The Future is today!

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

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7 June 2022

Disclaimer

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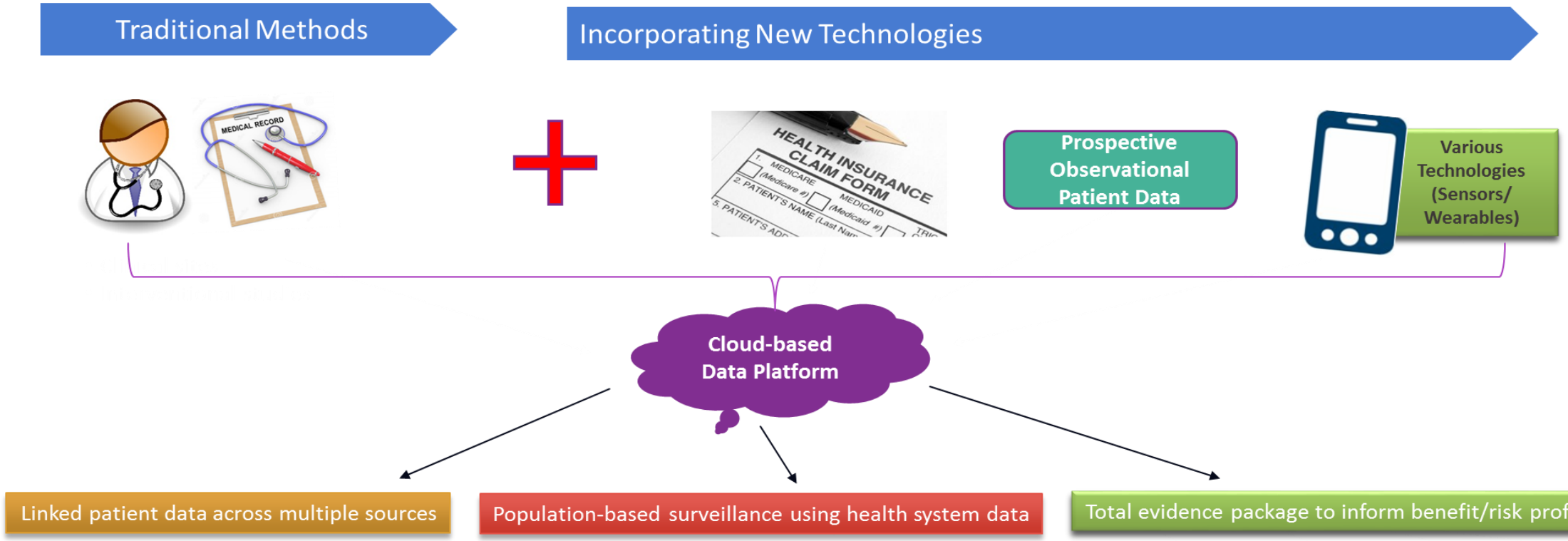
The way patients are diagnosed, treated and monitored has changed with advances in new technologies



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

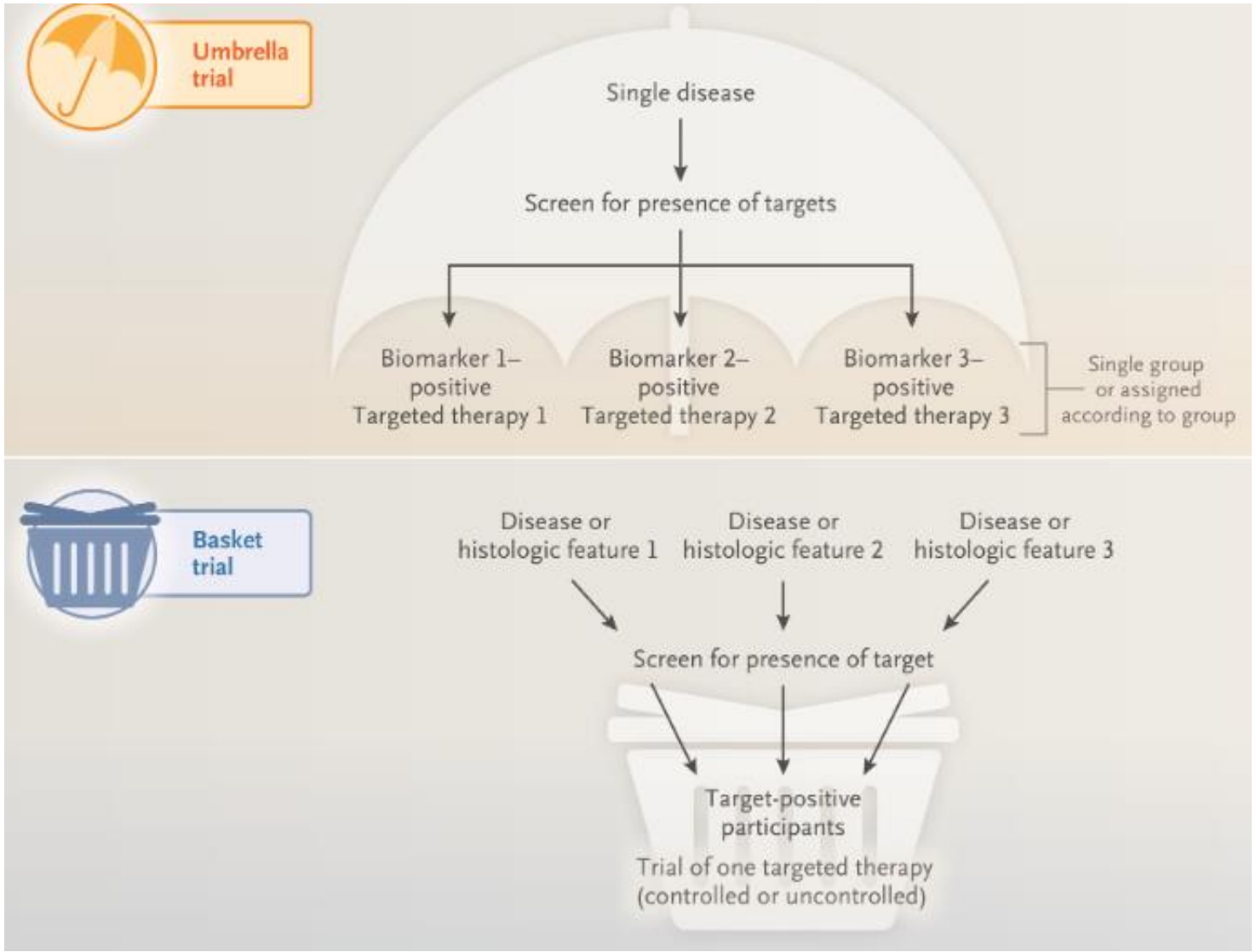
New era of complex clinical trial designs

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…

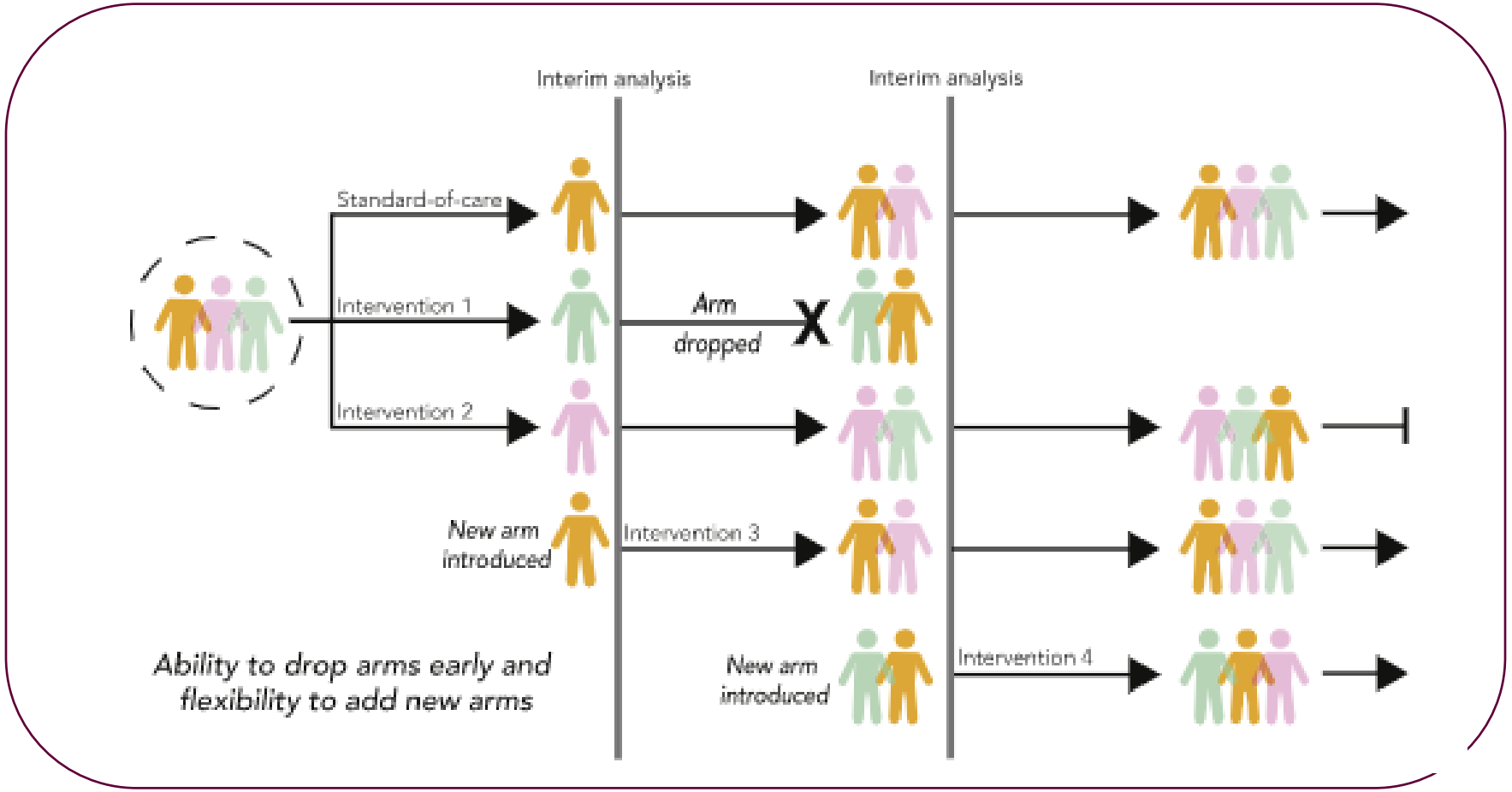
Mater Protocols, to Study Multiple Therapies, Multiple Diseases, or Both



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

Sjögren's Syndrome
Platform trial

Efficient clinical testing of **novel antimicrobial drugs**

Proof of Concept platform to run Phase II trials - **Alzheimer's disease**

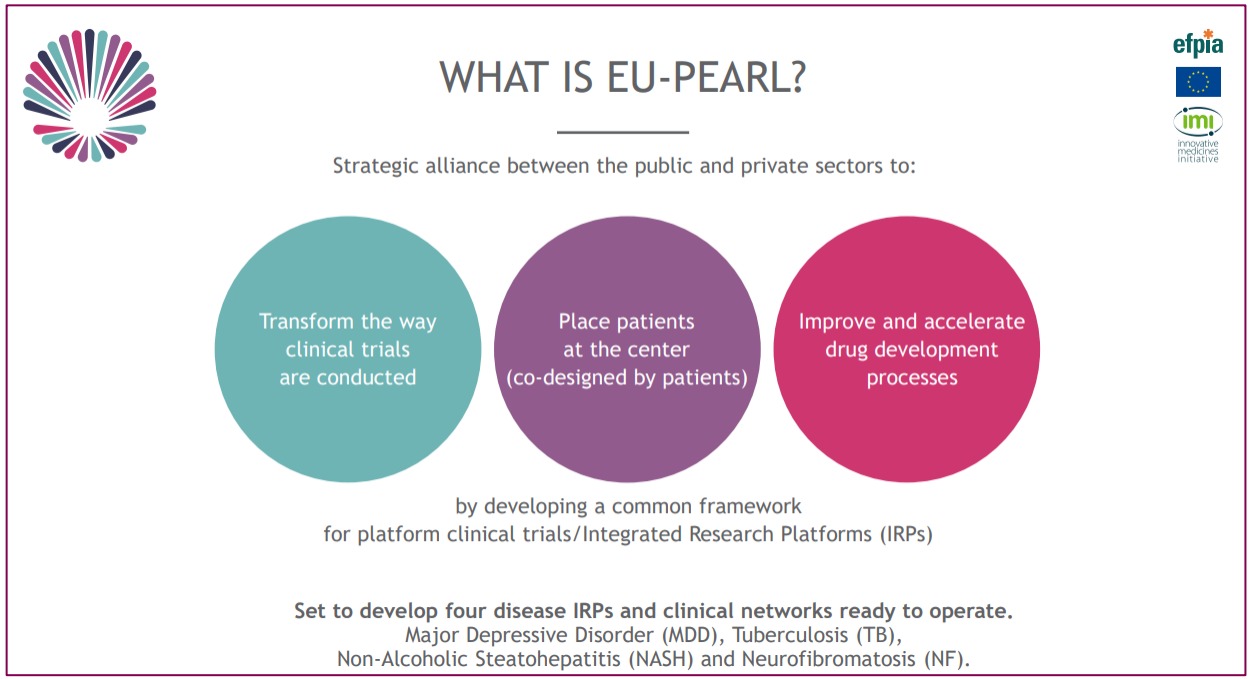
Methodological recommendations for robust and reproducible **personalised medicine research**

Multi-arm, adaptive CT
TB drugs

Master protocol for Phase 2 trials - **Type 1 diabetes**

EU expansion of the **DisCoVeRy** study - **COVID-19**
EU Adaptive Platform Trial: EU-SolidAct

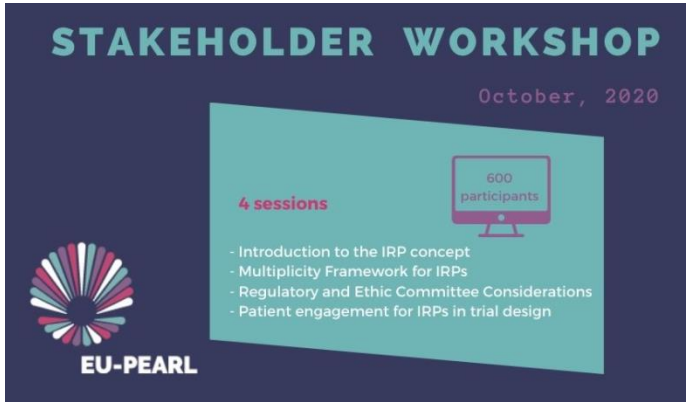
‘EU- PEARL - Patient centric clinical trial platforms’



- 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.

EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

Multistakeholder Workshop
Q4 2022



Some Complex Trials Initiatives in the US

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

- 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.

- 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.

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)

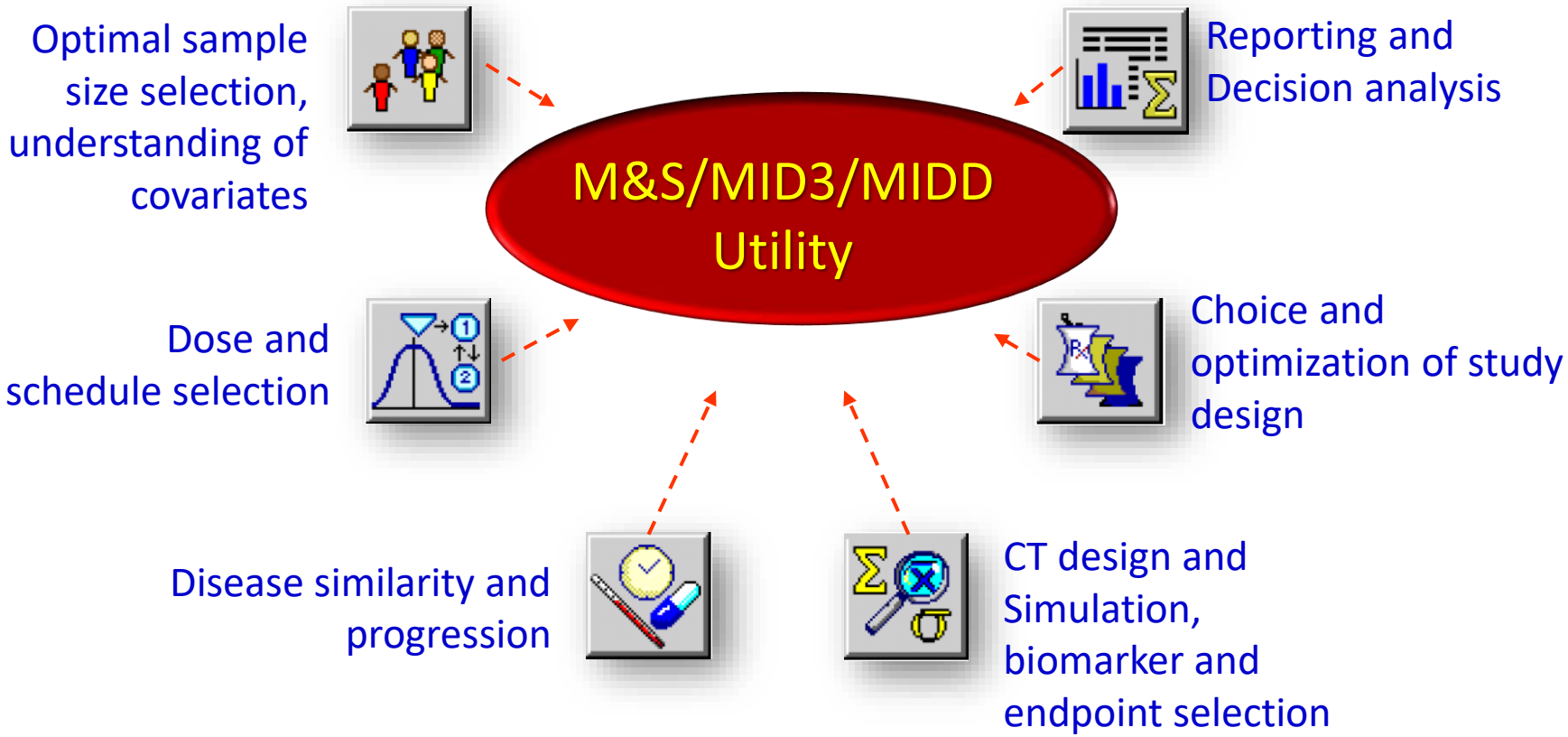
- Recognised use of adaptive designs to modify clinical trial designs to speed up drug development without lowering scientific and regulatory standards
- EMA/EFPIA workshops on adaptive designs (2007/2009)
  - FDA draft guidance released in 2010

➔ **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



Marshall et al. CPT&PSP2015

https://www.efpia.eu/news-events/events/efpia-event/accelerating-adoption-of-complex-clinical-trials-in-europe-and-beyond/

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

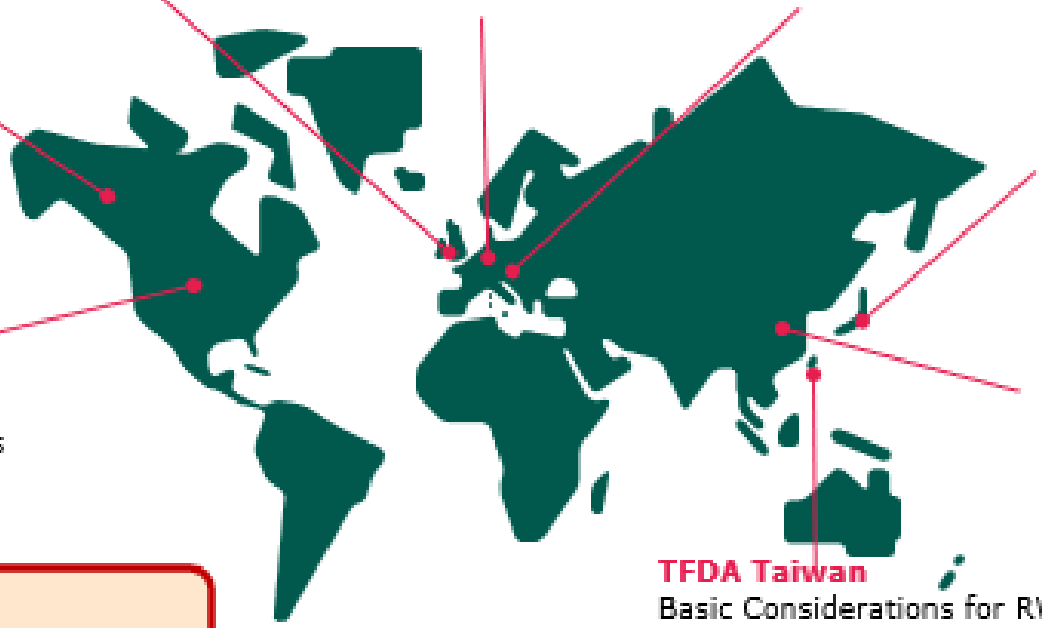
Projects aim to use of real-world evidence to support regulatory decisions across a product's life cycle for both drugs and medical devices. Issued several guidance on this topic

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

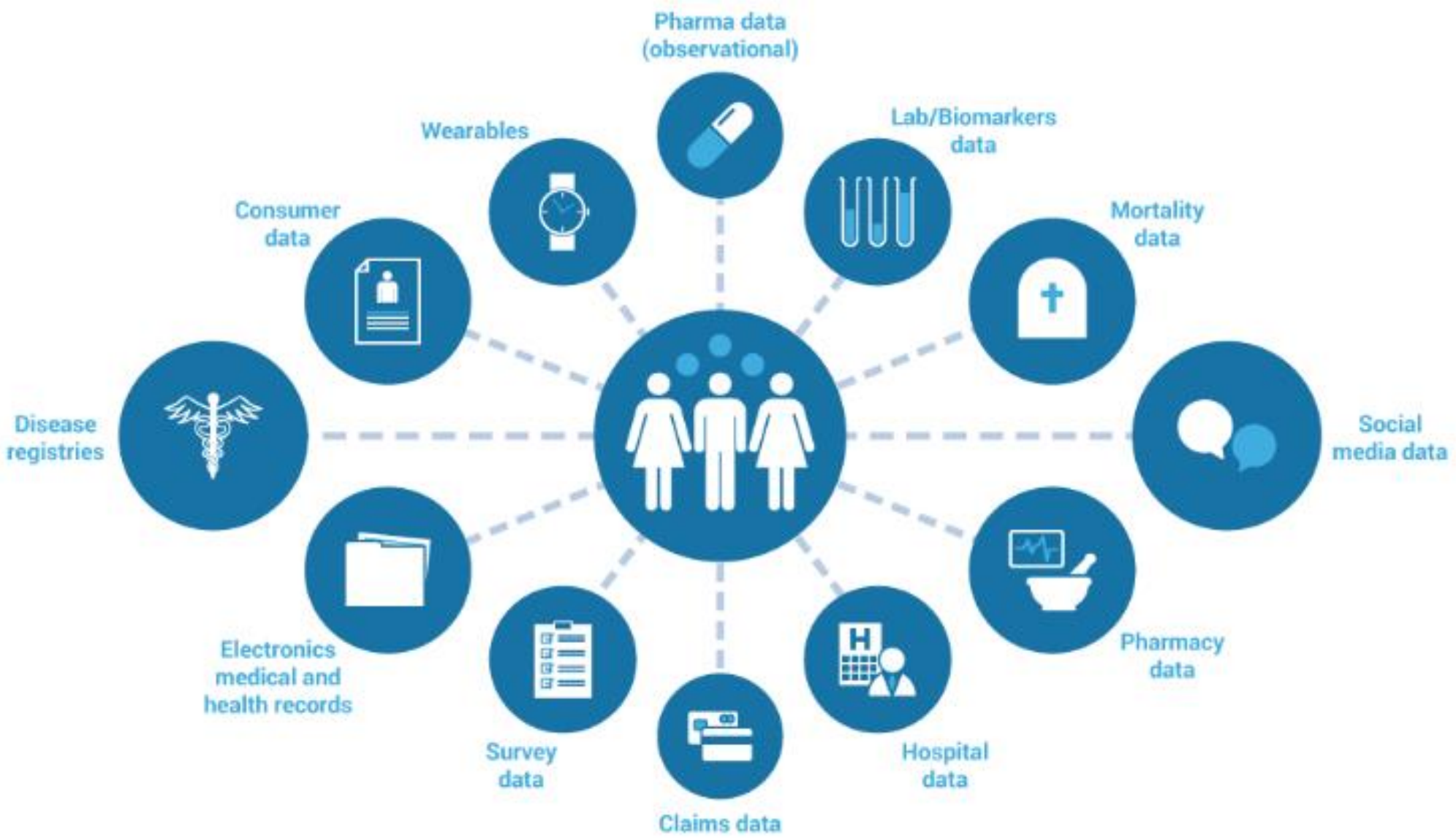
Potential Future Initiatives:

- ICH (selected topics under consideration)

Others discussing regulatory use of RWD/E:

- South Korea
- Brazil
- CIOMS (WHO)

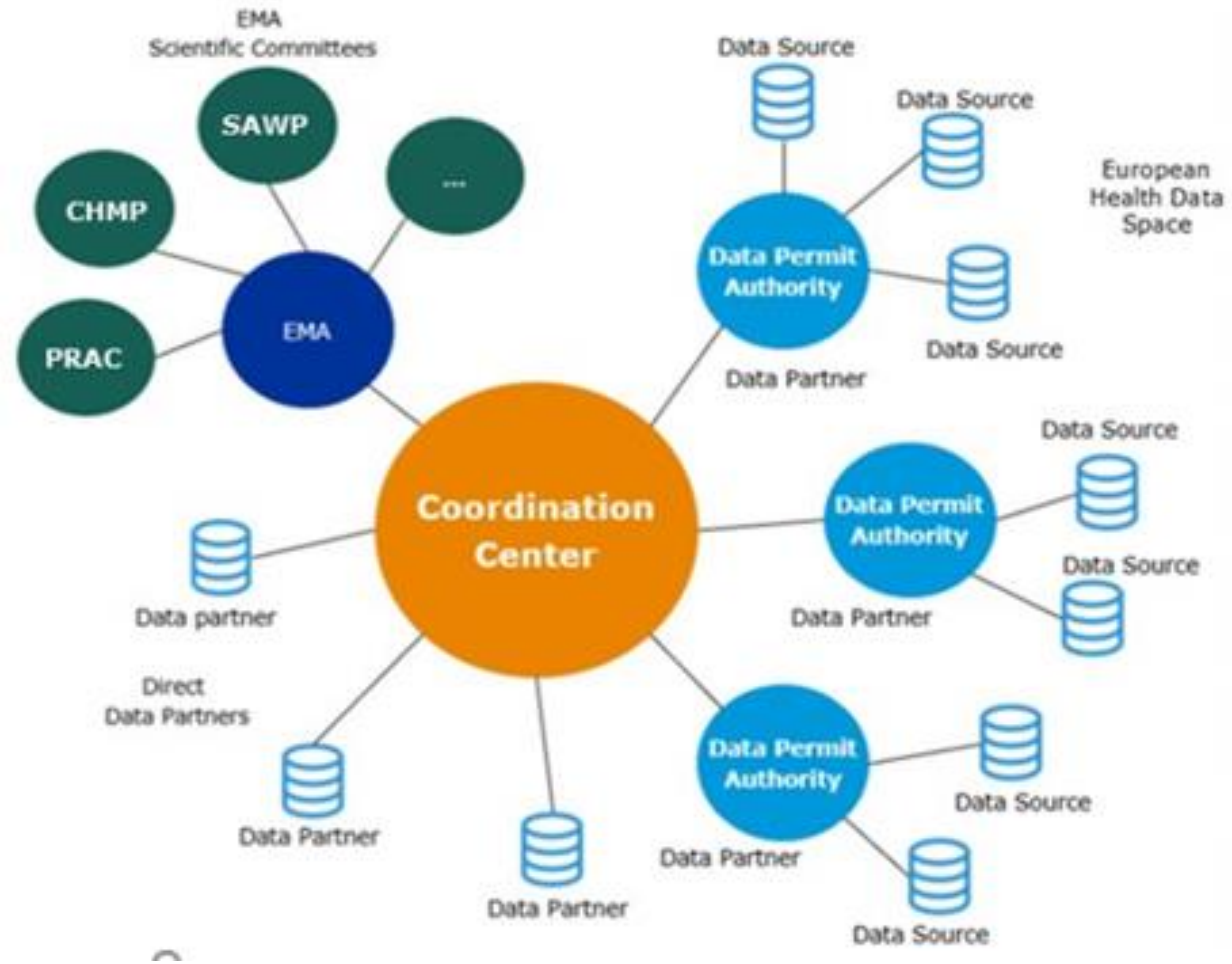
RWD – RWE Sources



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

RWE – EMA vision to 2025

PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett[1,*], Jesper Kjær[2], Karl Broich[3] and Emer Cooke[1]

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.

Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of the development, authorization, and supervision of medicines in the European Union. Their place in safety monitoring and disease epidemiology are well-established while their evidentiary value for additional use cases, notably for demonstrating efficacy, requires further evaluation.[1] During the coronavirus disease 2019 (COVID-19) pandemic, RWE rapidly provided impactful evidence on drug safety, vaccine safety, and effectiveness and we were reminded of the importance of robust study methods and transparency.[2] Our vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering 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.[4] In 2019 in the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological.[5] 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.[6] **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.[7]

Acknowledging different frameworks to conceptualize 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 EMRN 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, payers, 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 agreement of metadata for RWD and through a public catalogue of RWD sources[8] that builds on the early work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[9] extensively 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.[10]

The European Medicines Agency (EMA) and some national medicines agencies

Nov. 1, 2021 - doi:10.1002/cpt.2479

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Rea… eviden… regula… tion, a… Europ… monit… well-es… value … demor… evalua… ease 2… rapidly… drug s… and w… of robu… Our v… Medic… strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering this vision will support the development and use of better medicines for patients.

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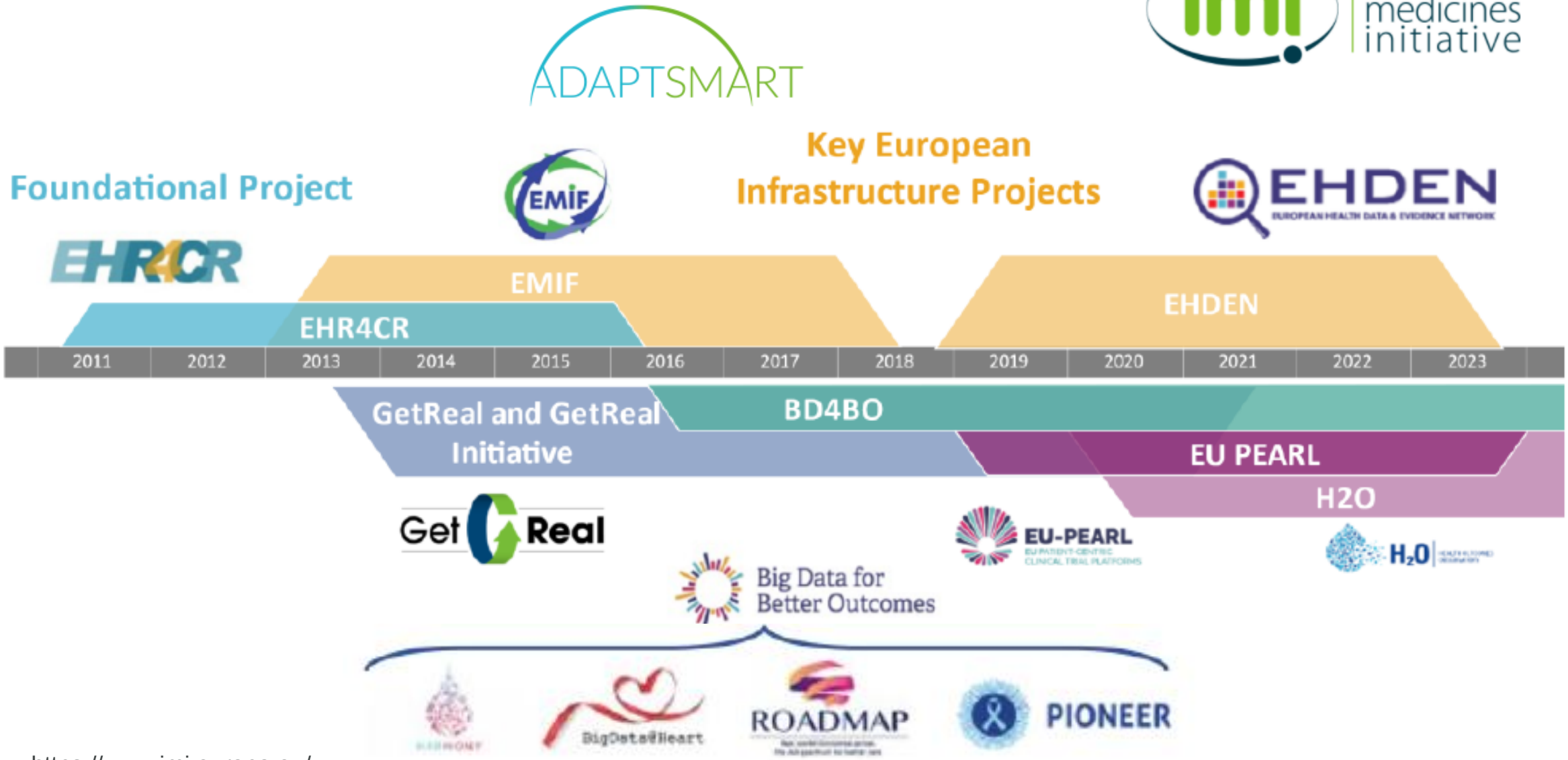
Ensuring the safe and effective use of medicines is not just an EU regulatory responsibility…

… 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

IMI & RWD/RWE



https://www.imi.europa.eu/

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

EU-AIMS
Autism Research in Europe

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

TRIALS @HOME

Decentralised Trials

Pan-EU pilot RADIAL study

Mobilise-D

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

WEB-RADR

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

IDEA FAST

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

innovative medicines initiative

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

efpia
European Federation of Pharmaceutical Industries and Associations

Special Populations

IMI – Advancing Paediatric Research

conect 4children
COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

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

conception SAFETY EVIDENCE ECOSYSTEM

ITCC P4 PAEDIATRIC PRECLINICAL PROOF OF CONCEPT PLATFORM

EU-AIMS Autism Research in Europe

RESCEU REspiratory Syncytial virus Consortium in EUrope

HARMONY

EU-PEARL EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

AIMS•2•TRIALS

INNODIA A PRIVATE PUBLIC PARTNERSHIP AGAINST TYPE 1 DIABETES

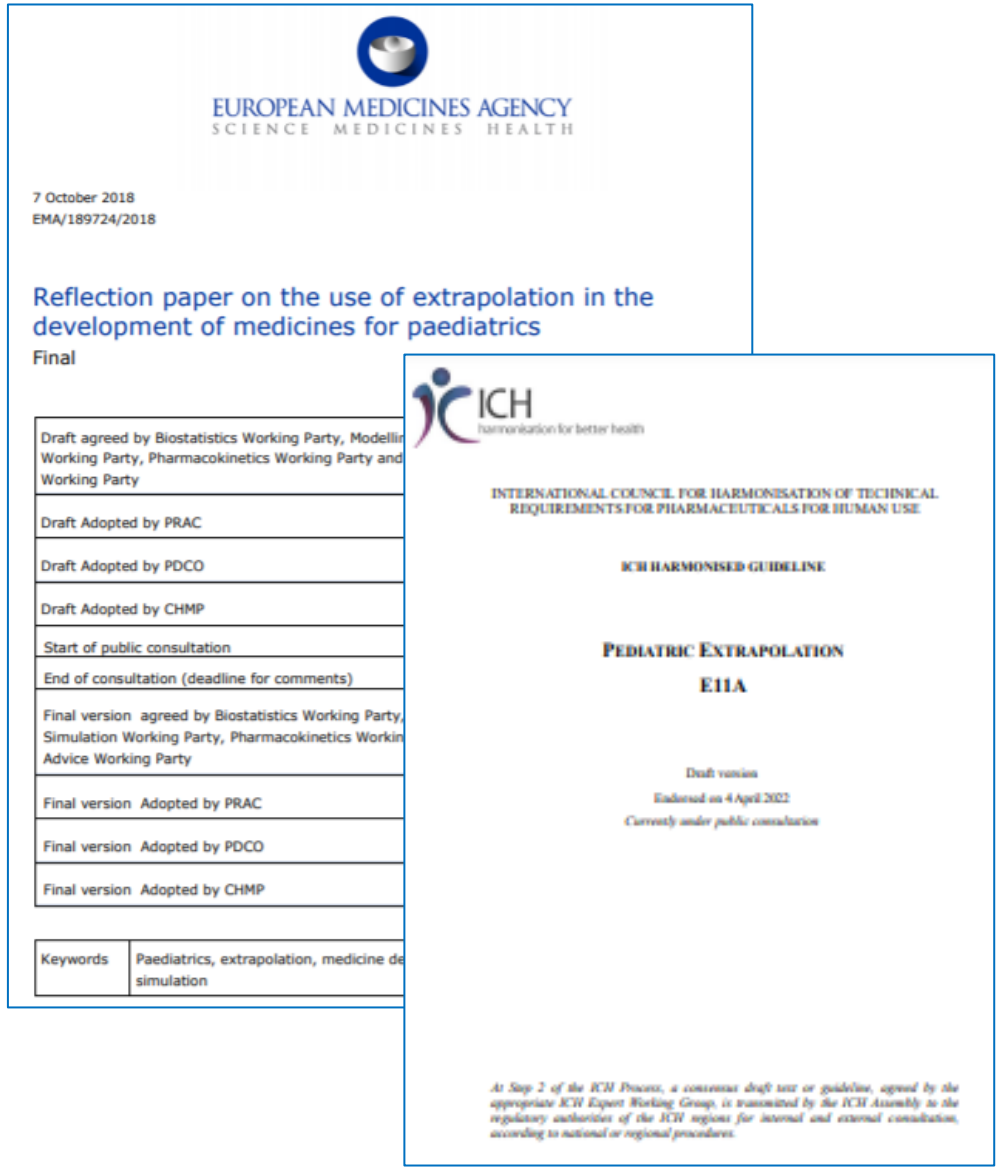
SCREEN 4CARE

Pre-Clinical → **Clinical**

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

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)**



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

7 October 2018
EMA/189724/2018

Reflection paper on the use of extrapolation in the development of medicines for paediatrics
Final

Draft agreed by Biostatistics Working Party, Modellin Working Party, Pharmacokinetics Working Party and Working Party
Draft Adopted by PRAC
Draft Adopted by PDCO
Draft Adopted by CHMP
Start of public consultation
End of consultation (deadline for comments)
Final version agreed by Biostatistics Working Party, Simulation Working Party, Pharmacokinetics Workin Advice Working Party
Final version Adopted by PRAC
Final version Adopted by PDCO
Final version Adopted by CHMP

Keywords	Paediatrics, extrapolation, medicine de simulation

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

PEDIATRIC EXTRAPOLATION

E11A

Draft version

Endorsed on 4 April 2022

Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

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

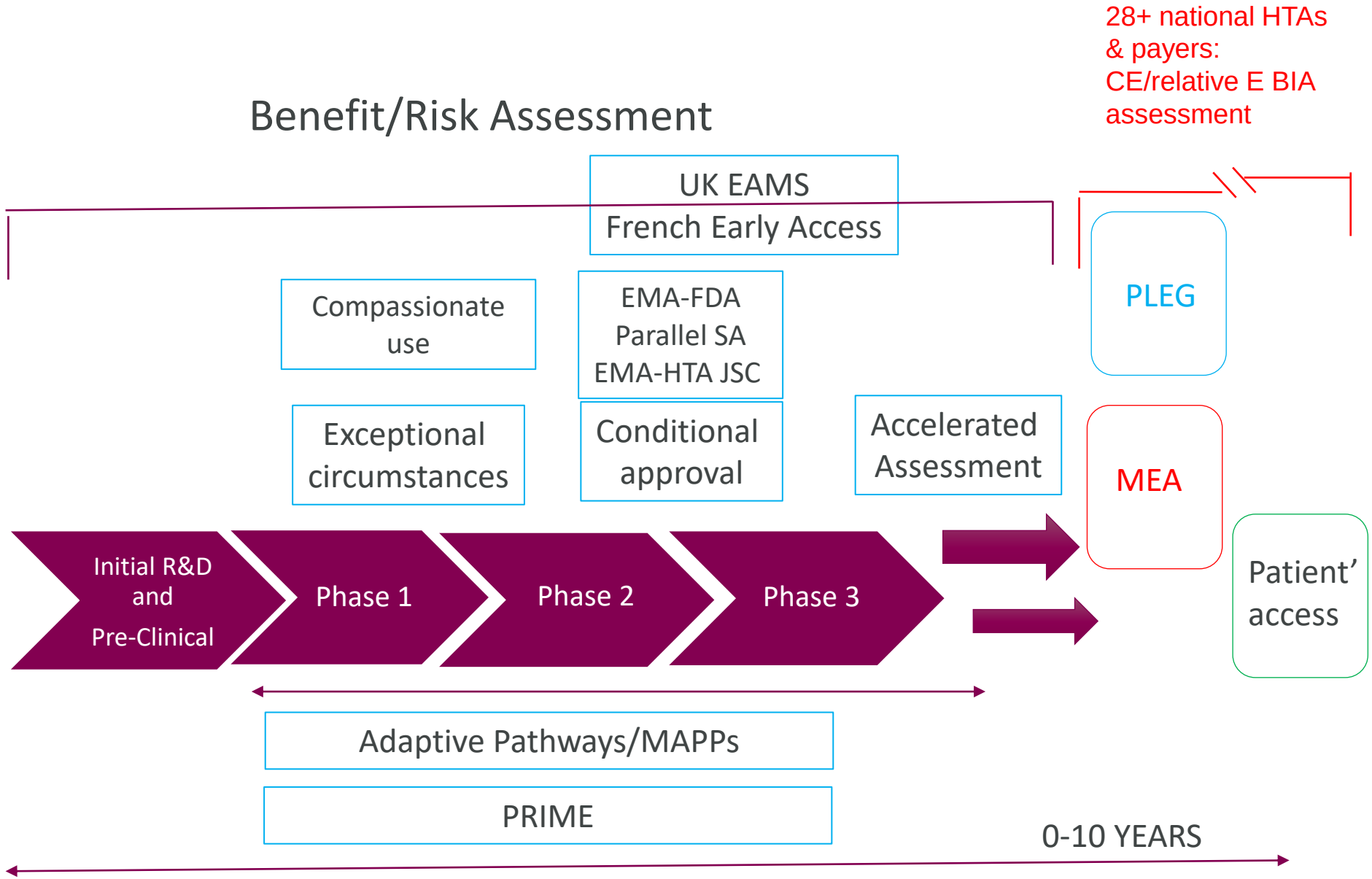
18 & 19 Oct. 2022

Processes & Operations

Tools and processes

Revision of the EU Pharma Legislation

HTA Regulation



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

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