# Challenges around Execution and Evaluation of Innovative Study Designs and their use in Regulatory Decision-Making: A Reflection from a Pharma Company

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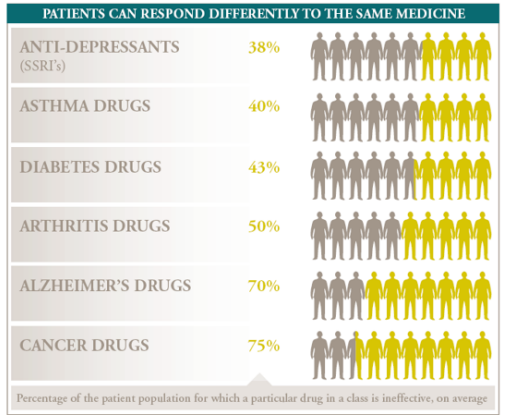
Global Product Development

TIME IS LIFE
Every Minute Matters

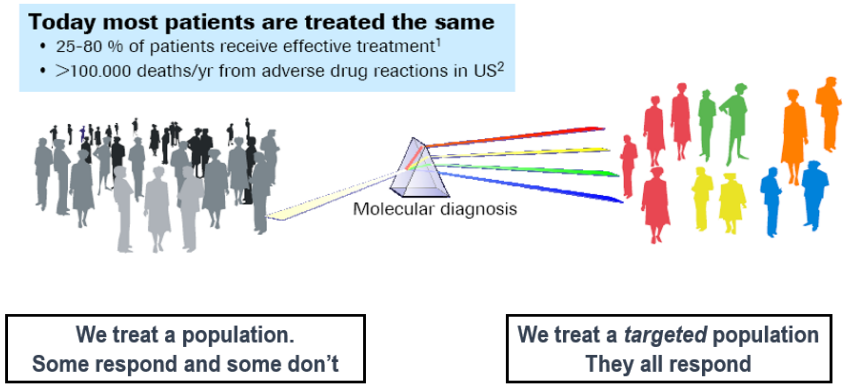
# The Case for Changing the Approach: Rise of Personalised Medicines

Traditional treatments have a high rate of non-response in the general population




"The Case for Personalized Medicine", http://www.gencat.cat/salut/ticsalut/flashticsalut/pdf/67_2_thecaseforpersonalizedmedicine_11_13.pdf

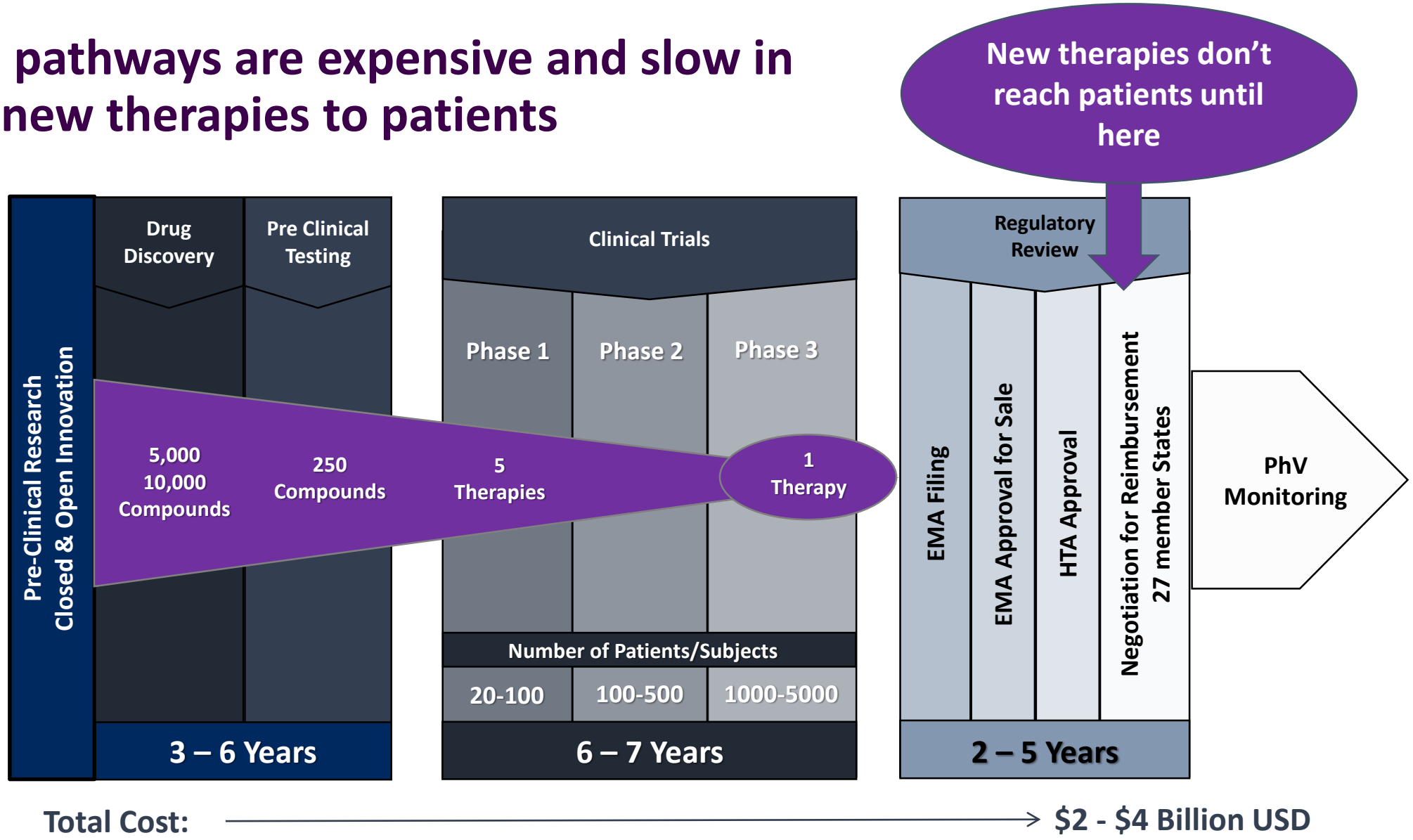
The way we treat patients is evolving from 'one size fits all' to targeted based on genetics.




Science is leading the revolution in targeted, personalised therapies:

- More precise diagnosis based on specific bio-markers of the patient
- Effective treatments designed to target the underlying cause of the disease
- Smaller, faster clinical trials
- Drugs given to those most likely to benefit
- Less waste + toxicity as only treat those who benefit

# Current pathways are expensive and slow in getting new therapies to patients




Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org;

CBO, *Research and Development in the Pharmaceutical Industry*, 2006;

Forbes, Matthew Herper, "The Truly Staggering Cost Of Inventing New Drugs", February 10, 2012

# Many Different Trial Designs to Choose From…

## Enhanced Use of RWE in Clinical Trials

**RWE for indirect comparisons**

## Model Informed Drug Development

**Modelling, simulation & extrapolation**

## Complex Innovative Trial Designs

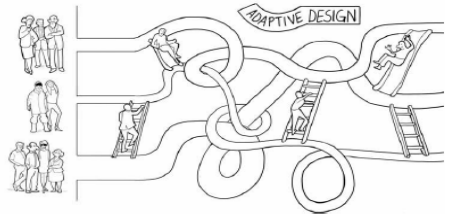
**Adaptive statistics**

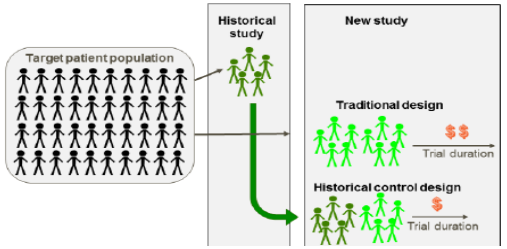
**Umbrella & Basket studies**

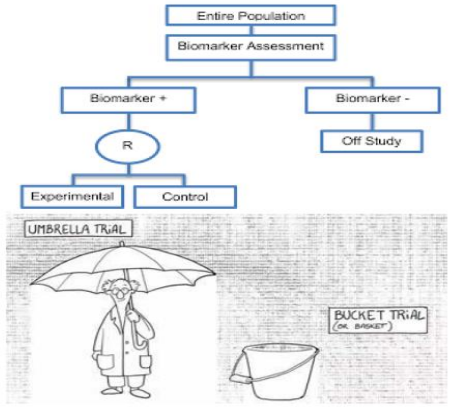
**Platform studies with Master protocols,**

**Historical controls**

## Biomarker validation



# Acceptability of New Evidence Sources

## Novel data gathering methods

- Electronic medical records, patient registries (RWE)
- Wearable devices, phone applications

## Novel data assessment methodologies

- AI & digital Tools

## Study Designs & Analyses

## Decision-making based on novel approaches

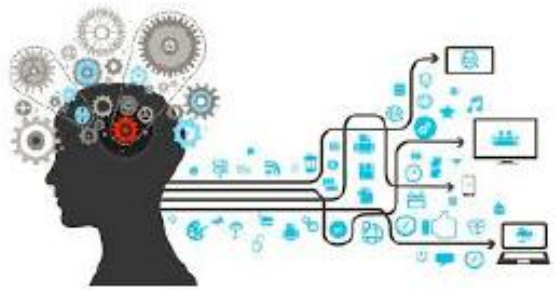
# The RWE Environment is Changing

**There is a growing regulatory application of RWE beyond Safety...**


PDUFA VI


**... with a particular interest in using RWE to bridge the evidentiary gap between regulators, HTAs, and payers...**


**... and this is enabled by the increase in the availability of real-world data and significant advancements in analytics tools and technologies.**



# …..but we are not there yet…

Regulatory, HTA and payer bodies have repeatedly stated that RWE is needed to reduce uncertainty about the benefits and risks of therapies in actual conditions for use

## Two Case Examples with Different Outcomes

- **RWE to support potential accelerated approval of an immunomodulator for a life- and organ-threatening autoimmune disease.**

  **Regulatory and reimbursement authorities showed a generally positive response to the use of RWE in granting conditional approval in area of high unmet medical need leading to a faster and lower cost development.**

- **MAH proposal to conduct a RWE study to meet a specific regulatory obligation for an oncology product rejected.**

  **Response was that *'RWE data would not provide a decisive comparison, since there could be a lot of bias and data analysis can be problematic'*. It was explicitly stated that they wanted data owned and generated by the company (i.e. conduct a confirmatory RCT).**

# Complex Innovative Design Trials

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

- Benefits well documented
- Accelerate 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 medicines earlier, reduce failure rate in Phase III and patient exposures to ineffective drugs

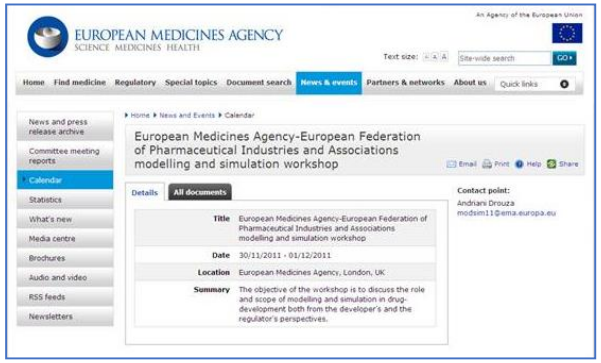




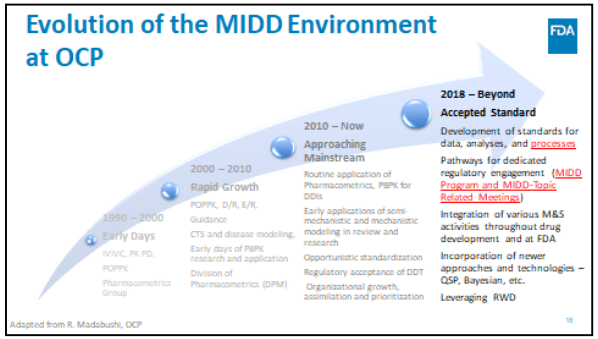
## Caveat: such designs are not suitable for every development question

# Modelling & Simulation to Model Informed Drug Discovery & Development (MID3)

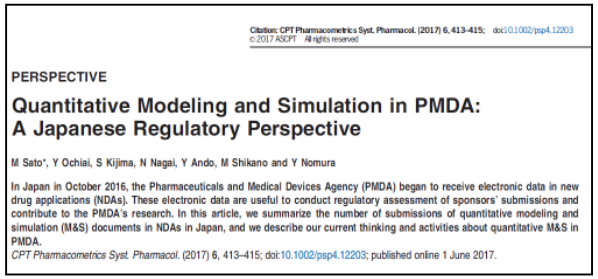
**EMA**




**FDA**




**PMDA**



PERSPECTIVE

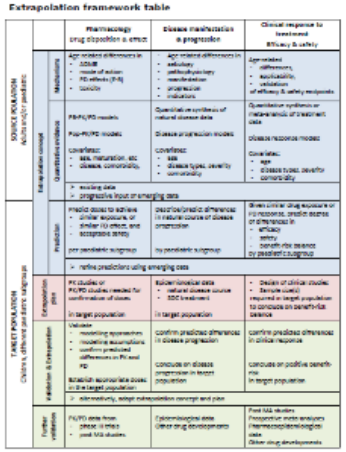
Quantitative Modeling and Simulation in PMDA: A Japanese Regulatory Perspective

M Sato*, Y Ochiai, S Kijima, N Nagai, Y Ando, M Shikano and Y Nomura

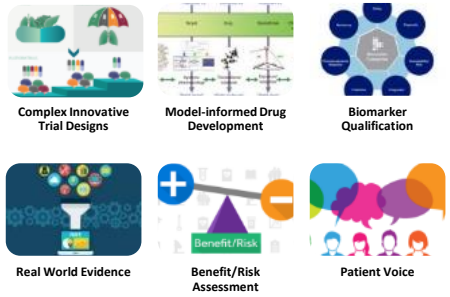
In Japan in October 2016, the Pharmaceuticals and Medical Devices Agency (PMDA) began to receive electronic data in new drug applications (NDAs). These electronic data are useful to conduct regulatory assessment of sponsors' submissions and contribute to the PMDA's research. In this article, we summarize the number of submissions of quantitative modeling and simulation (M&S) documents in NDAs in Japan, and we describe our current thinking and activities about quantitative M&S in PMDA.

*CPT Pharmacometrics Syst. Pharmacol.* (2017) 6, 413–415; doi:10.1002/psp4.12203; published online 1 June 2017.

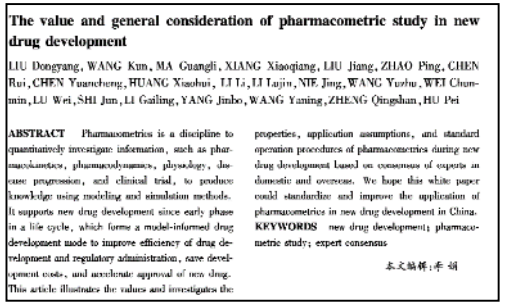
**Extrapolation Framework**




**PDUFA VI**




**China**



The value and general consideration of pharmacometric study in new drug development

LIU Dongyang, WANG Kun, MA Guangli, XIANG Xiaoqiang, LIU Jiang, ZHAO Ping, CHEN Rui, CHEN Yuancheng, HUANG Xiaohui, LI Li, LI Lanjin, NIE Jing, WANG Yuzhu, WEI Chunmin, LU Wei, SHI Jun, LI Gailing, YANG Jinbo, WANG Yaning, ZHENG Qingshan, HU Pei

**Global Regulators are embracing MID3 opportunity**

# Case Study: Modified Release Product – High Impact – Replaced Need for Study

**Traditional Approach to register a modified release product**

Clinical Efficacy Trial + Bioavailability Trials → FDA

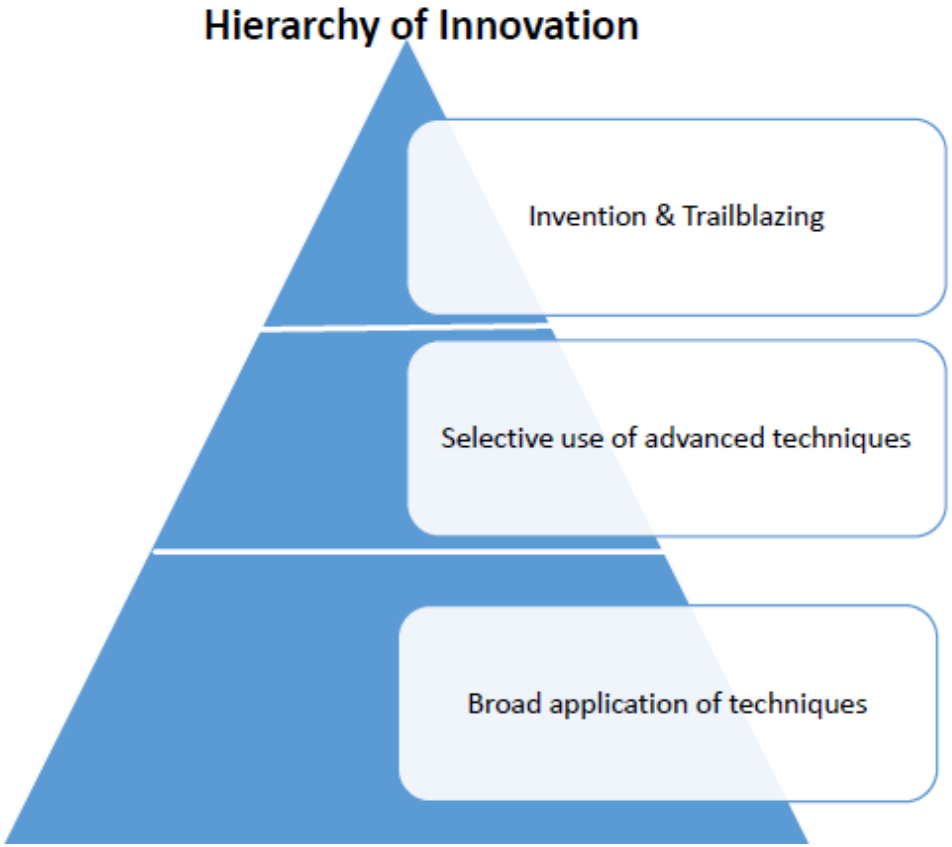
**MIDD Approach: PK/PD Bridge**

**PK/PD BRIDGE**
- PK-PD well understood
- Predicted equi-efficacious
- Safety assured (equivalent or lower concentrations)
- No Efficacy Trial

+ Bioavailability Trials → FDA

**But….**
**Approach not accepted by all decision-makers**

# Experience of complex trial designs varies




**Examples**

- Novel statistical methods and study designs
- Placebo substitution/historic control in P3 studies

- More complex adaptive trial designs (e.g. adaptive randomization)
- Platform designs (e.g. umbrella, basket)
- Placebo substitution/historic control
- Modelling & Simulation (e.g. pediatric extrapolation)

- Simple adaptive trial designs (e.g. dose dropping, group sequential)
- Trial simulation to inform design and program level decisions
- Increased utilization of RWD to inform trial design

# Longest experience is with adaptive designs where more complex designs have emerged

| ADAPTIVE DESIGN TYPE | BENEFITS |
|---|---|
| Adaptive randomization | Patients randomized to treatments which are more likely to be effective, may result with reduced sample size |
| Adaptive dose-finding | Better understanding of treatment doses to improve probability treatment is successful in phase 3 |
| Group sequential design | Stopping trials early for futility or efficacy, patients don't continue to receive an ineffective treatment |
| Sample size re-estimation | Checking assumptions still hold and trial retains sufficient power to assess trial objectives, |
| Seamless P2/3 design | Faster decision making and progressing promising treatments quicker for patients |
| Adaptive enrichment design | Targeting patients most likely to benefit from the treatment, reducing variability to treatment |

# Other examples of complex clinical trial designs published in the literature

- Platform designs (e.g. umbrella trials, basket trials, master protocols) to assess multiple treatments from one or more sponsor in a single trial
- Using historical placebo data to reduce (or replace) the size of placebo arm
- Advance modelling and simulation and Bayesian extrapolation from adults to paediatric to reduce generating clinical data in paediatrics
- Prognostic enrichment design prospectively seeking to optimize the trial population and decrease heterogeneity of patients enrolled e.g. biomarkers/gene expression
- Predictive enrichment designs identifying patients more likely to respond
- Trials with combination treatments and delayed-start design (e.g. Alzheimer's disease)

**Patients can benefit from advances in clinical trial designs as trials are designed with patients in mind, to be more efficient leading to improved decision-making**

# ….but convincing decision-makers is not easy…

## Elasser (2014) review of EMA submissions using adaptive design strategies highlighted:

- Unclear justifications for the designs selected
- Verification of Type I error rate control
- Potential bias introduced and how data integrity was maintained
- Problems for using of a complex design in a single pivotal trial
- Practical aspects for successfully implementing seamless phase II/III trial

## Convincing Ethics Committees is challenging

- Ensuring patient safety
- Committees and patients don't understand complex designs
  - E.g. randomisation schemes, when a trial will finish
- Patients are able to re-consent if needed

Elasser (2014) Adaptive clinical trial designs for European marketing authorization: a survey of scientific advice letters from the European Medicines Agency

# CTFG Paper on Complex Clinical Trials answers many questions but still poses many challenges

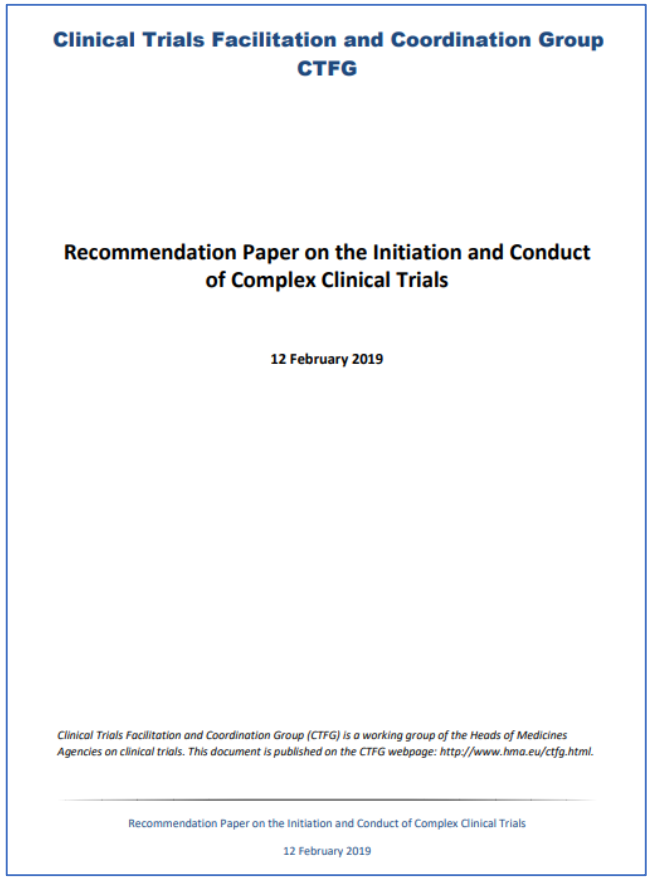
## Section 3: Potential Opportunities and Challenges of Complex Clinical Trials

However, complex trial designs also mean increased operational complexity due to the presence of several IMPs, populations, trial sites, multiple manufacturers and contract research organisations (CROs). Therefore, adaptations may cause challenges at both investigator and sponsor level and could jeopardise the safety oversight of the trials thus affecting the safety of trial subjects or the benefit-risk balance of the clinical trial.

Complex trial designs proposing extensive prospective adaptations such as the addition of new IMPs or populations also challenge the EU regulatory framework in terms of the definition of a clinical trial and data transparency, and they pose a challenge in terms of providing clear information particularly to the trial subjects.

summary reports is made available to the public on the EU Clinical Trials Register. Data transparency is thus of great concern for complex clinical trials submitted as one clinical trial, since publication of sub-protocol results will be delayed until after the overall clinical trial is completed.

There are also concerns regarding the scientific value or outcome of complex clinical trials due to the parallel testing of several IMPs in small numbers of trial subjects, difficulties to control type I error, and challenges created by shared control arms, which need to be thoroughly addressed. In addition, complex trial designs raise concerns regarding data integrity as emerging data from closed sub-protocols may affect the conduct of the ones that are still ongoing.



Clinical Trials Facilitation and Coordination Group
CTFG

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

12 February 2019

*Clinical Trials Facilitation and Coordination Group (CTFG) is a working group of the Heads of Medicines Agencies on clinical trials. This document is published on the CTFG webpage: http://www.hma.eu/ctfg.html.*

Recommendation Paper on the Initiation and Conduct of Complex Clinical Trials

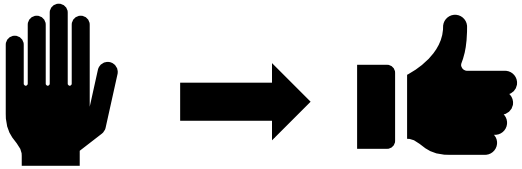
12 February 2019

# Questions to Consider:

**We are moving forwards, but how can we move forwards, faster?**

What will it take for decision-makers to regularly consider different evidence sources and innovative trial designs for decision-making?

- What are the blockers and how do we overcome them?



For industry to embrace innovative trial designs on a systematic basis, we need predictability of outcome – how can this be achieved?

# Thank you.

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