The challenges of evidence synthesis ahead: the Industry perspective

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Disclaimer

The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of GSK.

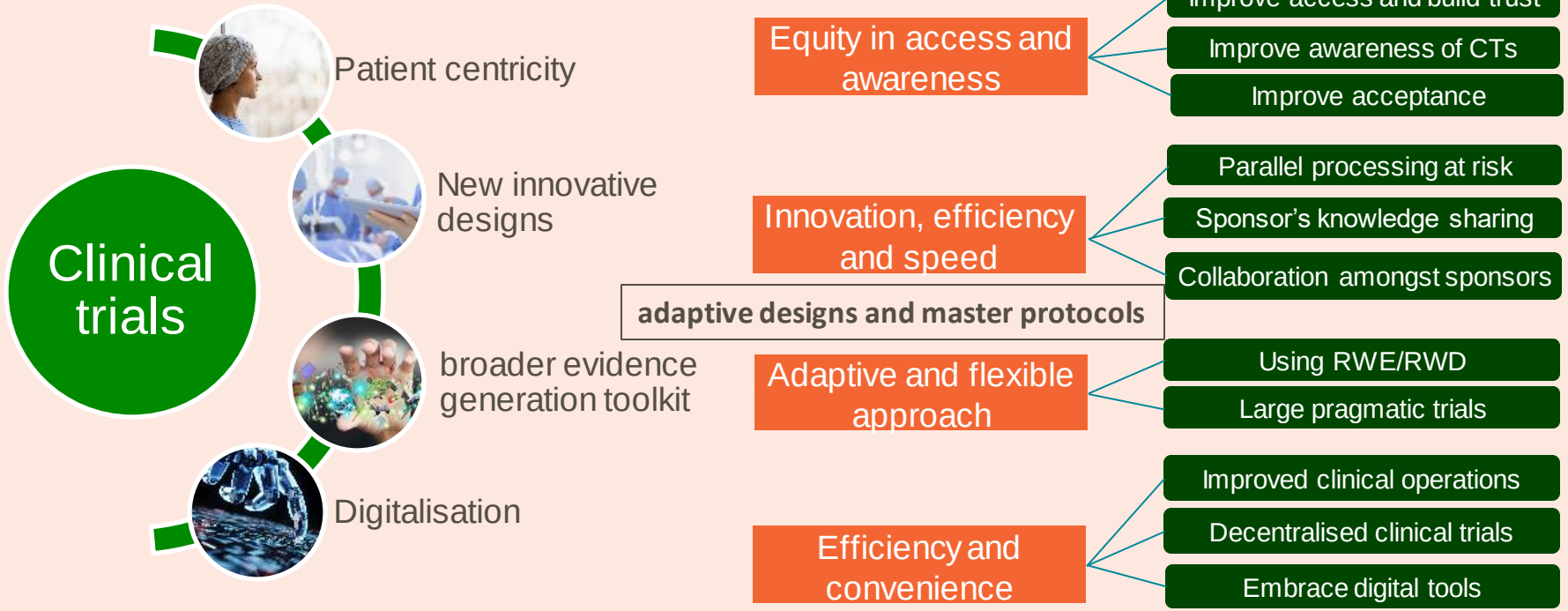
Agenda

- Innovation in Clinical Trials
- Regulatory considerations
- Reimbursement/Health Technology Assessment (HTA) considerations
- IMI GetReal evidence synthesis tools
- Access to data and clinical trial transparency
- Concluding remarks

Innovation in Clinical Trials

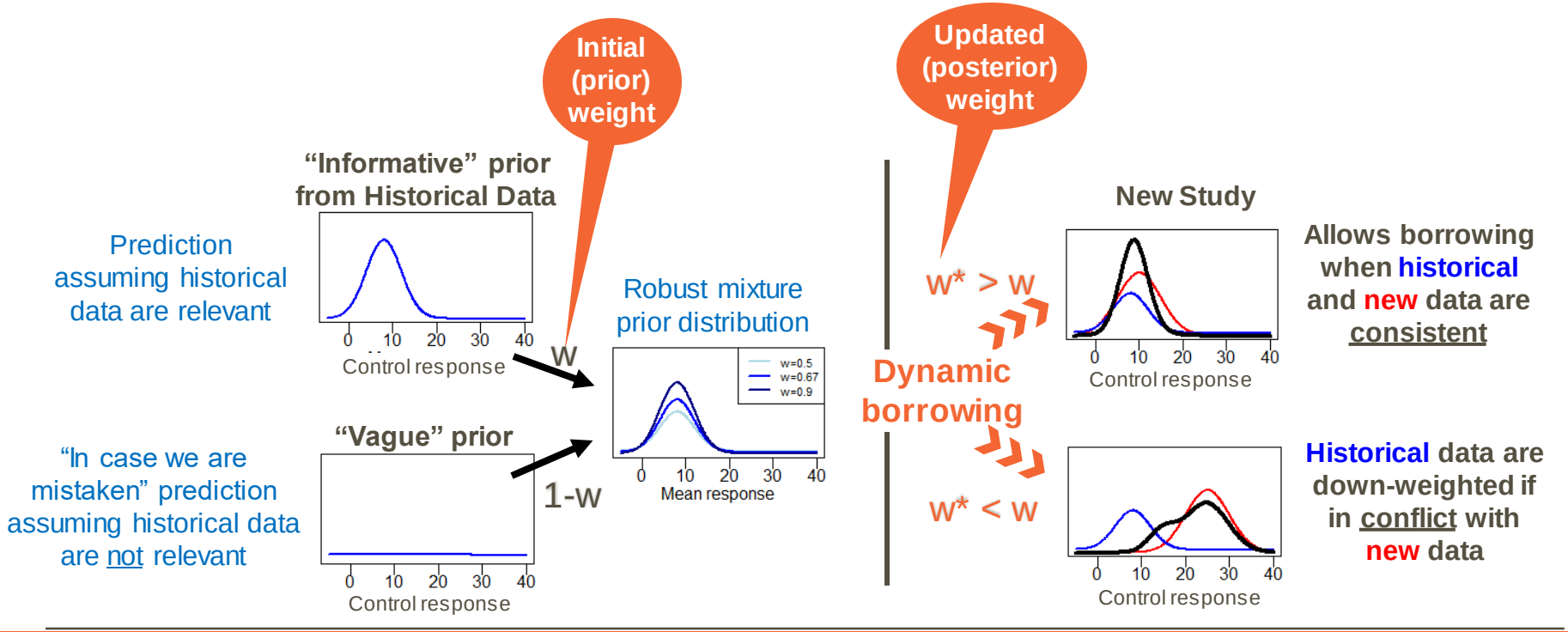
Innovation in clinical trials

Increase collaboration, flexibility, mutual recognition and reliance among regulators and other stakeholders



The increase use of more complex clinical trials will impact evidence synthesis strategies

Incorporating historical control data
Bayesian Dynamic Borrowing



Various types of evidence synthesis are being used in clinical trials

Regulatory considerations

Regulators are embracing innovation in clinical trials

Harmonisation in requirements for innovation in clinical trials

- **Adaptive Clinical Trials – ICH E20** – principles for the regulatory review of these studies in a global drug development program, i.e. design, conduct, analysis, and interpretation (expected 2023)
- **Good Clinical Practice Renovation - ICH E6(R3)** – increasing diversity of clinical trial designs and data sources (adopted by ICH April 2021)
- **Paediatric Extrapolation – ICH E11A** – study designs and statistical analysis methods used when incorporating paediatric extrapolation into a paediatric drug development plan (expected 2022)
- **MIDD – Model Informed Drug Development / Modelling & Simulation (M&S):** ICH MIDD Discussion Group recently established to develop an ICH MIDD guideline.

Accelerating Clinical Trials in the EU (ACT EU)

ACT EU is 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
- Read the press release and paper

ACT EU Priority actions and domains 2022-2023

Governance & Integration

1. Develop a **governance rationalisation strategy** (aligning different expert groups and working parties)

7. Reinforce the **coordination** between **scientific advice on CT approval and CT design** and link to the methodologies working party domain.

9. Successfully establish **CT safety monitoring** and bridge to the EU4Health Joint Action and start its integration into a pre- and post-marketing safety monitoring framework.

Engagement

3. Establish a **multi-stakeholder platform**, including patients, after stakeholder analysis.

6. Plan and launch a targeted **communication campaign** to engage all enablers.

10. Deliver a clinical trials **training curriculum** on drug development and regulatory science with links to SMEs & academia.

Methods & Practice

4. Implementing the **GCP modernisation** informed by the development of guidance at ICH.

8. Develop and publish key **methodologies guidance** e.g. on AI/ML impacted CTs, complex trials, decentralised CTs and IVDR/CTR interface (to strengthen links between innovation and scientific advice fora).

Impact

2. The successful and timely **implementation of the CTR** and its implementing acts.

- **KPIs** to track performance of the European CT environment.
- **Promote larger, multinational trials** specifically in academia

5. **Analyse data about clinical trials** leveraging academic, non-profit, European, and international initiatives, improving the impact of policymaking and funding to support evidence-based decision making.

FDA MIDD and CID pilots

Opportunities to innovate and accelerate clinical development

Model-Informed Drug Development Pilot Program

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As displayed in the Federal Register notice on April 16, 2018, the FDA is conducting a Model-Informed Drug Development (MIDD) Pilot Program to facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, referred to as MIDD approaches. MIDD approaches use a variety of quantitative methods to help balance the risks and benefits of drug products in development. When successfully applied, MIDD approaches can improve clinical trial efficiency, increase the probability of regulatory success, and optimize drug dosing/therapeutic individualization in the absence of dedicated trials.

What's New

Did you know that under the Pilot Program we are asking the MIDD meeting requests and meeting packages to include elements of a credibility framework to facilitate alignment and streamline review?

For more information or questions see:

Content & Format of the Meeting Request
Content & Format of the Meeting Information Package
MIDD Pilot Program Frequently Asked Questions

Or send an email to MIDD@FDA.HHS.GOV

Complex Innovative Trial Design Meeting Program

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On this page

- Goals of the CID Pilot Meeting Program
- Procedures and Submission Information
- Frequently Asked Questions
- Contact Us
- CID Pilot Program Trial Design Case Studies
- Learn more about CID

As displayed in the *Federal Register* notice on August 29, 2018, FDA is conducting a Complex Innovative Trial Design (CID) Pilot Meeting Program to support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs. The CID Pilot Meeting Program fulfills a performance goal agreed to under PDUFA VI, included as part of the FDA Reauthorization Act of 2017.

This pilot meeting program offers sponsors whose meeting requests are granted the opportunity for increased interaction with FDA staff to discuss their proposed CID approach.

Meetings will be conducted by FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) during fiscal years 2019 to 2022. To promote innovation in this area, trial designs developed through the pilot meeting program may be presented by FDA (e.g., in a guidance or public workshop) as case studies, including trial designs for medical products that have not yet been approved by FDA.

ICH E9(R1) Estimands and sensitivity analyses

Addendum to Statistical Principles in Clinical Trials (E9)

ICH
harmonisation for better health

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

ICH HARMONISED GUIDELINE

ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS
TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS

E9(R1)

Final version

Adopted on 20 November 2019

Precise description of

?

"WHAT do we want to find out in our clinical study?"

Why are estimands important in evidence synthesis?

- Estimands will clarify what treatment effects are being estimated
  - Many estimates of treatment effects in publications labelled ‘intent-to-treat’ but they represent something else
  - It wasn’t easy to understand how treatment effects were being adjusted for the use of rescue medication, switching treatments, discontinuing treatment
- New definition of ‘sensitivity analysis’ for addressing assumptions relating to missing data or possible limitations of data
- More careful evaluation will be needed in what treatment effects are being included in evidence synthesis e.g. network meta-analyses
- Implementation of new estimand framework is still ongoing

EFPIA/EFSPI Estimand Implementation Working Group (EIWG) Key areas of focus

1. Variety of sub-teams focussing on:
   - Incorporating estimands into clinical trial protocols (publication under review 'Trials')
   - Estimands in early phase studies, non-inferiority studies, non-interventional studies
   - Reporting and communicating estimands
   - Estimation methods
   - EIWG central resource for all materials
2. Developing publications, white papers and discussing other publications emerging
3. Estimand Academy – training via case studies
4. Reviewing guidelines e.g. ICH M11 and new protocol template, EUnetHTA methodology guidelines
5. Discussing with NIH how to incorporate estimands in CT.GOV
6. Discussing with authors of CONSORT/SPIRIT how estimands are incorporated

Therapeutic Innovation & Regulatory Science
https://doi.org/10.1007/s43441-022-00402-3

DIA

ORIGINAL RESEARCH

Check for updates

Marking 2-Years of New Thinking in Clinical Trials: The Estimand Journey

C. Fletcher[1] · N. Hefting[2] · M. Wright[3] · J. Bell[4] · J. Anzures-Cabrera[5] · D. Wright[6] · H. Lynggaard[7] · A. Schueler[8]

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Abstract

The ICH E9(R1) addendum on *Estimands and Sensitivity Analyses in Clinical Trials* has introduced a new estimand framework for the design, conduct, analysis, and interpretation of clinical trials. We share Pharmaceutical Industry experiences of implementing the estimand framework in the first two years since the final guidance became available with key lessons learned and highlight what else needs to be done to continue the journey in embedding the estimand framework in clinical trials. Emerging best practices and points to consider on strategies for implementing a new estimand thinking process are provided. Whilst much of the focus of implementing ICH E9(R1) to date has been on defining estimands, we highlight some of the important aspects relating to the choice of statistical analysis methods and sensitivity analyses to ensure estimands can be estimated robustly with minimal bias. In particular, we discuss the implications if complete follow-up is not possible when the treatment policy strategy is being used to handle intercurrent events. ICH E9(R1) was introduced just before the start of the COVID-19 pandemic, but a positive outcome from the pandemic has been an acceleration in the adoption of the

Reimbursement/HTA considerations

Concerns raised by HTA agencies on evidence being generated to support assessment of added clinical benefit

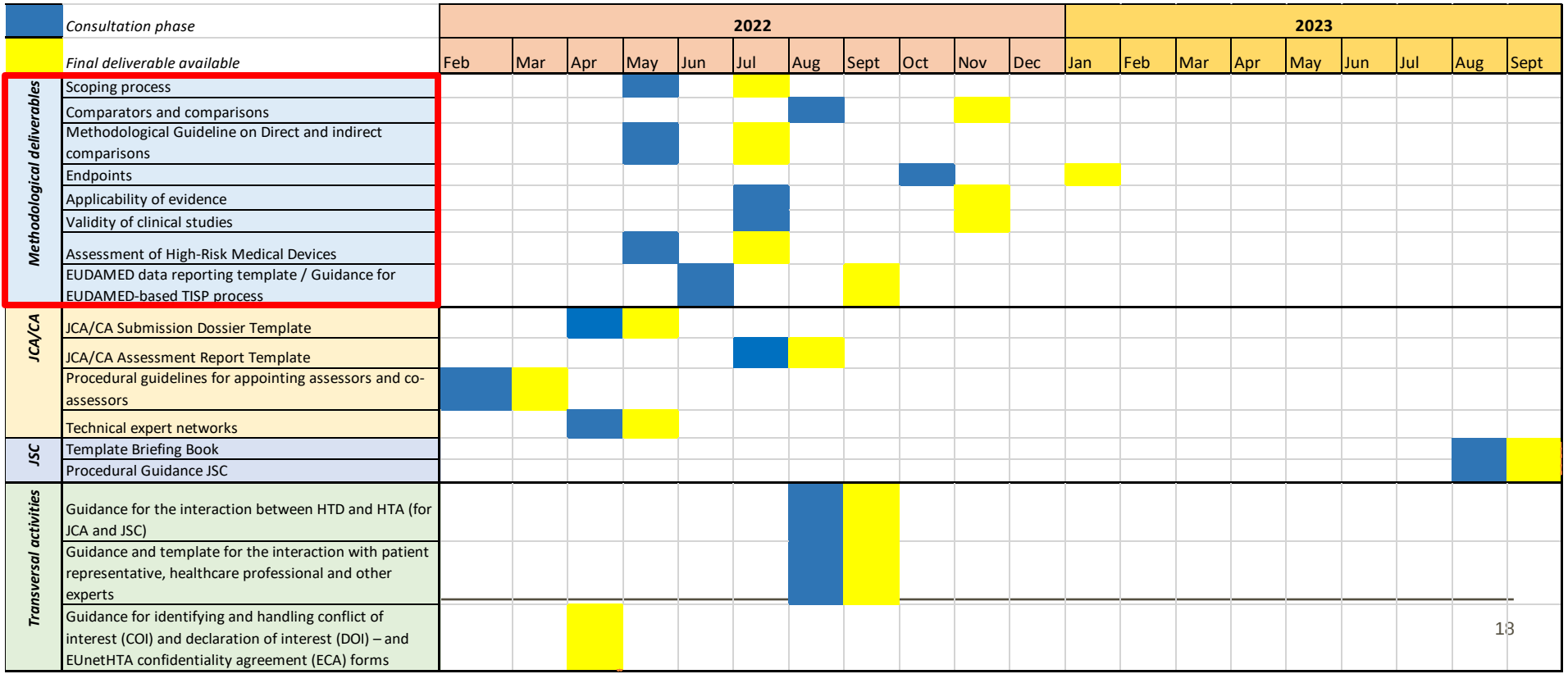
Increased alignment on trial design needed between regulatory and HTA agencies

Accelerating Adoption of Complex Clinical Trials in Europe and beyond (efpia.eu)

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

EUnetHTA 21 consortium: New EU HTA regulation

The new methodology guidelines will influence future evidence synthesis



EUDAMED=European Databank on Medical Devices; CA= collaborative assessments of medical devices (on clinical evidence); TISP= Topic identification, selection and prioritisation

However consolidated PICOs across Member State requests could lead to an explosion of evidence synthesis

D4.2 Scoping Process

	PICO 1	PICO 2	PICO 3	PICO 4	PICO 5
P	Full licensed indication	Full licensed indication	Full licensed indication	Subpopulation A	Subpopulation B
C	Comparator 1 OR Comparator 2[14]	Comparator 3	Comparator 4	Comparator 1	Comparator 3
O	All outcomes	All outcomes	All outcomes	All outcomes	All outcomes

Draft guideline on direct and indirect comparisons recognises advances in methodology but only evidence synthesis based on connected networks is supported

eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA 21

METHODOLOGICAL GUIDELINE

D4.3.2: DIRECT AND INDIRECT COMPARISONS

Version 0.3; May 2, 2022

Contents

IMI GETREAL

Evidence synthesis was a core topic of the IMI GetReal initiative focussing on integration of RCT and RWE and using aggregate and individual patient level data

Evolution of GetReal over the years

Achievements

- Brought together healthcare decision makers, academics, pharmaceutical companies, clinicians and other societal stakeholders
- assessed existing processes, methodologies and key research issues
- Proposed innovative trial designs and assessed the value of information
- Proposed and tested innovative analytical and predictive modelling approaches
- Assessed operational challenges, and proposed and tested the impact of solutions
- Created new tools to support decision-making, and to use in evaluating development programmes and assessing the value of new medicines
- Shared and discussed project outputs with healthcare decision makers, academics, pharmaceutical companies, clinicians and other societal stakeholders
- Developed training for researchers, healthcare decision makers and societal stakeholders in the public and private sector to increase knowledge about the use of RWE in demonstrating relative effectiveness of medicines.

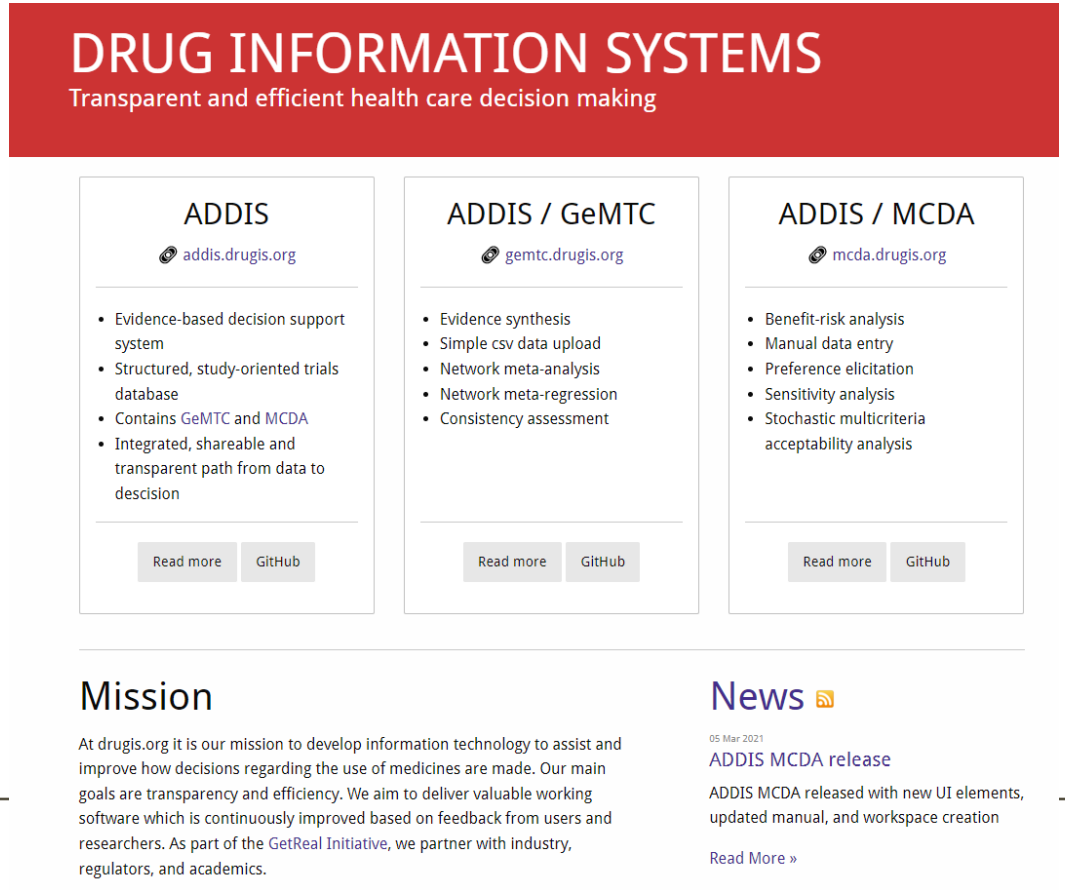
Recommendations

In 2017 GetReal produced recommendations in **Advancing Evidence Generation for New Drugs**.

Download report

Homepage - GetReal Institute (getreal-institute.org)

The ADDIS platform provides a range of tools and analyses for evidence synthesis



Access to data and clinical trial transparency

Clinical trial transparency

The ABPI is committed to greater clinical trial transparency: we believe that clinical trial results should be posted in publicly accessible registries and databases and published in the scientific literature in a timely manner.

To help companies achieve this, the ABPI launched its clinical trial disclosure toolkit in the summer of 2013.

Clinical trial transparency has improved over five years of monitoring. Latest results show that for newly licensed medicines approved in 2014 the disclosure rate has reached 93% at 12 months (up from 71% in 2009) and 96% overall.

The ABPI Code of Practice refers to the IFPMA joint positions on the disclosure and publication of clinical trial information and results in that trials must be registered within 21 days of enrolling the first patient, and results must be published within one year of marketing authorisation or one year from completion for marketed products. This is in line with the IFPMA Code of Practice to support a global position on trials transparency.

The industry is also committed to enhancing public health through responsible sharing of clinical trial data consistent with the EFPIA/PhRMA principles of data sharing.

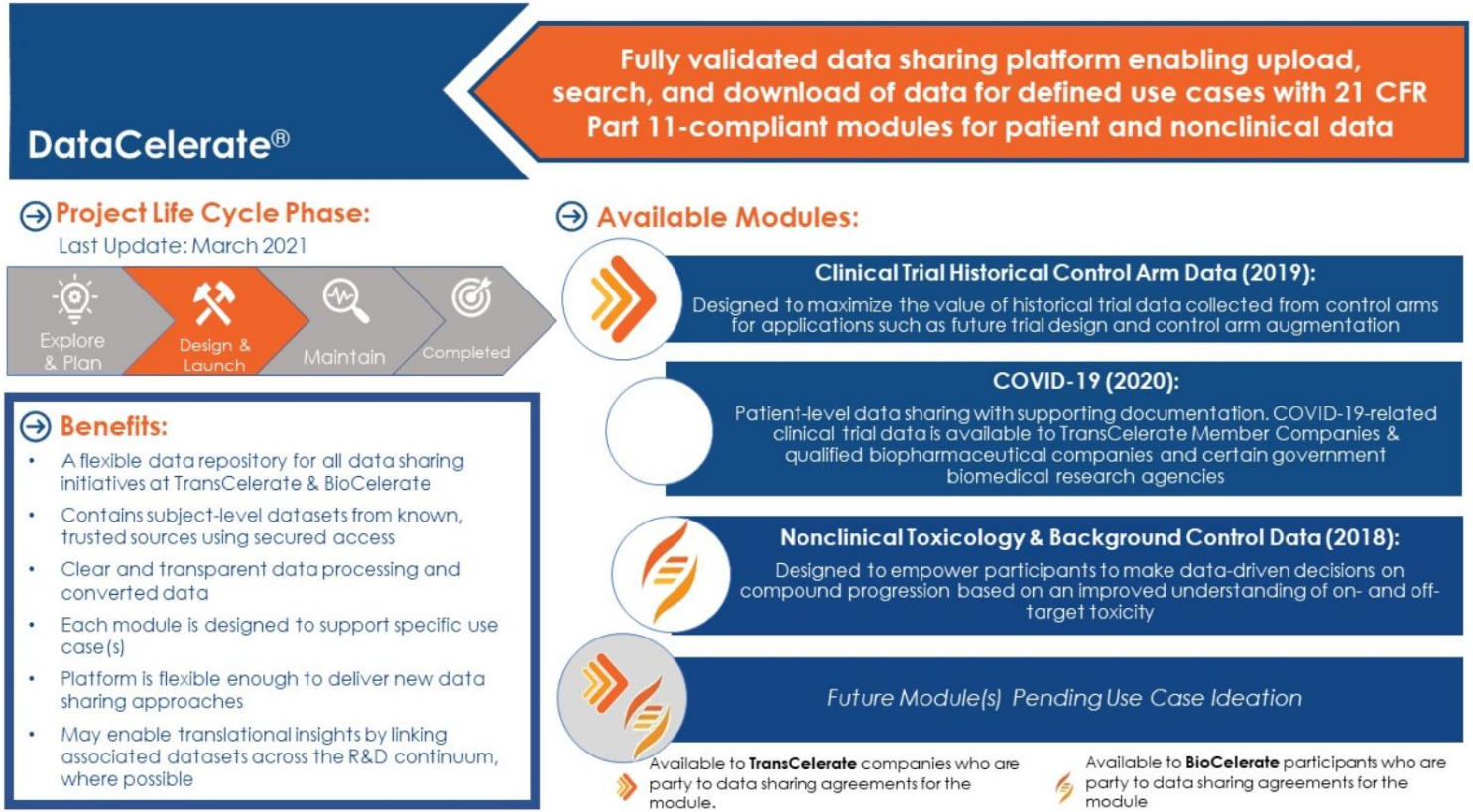
During 2017 pharmaceutical companies spent £370.9 million on research and development activities with healthcare professionals and healthcare organisations, the majority of this is for clinical trials.

Many companies have also collaborated to develop ClinicalStudyDataRequest.com and Vivli.org providing researchers with access to clinical trial data to further research that can help advance medical science or improve patient care.

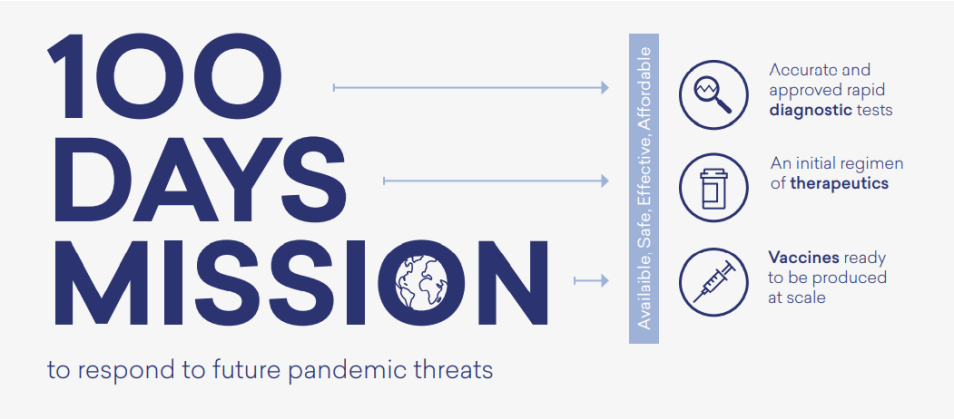
Access to data is a key enabler for evidence synthesis

TransCelerate

TransCelerate - Pharmaceutical Research and Development (transceleratebiopharmainc.com)



COVID-19 has taught us to be ready for future pandemic threats including ability to synthesize evidence quickly



Embedding Best Practice

International network of clinical trials with effective data-sharing

56 Capability for high quality, efficient and rapid clinical trials and regulation is crucial to enable effective preparation for pandemics as well as rapid responses during pandemics. There are a number of improvements we can make to clinical trials capability and regulation processes to embed best practice between pandemics. Enhancing clinical trials infrastructure and use will enhance healthcare by providing a stronger evidence base and sharing of best practice globally.

57 The success of clinical trials depends on how well they are designed and the extent to which busy healthcare staff, patients, and healthy volunteers are able and willing to participate. Trials need to be set up in a way that focuses on the aspects that are critical to the generation of actionable results and keeps additional work to a minimum.

58 During COVID-19 large, randomised controlled trials were transformational in identifying which interventions were effective and how best they should be used - the discovery that dexamethasone reduces mortality for patients in hospital is estimated to have saved one million lives worldwide.[55] Innovations in trial design and trial methodologies expedited robust evidence. Adaptive platform trials were particularly successful as they enabled many different treatments to be studied simultaneously, giving researchers and regulators the evidence needed to make decisions on which treatments were effective (and which were not). Incorporating data that was already being routinely collected via health systems also streamlined significantly what needed to be collected manually at a patient's bedside. These

100 Days Mission to respond to future pandemic threats (publishing.service.gov.uk)

Concluding remarks

Evidence synthesis plays a vital role in a new era of innovative drug development

- Strategies to synthesize evidence need to accommodate more complex trials
- Estimands will enable similar treatment effects to be compared
- Methods are continuing to advance to accommodate different types of evidence but their use needs to be justified and key assumptions and limitations discussed
- Regulatory and HTA agencies on not aligned on what evidence is acceptable for key decision making
- There is a continued focus to improve access to data to support evidence synthesis
- More tools continue to become available for implementing new methods
- Sharing best practices for evidence synthesis would help to increase quality and further promote the appropriate use of the range of methods available