Breakout Session #5
Implementation & Operational aspects

Chairs: Olga Kholmanskikh (CTFG, FAMHP), Josse Thomas (BAREC)

EFPIA European Federation of Pharmaceutical Industries and Associations

Norwegian Medicines Agency

Day 2
6 October 2021

Breakout session 5

Operation & Implementation

Multi-stakeholder workshop
5 - 6 October 2021

Chairs:

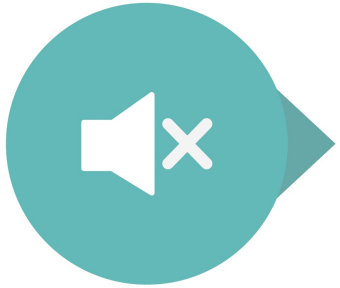
Olga Kholmanskikh (CTFG, FAMHP)

Josse R. Thomas (Ethics Committee, BE)

Complex innovative trial designs require much more upfront planning, anticipation, strong communication and flexible problem-solving approaches across multiple stakeholders. This session will discuss each of the steps: planning, implementation, execution and oversight of complex clinical to identify the most important challenges in the implementation of complex innovative clinical trials. Aspects such as collaboration vs. competition, use of common templates and governance will be discussed to elaborate best practices and recommendations.

House-keeping rules

(For active participants in the Zoom call)



- Mute your sound and video when not speaking

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- Introduce yourself (name, company, role) when taking the floor

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

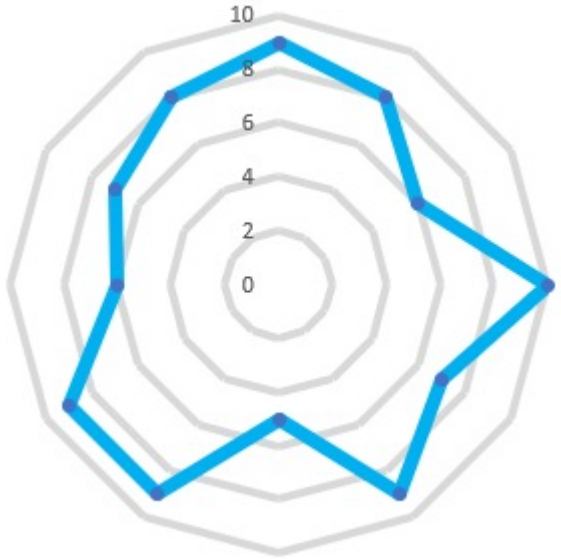
You can scan the QR-code with your mobile device for direct access to the Q&A

Topics for discussion during this break-out session

1. Collaborative, competitive and mixed approaches for planning, conducting and reporting of CCTs

2. Practical aspects and solutions to transform challenges to opportunities

3. Best practices sharing: the way forward



Complexity in clinical trials

Potential sources/determinants of complexity

Population (vulnerability, clinical complexity, prevalence)

Treatment (medicinal product and its characteristics, administration, combinations, length of treatment phase)

Development status (FIH, different phases, exploratory, confirmatory)

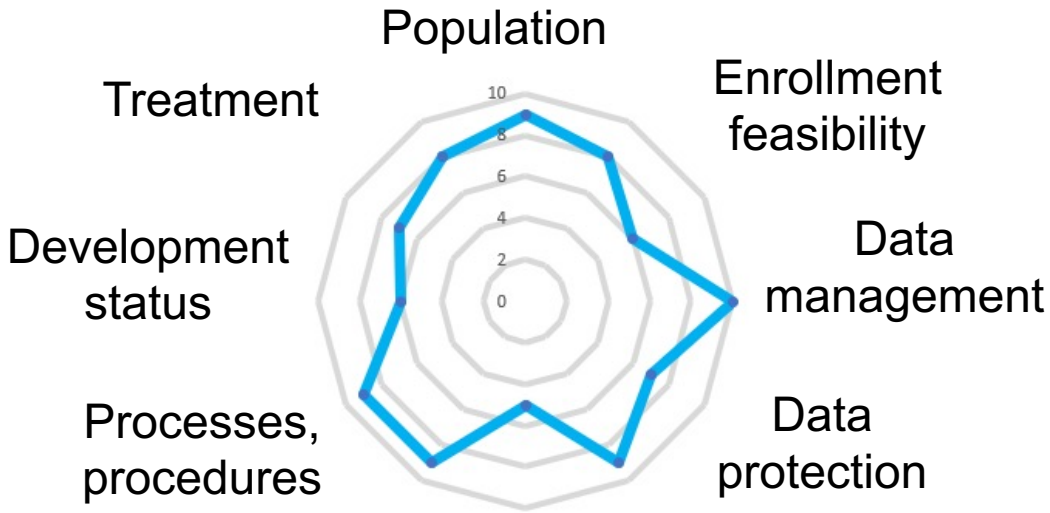
Design elements and analysis (number of arms/cohorts/sub-protocols; fixed vs adaptive, randomisation, enrichment, operating characteristics)

Processes and procedures (informed consent, operational complexity)

Data collection, protection, follow-up phase requirements etc.

Complexity in clinical trials

Combinatorial complexity

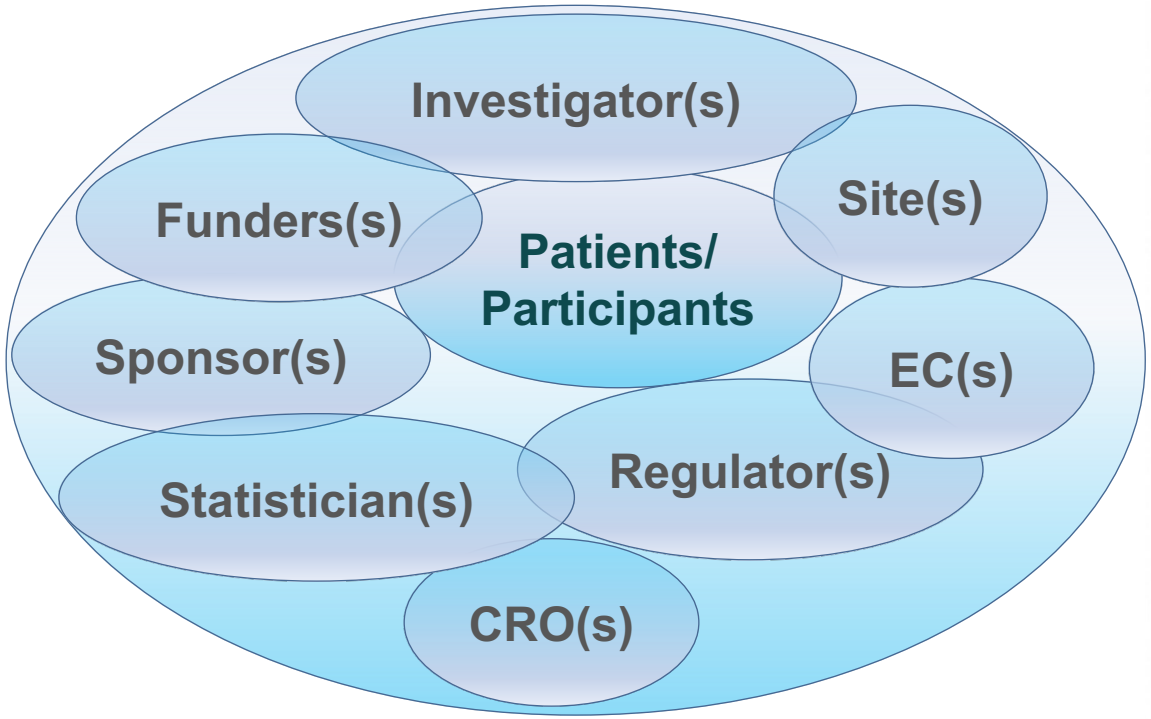


Design and analysis

One of the elements/features/methods and/or combination thereof

-Master protocol elements
(e.g. basket, umbrella, platform)
-Adaptive features
-Enrichment strategies
(+biomarkers / IVD medical devices)

Operational complexity
Inter-/multi-stakeholder relationships



CTFG

1. Collaborative, competitive and mixed approaches for planning, conducting and reporting of CCTs

Innovation in collaboration:

early and continuous

stakeholders' collaboration to mitigate complexity

Impact on clinical decision-making

Collaborative efficiency

Collaborative vs competitive vs mixed approches and operational consequences

Examples, working definitions

- **Collaborative approach**
  - **One or several non-commercial sponsors** (e.g. academic centres, not-for-profit organisations, investigator networks, government-funded cooperative groups, patient organisations, etc.), pharma/biotech/medtech companies may offer medicinal products/IVD medical devices and/or funding
  - **Consortium of commercial and/or non-commercial sponsors**, common funding
- **Competitive approach**
  - **Individual commercial sponsors**, one-sponsor funding, similar CCTs within the same therapeutic area
- **Mixed approaches**

  (e.g. in terms of funding within one complex clinical trial; change from competitive to collaborative approach within the same therapeutic area; collaborative competition: prioritisation within the same therapeutic area)

Examples from different therapeutic areas

Oncology +++

Adult: **- 1 commercial sponsor/funder**
(e.g. >1 IMPs/combo in > 1 trials in > 1 histology)
- **1 non-commercial sponsor, >1 funders**
(e.g. 1 trial, >1 IMPs/combo in 1 histology)

Paediatric: **1 non-commercial sponsor, >1 funders**
(e.g. >1 IMPs/combo, > 1 histology)

Neurology

- Alzheimer's disease (DIAN-TU)
- Amyotrophic lateral sclerosis (HEALEY ALS)

Infectious diseases

- COVID-19 (++)
- Tuberculosis (PanACEA-TB)
- Antibiotics targeting resistant pathogens (ADAPT)

-Ebola (PREVAILII)
- Severe acute respiratory infection (PREPARE/PRACTICE/ Study C)

Clinical trials ongoing and coming in other areas: gastrointestinal diseases, endocrinology …

EU-PEARL examples…

Examples of collaborative, competitive or mixed approaches

Cecile Spiertz (EU-PEARL/J&J)

Implementation & Operational aspects

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

EU-PEARL
EU PATIENT-CENTRIC
CLINICAL TRIAL PLATFORMS

SHAPING THE FUTURE OF CLINICAL TRIALS

We are transforming the future drug development
by creating a sustainable entity
available for industry and academia
to conduct platform trials in any disease area
codesigned by patients

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 853966.
The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and CHILDREN'S TUMOR FOUNDATION, GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT NON PROFIT ORGANISATION, SPRINGWORKS THERAPEUTICS INC.

WHAT IS EU-PEARL?

Strategic alliance between the public and private sectors to:

by developing a common framework
for platform clinical trials/Integrated Research Platforms (IRPs)

WHO IS INVOLVED

EUROPEAN UNIVERSITY HOSPITAL ALLIANCE (EUHA) HOSPITALS

Vall d'Hebron Institut de Recerca
Vall d'Hebron
Erasmus MC University Medical Center Rotterdam
Assistance Publique Hôpitaux de Paris
UniSR Università Vita-Salute San Raffaele
Medizinische Universität Wien
King's College London
KU Leuven
Charité Universitätsmedizin Berlin

OTHER HOSPITALS

LMU Klinikum der Universität München

UNIVERSITIES

University of Oxford
Manchester 1824 The University of Manchester
Università degli Studi di Milano
Newcastle University
Tartu Ülikool 1632 Universitas Tartuensis

PATIENT ORGANISATION

EPF European Patients Forum

DATA, STATISTICS

The European Institute For Innovation Through Health Data
Berry Consultants Statistical Innovation
Custodix

REGULATORY

Paul-Ehrlich-Institut
euroscan

PROJECT MANAGEMENT

teamit Research

EUROPEAN RESEARCH INFRASTRUCTURES

eatris
ECRIN European Clinical Research Infrastructure Network

BIOPHARMACEUTICAL COMPANIES / EFPIA / ASSOCIATED PARTNERS

AstraZeneca
Novartis
Janssen
Allergan
novo nordisk
Otsuka
teva
Sanofi
Pfizer
TB Alliance Global Alliance for TB Drug Development
SpringWorks Therapeutics
Children's Tumor Foundation Ending NF Through Research
Servier

imi innovative medicines initiative
efpia
SpringWorks Therapeutics
TB Alliance
Children's Tumor Foundation Ending NF Through Research

INTEGRATED RESEARCH PLATFORMS
IRPs

An Integrated Research Platform is a novel clinical development concept which centers around a **master trial protocol**

It can accommodate multi-sourced interventions using the existing infrastructure of hospitals and federated patient data in design, planning and execution

An optimized regulatory pathway
for these novel treatments has been established.

EU-PEARL WILL DELIVER

1 A trusted sustainable entity ready to setup and coordinate the operation of Integrated Research Platforms in any disease.

2 A Clinical Trial Platform Framework that can be used for any disease, plus four disease clinical trial platforms ready to operate at the end of the project

3 Four disease trial-ready clinical networks

- Major Depressive Disorder
- Tuberculosis
- Non-Alcoholic Steatohepatitis (NASH)
- Neurofibromatosis

COLLABORATION & SHARING

- EU-PEARL brings together patients, clinicians, industry, academia, researchers, and authorities to collaborate in shaping the future of clinical trials
- An open and trusted environment for knowledge sharing and science-driven debate amongst all stakeholders
- Advancing science together: this is the driving force behind EU-PEARL – interested and open to collect best practices, and drive discussions to create a general framework

DISEASE-AGNOSTIC WORK PACKAGES

WP1 IRP Governance, Quality, Sustainability

- Information governance and Ethics
- Certification of Implemented ICT platform components
- Legal Framework
- Interoperability and Data Quality
- Project and Sustainability KPIs
- Sustainability and Scale Up
- Patient Engagement Platform

WP2 Scientific, Regulatory and Operational Methodology

- Qualitative Methods and Statistical Design
- Regulatory Aspects
- Clinical Operational Best Practices (Master Protocol Template)

WP3 Clinical network and patient level data

- Clinical Network
- Patient Data Network
- Deployment and Evaluation

WP8 Project Oversight, Project Management and Outreach

- Project plan
- Reporting and timely presentation of deliverables
- Internal and external communications
- Risk management
- Alliances with other initiatives

DISEASE-SPECIFIC WORK PACKAGES

WP4 IRP for Major Depressive Disorder (MDD)	WP5 IRP for Tuberculosis (TB)	WP6 IRP for **Non-Alcoholic Steatohepatitis (**NASH)	WP7 IRP for NeuroFibromatosis (NF)

Define scientific challenges for each disease area

Design Master Protocol (disease specific)

Establish hey operational requirements for the implementation of specific IRPs

Endorsement of Master Protocols by regulatory and ethics

Build patients and clinical networks

Sustainability and dissemination

Examples of collaborative, competitive or mixed approaches

Sharon Love (MRC Clinical Trials Unit at UCL)

Implementation & Operational aspects

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

MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

UCL

Examples of collaborative, competitive and mixed approaches for planning, conducting and reporting of complex clinical trials

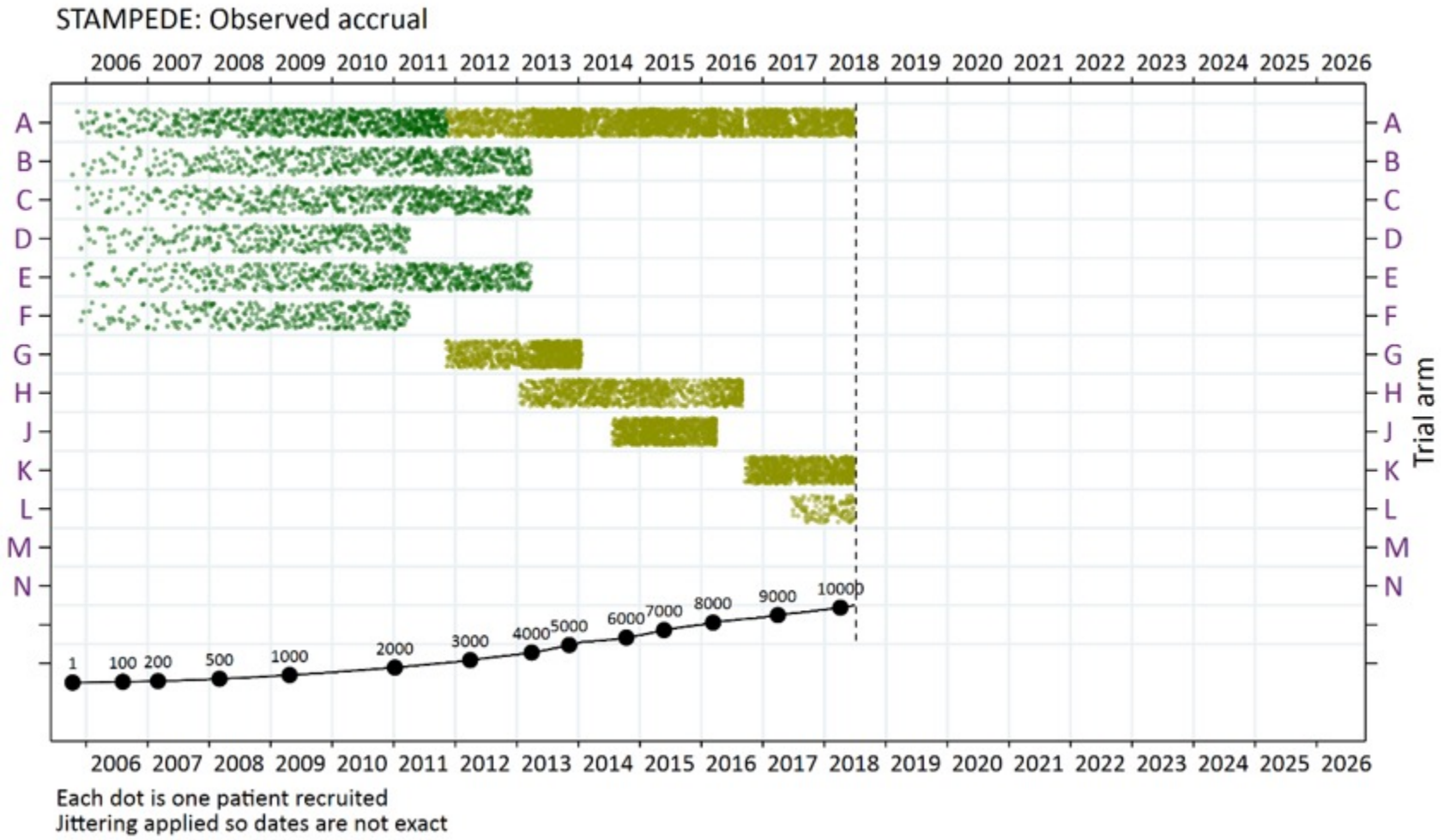
Sharon Love

MRC Clinical Trials Unit at UCL

Institute of Clinical Trials & Methodology

6-Oct-2021

STAMPEDE


STAMPEDE: Observed accrual
2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026
A
B
C
D
E
F
G
H
J
K
L
M
N
Trial arm
1 100 200 500 1000 2000 3000 4000 5000 6000 7000 8000 9000 10000
Each dot is one patient recruited
Jittering applied so dates are not exact

RECOVERY

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- 9 completed arms
- 4 currently open arms
- 1 sponsor – Oxford university
- >6 funders, all grant funders ie no commercial funders
- Licensed drugs supplied as usual for treatments in UK / some by the pharmaceutical company
- Unlicensed drugs supplied correctly labelled by the pharmaceutical company

Commercial and non-commercial sponsors

Organisation leading trial		
Non-commercial	55	89%
Commercial	7	11%

Acknowledgements

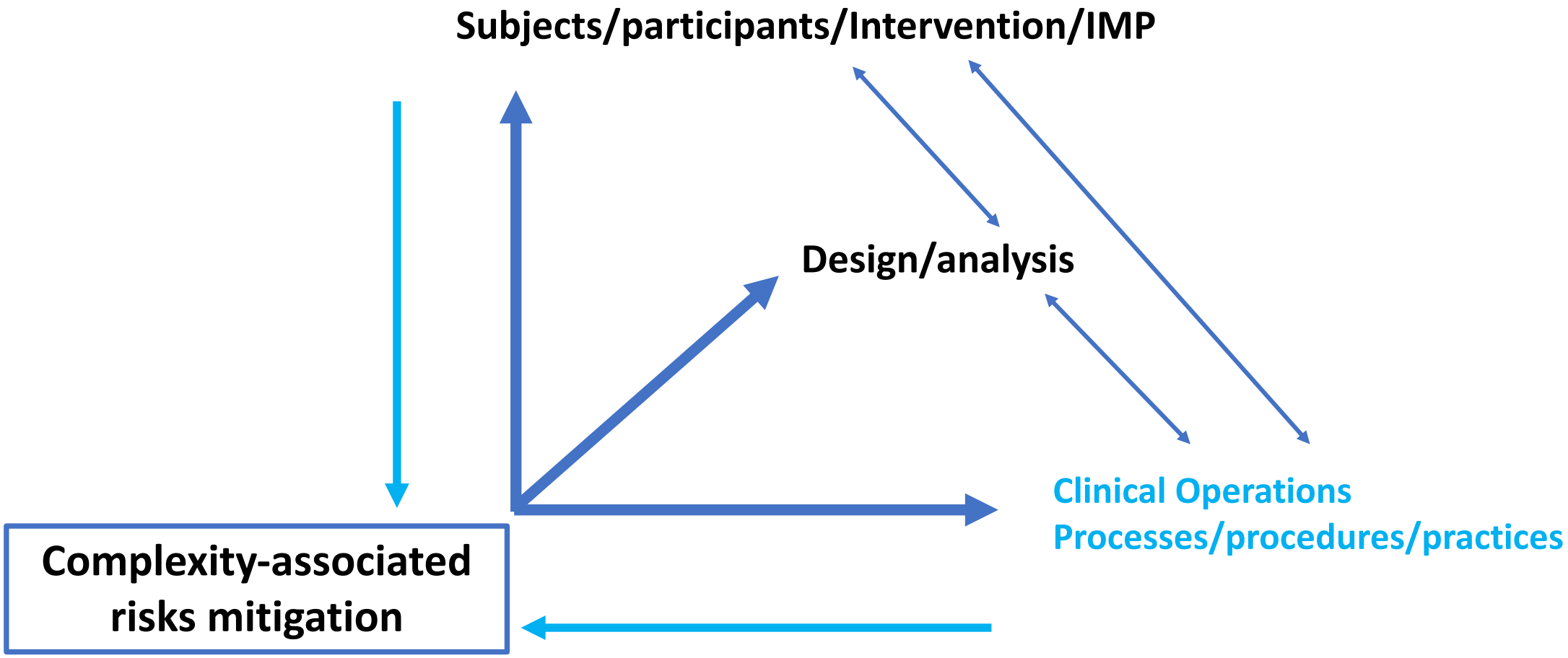
- Industry partners
- Dr Nurulamin Noor

1. Collaborative, competitive and mixed approaches for planning, conducting and reporting of CCTs

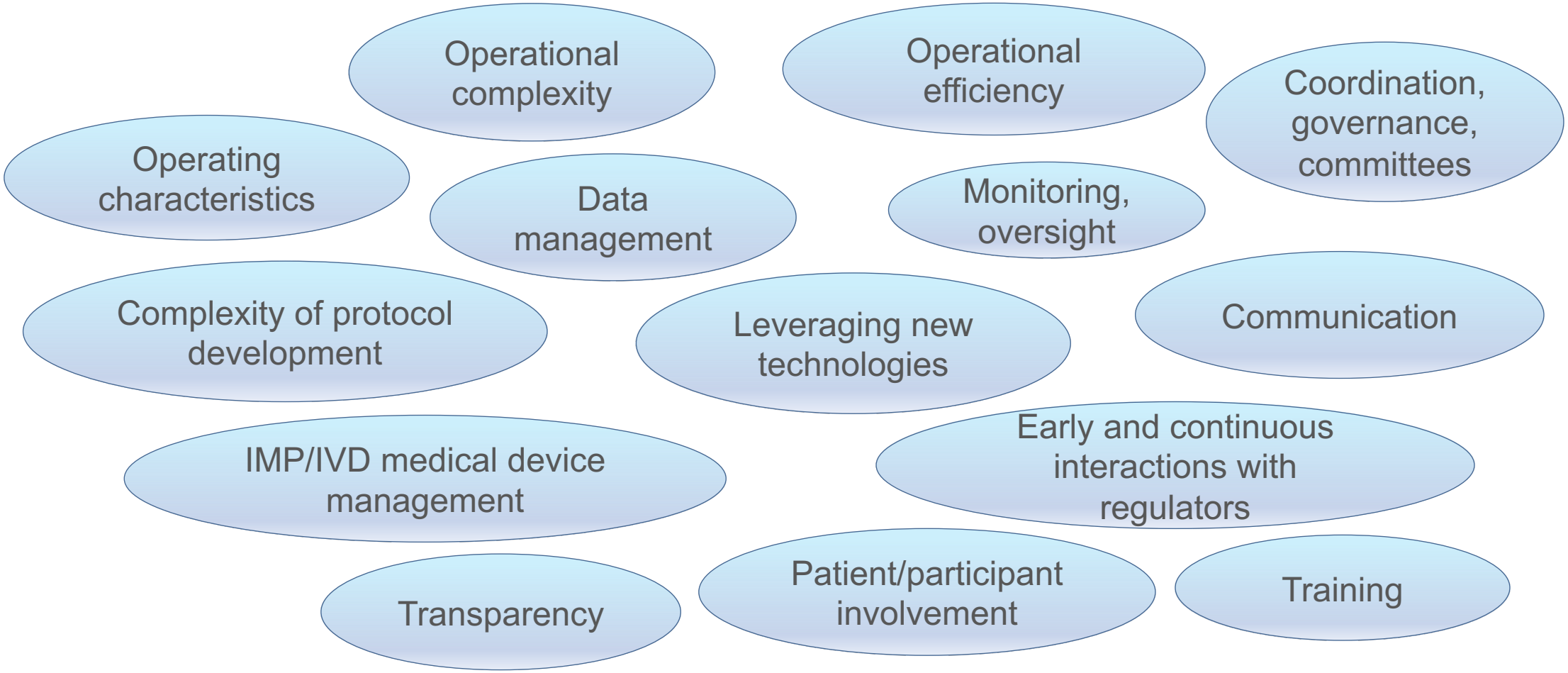
- In which therapeutic areas do you have experience with CCTs?
- What are advantages and disadvantages of different approaches?
- Are there priorities for specific areas/diseases/conditions?

Discussion

2. Practical aspects and solutions to transform challenges to opportunities

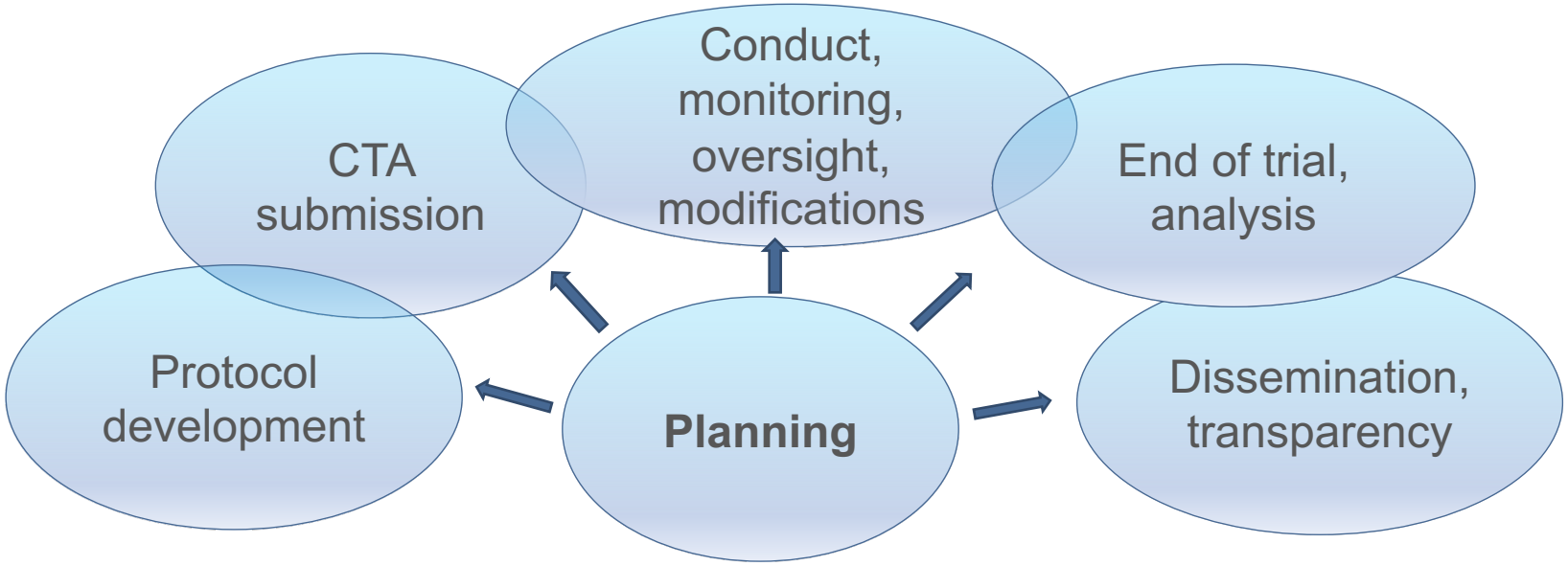

Subjects/participants/Intervention/IMP
Design/analysis
Clinical Operations
Processes/procedures/practices
Complexity-associated risks mitigation

Challenges ⟷ Opportunities



CTFG key recommendations for initiation and conduct of complex clinical trials (2019)

Clearly describe and justify design
Maintain scientific integrity
Ensure quality of trial conduct and optimise clinical feasibility
Ensure safety of trial subjects
Maintain data integrity
Reassess benefit-risk balance at critical steps throughout clinical trial
Validate companion diagnostics
Consider data transparency



2. Practical aspects and solutions to transform challenges to opportunities

- What to think about during planning, conducting and reporting?

Experience from

MRC Clinical Trials Unit at UCL

What to think about during planning, conduct and reporting of CCT

Sharon Love (MRC Clinical Trials Unit at UCL)

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What to think about during planning, conduct and reporting of CCT

Sharon Love

MRC Clinical Trials Unit at UCL

Institute of Clinical Trials & Methodology

6-Oct-2021

Planning

- Chief investigator responsibilities
- Simultaneous vs sequential

Conduct

- Communication
- Change of the standard of care
- Staffing

Reporting

- Telling participants about their arm or all arms
- When to upload to EudraCT

Acknowledgements

- STAMPEDE and FOCUS4 Trial Management Group and Teams
- Sponsor: MRC and UCL
- Funders
  - CRUK
  - MRC/NIHR EME Programme
- Industry partners
- Registered CTU running platform trials in the UK

FOCUS4

MRC Medical Research Council

NHS National Institute for Health Research

CANCER RESEARCH UK

MRC Clinical Trials Unit

UCL

UNIVERSITY OF OXFORD

The FOCUS4 Trial Programme is jointly funded by the MRC-NIHR Efficacy and Mechanism Evaluation Programme (11/100/50) and Cancer Research UK (A13363).

Practical aspects and solutions to transform challenges to opportunities

Cecile Spiertz (EU-PEARL/J&J)

Implementation & Operational aspects

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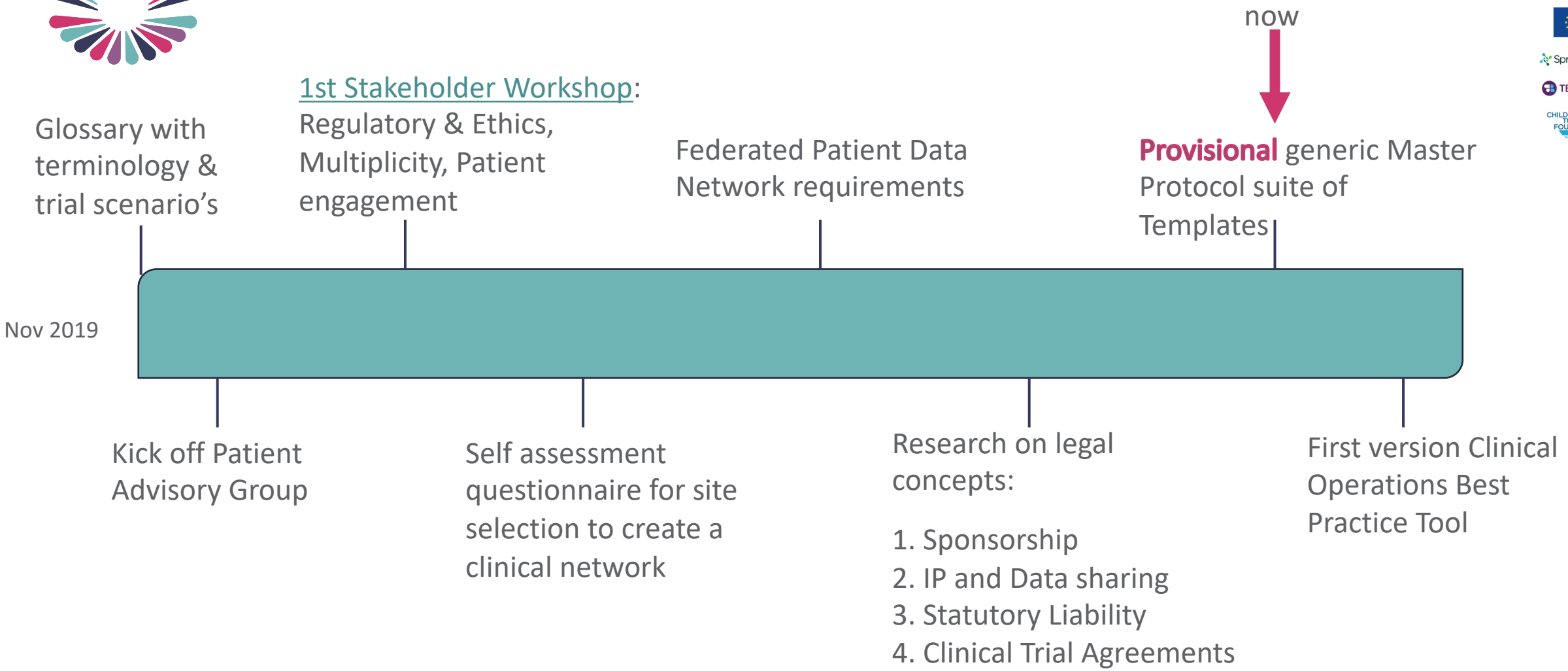
OVERVIEW ON PROGRESS

Disease-agnostic IRP framework



SET OF PROVISIONAL GENERIC PLATFORM TRIAL TEMPLATES

I. Provisional Master Protocol Template

•

II. Provisional Intervention Specific Appendix (ISA)

•

III. Provisional Statistical Analysis Plan Template

•

Based on TransCelerate BIOPHARMA INC. Common Protocol Template V8 (2020)

Based on TransCelerate BIOPHARMA INC. Statistical Analysis Plan V3 (2020)

OTHER DOCUMENTS THAT SUPPORT PLATFORM TRIAL TEMPLATES

- Clinical Operations Checklist (Study design, setup, execution, and analysis)

- Structured Cover Letter (Used for tracking changes through amendments to Master Protocol and individual Intervention Specific Appendices (ISA's))

DEVELOPMENT PROCESS OF THE GENERIC TEMPLATES

Starting point was the TransCelerate CPT

Cross-functional experts provided input

Review rounds within EU-PEARL and with Associated Collaborator

EU-PEARL disease teams assess templates

Refinement based on feedback from disease teams and experts within EU-PEARL

Input from EU-PEARL's Patient Advisory Group

Seek opportunities to collect external feedback

CONTACTS IN WP2

Thank you!

We very much welcome follow up discussions

WP2 operational task team

Peter Mesenbrink (Novartis); Madhavi Gidh-Jain (Sanofi); Kathryn Hersh (Janssen); Franz König (MUW); Tom Parke (Berry); Clelia Di Serio, Paola Rancoita (USR); Olga Sánchez-Maroto (VHIR); Burç Aydin, Christine Kubiak (ECRIN); Edwin van de Ketterij (EATRIS); Cecile Spiertz, Tobias Mielke, Heidi De Smedt, Sal Morello, Eva-Maria Didden, Tom Reijns, Ingela Larsson (Janssen); Ekkehard Glimm, Sabina Hernandez Penna, Fabienne Baffert; Ian Carbarns (Novartis); Yingwen Dong (Sanofi)

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SpringWorks THERAPEUTICS TB Alliance CHILDREN'S TUMOR FOUNDATION

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CLINICAL TRIAL PLATFORMS

Project dates	1 November 2019 –30 April 2023
Project Coordinator	Joan Genescà *((Vall d'Hebron University Hospital, Vall d'Hebron Research Institute (VHIR))*
Project Leader	Ann Van Dessel *(Janssen Pharmaceutica)*
Contributions	EFPIA contribution: 14.2 MM € IMI2 JU funding: 12 MM € Grant Agreement number: 853966
IMI2 Project Fact sheet:	www.imi.europa.eu/projects-results/project-factsheets/eu-pearl
Website	www.eu-pearl.eu
Questions?	info@eu-pearl.eu
Twitter	@imi_eupearl
Linkedin	www.linkedin.com/company/imi-eu-pearl

2. Practical aspects and solutions to transform challenges to opportunities

- What to think about during planning, conducting and reporting?
- What could be recommendations for an ideal governance structure?
- How to ensure a balance between transparency and integrity?

Discussion

Introduction to the discussion

- Some **challenges** are specific for CCTs and/or the operational approach

  Others are just exacerbations of known issues due to the sheer complexity and scale

- **Solutions/Recommendations** should be fit-for-purpose, modular, and flexible

Challenges concerning trial planning

- Study design: e.g. study type (single vs master + sub-protocols), adaptations
- Regulatory: e.g. scientific advice, CTA (initial + each SM)
- Operational approach: e.g. collaborative, competitive, mixed
- Sponsorship/funding: e.g. commercial, non-commercial, mixed
- Patient involvement: e.g. design, study docs
- Study materials: e.g. documents, supplies, database, website
- Site selection/investigator involvement: e.g. capacity, experience
- Service providers: e.g. needs, selection, collaboration
- Oversight bodies: e.g. trial mgt group, SteerCom, (i)DMC, safety mgt
- Resources: e.g. numbers (flexible, scalable), training

Recommendations concerning trial planning

Careful planning is key to success

Very important initially,
but also with each substantial modification

- First and foremost: start early,
  and don't underestimate the challenges
- Interact early with regulators and ECs
- Properly involve all stakeholders
- Pay attention to details in the contracts
- Don't underestimate resource needs
  Foresee flexibility and scalability
- …

Challenges during trial conduct

- Data management issues: e.g.
  - CRF and DB updates: applicable to all arms or arm-specific
  - DB growth: performance issues, DB split
- Trial management issues: e.g.
  - Finding additional funding, gaining additional approvals
  - Fluid implementation at centres
  - New safety issues
- Human resources issues: e.g.
  - Added complexity > added resources
  - Multiple overlapping tasks > priority setting
  - Attn. to increased workload and stress
- Applying Substantial Modifications:
  - e.g. adding or closing arms/comparisons, adapting the control arm or the SOC

...

Recommendations concerning trial conduct

- Start small and scale up as needed

  You’re in for a long ride

- Regularly re-estimate resource needs (systems and staff)

- Prioritise competing and concurrent tasks

- Assure continuity of staff and oversight body members

- Pay attention to workload, stress and motivation of staff

Challenges and recommendations for trial reporting
(Agencies, ECs, participants, investigators, public at large)

- **Main challenges**:
  - Timing of the communications
  - Arm-specific vs overall results

- **Recommendations**:
  - Specific regulatory guidelines needed
  - Foresee modularity and flexibility
  - Leave some choice to participants

Challenges and recommendations for trial oversight
(Trial Management Group, (i)Steering Committee, (i)DMC)

- **Challenges**:
  - Manage multiple arms/comparisons
  - Long trials
  - Independency

- **Recommendations**:
  - Install arm-specific expert subgroups
  - Assure continuity of membership
  - Guarantee independence (independent DMC for all CCTs?)

3. Best practices sharing: the way forward

- Is there a need to share best practices within and among stakeholders?
- Are initiatives like EU-PEARL helpful?
- What to do next?

Conclusions

How to go back to the plenary session?

As a viewer

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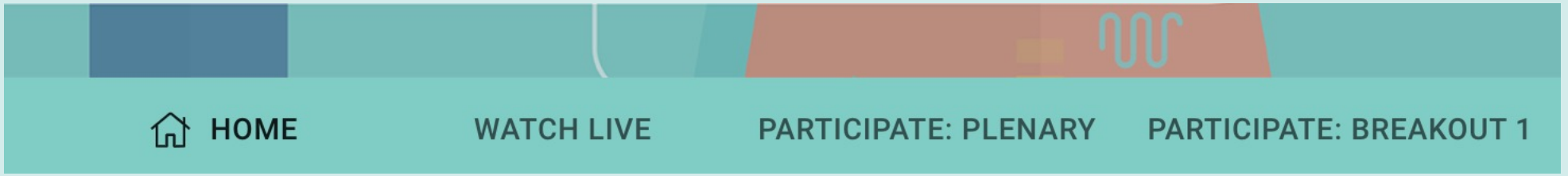

As an active participant

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