** +31 (0)88 781 6000
**Send us a question** Go to www.ema.europa.eu/contact

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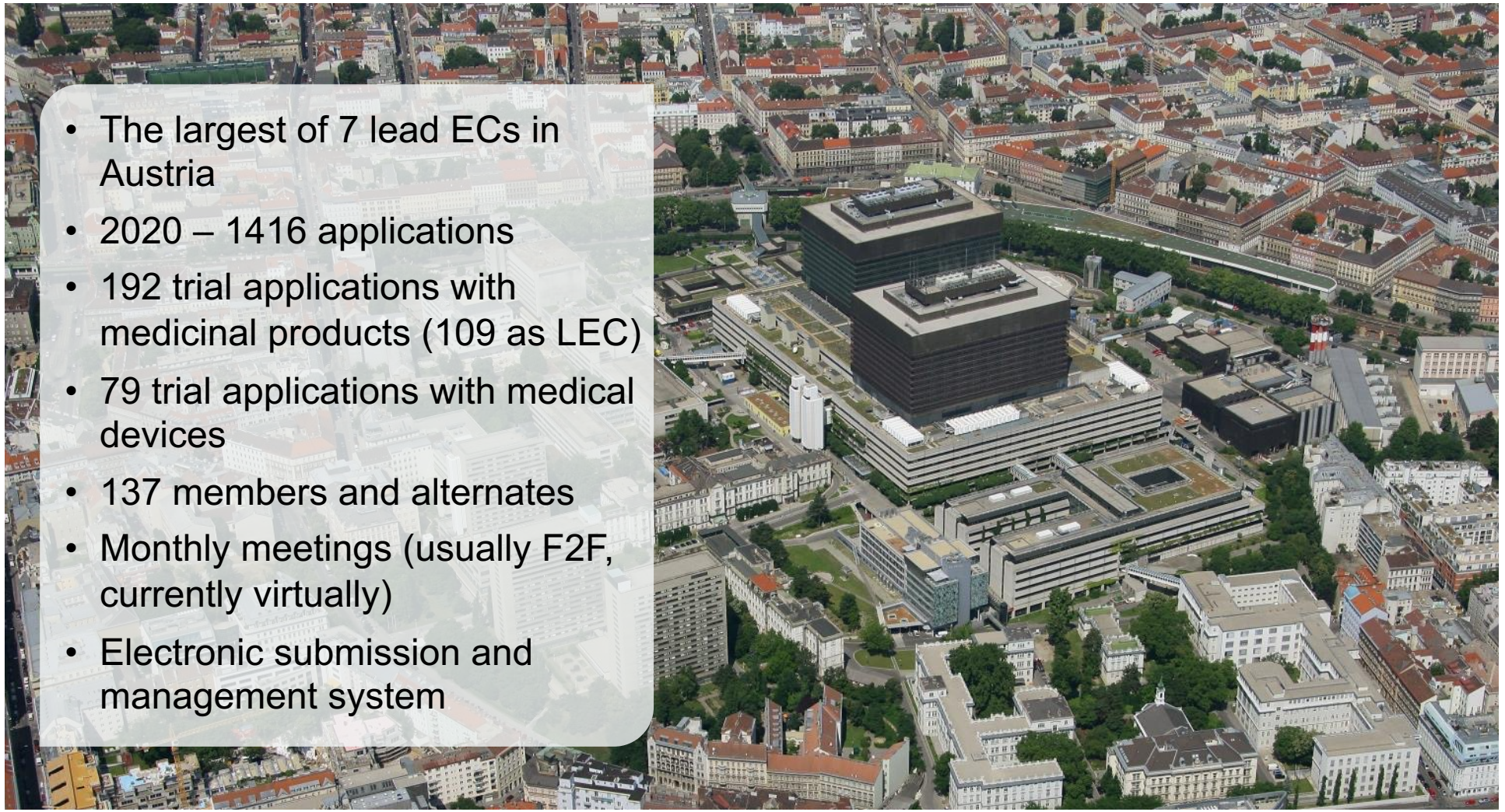
# Ethics Committees

**Martin Brunner, MD, Medical University of Vienna, Austria**

## Session 2 - Stakeholders´ priorities & expectations


EUPATI Patients United · efpia European Federation of Pharmaceutical Industries and Associations · BARC · PPD · Norwegian Medicines Agency

# Ethics Committee of the Medical University of Vienna



- The largest of 7 lead ECs in Austria
- 2020 – 1416 applications
- 192 trial applications with medicinal products (109 as LEC)
- 79 trial applications with medical devices
- 137 members and alternates
- Monthly meetings (usually F2F, currently virtually)
- Electronic submission and management system

# Ethics Committee

An independent body constituted of medical, scientific and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety and wellbeing of human subjects involved in a trial by, among other things, reviewing, approving and providing continuing review of trial protocol and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

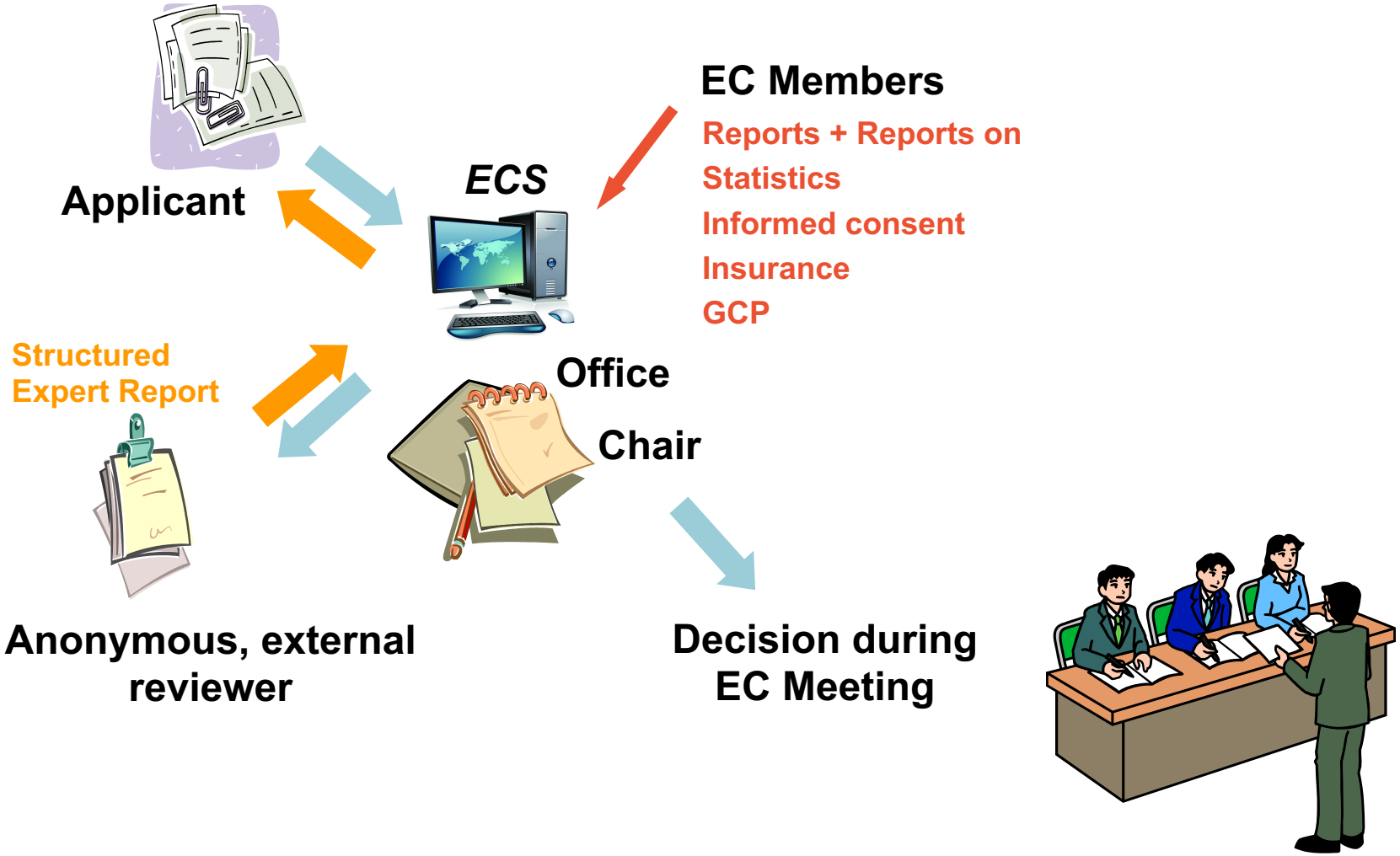
*ICH GCP*

# Ethics Committee responsibilities

In preparing its opinion the EC shall consider…

- Relevance of the trial
- Trial design
- Sample Size, Statistical Analysis (SAP)
- Protocol + Amendments
- Benefit/Risk assessment
- Quality of investigator/facility
- Informed Consent (other information to subjects)
- Insurance, Compensation

# EC workflow at the Medical University of Vienna



# Complex study designs submitted to EC

**(according to key word in study title; since 2012)**

- Platform Trials: 4 (all in 2020 and 2021)
- Basket: 3 (2019-2020)
- Adaptive: <10 (2014-2021)
- Phase II/III: <10 (2012-2021)
- Seamless: 1 (2021)
- Umbrella: 0
- Note: Many trials with complex designs submitted to the EC do not use the relevant terms (such as "adaptive") in the study title. Sponsor must be willing to label the adaptive character already in the title (as suggest by the Consort Extension on adaptive designs).

Platform trials:

- Phase II/III, industry, oncology, masterprotocol, future cohorts anticipated, EMA SA available, conditional positive EC decision due to ICON issues.
- Phase II, industry, dermatology, masterprotocol, future cohorts anticipated, already going on with 2 amendments, positive EC decision.
- Phase II, academia, infectiology, masterprotocol with substudies, positive EC decision.
- Phase Ib, industry, hematology, masterprotocol with drug- specific appendices, amendments, ICON 50 pages, positive EC decision.

# EC experience I

- EC specialists know and support underlying concept and clinical relevance of complex study designs.
- Protocols are complex, long, difficult to read in particular when amendments are already incorporated. Many cross-references.
- Study conduct difficult to follow as investigator.
- Statistics might be based on comprehensive simulations (including references to documents that might not be available) with little information to allow reproducability in the short time given for EC assessment.
- ICONs not suitable for patients (too long, too complicated, no seperate documents for substudies).

# EC experience II

Phase II/III study with local center only foreseen for phase III.

- EC assessment practically impossible, because no information on status of earlier study phase was included. Interim report needed.

Phase Ib/III study with progress dependent on dose finding. Whole study design incl. transition of phases submitted for approval.

- Approval only for first study phase possible. Thereafter, re-evaluation based on results of interim report necessary.

# Prerequisites for EC review

- Involvement of ECs in the implementation of novel concepts.
- Availability of statisticians with expertise in assessment of complex study designs.
- EC member training (vs. professionalisation?)
- (Master)-Protocol that follows CTFG and FDA recommendations that specifically justifies the need for a complex study design.
- Details as Intervention Specific Appendices (ISA).
- Documents that provide investigator and EC/CA sufficient details to a priori understand study conduct (as a prerequisit to adequately inform patients).
- Minimum number of amendments.
- Clearly defined stopping rules and rules for continuation.
- Details on DSMB (study oversight)
- Any risk/benefit change that leads to change in study documents needs to be submitted to the EC.

# Challenges and open questions I

- Clear process when and how new treatment arms (drugs) are added to a platform required. Which board is responsible for the decision?
- How to adequately handle and communicate changes of SOC?
- Total sample size often unknown/sample size adaptations – how will contracts with insurance companies and EC insurance review will be affected ?
- How to ensure study oversight and risk/benefit assessment (independent DSMB) for the duration of the trial?
- Informed consent is a process not a document. How can patients be adequately informed about the study/sub-study they are assigned to (initially and during the trial) to con/reconsider participation?

# Challenges and open questions II

- Substantial amendments/modifications need to be discussed during EC meetings – potential delay of study conduct. Are more frequent/ad hoc meetings an option? How can amendments kept to a minimum?
- Impact of the CTR-implementation?
- Usually one IB and one DSUR. How to proceed with several arms and different sponsors? Several IBs? Integrated report?
- Trials with multiple drugs from multiple sponsors – comparison between treatments absolutely desirable/necessary.
- EC involvement later in the process, e.g. when a new arm is added or a center joins after some time
  - What if key aspects of the initial design are criticized in an already on-going trial?

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TANDVÅRDS- OCH
LÄKEMEDELSFÖRMÅNSVERKET

# CCT – Stakeholders´ priorities and expectations HTA bodies

Niklas Hedberg
Chief Pharmacist
October 5, 2021

# Disclaimer

- The observations in this presentation are my own, made from many years experience in HTA.
- It is based on what I hear, which is not necessary what I personally think is right.
- It does not represent the position of any HTA agency.

# Two different missions

**EMA**

- Is it good? (efficacy)
- Is it safe?

**HTA bodies**

- How good is it? (effectiveness)
- Is it better that the alternatives?
- How much better?

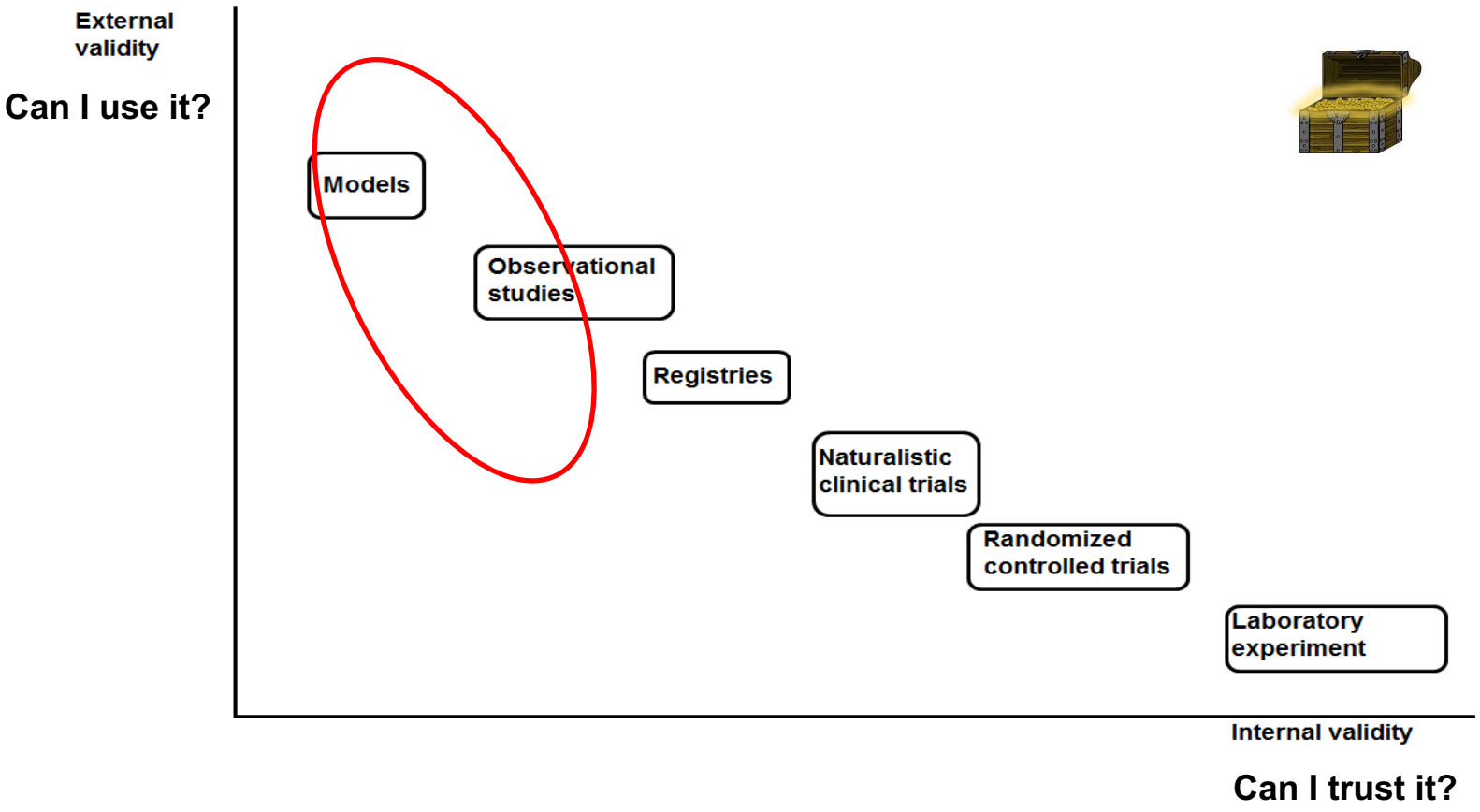
And for some of us:

- Is it worth its price??

# What is a complex clinical trial?

- From the internet I take this definition:
  - *"Complex innovative clinical trial designs enable researchers to address multiple **clinical** questions within a single study. With this trial design, a novel drug can be assessed for **safety and effectiveness** at the same time and patients are selected based on biomarkers rather than the origin of the tumour."*
- The definition does not (fully) cover the needs of HTA bodies.
- Yet, it appears to us, it is now used in regulatory decision making.

# Where do I find my evidence?




Picture from: Anders Sköldunger, Dementia and use of drugs: economic modelling and population-based studies thesis, Karolinska Institutet, 2015

# What I want to see in the field of CCT

- More information about CCT, preferably from independent bodies like EMA.
- Involvement of HTA perspective from early stages.
- A nuanced discussion about *impossible* vs *inconvenient* trial designs.
- Joint efforts to develop and validate new methods.
- Investments in longitudinal data sets.
- Investment in trust!

# Thank you!

For more information,
please visit us at
www.tlv.se on on LinkedIn

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# Industry perspective


## Lucia D'Apote, Director Global Regulatory and R&D Policy Amgen (EFPIA)


Session 2 - Stakeholders' priorities & expectations


EMA Patients United · efpia European Federation of Pharmaceutical Industries and Associations · BARC · PPD · Norwegian Medicines Agency

# Innovation in Clinical Trials accelerates patients' access to treatments addressing UMNs

- Incorporating innovative methodologies into clinical trials can "dramatically change the prospects for success" in drug development
- Transforming data into insights informs the best possible decision, at the earliest time-point, in the most efficient manner
- Global development programmes require convergence of acceptance of new regulatory approaches

# CCT Challenges are well identified

Complex Clinical Trials – A multi-stakeholder initiative

Author:

Date: 11/2/2020 Version: FINAL

ACRO efpia EUCOPE EuropaBio

## 3. CCT Challenges

Limited awareness and understanding of CCTs and lack of alignment across stakeholders are key barriers to accelerating innovation in clinical trials in the European Union. Overall, the following can be highlighted:

1. There is limited understanding in EU National Competent Authorities (NCAs) and Ethic Committees of clinical trials with complex designs;
2. There is limited subject matter expertise in NCAs and Ethic Committees to assess and critique CCT designs and methods;
3. There is limited opportunity for CCT sponsors and drug developers to provide input on practical considerations when developing guidelines;
4. In Industry, there is conservatism and scepticism about CCTs: concerns regarding risk of excessive justification to regulators, non-acceptance of the ultimate CCT design, lack of prior experience and of available data management infrastructure.
5. It is unclear how different groups and stakeholders could be brought together for a shared dialogue, something which is known to bring value;
6. There is a need to develop best practices in a timely manner involving all relevant stakeholder perspectives;
7. There is the need to accelerate and drive innovation in clinical trials to address significant unmet needs across a range of diseases as well as public health threats, e.g. COVID-19 pandemic.

| Scientific/technical challenges | Operational challenges | Regulatory/Ethic Committee challenges |
|---|---|---|
| **Adaptation vs. integrity:** How to adapt repeatedly a CCT protocol while preserving the overarching hypothesis and avoiding biases? The scientific consistency of the CCT is paramount to justify its execution as single study rather than stand-alone studies. Finally patient favourable risk-benefit ratio will need to be preserved.<br><br>As in traditional RCTs, sample size reassessment in an ongoing trial could be seen as a substitute for careful planning. | **Preplanning of all aspects of the trial design prior to any CCT starting** including changing IMPs, modifying the patient selection criteria, etc.. and anticipating all possible changes: such foreseen changes should be anticipated/known before starting the trial, described with sufficient details in the protocol and scientifically justified. The challenge is how to initially predict future study adaptations and their rationale. This might not be entirely possible for some master protocols such as platform trials. | **Regulatory uncertainties:** Different regulatory bodies (i.e. national competent authorities, ethics committees, SAWP, GCP inspectors and HTA bodies) do not have a common approach across the medicine development pathway and are known to have different requirements and expectations.<br><br>Requirements and expectations from different regulatory bodies (i.e. national competent authorities, ethics committees, EMA SAWP, GCP inspectors and HTA bodies) result in request for additional data and different level of acceptance of CCTs, along the medicine development pathway. |
| **Multiplicity and control of type I error:** CCT design and planned analyses plan should consider features preventing multiplicity issues and control for type I error. Valid statistical procedures should be used to ensure robust clinical interpretation of the study results.<br><br>Lack of regulatory guidance on what can be considered acceptable for CCT where strict control of type I error is not possible.<br><br>Evaluating operating characteristics through extensive simulations is recommended. | **Regional variations**, e.g. Standard of Care might evolve over time but differently according to the regions/countries. Therefore, it is important to consider the impact of such variations on the relevance of the generated data for any comparison in the context of a global development. | **Acceptability of external data sources:** Challenge for regulators/downstream decision makers to determine acceptability of external data sources, particularly when used as control data for single arm studies. |
| **Data leakage (at interim analysis) may compromise data integrity:** The release of interim analysis (positive or negative) results could impact the decision to participate to the other study arms or sub-protocols by the investigators or by the patients .<br><br>Transparency requirements need to be balanced with preserving study integrity. | **Requirement for many substantial amendments:** Repeated adaption of the study protocol will request efficient communication with regulators and ethics committees. The challenge is to communicate and justify changes to an already complex study design while avoiding misunderstanding and miscommunication that may hamper CCT progress. | **CCT case studies and experience:** Limited number of CCT case examples used for decision making (late phase of development) to facilitate practical learning.<br><br>Inconsistencies in views among different regulators across globe create uncertainties that hinder the acceptance of CCTs which are often designed as multi-regional clinical trials. |

# 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

**…discussion at breakout sessions**

Multi-stakeholder workshop

5 - 6 October 2021

Day 1
5 October 2021

15:00

# SESSION 2
# Stakeholders' priorities & expectations

## Claas Röhl (NF Patients United)

- 10' **Patients**
  Dominique Hamerlijnck (EUPATI)
- 10' **Regulators - EU & beyond**
  Anthony Humphreys (EMA)
- 10' **Ethics Committees**
  Martin Brunner
  (Ethics Committee, AT)
- 10' **HTA bodies**
  Niklas Hedberg
  (TLV SE, EUnetHTA)
- 10' **Sponsors: Industry, Academia & non-profit organisations**
  Lucia D'Apote
  (Amgen, EFPIA)
- 10' **Investigators**
  Birgit Geoerger
  (Gustave Roussy Institute, FR)
- 25' **Panel discussion**

# Investigators - AcSé-ESMART

**Birgit Geoerger, MD, PhD**
**Gustave Roussy Cancer Campus, Pediatric and Adolescent Oncology, INSERM U1015, Université Paris-Saclay, Villejuif, France**

## Session 2 - Stakeholders' priorities & expectations


NF Patients United · efpia European Federation of Pharmaceutical Industries and Associations · BARC · PPD · Norwegian Medicines Agency

# European Pediatric Precision Cancer Medicine Program in Q4 2021

***1. Generate invididual molecular information at relapse***

## Molecular Matching Trials

**MAPPYACTS > FMG2025 MAPPYACTS 2**
(France, Spain, Italy, Ireland > + Denmark, Lithuania, Israel)

**INFORM**
(Germany, Austria, Sweden, Switzerland, Belgium)

**iTHER (The Netherlands)**

**SM-PAEDs (UK)**

**M A T C H**

***Match treatment and tumor profile***

***3. Evaluate activity of drugs and combinations***

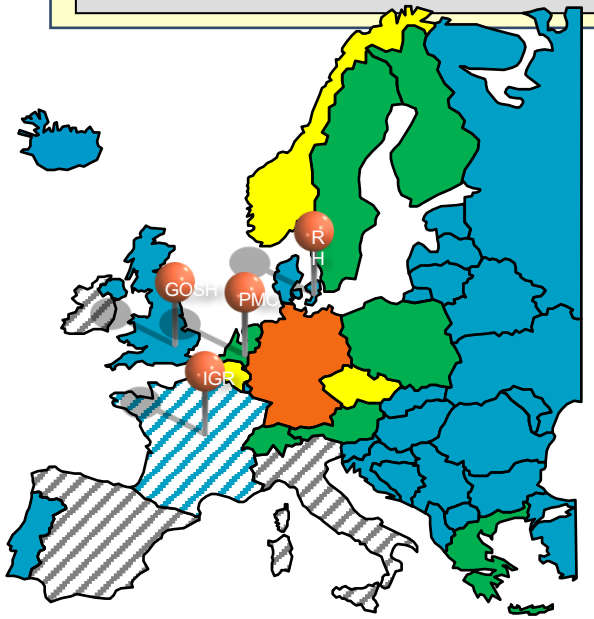
**Phase 1 Trials (Industry and ISTs)**

**Phase 2 Trials (Industry and ISTs)**

**Genentech Roche Matrix Trial**

**AcSé-ESMART Multiarm trial**
European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors in children (ESMART)

**INFORM2 trial series**




**SHARE**

**EU Clinico Biological (WES/RNAseq Data Base**

Project A

Project B

Project C

Project D

GUSTAVE ROUSSY
Princess MÁXIMA center for pediatric oncology
THE ROYAL MARSDEN
institutCurie
ITCC
Great Ormond Street Hospital for Children NHS
dkfz. German Cancer Consortium Core center Heidelberg

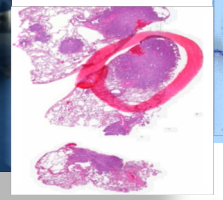
Pediatric New Drug Development

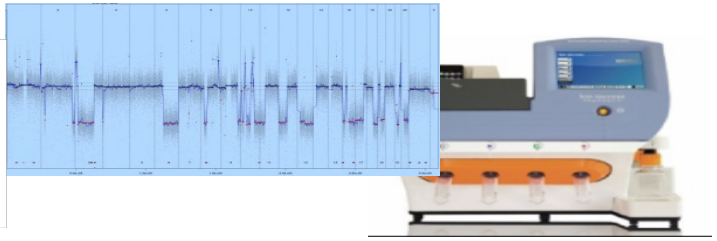
***4. Generate new knowledge, new druggable pathways***

# MAPPYACTS Design & Workflow

MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification

**Sample collection** → **Molecular analysis** → **Molecular Tumor Board** → **Clinical Molecular Tumor Board** → **Treatment**





On-purpose image-guided biopsy or tumor resection

15-30 centers

**Whole Exome & RNA Sequencing**

**≥ 30% tumor cells**

2 platforms

Biologists, bio-informaticians, physician-scientists

Weekly discussion with treating physicians

Early phase clinical trials or off-label or compassionate use

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

institutCurie Together, let's beat cancer.

Ancillary: cf DNA, Immune contexture, Patient-Derived Xenografts

Aims:

- To screen relapsed or refractory pediatric patients

To provide them with their individual molecular tumor profile

- Treat them with matched innovative targeted agents

# MTB and CMTB recommendations: Evidence of reported “actionable” molecular alterations

## Modified ESMO ESCAT Scale:

| LEVEL OF EVIDENCE |
|---|
| Ready for routine use |
| Investigational |
| Hypothetical target |
| Mutation associated to resistance to targeted treatment |
| Oncogenic without a level of evidence |
| Oncogenic not targetable |

**Ready for routine use: 7%**

NPM1/ALK , KIAA1549/BRAF, ETV6/NTRK3, KANK2/NTRK2, CCDC6/RET fusions; BRAF p.V600E, PTCH1, NF1 mutations

**Investigational: ~40%**

CDK4 ampli, CDKN2A/B del, PI3KCA, PTEN loss, FGFR ampli/mut, MYC ampli, ATR, ATM mut, SMARCA1 …

**Hypothetical target: ~ 20%**

Histone mut, CNA gains, TP53 mut, …

**Resistance mutations: 1%**

SMO p.I408V, NTRK3 p.G623R

**Oncogenic without level of evidence**:

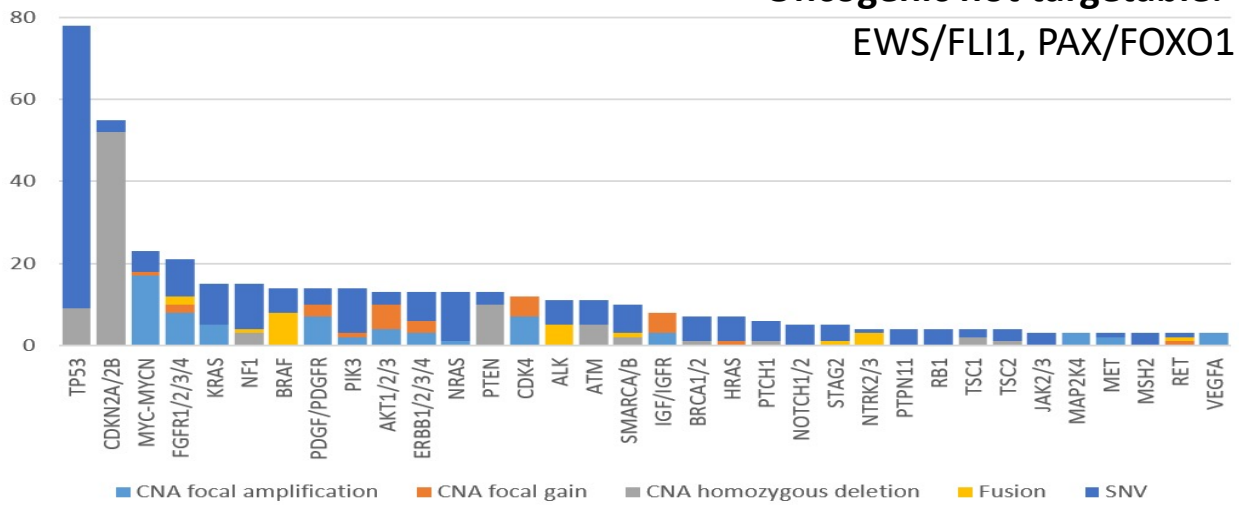
TP53 mut?, VUS, subclonal events

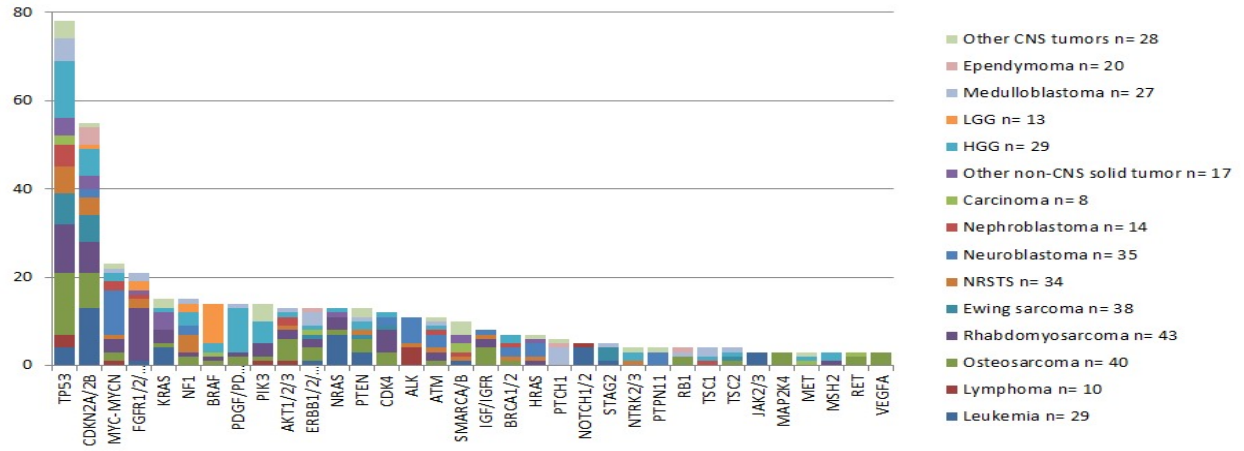
**Oncogenic not targetable:**

EWS/FLI1, PAX/FOXO1

*P Berlanga et al.*
*In revision*

- **Facing cancer complexity**
- **Need for dynamic trials with limited patient numbers**



**Main Inclusion Criteria:**

- Patients < 18 years with relapsed or refractory malignancy (solid tumor or leukemia)
- Evaluable disease
- Lansky/Karnofsky ≥70%
- No toxicity ≥ G2
- Deep tumor molecular analysis available is mandatory

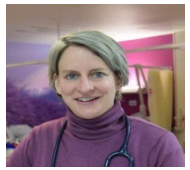
**Proof-of-concept trial with enrichment strategy in case of no clearly defined biomarker**

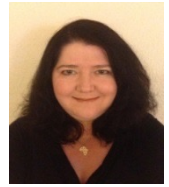
AcSé INSTITUT NATIONAL DU CANCER

e★smart
European proof of concept therapeutic stratification trial of molecular anomalies in relapsed or refractory tumors in children



| ARM | Pathway | Target | Treatment | Enrichment | Pharma | Investigator |
|---|---|---|---|---|---|---|
| Arm A | Cell Cycle | CDK4/6 | Ribociclib + TOTEM* | 50% | NOVARTIS | Francisco Bautista |
| Arm B | | | Ribociclib + Everolimus | 50% | | Francisco Bautista |
| Arm C | DNA repair | WEE1 | AZD1775 + Carboplatin | 50% | AstraZeneca | Francisco Bautista |
| Arm D | | PARP | Olaparib + Irinotecan | 50% | | Susanne Gatz |
| Arm E | PI3K/AKT/mTOR | mTORC1/TORC2 | Vistusertib | 100% | | Lynley Marshall |
| Arm F | | | Vistusertib + TOTEM | 50% | | Lynley Marshall |
| Arm G | Immune checkpoints | PD1 | Nivolumab + Cyclophosphamide +/-RT | NA | Bristol-Myers Squibb | Claudia Pasqualini |
| Arm H | PI3K/AKT/mTOR Ras-Raf-MEK-ERK | MEK + mTOR | Selumetinib + Vistusertib | 100% | AstraZeneca | Pablo Berlanga |
| Arm I | Metabolic pathway | IDH2 | Enasidenib | 100% | Celgene | Stephane Ducassou |
| Arm J | Immune checkpoints | PD1 + KIR | Nivolumab + Lirilumab | NA | Bristol-Myers Squibb | Nicolas Andre |



# ESMART – Overview + New arms (Amendment #9)

**Protocol v1.0 Approved 25/05/2016** ⇨ **Protocol v2.0 Approved 28/02/2018** ⇨ **Protocol v4.0 Approved September 2020**

| ARM | Target | Treatment |
|---|---|---|
| Arm A | CDK4/6 | Ribociclib + TOTEM |
| Arm B | | Ribociclib + Everolimus |
| Arm C | WEE1 | Adavosertib (AZD1775) + Carboplatin |
| Arm D | PARP | Olaparib + Irinotecan |
| Arm E | mTORC1/TORC2 | Vistusertib |
| Arm F | | Vistusertib + TOTEM |
| Arm G | PD1 | Nivolumab + Cyclophosphamide +/-RT |

AstraZeneca NOVARTIS

Bristol-Myers Squibb

| ARM | Target | Treatment |
|---|---|---|
| Arm H | MEK + mTOR | Selumetinib + Vistusertib |
| Arm I | IDH2 | Enasidenib |
| Arm J | PD1 + KIR | Nivolumab + Lirilumab |

Celgene

**Protocole v3.0** (20/03/2019)

→ Harmonisation Européenne

| ARM | Target | Treatment |
|---|---|---|
| Arm K | CDK2/9 | Fadraciclib (CYC065) + Temozolomide |
| Arm L | | Fadraciclib (CYC065) + Cytarabine |
| Arm M | CDK4/6 + mTOR | Ribociclib + Everolimus |
| Arm N | ATR + PARP | Ceralasertib (AZD6738) + Olaparib |
| Arm O | pan-FGFR | Futibatinib (TAS-120) |

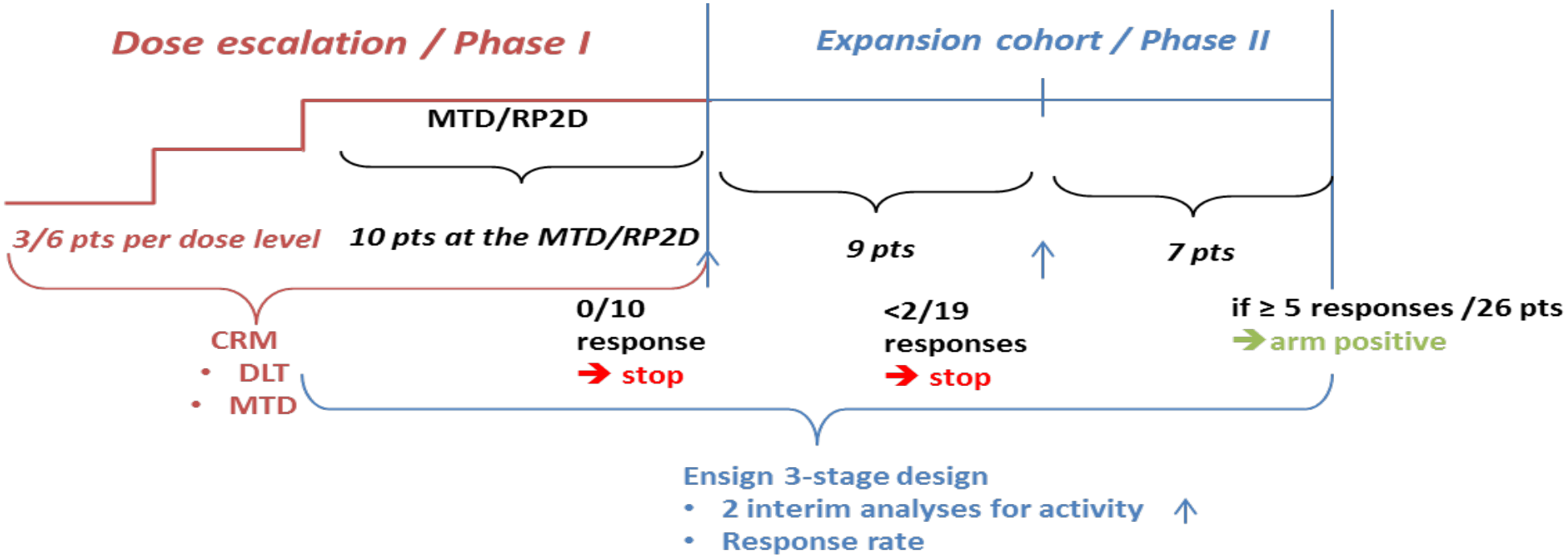
AstraZeneca CYCLACEL TAIHO

NOVARTIS

10 centers in France, 1 Netherlands, 2 Spain, 3 UK, 3 Italy & 1 Denmark

# AcSé-ESMART Statistical Design

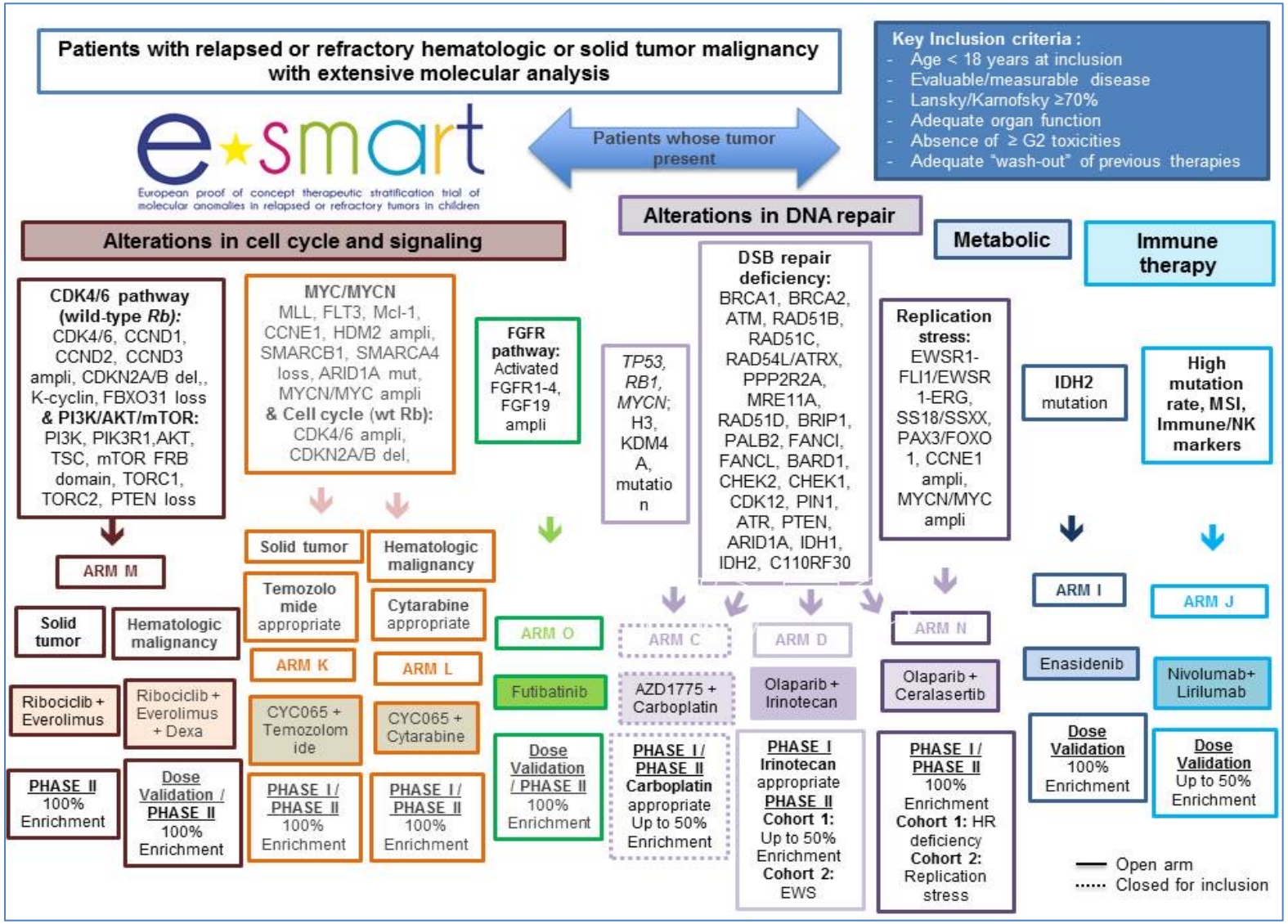
- Each arm is run independently (6-38 patients/arm)
- 2 parts : Phase I et Phase II
  - Evaluation of safety (DLT, MTD, RP2D) AND activity




Xavier Paoletti

  - Max 460 evaluable patients in 9 years for 15 arms
  - IDMC (1 pediatric oncologist, 1 medical oncologist, 1 pharmacovigilant, 1 statisticien)

# Complexity of Hypothesis Driven Enrichment Strategy & Proof-of-Concept for the Clinical Roles of Molecular Alterations

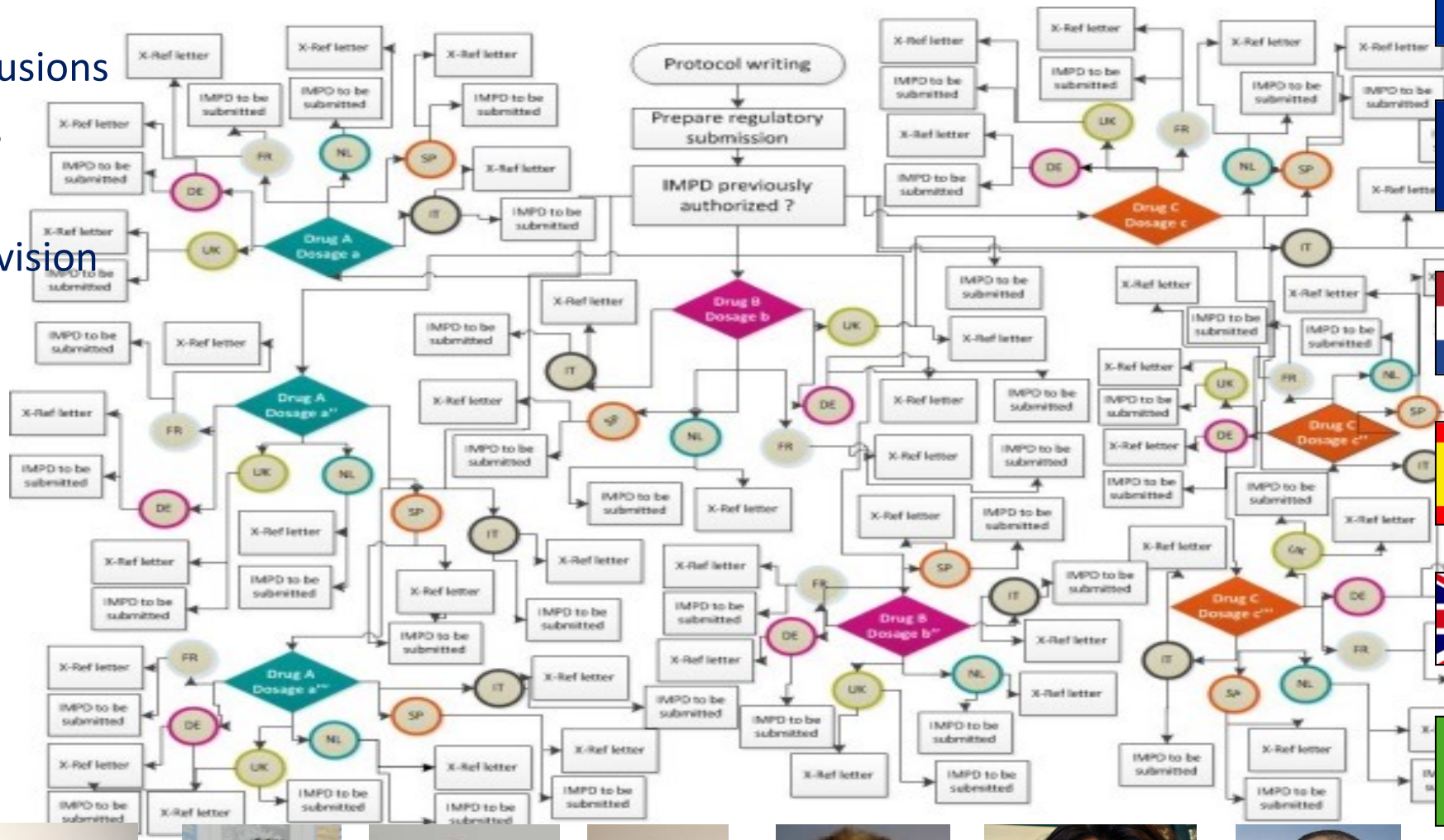



- **Molecular alterations:**
  - Variable level of biological evidence
  - Fusions – CNA – VP/VUS/VNP
  - Homozygotic *vs* heterozgotic events
  - Subclonal events
- **Hierarchy of multiple alterations**
- **Lack of gene methylation, protein expression and functional data**

- Profiles of patients in each arm are currently further explored
- Each patient counts and contributes!

# Coordinate the Complexity of ESMART

- Pre-screening for inclusions
- Weekly tumor boards
- Close toxicity update
- Reactivity in data provision
- High commitment
- Regulatory issues
- Amendments
- Reports
- .....
- .....












# Thank you for your attention

Many thanks to
All patients and parents
Our teams
Funders
Pharmaceutical companies
Regulatory bodies

Multi-stakeholder workshop

5 - 6 October 2021

Day 1
5 October 2021

15:00

# SESSION 2
# Stakeholders' priorities & expectations

## Claas Röhl (NF Patients United)

- 10' **Patients**
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- 10' **Investigators**
  Birgit Geoerger
  (Gustave Roussy Institute, FR)
- 25' **Panel discussion**

Multi-stakeholder workshop

5 - 6 October 2021

Day 1
5 October 2021

16:45

# Breakout Sessions

1. **Design of Master Protocols**
   Chairs: Christine Fletcher (GSK, EFPIA)
   Lada Leyens (Roche, EFPIA)
2. **Regulatory processes and system**
   Chairs: Anja Schiel (EMA SAWP, NoMA)
   Lucia D'Apote (Amgen, EFPIA)
3. **Patient involvement**
   Chairs: Claas Röhl (NF Patients United, AT)
   Solange Corriol-Rohou (AZ, EFPIA)

Day 1
5 October 2021

# Breakout session 1
# Design of Master Protocols

Multi-stakeholder workshop
5 - 6 October 2021

*Chairs:*

Christine Fletcher (GSK, EFPIA)
Lada Leyens (Roche, EFPIA)

Master protocols designs are supporting innovation strategies for evidence generation. This session will use 2 case studies, one in oncology and one in non-oncology, to illustrate some of the key challenges and sources of complexity when designing master protocols. The discussion will focus on key and critical points for different stakeholders. Their views will be shared and solutions proposed to enable recommendations and increased alignment across stakeholders regarding an optimal design of master protocols.

Day 1
5 October 2021

# Breakout session 2
# Regulatory processes and system

Multi-stakeholder workshop
5 - 6 October 2021

*Chairs:*

Anja Schiel (EMA SAWP, NoMA)

Lucia D'Apote (Amgen, EFPIA)

As the EU regulatory landscape and policy initiatives continue to evolve, this session will provide a platform for exchange between drug developers, regulators (EMA, CTFG, EU-IN) and other stakeholders to discuss the current regulatory process and system for CCT trial advice and authorisation. The session will use case studies and research on CTT proposals accepted by regulators to highlight learnings and opportunities for regulatory convergence. A panel discussion at the end of the session will provide perspective on policy opportunities from all experts.

Day 1
5 October 2021

# Breakout session 3
# Patient Involvement

Multi-stakeholder workshop
5 - 6 October 2021

*Chairs:*

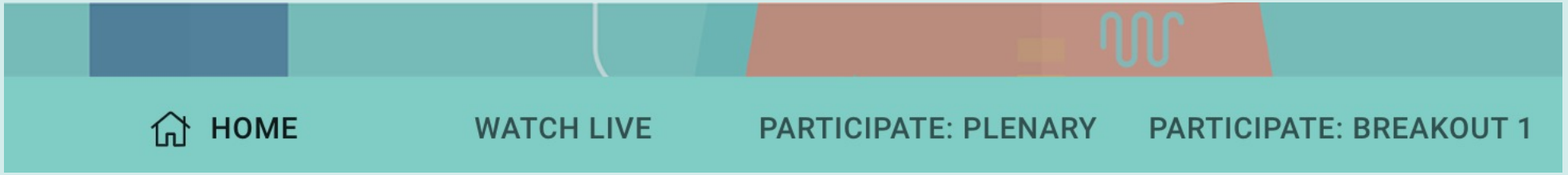
Claas Röhl (NF Patients United, AT)
Solange Corriol-Rohou (AZ, EFPIA)

Patient involvement in clinical trials is attracting more and more interest, and experience is growing. This interactive breakout session will be not only the opportunity to share the experience so far but also to identify recommendations to optimise patient's involvement in the design and conduct of complex trials. A few flash presentations will open up the discussion by representatives of key stakeholders. We cannot expect to solve all the issues through this session, but the goal is to identify recommendations and next steps including synergies with the Education & Training breakout session.

# How to go to the breakout session?


## As a viewer

Click on the “home” and “Watch Live” respectively in the navigation and find the breakout session you want to follow and click on “Live”.




## As an active participant

If you have been selected as an active participant, you will see the link e.g. ”Participate: Breakout 1” in the navigation of the webinar platform. Open the link and click “Live”. This will invite you to a zoom-session.


Coffee
break

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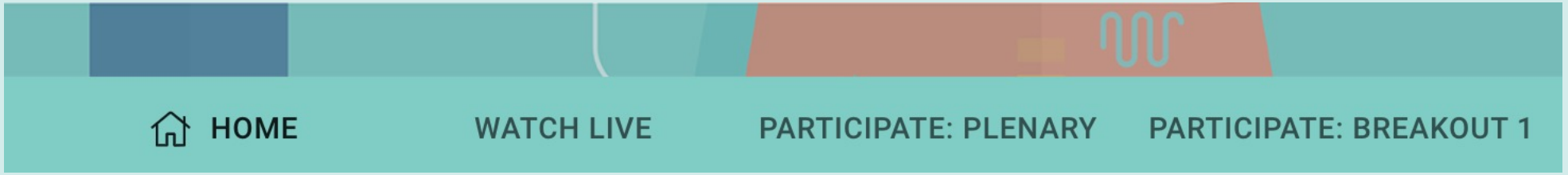


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Multi-stakeholder workshop

5 - 6 October 2021

Day 1
5 October 2021

16:45

# Breakout Sessions

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   Solange Corriol-Rohou (AZ, EFPIA)

Multi-stakeholder workshop

5 - 6 October 2021

18:45

Day 1
5 October 2021

# Concluding remarks

Christine Fletcher (GSK, EFPIA)

Mireille Muller (Novartis, EFPIA)

Anja Schiel (EMA SAWP, NoMA)

# Multi-stakeholder workshop 5 - 6 October 2021

Day 2
6 October
2021

**14:00**

## Introduction to Day 2

Sini Eskola (EFPIA)
Peter Arlett (EMA)

**14:10**

## SESSION 1

### Feedback from Day 1 Breakout sessions

Breakout Sessions Chairs

Christine Fletcher (GSK, EFPIA)
Lada Leyens (Roche, EFPIA)

Anja Schiel (EMA SAWP, NoMA)
Lucia D'Apote (Amgen, EFPIA)

Claas Röhl (NF Patients United, AT)
Solange Corriol-Rohou(AZ, EFPIA)

**14:40**

## SESSION 2

### Breakout Sessions

4. **Trials incorporating historical controls or with adaptative features**
   Christine Fletcher (GSK, EFPIA)
   Frank Bretz (Novartis, EFPIA)
5. **Operation & implementation**
   Olga Kholmanskikh (CTFG, FAMHP)
   Josse R. Thomas (Ethics Committee, BE)
6. **Education & Training**
   Begonya Nafria Escalera (eYPAGnet, ES)
   Mireille Muller (Novartis, EFPIA)

**16:40 Coffee break**

**16:50**

## Feedback from Day 2 Breakout sessions

Breakout Sessions Chairs

**17:20**

## Panel session to discuss main outputs & propose next steps/action plan

Anja Schiel
(EMA SAWP, NoMA)

Nick Sykes (Pfizer, EFPIA)

**EU Commission**
Kristof Bonnarens
(EC DG SANTE)

**FDA**
Dionne Price
(FDA)

**CTFG**
Elke Stahl
(CTFG Co-Chair,
BfArM)

**Ethic Committees**
Josse R. Thomas
(Ethics
Committee, BE)

**Patient representatives**
Rita Magenheim
(GENTURIS)

**HTA bodies**
Niklas Hedberg
(SE TUV,
EunetHTA)

**Industry**
Christine Fletcher
(GSK, EFPIA)

**NGO**
Stephane Lejeune
(EORTC)

**18:45**

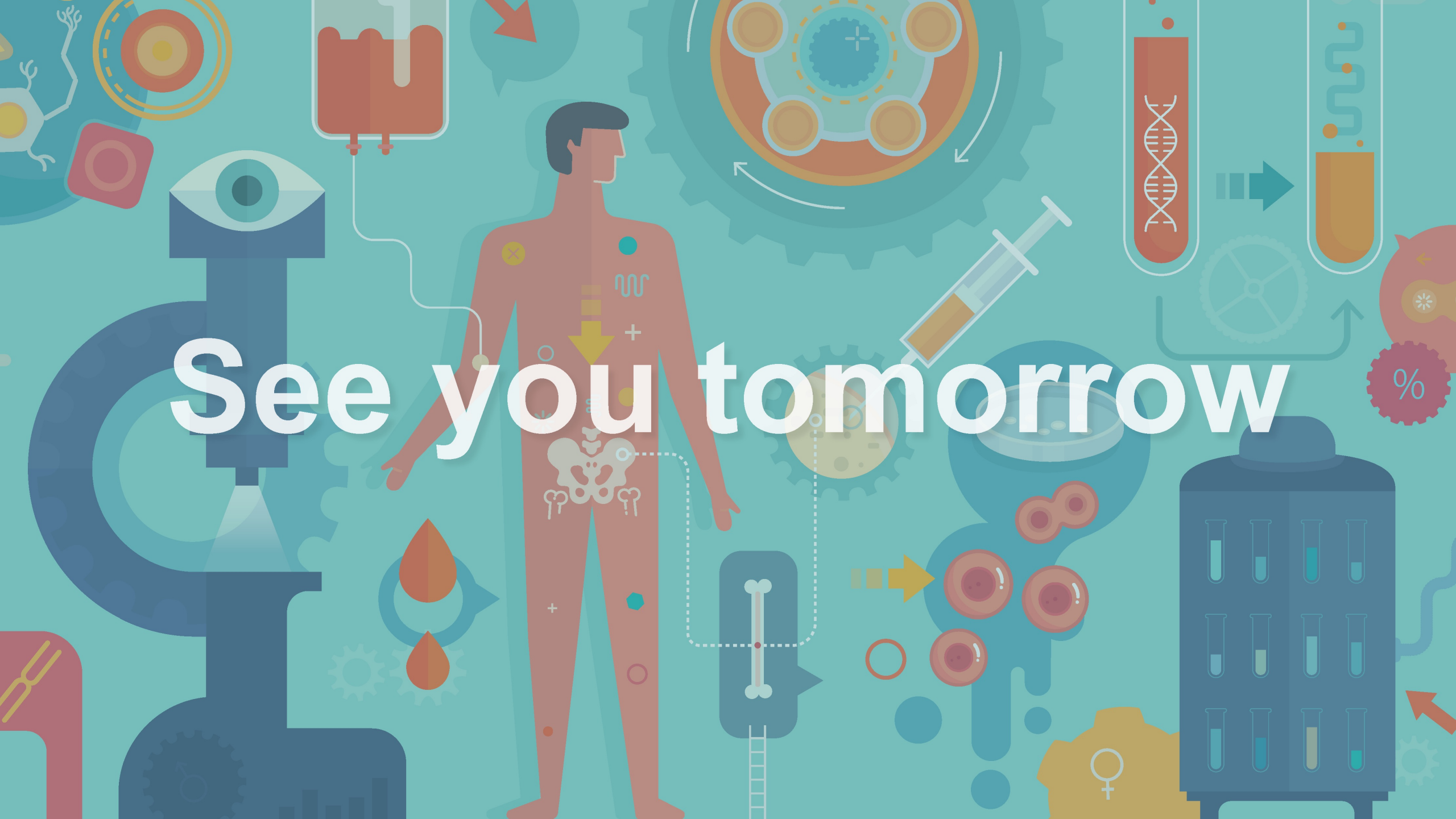
## Concluding remarks

Christine Fletcher
(GSK, EFPIA)

Mireille Muller
(Novartis, EFPIA)

Anja Schiel
(EMA SAWP, NoMA)

**18:30 End of Day 1**


See you tomorrow