The Future is today!

Future Clinical Trials conference – from tomorrow to 2030 – Why choose the Nordics?

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The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to AstraZeneca.
The way patients are diagnosed, treated and monitored has changed with advances in new technologies.

Clinical trial designs have evolved to take advantage of the new environment and change how new treatments are being developed.
Opportunities and Challenges in clinical research

• Complex Clinical trials
• Use of Digital Health tools
• Use of RWD/RWE
• Special populations
• Processes and Operations
• Conclusion
Complex Trial Designs
New era of complex clinical trial designs

Innovative clinical trial designs can speed up drug development without lowering scientific and regulatory standards

- Accelerated drug development and approval
- Increased and earlier patient access to targeted therapies
- Efficiently study multiple compounds / multiple targets in one operational set-up
- Identify ineffective medicine earlier, reduction of failure rate in Phase III and patient exposure to ineffective drug
Some examples of complex designs...

Mater Protocols, to Study Multiple Therapies, Multiple Diseases, or Both

Woodcock et LaVange N Engl J Med 2017
Some examples of complex designs...

**Platform Trials:** multiple interventions can be evaluated simultaneously against a common control group within a single master protocol

*Park et al. Journal of Clinical Epidemiology 2020*
Some EU-funded projects

- Rare diseases Final report
- Efficient clinical testing of novel antimicrobial drugs
- Methodological recommendations for robust and reproducible personalised medicine research
- Multi-arm, adaptive CT TB drugs
- EU expansion of the DisCoVeRy study - COVID-19 EU Adaptive Platform Trial: EU-SolidAct
- Proof of Concept platform to run Phase II trials - Alzheimer’s disease
- Master protocol for Phase 2 trials - Type 1 diabetes
‘EU- PEARL - 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.

Multistakeholder Workshop
Q4 2022
Some Complex Trials Initiatives in the US

- 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.


**FDA Pilot Program** – PDFU VI Goals

Several therapeutic areas
- Neurology
- Analgesia
- Rheumatology
- Oncology

Designs incorporated
- Bayesian hierarchical modelling
- Use of formal priors
- Formulation of a master protocol
At the global level, Regulators are embracing innovation in clinical trial design

+ 10 years since EMA Reflection Paper on Adaptive Designs (2007)
  • Recognised use of adaptive designs to modify clinical trial designs to speed up drug development without lowering scientific and regulatory standards
  • EMA/EFPIA workshops on adaptive designs (2007/2009)
    • FDA draft guidance released in 2010
  ➔ ICH E20 EWG to issue a guideline by end 2024

Further to EMA workshop on M&S (2011) and on Dose Finding (2014)
  • ICH E11A – Paediatric Extrapolation
  • ICH M15 – MIDD (Model Informed Drug Development)
Use of Pharmacometrics Approaches in clinical development

- Optimal sample size selection, understanding of covariates
- Dose and schedule selection
- Disease similarity and progression
- CT design and Simulation, biomarker and endpoint selection
- Reporting and Decision analysis
- Choice and optimization of study design

M&S/MID3/MIDD Utility

Multi-stakeholder workshop

Accelerating Adoption of Complex Clinical Trials in Europe and beyond

5 - 6 OCTOBER 2021

Use of RWD/RWE
RWD/RWE - Different level of maturity in different geographies

**UK MHRA**
Draft guidance on randomised controlled trials generating real-world evidence to support regulatory decisions

**Health Canada**
Projects aim to use of real-world evidence to support regulatory decisions across a product’s life cycle for both drugs and medical devices. Issued several guidance on this topic

**US-FDA**
PDUFA VI, 21st Century Cures Act;
Label Expansion
Fulfilling PMR/C
PDUFA VII- Pilots, Guidance, Workshops

**EU**
EMA Regulatory Science Strategy 2025
HMA/EMA Network Strategy to 2025
EMA PAES and draft registry guidelines
EMA/HMA Big Data Taskforce

**Swissmedic**
Addressing the real-world approach for drugs is integrated in Swissmedic Strategic Objectives 2019 – 2022.

**PMDA Japan**
Policy and guidelines on use of RWD for pharmacovigilance, such as electronic medical records and data of patient registries for drug safety assessment. Points to Consider for Ensuring Reliability when using Registry Data for Approval Applications

**NMPA China**
Several guidance on use of RWD to support regulatory decision making across product life cycle

**TFDA Taiwan**
Basic Considerations for RWE to Support Drug Research and development, Guidelines Study Design for RWE—Main Considerations for Pragmatic Clinical Trial and for clinical investigation using EHRs

**Potential Future Initiatives:**
- ICH (selected topics under consideration)

**Others discussing regulatory use of RWD/E:**
- South Korea
- CIOMS (WHO)
- Brazil
RWD – RWE Sources
RWD – RWE Sources
DARWIN EU – a federated network of data, expertise & services

To support better decision-making throughout the product life cycle by generating reliable evidence from real-world health care data

FEDERATED NETWORK PRINCIPLES

- Data stays local
- Use of Common Data Model (where applicable) to perform studies in a timely manner and increase consistency of results
Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlert1*, Jesper Kjær2, Karl Broich3 and Emer Cooke1

We outline our vision that by 2025 the use of real-world evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

In December 2018, the US Food and Drug Administration (FDA) published its framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study design can provide adequate evidence, and whether the study conduct meets regulatory requirements. In 2019 the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological. More recently, the EU approach places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021. Figure 1 represents the workplan with its 11 workstreams which will deliver our vision for RWE by 2025. The workplan places emphasis on collaboration across stakeholders and with international regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission’s plans for a European Health Data Space. Acknowledging different frameworks to conceptualise the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMA is working to deliver on both priorities through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the central role of industry in generating evidence.

ENABLING USE
To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry, regulatory and public health agencies, health technology assessment bodies, patients, and academia. We are initiating work to establish a data quality framework, not just for RWD but for all data used in regulatory decision making. We are striving to improve the discoverability (findability) of RWD through agreements on metadata for RWD and through a public catalogue of RWD sources that builds on the early work of the European Network of Centres for Pharmaceutical Economics and Pharmacoeconomics (ENC-P). The ENC-P Guide on Methodological Standards in Pharmacoepidemiology recently updated in 2021, is the core of our efforts to drive up the standards of study methods for RWE, and this is complemented by recently published guidance on conducting studies based on patient registries. The European Medicines Agency (EMA) and some national medicines agencies...
Ensuring the safe and effective use of medicines is not just an EU regulatory responsibility…

… it’s a global responsibility for all stakeholders to support

Ensuring the appropriate use of RWE to inform regulatory decision-making is not just an EU regulatory responsibility…

… it’s a global responsibility for all stakeholders to support
Use of Digital Health Technologies
Building better measures for clinical trials with digital health technologies

Digital Health Technology
A system that uses computing platforms, connectivity, software, and sensors for healthcare and related uses.

Smartphones and Tablets
Can be used to complete daily tasks or questionnaires. When carried, sensors can record behavior such as body movement and location.

Wearables
Can be used to record behavior and physiological changes such as heart rate.

Nearables
Can be used to record behavior and physiology with minimal disturbance to the participant.

DHTs can measure signs of a disease outside of the clinical environment
IMI & Digital Health Tools

A mobile app that allows users to report adverse drug reactions and receive reliable information about their treatments.

MRI methodology to stratify populations of people with Autism spectrum disorders.

Identify and validate a set of Digital Mobility Outcomes that can be used as reliable quantification of the mobility performance.

Decentralised Trials
Pan-EU pilot RADIAL study

Identifying digital endpoints to measure fatigue, sleep quality and impact of sleep disturbances in neurodegenerative (Parkinson, Huntington’s disease) and immune mediated inflammatory diseases (RA, SLE, IBD)
IMI & Digital Health Tools

2 hybrid tools qualified to assess COPD patients’ perception of Physical Activity
• To be used as endpoint in CTs
• To support labelling claims

ActiMyo - developed to evaluate the physical condition of subjects suffering from pathologies associated with movement disorders; e.g., Duchenne Muscular Dystrophy

EMA QUALIFICATION PROCESS
EMA Q&A Document: Qualification of digital technology-based methodologies to support approval of medicinal products
Horizon scanning: survey to complete by end of July: https://survey.zohopublic.eu/zs/peDHfj
Some Critical-Path Institute’s initiatives

Critical Path for Parkinson’s Digital Drug Development Tools (3DT) initiative

DHTs as disease progression biomarkers

To advance the science of CT endpoint assessment by collaboratively supporting and conducting research, designing and delivering educational opportunities, and developing and disseminating best practice recommendations for electronic collection of clinical outcome data.

https://c-path.org/
SAVE THE DATE

Enhancing patient-centric outcome measures and clinical trials with the use of Digital Health Technologies

A multistakeholder workshop to facilitate dialogue on the use of Digital Health Technologies in clinical trials, including digital endpoints, and to identify opportunities for optimising regulatory pathways and solutions to some of the challenges faced

8-9 November 2022 (13:45 - 19:00 CET)
Virtual interactive event
Special Populations
IMI – Advancing Paediatric Research

Innovative trial designs, e.g. Master Protocol
Use of RWD, Big Data, Artificial Intelligence...

Pre-Clinical

Clinical

Autism  Resp. Syncitial Virus  Neurofibromatosis  Type 1 Diabetes  Rare diseases
Blood cancers  Autism  Pregnancy & Breast feeding

November 10, 2021
ICH guidelines

• ICH E11(R1) – Paediatric addendum
  • Finalised in Sept. 2017, implementation is ongoing

• ICH E11 A Paediatric extrapolation guideline
  • Based on existing guidelines including the EMA RP on Paediatric Extrapolation, and published case examples
  • Step 2 guideline reached in April 2022
    • Public consultation until early August

• New topic: Pregnant & Breastfeeding Individuals in Clinical Trials (June 2022)
Upcoming events

EFGCP Better Medicines for Children Pre-Conference Workshop

The Fundamentals of Paediatric Extrapolation

Virtual Event English

1 Day 4 hours/ day

17 Oct. 2022

EFGCP Better Medicines for Children Conference 2022 Conference

Global Paediatric Drug Development: Progress made & always remaining challenges

Virtual Event English

2 Day 8 hours/ day

18 & 19 Oct. 2022
Tools and processes

Revision of the EU Pharma Legislation

HTA Regulation

Benefit/Risk Assessment

Initial R&D and Pre-Clinical

Phase 1

Phase 2

Phase 3

Adaptive Pathways/MAPPs

PRIME

UK EAMS

French Early Access

EMA-FDA Parallel SA

EMA-HTA JSC

Conditional approval

Accelerated Assessment

Exceptional circumstances

Compassionate use

28+ national HTAs & payers:
CE/relative E BIA assessment

MEA

Patient access

PLEG

0-10 YEARS

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Sustainable clinical trials – Reducing carbon emissions in clinical trials – regulatory perspective

AZ Ambition Zero Carbon

Through our Ambition Zero Carbon programme we are on track to reduce greenhouse gas emissions from our global operations by 98% by 2026 and halve our entire value chain footprint by 2030 on the way to a 90% reduction by 2045.

Clinical trials produce significant carbon emissions

- We recently conducted a Life Cycle Assessment* of clinical trials across therapy areas to identify CO2 hot spots and opportunities for reduction including travel, samples, and waste
- AZ Objectives to reduce CO2 in clinical trials include:
  - Incorporate CO2 reduction thinking into design of new clinical trials
  - Introduce in 2022 a Carbon emissions calculator to use during Study Design
  - Evaluate CO2 reduction efforts during governance decision making including innovative trial designs, endpoints
  - Increasing awareness and training across AZ R&D
- Health authorities’ positions and/or guidelines have not emerged to date
- We welcome opportunities to engage in conversations with stakeholders. Point of contact: zofia.chmielewska@astrazeneca.com

Halve emissions from total value chain by 2030

*Sustainability at AstraZeneca https://www.astrazeneca.com/media-centre/articles/2020/ambition-zero-carbon-22012020.html#

AZ Sustainability Report 2021

*A Life Cycle Assessment (LCA) is an internationally accepted and scientifically robust technique for assessing the environmental impacts of a product, process or service from raw materials, processing, manufacturing and assembling, distribution to use and end of life. (ISO 14040 and ISO 14044)
To conclude – the future is today!

• All stakeholders involved in R&D are taking steps to promote alternative clinical study designs, and methods that go beyond randomised clinical trials, said to be the ‘gold standard’

• Devising more efficient, less costly strategies to answer questions about treatment effects and patient benefits, are key to shift to personalised medicine for targeted patients with high unmet medical need

• This could involve developing and qualifying new biomarkers or Patient Reported Outcomes as ‘fit for purpose’, or designing pragmatic, adaptive, or platform trials with master protocols to evaluate multiple treatments more efficiently

• This will also imply improving existing tools, or methods (e.g., Modelling & Simulation) and regulatory processes (e.g., conditional approvals, scientific advice, registries) to optimise drug development pathway and support early patient access to innovative medicines

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

• Benefit to seek regulators’ early feedback