AstraZeneca

Towards successful paediatric medicines development and access

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Agenda

- Regulatory & Access framework
- Complex Clinical Trials
- Paediatric Extrapolation
- Paediatric Oncology Development
- Inclusion of Adolescents in Adult Trials
- Other Tools and Methods to optimise paediatric drug development
- Conclusions

Challenges with Paediatric Drug Development

- **Conceptually**
  - Unmet medical needs
  - Target population
  - Timing
- **Content**
  - Standard of Care
  - Study design – endpoints; placebo; use/acceptance of complex innovative designs, decentralised trials, RWD…
- **Operational**
  - Different regulations
  - Research network infrastructures and capabilities
  - Trial enrolment/retention

EMA Regulatory Science Strategy to 2025

- Foster innovation in CTs
- Exploit DHT and AI in decision making
- Develop the regulatory framework for emerging data generation

- Reinforce patient relevance in evidence generation
- Promote the use of high-quality RWD in decision making

Accelerating CT in the EU

An initiative to transform the EU clinical research environment in support of medical innovation and better patient outcomes.

- Builds on the momentum of the Clinical Trials Regulation and CTIS
- Driven by the Network Strategy to 2025 and the EU Pharmaceutical Strategy
- Launched 13 January 2022

More details: https://www.ema.europa.eu/en/documents/presentation/presentation-accelerating-clinical-trials-eu-act-eu-iden-rooijen-fpetavy-fsweeney-ema_en.pdf

Regulatory and Access Pathways

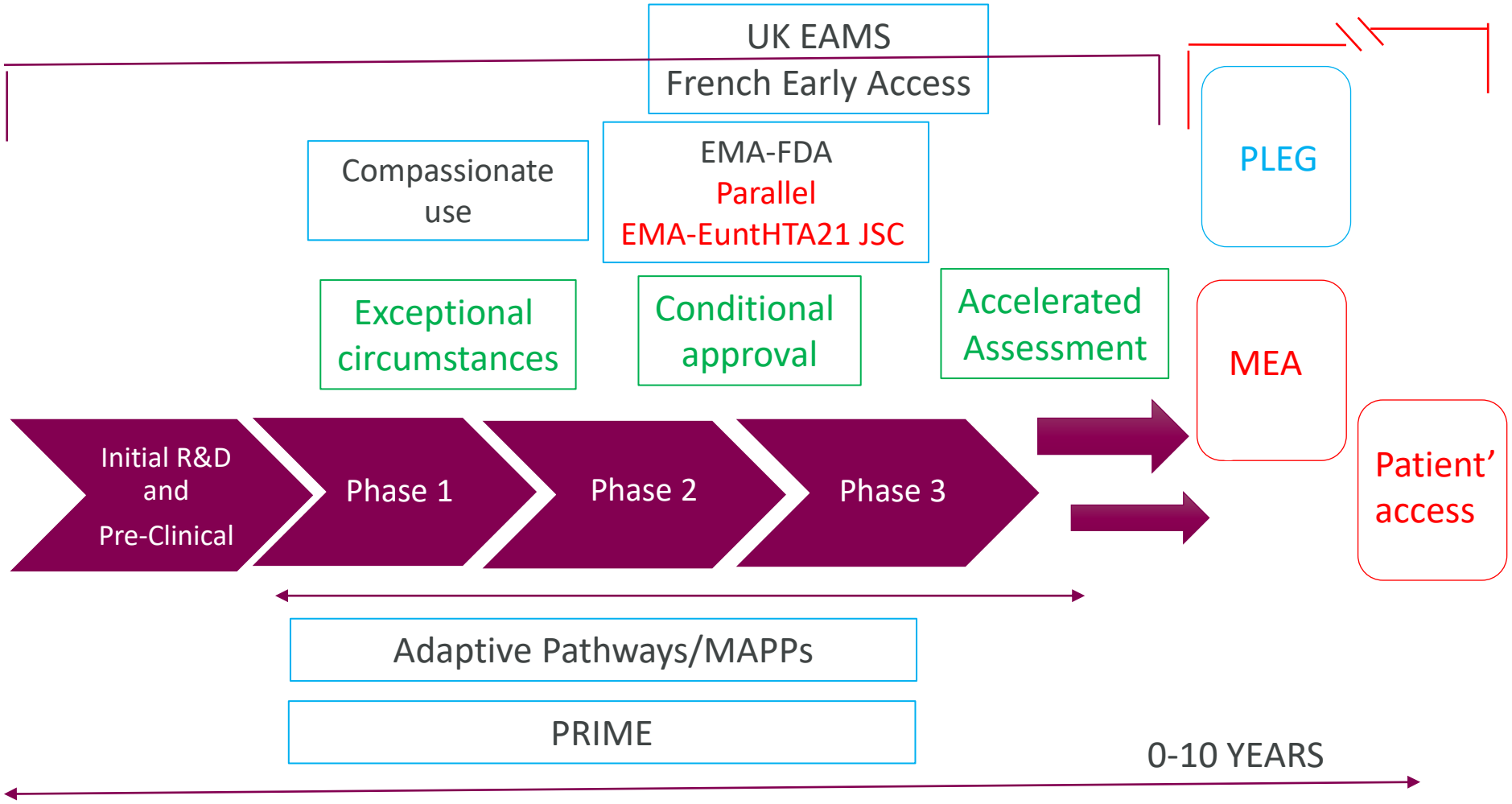
Revision of the EU Pharma Legislation

HTA Regulation

Cost/Effectiveness appraisal

27+ national HTABs & payers

Benefit/Risk Assessment



New era of complex innovative clinical trial designs

Innovative clinical trial designs, e.g., platform or adaptive trials, 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 initiatives of interest

MSH Workshop

European Commission

EU-funded projects

EUROPEAN MEDICINES AGENCY

HMA Heads of Medicines Agencies

- 2019 Recommendation Paper on the Initiation & Conduct of Complex CTs
- 2022 EMA-HMA Q&A document

ICH harmonisation for better health

ICH E11A; ICH E20; ICH M15; ICH E21

CLINICAL TRIALS TRANSFORMATION INITIATIVE

imi innovative medicines initiative

Public-Private Partnerships

IMI – Advancing Paediatric Research

New models
Novel biomarkers
Predictive models for efficacy
Novel assays

New taxonomy
Better disease understanding

Innovative trial designs, e.g. Master Protocol

Use of RWD, Big Data, AI, M&S…

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COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

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

AIMS2TRIALS

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

B/R methodologies
New outcome measures
RWD/RWE – Patient engagement

New endpoints
Clinical networks

ICH E11A Paediatric Extrapolation Guideline

- Expert Working Group assembled in 2017 to provide a systematic framework for the utilization of paediatric extrapolation
  - Not intended to be standard, harmonized regulatory "recipe book"
- Use of well-conceived and well-designed models and statistical methodologies can greatly aid in addressing gaps in knowledge in paediatric extrapolation approaches
  - Early discussion with regulatory authorities encouraged
- Step 3 guideline is under public consultation
- Case example: Polyarticular Juvenile Idiopathic Arthritis

ICH
harmonisation for better health

The 2021 FDA ADEPT 7 Workshop

FDA U.S. FOOD & DRUG ADMINISTRATION

Advancing the Development of Pediatric Therapeutics Complex Innovative Trial Design

https://www.fda.gov/drugs/news-events-human-drugs/fda-m-cersi-advancing-development-pediatric-therapeutics-complex-innovative-trial-design-public

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-022-00445-6

DIA

ORIGINAL RESEARCH

Check for updates

Innovations in Pediatric Therapeutics Development: Principles for the Use of Bridging Biomarkers in Pediatric Extrapolation

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RACE FOR CHILDREN ACT

U.S. FOOD & DRUG ADMINISTRATION

- **Effective since Aug. 18, 2020**
- **Requires** evaluation of new molecularly targeted drugs and biologics "*intended for the treatment of adult cancers and directed at a **molecular target** substantially relevant to the growth or progression of a pediatric cancer*"
- Eliminates the **orphan exemption for pediatric studies** for cancer drugs directed at relevant molecular targets.

Global Impact

- Cancer drug development is a global enterprise
- Clinical studies in small patient populations require international collaboration
- Regulatory requirement in U.S. and EU, although similar in intent, differ: PIPs and iPSPS differ in content and timing of submission
- Regulatory alignment is critical to accelerate cancer drug development for children
  - ➔**Call for simultaneous submission of PIPs and iPSPs**: Reaman G, Karres D et al. 2020
  - ➔**EMA/FDA Common Commentary Template**: Karres D, Reaman G et al. 2021

Inclusion of adolescents (12-17) adult oncology trials

- **2019 FDA Guidance**
  - Appropriate criteria for the inclusion of adolescent patients in adult oncology clinical trials at various stages of drug development
  - Dosing and pharmacokinetic and pharmacodynamic evaluations
  - Safety monitoring
  - Ethical considerations

- **ACCELERATE FAIR (Fostering Age Inclusive Research) Initiative**
  - **FAIR for AYA STAMP** offered for **trials** which actively avoid unnecessary barriers based on age
  - Tool Kit: eCRF Standard Analyses, PROS, Assent templates for adolescents, Protocol Elements, Examples of HA/EC considerations on AYA, List of AYA-clinical sites

- **ACCELERATE – Paediatric Strategy Forums**
  - multi-stakeholder meetings in which strategies regarding new drug development are discussed ➔ DNA Damage Repair Pathway Inhibitors (Oct. 2022)

Problem Statement & Study Aim

- **The average time between approval and labelling of a new medicine for adults and children is nearly a decade**
- Adolescent trials are typically not initiated until after the benefit-risk of a new medicine has been established in adults
- Where appropriate, Inclusion of adolescents in disease- and/or target-appropriate adult trials may facilitate earlier adolescent access to effective therapies

- **Study Aim:** to understand how adolescent inclusion in adult trials is positioned in regulatory guidance (RG) as they set critical expectations for trial design and regulatory decision-making for innovative medicines

Study results

- Using **a qualitative analysis approach, FDA and EMA guidance documents were assessed for their recommendations about adolescent inclusion in clinical trials**.

- **32% of FDA** and **15% of EMA guidance documents include recommendations** supporting adolescent inclusion in adult CTs
  - 14% and 21% respectively, were found to be **exclusionary**
  - In both regions, **more than half of all guidance documents were silent**
- **FDA guidance for infectious diseases** and **EMA guidelines for conditions requiring blood products** are **the most permissive**.
- A more inclusive approach was identified to disease guidance published by the FDA Oncology Center of Excellence.

➔ **CALL FOR ACTION - important opportunities for enhancement of guidance** which, if addressed, could facilitate inclusion of adolescents in adult trials, and accelerate adolescent access to life-changing medicines.

➔ ***Correcting Disparities in Adolescent Access to Medicines By Promoting Age Inclusive Research*: A Review of Regulatory Guidance** - to be published soon in Clinical Trials Journal

Digital Technologies to enable Clinical Trials

Designed to overcome clinical & regulatory roadblocks

Patient Generated Outcome Data	Continuous Data	Digitalised Monitoring Process
Remote Disease Monitoring	Real Time Data	Real Time Flags
Passive Data Capture	Paperless Data Capture	Medication Prompts

- ✓ Improved understanding of diseases
- ✓ Increased chance of regulatory approval
- ✓ Better, cheaper & faster drug development
- ✓ Higher patient empowerment & quality of life
- ✓ More participants & engagement
- ✓ Lives Saved & Improved

Some Digital Health Initiatives

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

Decentralised Trials

Pan-EU pilot RADIAL study

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

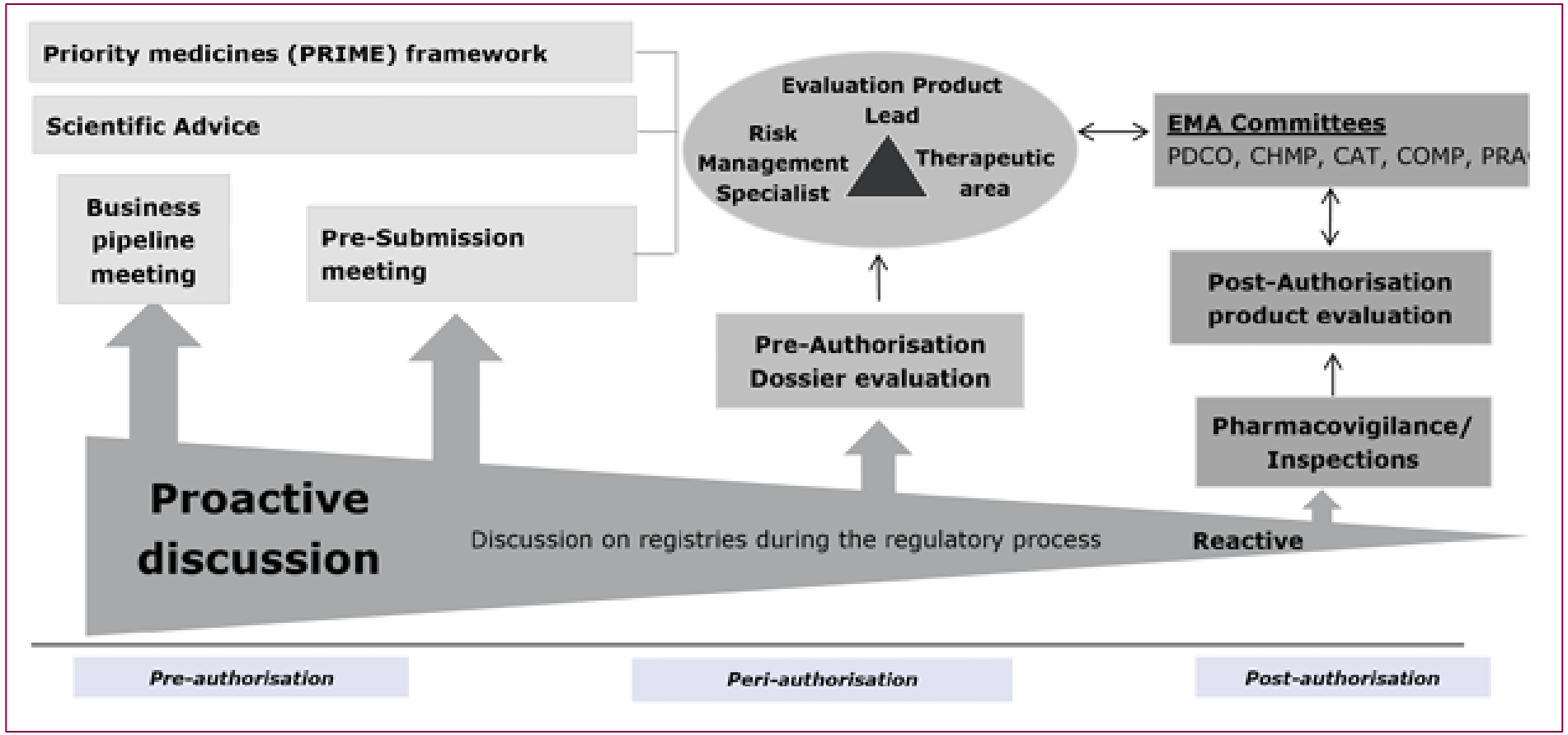
EMA QUALIFICATION PROCESS

EMA Q&A Document: Qualification of digital technology-based methodologies to support approval of medicinal products

Paediatric DCTs are well-poised for field implementation

- There are **multiple advantages** to implement paediatric DCTs, including keeping children and families in the places where they live (i.e., less stress and disruptions)
- Paediatric DCTs require **careful planning** to cover key medical aspects such as dealing with heterogeneous populations (e.g., multiple developmental ages that may introduce variability)
- A **multidisciplinary team** is needed in paediatric DCTs to cover all operational aspects of these trials and to mitigate sources of variability
- Paediatric DCTs and traditional paediatric trials have the **same regulatory expectations**
- E-consent/assent for pediatric DCTs is doable when **working closely with parents**/ guardians/Legally Authorised Representatives
- Using central Institutional Review Boards offer consistency and mitigation of variability in decisions made for paediatric Decentralised CTs

Patient registries are potentially valuable sources of data for supporting regulatory decision-making on medicines, but they are greatly underused owing to heterogeneity in registry design, the data collected and its quality, as well as to data sharing impediments (McGettigan et al. 2019)



2021 EMA guideline on Registry-based studies

To tackle the challenges of rare and paediatric diseases

EURORDIS and EFPIA call for a Moonshot for basic and translational research for adult and paediatric rare disease

EFPIA has suggested a Moonshot to develop science for rare diseases, thus supporting innovation in underserved areas. Typically, a Moonshot refers to an open-science model aimed at making knowledge generated from scientific research transparent and accessible through shared collaborative networks. A recent example is the cancer Moonshot launched in 2016 with an ambition to reduce cancer deaths in the United States by 50%, by accelerating scientific discovery, fostering greater collaboration and improving data sharing[46].

In many rare and paediatric diseases, limited understanding of disease pathophysiology and of potential drug targets precludes any investment. The Moonshot for rare diseases aims to establish a mindset of concerted effort towards developing the basic science and accelerating the translational research that are prerequisites for clinical development[47].

This shared goal would encourage all stakeholders to work together on defined areas of priority based on better coordination of basic research, investment, and infrastructures. The model would be built on public-private partnerships, leveraging existing European initiatives such as the IMI and its successor, the Innovative Health Initiative (IHI), as well as enabling collaboration opportunities for industry in any Commission programme dealing with rare diseases (e.g., ERNs for rare disease and potential European Rare Disease Partnership in Horizon Europe).

This proposal has the potential of contributing to faster, better, and more efficient and coordinated development of innovative products. EURORDIS is fully supportive of this initiative; EURORDIS and EFPIA will actively partner to design and implement the Moonshot.

Some PPPs* to Advance Paediatric Research

Integrated DEsign and AnaLysis of small population group trials

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COLLABORATIVE NETWORK FOR EUROPEAN CLINICAL TRIALS FOR CHILDREN

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

InSPiRe
Innovative methodology for small populations research

SCREEN 4CARE

asterix

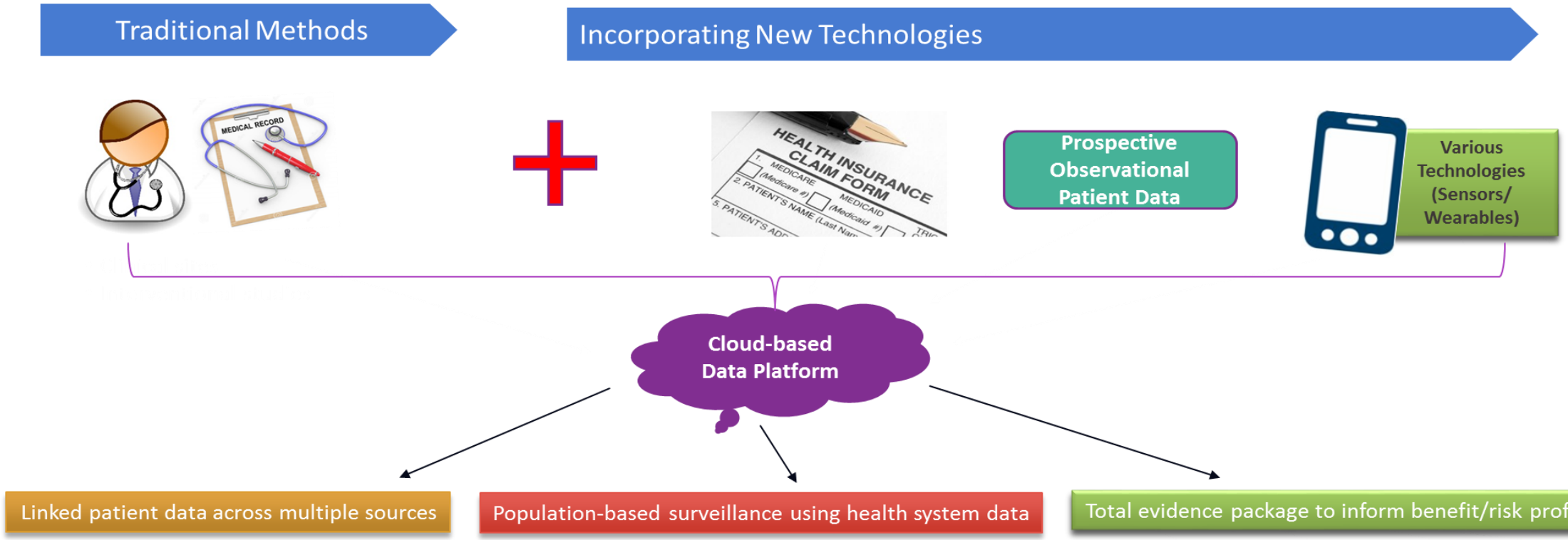
EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

Pre-Clinical → **Clinical**

RDCA-DAP®
Rare Disease Cures Accelerator
Data and Analytics Platform

*Public Private Partnerships

To conclude: 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

To conclude

- All stakeholders involved in R&D are taking steps to promote alternative clinical study designs, and methods that go beyond randomised clinical trials
- 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 ‘fit for purpose’ Patient Reported Outcomes, 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., M&S, registries) and regulatory processes (e.g., conditional approval, scientific advice, qualification) to optimise drug development pathways 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

Upcoming virtual events

https://efgcp.eu/event.php?eid=44

New Horizons in Pediatric Drug Development

CERTARA – Oct. 27, 28 – 9am to 1pm ET
https://www.newhorizonpdd.org/2022-symposium/

EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

Multistakeholder Workshop
Nov. 10, 2022

https://medicinedevelopment.eu/

Thanks for your attention!