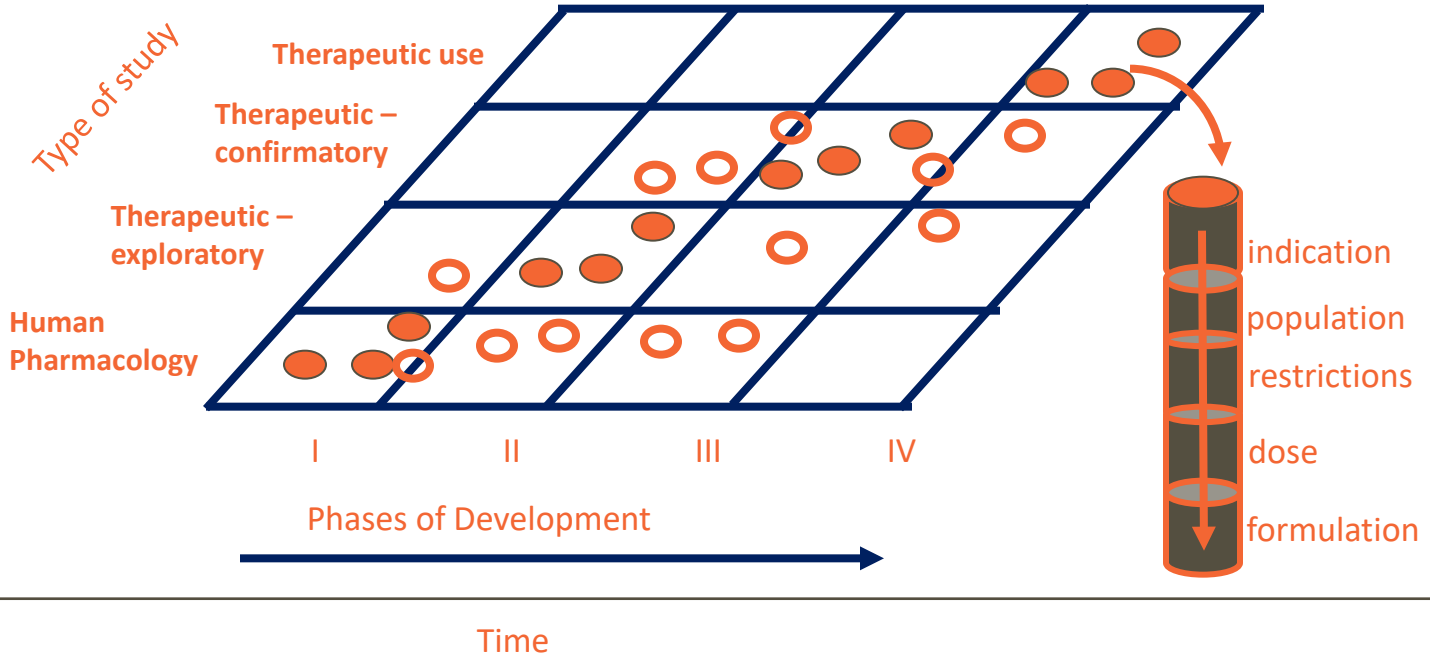
Concrete examples of trials approved with innovative design(s)

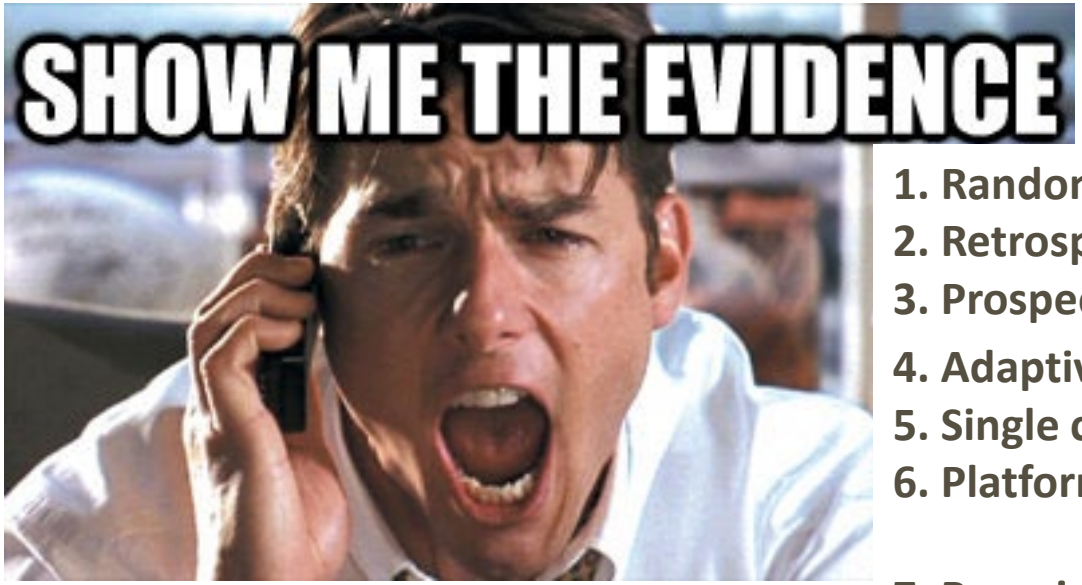
Oscar Della Pasqua
Chair Clinical Pharmacology & Therapeutics

Where can one innovate?



Evidence generation in clinical development

How has the process for evidence generation evolved?



1. Randomised controlled clinical trials
2. Retrospective observational studies
3. Prospective observational studies
4. Adaptive (Bayesian) designs
5. Single case designs
6. Platform trials

7. Bayesian dynamic borrowing
8. Digital twins
9. Synthetic arms
10. Virtual cohorts

Efficiency vs Innovation

Planning, execution, integration

Scientific advances are incorporated into guidelines

Stakeholders acknowledge the value of alternative approaches for evidence generation

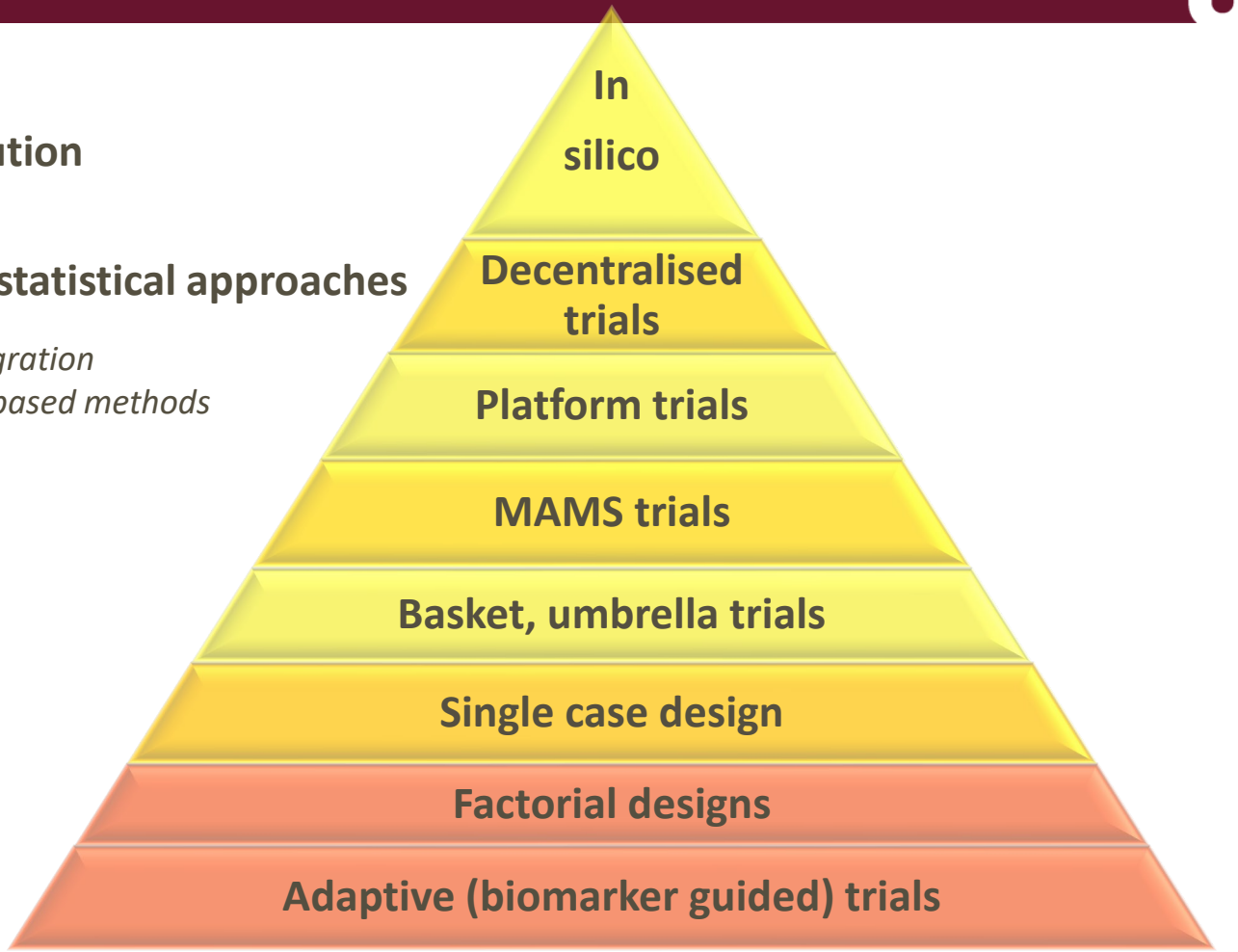
Efficiency vs Innovation in Clinical Trial Design

Efficiency in execution

Novel (pharmaco)statistical approaches

(Prior) knowledge integration
(Drug-disease) model-based methods

Digital twins
Synthetic controls
Virtual patients



Basket, umbrella, and platform trials

Clinical Therapeutics/Volume 42, Number 7, 2020

The Evolution of Master Protocol Clinical Trial Designs: A Systematic Literature Review

Elias Laurin Meyer, MSc[1]; Peter Mesenbrink, PhD[2]; Cornelia Dunger-Baldauf, PhD[3]; Hans-Jürgen Fülle, MD PhD[3]; Ekkehard Glimm, PhD[3]; Yuhan Li, M.S.[2]; Martin Posch, PhD[1]; and Franz König, PhD[1]

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPE

SOUNDING BOARD

The Magic of Randomization versus the My Real-World Evidence

Authors: Rory Collins, F.R.S., Louise Bowman, M.D., F.R.C.P., Martin Landray, Ph.D., F.R.C.P. , an F.R.S. Author Info & Affiliations

Published February 12, 2020 | N Engl J Med 2020;382:674-678 | DOI: 10.1056/NEJMsb1901642

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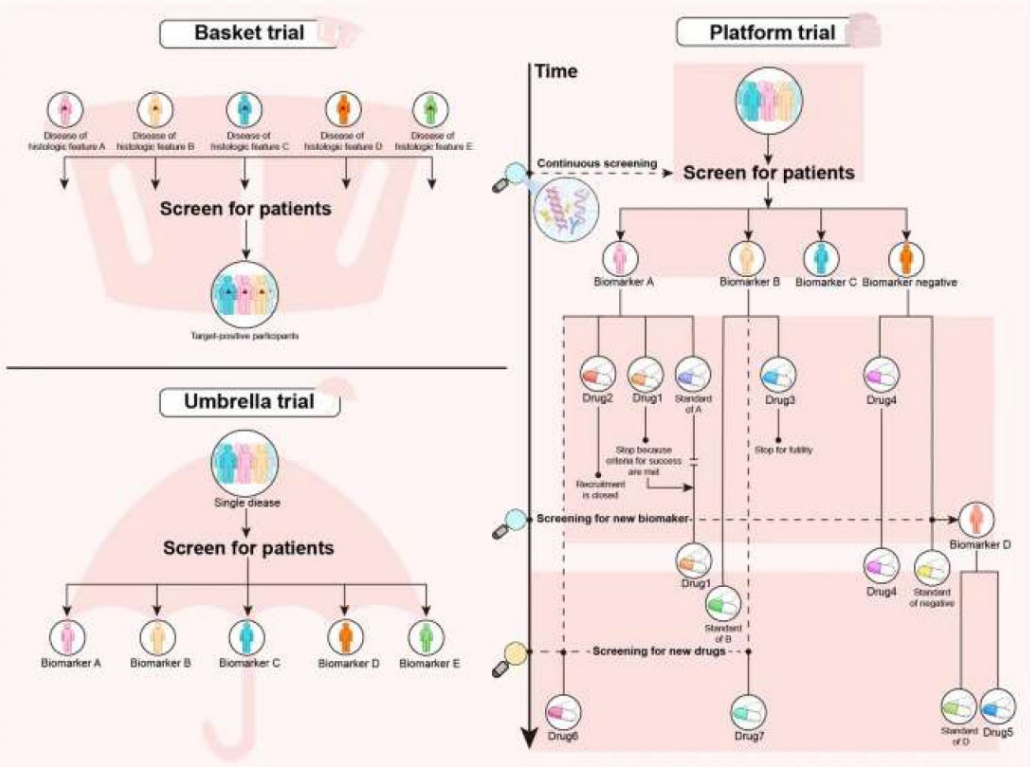
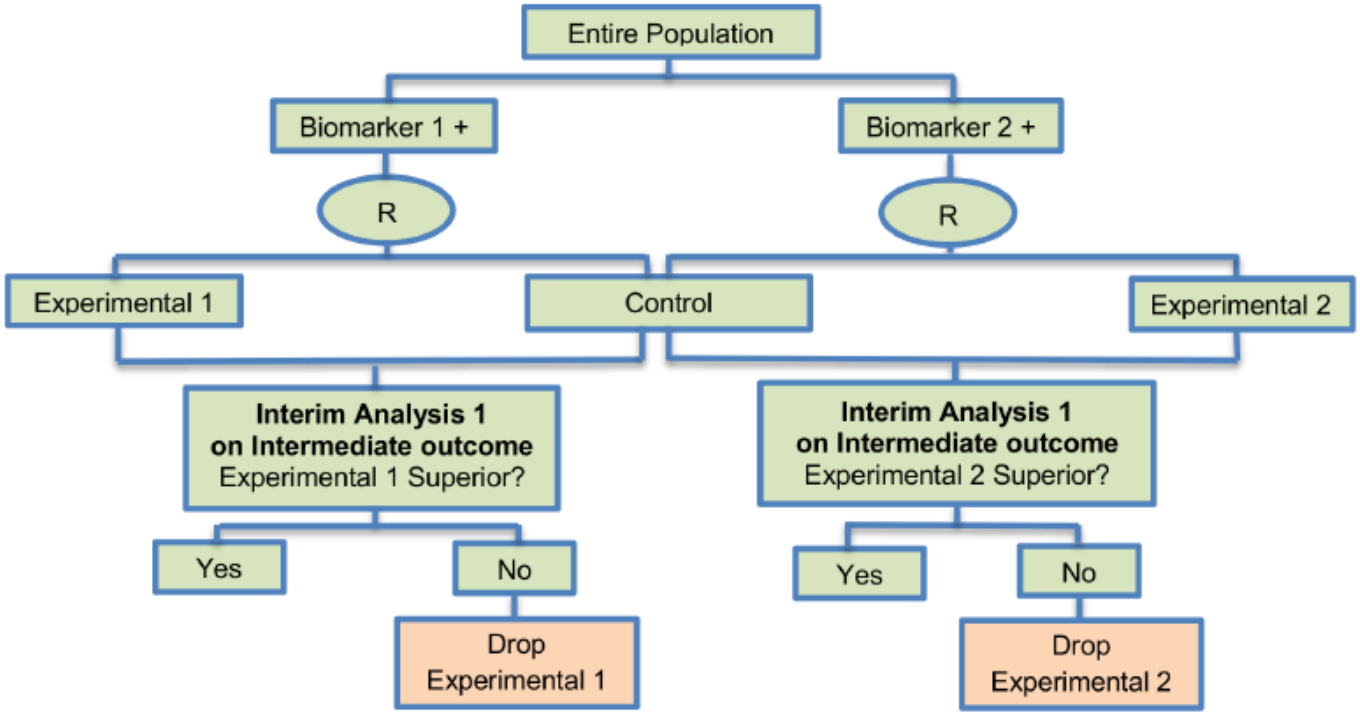


MAMS and adaptive platform trials



Multi-arm multi-stage (MAMS) design. "R" refers to randomization of patients.

https://www.phctrials.ox.ac.uk/platform-trials-an-explainer
doi: 10.1371/journal.pone.0149803.g007

MAMS and adaptive platform trials

Platform design	Intervention(s)
RECOVERY (adaptive, multi-arm, pragmatic)	Dexamethasone; Tocilizumab; others
REMAP-CAP (Bayesian, multifactorial adaptive platform)	IL-6R antagonists; anticoagulation; statins

REMAP-CAP

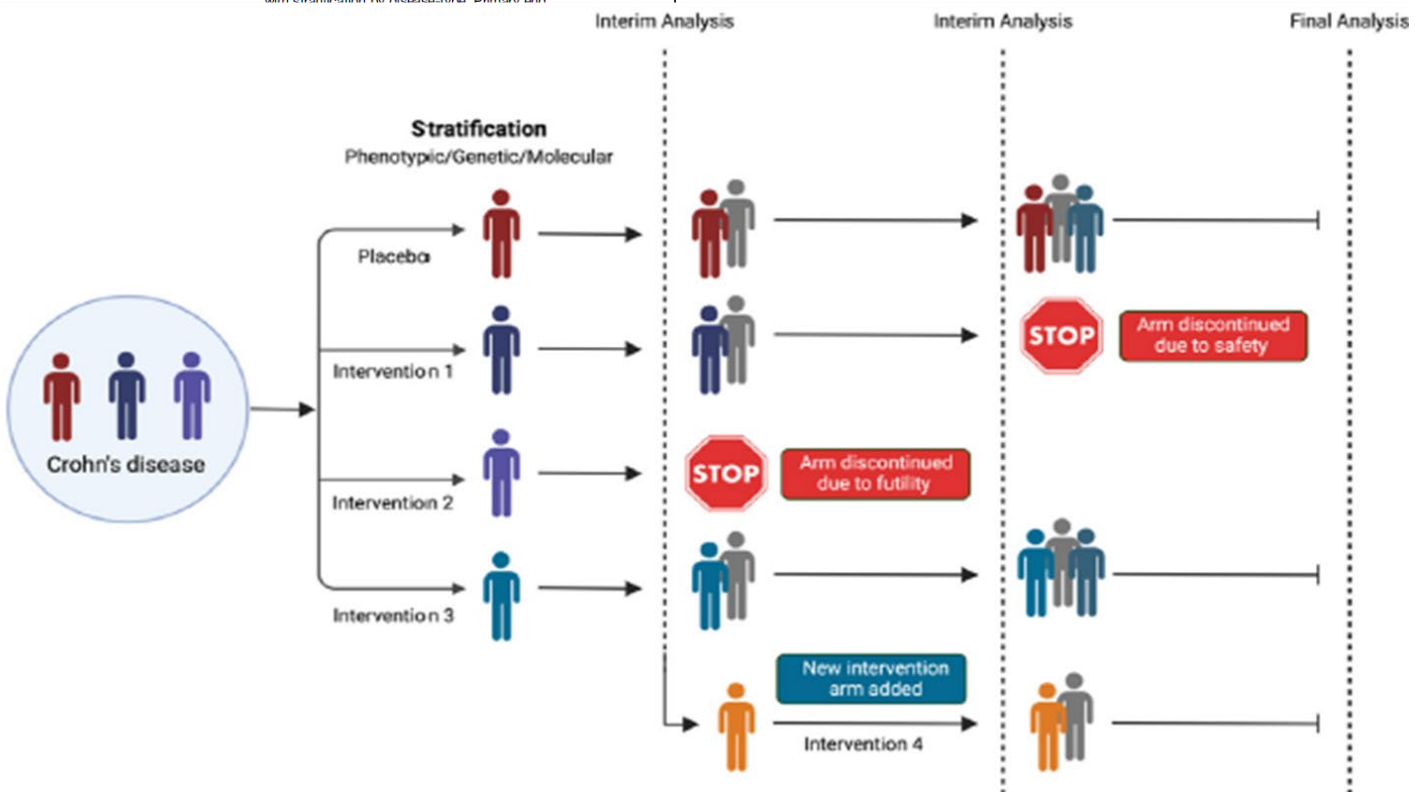
A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia

26,659	18,652	66
Patient randomisations	Patient randomisations with suspected or proven COVID-19	Current or completed interventions in 18 Domains
15,639	10,500	244
Total patients	Patients with suspected or proven COVID-19	Active Sites

Basket, umbrella and platform trials

Trial name	Type	Phase	Disease	n[a]	Intervention	Within-trial adaptations	Sub-type stratification	Details	Status
TRANSREG[7]	Basket	IIa	UC, CD	12	Low-dose IL-2	No	Yes	Open-label trial across 13 autoimmune diseases with stratification by disease-type. Primary end	Completed
POLARISE[8]	Basket	II	CD, PSC, RA, LN	60	Mese st				
RELIEVE UCCD[9]	Basket	IIb	UC, CD	240	TEV-				
VIBRATO[13]	Umbrella	IIb	UC	292	Ritlec bi				
MACARONI-23[21,22]	Platform	III	CD	120	Guse m				

CD, Crohn's disease; IL, interleukin; JAK, Janus kinase; LN, lupus r
sclerosing cholangitis; RA, rheumatoid arthritis; RCT, randomized co
T-regulatory cells; UC, ulcerative colitis.
[a]Number of IBD patients enrolled or expected to enroll.



Gastroenterology 2024;167:636–642

Decentralised clinical trials

REVIEW OPEN ACCESS

Decentralized Clinical Trials in the Era of Real-World Evidence: A Critical Assessment of Recent Experiences

Hongwei Wang[1] | Nadia Daizadeh[2] | Yuan-Li Shen[3] | Jie Chen[4] | Frank W. Rockhold[5] | Herbert Pang[6] | Hana Lee[3]

- **Diabetes trials:** Approximately 35% of all paediatric diabetes studies initiated since 2010 have used a decentralized approach, leveraging tools like remote blood glucose monitors.

- **Genetic disorders:** Trials for genetic disorders, including a study on children with SCN2A-DEE and SCN8A-DEE, have used decentralized methods to manage complex needs, such as continuous feeding and ventilation equipment, by pivoting to a fully remote model.

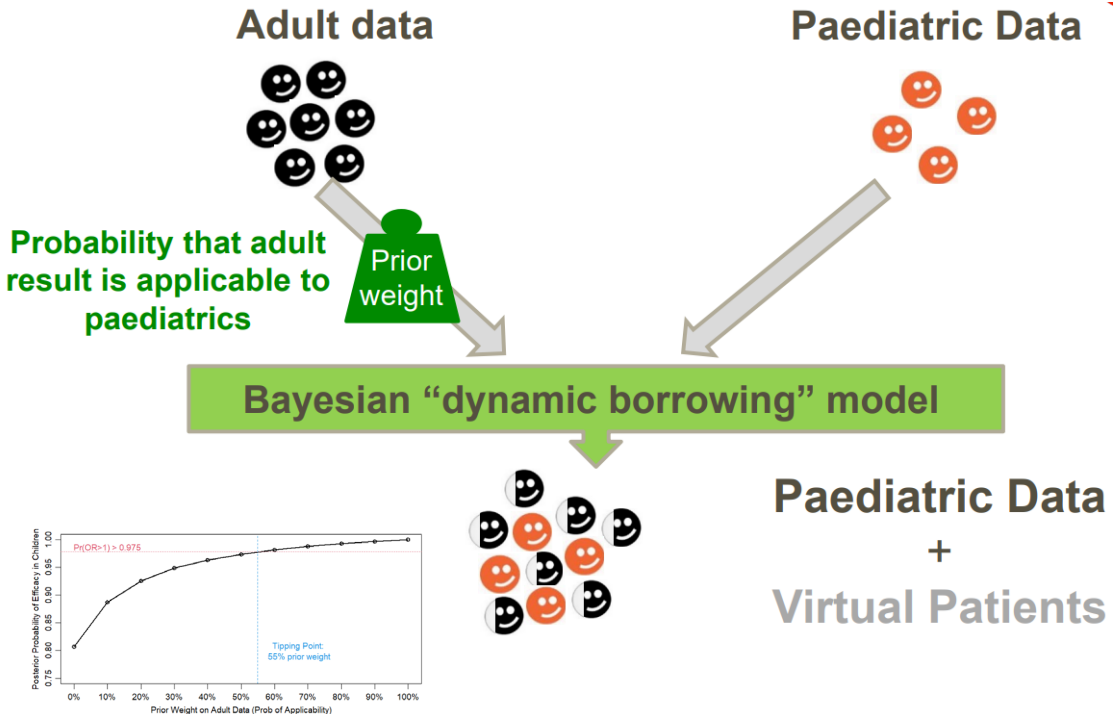
- **Duchenne muscular dystrophy:** A trial for heart failure prevention in this condition integrated decentralized elements such as remote recruitment and electronic patient-reported outcomes (ePRO).

- **Cystic fibrosis:** A Phase 4 study used wearable technology for remote data collection on physical activity, cough, and sleep quality, with home-based visits conducted via telemedicine.

Clinical and Translational Science, 2025; 18:e70328

Bayesian Dynamic Borrowing

Systemic lupus erythematosus



ICH harmonisation for better health

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

ICH HARMONISED GUIDELINE

PEDIATRIC EXTRAPOLATION
E11A

Final version
Adopted on 21 August 2024

DOI: 10.1002/cpdd.889

https://www.fda.gov/media/152385/download
10.1136/annrheumdis-2020-217101

N-of-1 trials and single case design

Rheumatology, 2025, **00**, 1–8
https://doi.org/10.1093/rheumatology/keaf393
Advance access publication 17 July 2025
Original Article

British Society for Rheumatology RHEUMATOLOGY OXFORD

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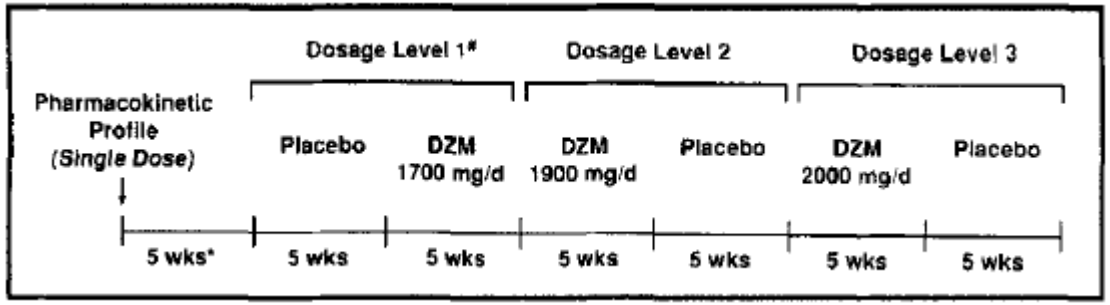
Dezinamide for partial seizures:

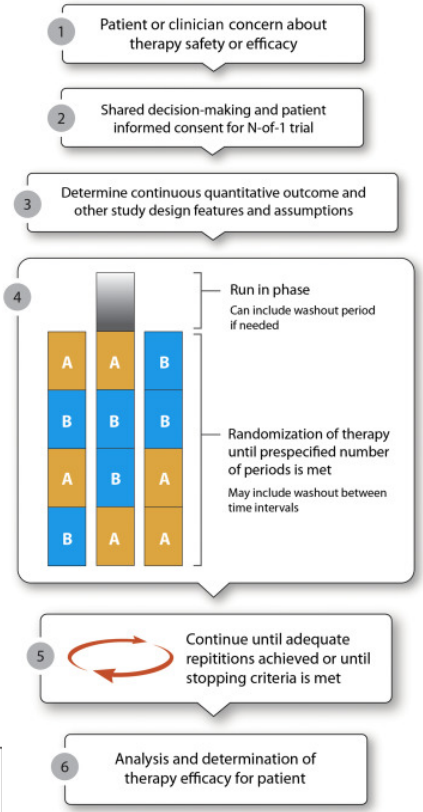
Results of an n-of-1 design trial

M.D. Privitera, MD; D.M. Treiman, MD; G.W. Pledger, PhD; J.T. Sahlroot, PhD; A. Handforth, MD; M.S. Linde, RN; C.R. France, RN; J.J. Cereghino, MD; C.B. McCutchen, MD; and J.H. Wood, PhD

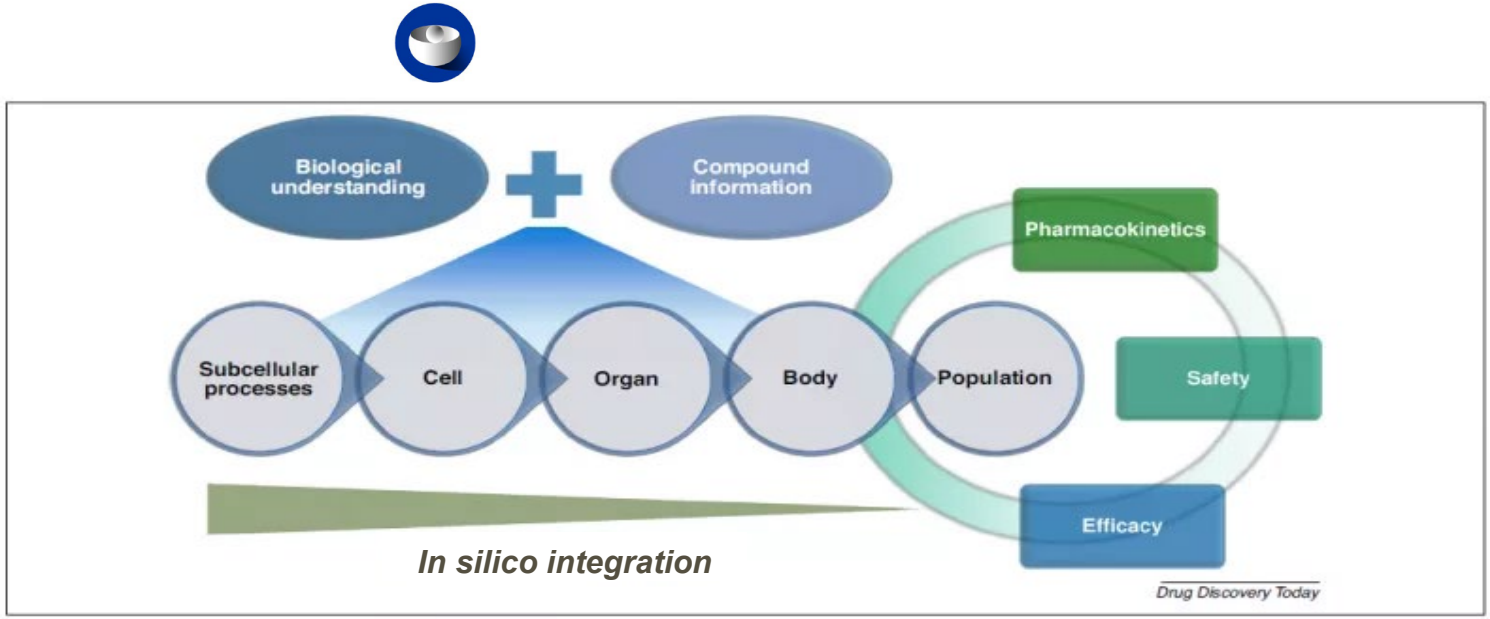


Rheumatology key messages

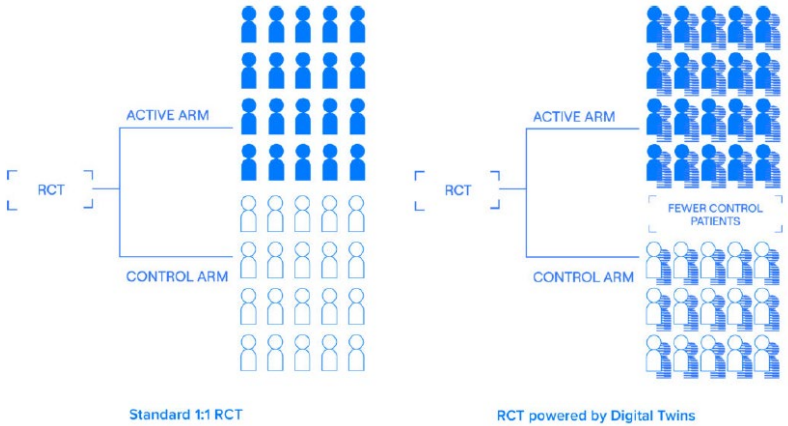
- NSAID response in axial spondyloarthritis varies widely, complicating optimal treatment selection.
- Bayesian hierarchical models enabled personalized NSAID comparisons using data from double-blind N-of-1 trials.
- This individualized approach supports shared decision-making and may guide therapy.



From digital twins to synthetic controls to virtual cohorts and *in silico* trials Trials



Digital twins in ALS



PROJECT ALS

Four-part study PRO-101 (NCT05279755)

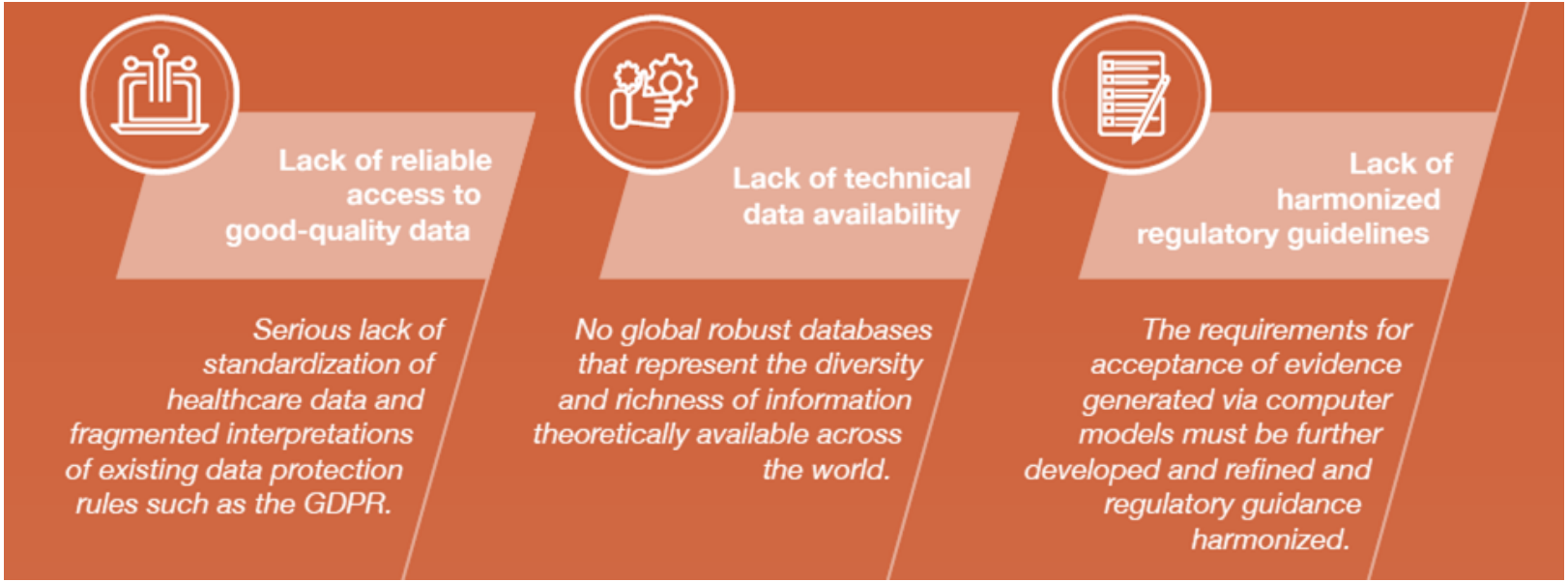
Prosetin is an orally administered MAP4K inhibitor under investigation for the treatment of amyotrophic lateral sclerosis.

Patients who complete part C — running up to 56 days (about two months), including 14 days of daily oral solution treatment (prosetin) or a placebo solution, and seven hospital visits — will be invited to enter part D. In this open-label extension phase, all will be given prosetin for 52 weeks (about one year).

The digital twins will serve as a placebo group during part D's long-term extension.
Unlearn will use its ALS Digital Twin Generator, an AI-based model that's been trained on patient-level data, to generate digital twins. These counterparts of treated patients will act as a trial placebo group, allowing comparison between prosetin and changes in a patient's health without the medication.

Challenges and barriers

Barriers to the implementation of digital twins in clinical trials



Drug-disease modelling and simulation framework

Disease model

Biology
- Biomarker(s)/outcome relationship
- Natural progression

Placebo effect

Drug model

Pharmacology
- Effectiveness
- Safety

Preclinical/Healthy/Patient

Product features

Not-in-trial model

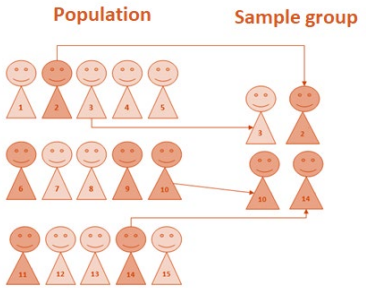
Co-morbidities

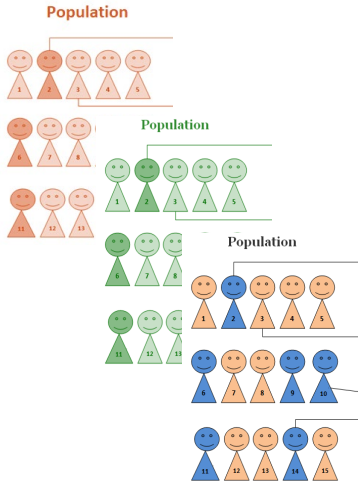
Drop-out

Adherence

Medical practice

Patient pop. model





Gobburu & Lesko, Annu Rev Pharmacol Toxicol. 2009;49:291-301.

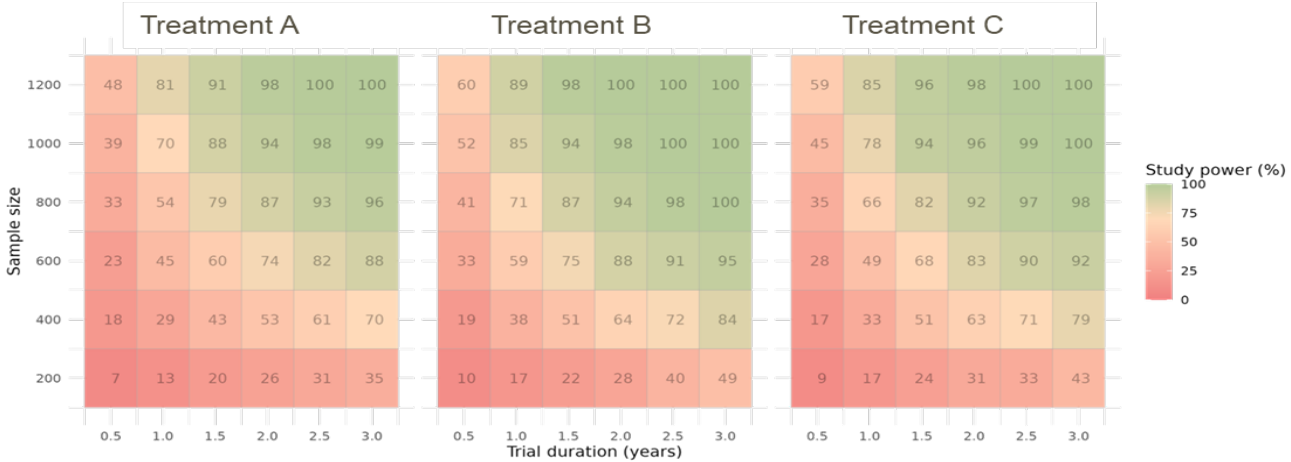
Generating Virtual Patients

Adv Ther (2024) 41:4065–4088
https://doi.org/10.1007/s12325-024-02962-2

ORIGINAL RESEARCH

Baseline Characteristics and Maintenance Therapy Choice on Symptom Control, Reliever Use, Exacerbation Risk in Moderate–Severe Asthma: A Clinical Modelling and Simulation Study

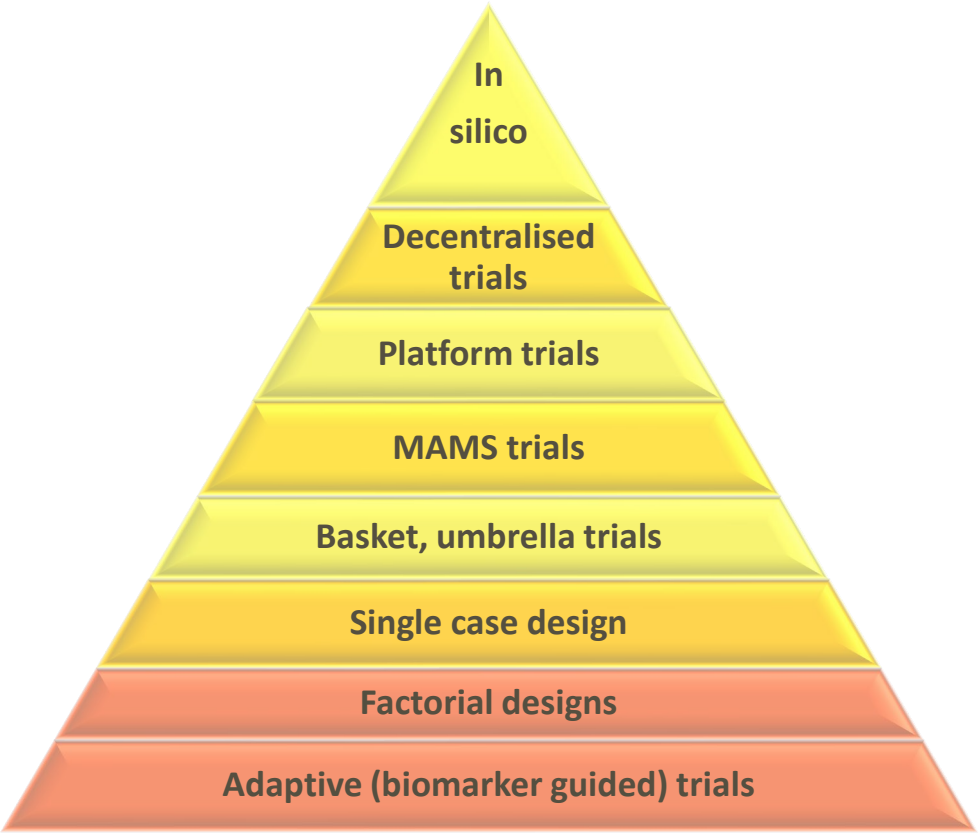
Pierluigi Paggia



Results

Heat map shows the study power that is predicted based on an alpha of 0.05

Summary



Efficiency in execution

Significant attention has been given to approaches that enhance efficiency from an operational perspective.

Ongoing initiatives focus on patient-centric elements, including the incorporation of advancing technologies such as wearable devices and continuous monitoring.

Novel (pharmaco)statistical approaches

Acceptance of novel methodologies for evidence generation and analysis of clinical trial data remains challenging.

Advanced data analytical approaches (AI, ML, MIDD) require further evaluation, standards and guidance on best practices.

Drug-disease modelling and simulation methods will enable more mechanism-based representation of the patient population.

Hybrid protocols including real patients and virtual cohorts may become critical to address gaps in areas such as rare paediatric diseases.

Thank you

“Not everything that is faced can be changed, but nothing can be changed until it is faced.”

— **James Baldwin**

Back-up slides

Digital twins, Synthetic controls, Virtual patients

A digital twin is a comprehensive, longitudinal, clinical record created using baseline data collected from a patient –BEFORE they receive their first treatment – that predicts how that patient would likely evolve over the course of the trial if they were to be given a placebo. That is, a digital twin is like a simulated control group for a particular patient. Digital twins are treated as covariates optimised to explain variability in the outcome. They improve power and efficiency without introducing bias.

Digital twins are not synthetic controls. Synthetic controls refer to the inclusion of patients who were not in the original patient sample of the trial. Digital twins add information about patients already in the trial. Synthetic controls may increase Type I error, use cases are limited based on regulatory guidance.

Virtual patients (in silico cohorts). These are model-based simulation of the characteristics and responses of real patients for use in in silico clinical trials. These models, derived from population data and other information, can represent a single hypothetical patient or a cohort of virtual patients to theoretically conduct trials in a computer environment.

Overview
Pivotal evidence relied on single-arm data vs. an external comparator

Drug (year)	Disease	Trial design & "synthetic/external" element	Primary endpoint(s) / Phase	Regulatory outcome
Cerliponase alfa (Brineura) (2017)	CLN2 Batten disease (paediatric)	Single-arm open-label trial (Studies 201/202) compared **to an external natural-history cohort (Study 901) after scale-bridging (Hamburg scale).**	Motor-language decline rate; Phase 1/2 with extension	FDA approval (2017); natural-history cohort explicitly served as the control.
Onasemnogene abeparvovec (Zolgensma) (2019 EU; 2019 US)	SMA Type 1 (paediatric)	Open-label pivotal program where comparison **to natural-history controls provided the primary effectiveness evidence (survival & milestones).**	Survival at 14 months; motor milestones; Phase 3 open-label	FDA/EMA approvals citing comparison to natural-history datasets.
Risdiplam (Evrysdi) (2020)	SMA Type 1 (infant cohort)	Single-arm infant cohort with context from natural-history studies to interpret survival/motor outcomes.	CHOP-INTEND, HINE-2; survival; early-phase program supporting approval	FDA approval (2020) with explicit natural-history benchmarking in review.
Avelumab (Bavencio) (2017)	Metastatic Merkel cell carcinoma (mMCC)	Single-arm Phase 2 (JAVELIN Merkel 200). Approval primarily on durable ORR; literature and reviews discuss contextual historical controls for unmet-need settings.	ORR with durability; Phase 2	FDA accelerated approval (2017); external/historical data used contextually in reviews.
GEN-1 (Celsion) neoadjuvant ovarian cancer	Advanced epithelial ovarian cancer	Phase Ib single-arm re-analyzed vs. a Medidata Synthetic Control Arm® built from prior trials;	PFS/safety comparisons vs. matched historical patients	Peer-reviewed case study and sponsor reports of the SCA's impact.

Overview
Pivotal evidence relied on single-arm data vs. an external comparator

Design	Drug	Disease/Condition	Phase (pivotal)	Primary endpoint(s)	What happened	Key refs
Single-arm with external/lead-in comparator	Valoctocogene roxaparvovec (Roctavian)	Severe haemophilia A	Phase 3 GENEr8-1 (single-arm; compared vs prior prophylaxis from lead-in)	Annualized bleeding rate (ABR), FVIII usage	FDA approval 2023 (regular). ABR reduced vs prior standard prophylaxis.	FDA SBRA; Phase 3 publications.
Single-arm with baseline/prophylaxis comparison	Etranacogene dezaparvovec (Hemgenix)	Haemophilia B	Phase 3 HOPE-B (single-arm)	ABR, FIX activity	FDA approval 2022 (first for haemophilia B). Substantial ABR reduction and ↑FIX.	FDA SBRA; Lancet Haematology 24-mo data; CADTH review.
Single-arm + historical controls; milestone endpoints	Onasemnogene abeparvovec (Zolgensma)	Spinal muscular atrophy (SMA)	Phase 1 (START) + Phase 3 (ongoing)	Survival / milestone achievement	FDA approval 2019; survival/motor milestones vs natural history.	FDA SBRA; review & long-term follow-up.
Surrogate biomarker (Bayesian inference in review; interim)	Casimersen (Amondys 45)	Duchenne muscular dystrophy (exon 45 skipping)	Pivotal ESSENCE (blinded RCT) but approval based on interim biomarker	Dystrophin % at 48 weeks (biomarker surrogate)	Accelerated approval 2021 (continued clinical-benefit confirmation pending).	FDA approval letter/label; reviews.
Single-arm targeted oncology	Sotorasib (Lumakras)	KRAS G12C-mutated NSCLC (post-line)	Phase 2 CodeBreaK-100 (single arm)	ORR, DOR	Accelerated approval 2021; first KRAS G12C inhibitor to market via single-arm pivotal.	NEJM CodeBreaK-100.

Prevention / stage-based “disease-modifying” (immunology/endocrinology)

Design	Drug	Disease/Condition	Phase	Primary endpoint(s)	What happened	Key refs
Randomized, placebo-controlled prevention in at-risk population	Teplizumab (Tzield)	Stage 2 type 1 diabetes (abnormal OGTT & 2+ autoantibodies)	TN-10 (Phase II)	Time to Stage 3 T1D diagnosis	FDA approval 2022 to delay onset of Stage 3 T1D (first disease-modifying therapy for T1D).	FDA clinical review