Complex Clinical Trial Designs – A Review of the Landscape

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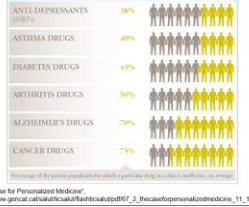
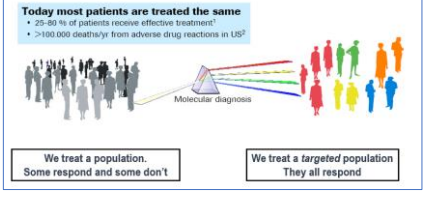
The Case for Changing the Approach: Rise of Personalised Medicines

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

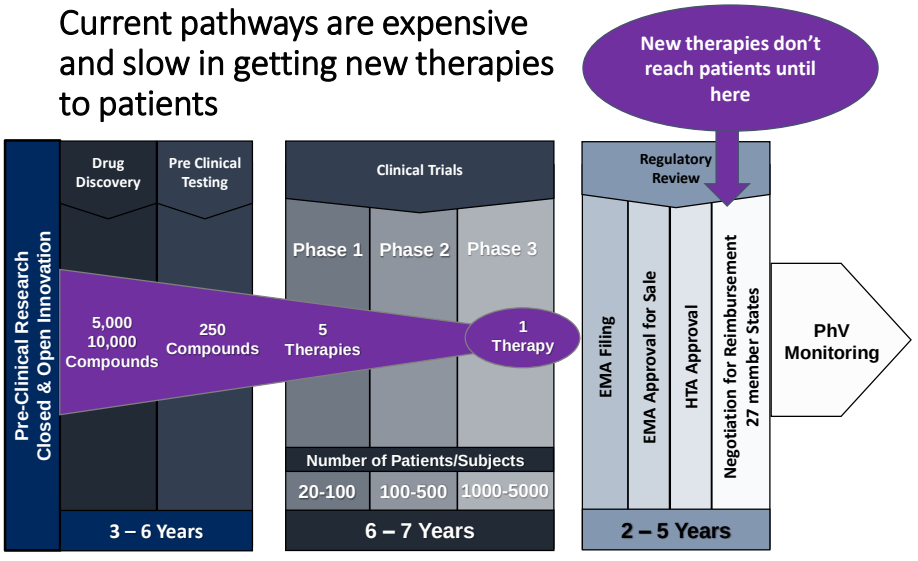
The way we treat patients is evolving from 'one size fits all' to targeted based on genetics.



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

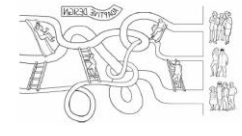
Current pathways are expensive and slow in getting new therapies to patients

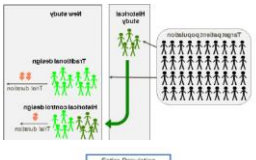


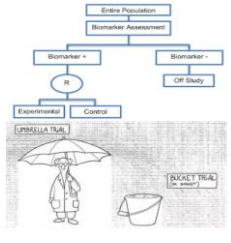
Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org;
CBO, *Research and Development in the Pharmaceutical Industry*, 2006;
Forbes, Matthew Herper, "The Truly Staggering Cost Of Inventing New Drugs", February 10, 2012

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...

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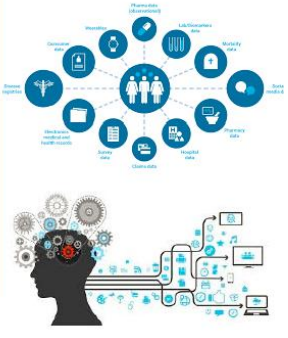
... with a particular interest in using RWE to bridge the evidentiary gap between regulators, HTAs, and payers…

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



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…..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 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 patient access to an innovative treatment

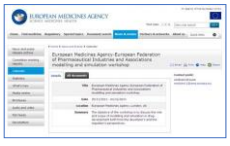
- MAH proposal to conduct a RWE study to meet a specific regulatory obligation for an oncology product rejected
  Response was that *'RWE data would not provide a decisive comparison, since there could be a lot of bias and data analysis can be problematic'*.
  The company was explicitly told that they wanted data owned and generated by the company (i.e. conduct a confirmatory RCT).

Complex Innovative Design Trials

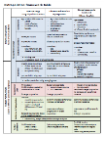
- Innovative clinical trial designs can speed up drug development without lowering scientific and regulatory standards
  - Accelerate drug development and approval
  - Increased and earlier patient access to targeted therapies
  - Efficiently study multiple compounds / multiple targets in one operational set-up
  - Identify ineffective medicine earlier, reduction of failure rate in Phase III and patient exposure to ineffective drug
- **Caveat: such designs are not suitable for every development question**

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

EMA



Extrapolation Framework



FDA

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PMDA

China

Global Regulators are embracing MID3 opportunity

Case Study: Modified Release of an RA Product
- High Impact – Replaced Need for Study

Traditional Approach to register a modified release product

Clinical Efficacy Trial + Bioavailability Trials → FDA

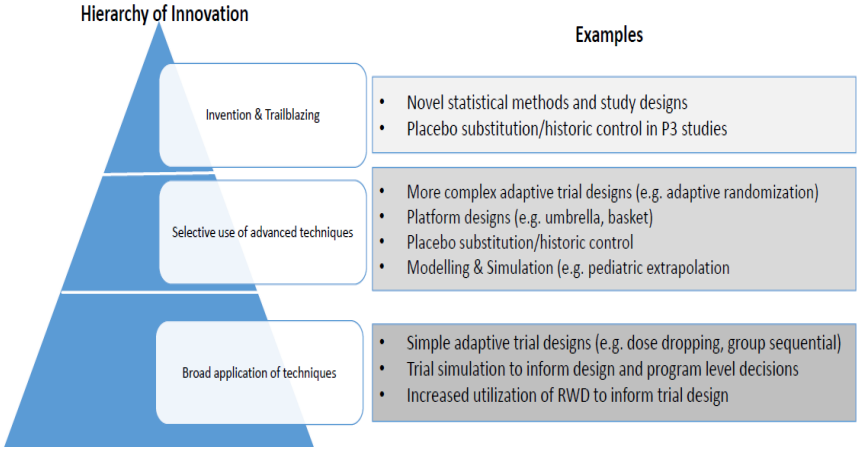
MIDD Approach: PK/PD Bridge

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:
  - Not accepted by Japan
  - No decision from EU

Experience of complex trial designs varies



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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

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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

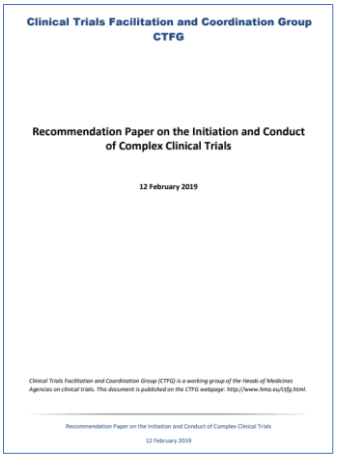
Convincing Ethics Committees is challenging

- 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

- Definitions of complex innovative designs
- Applicability of CTFG recommendations to different types of complex innovative designs
- The level of information needed in the CTA describing how the trial will be conducted
- Clarity on what adaptations during the trial require substantial modifications
- Maintaining trial integrity takes precedent over transparency requirements


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

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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?

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