School of Medicine
& Health Sciences
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Overview of Modern Clinical Trial Designs

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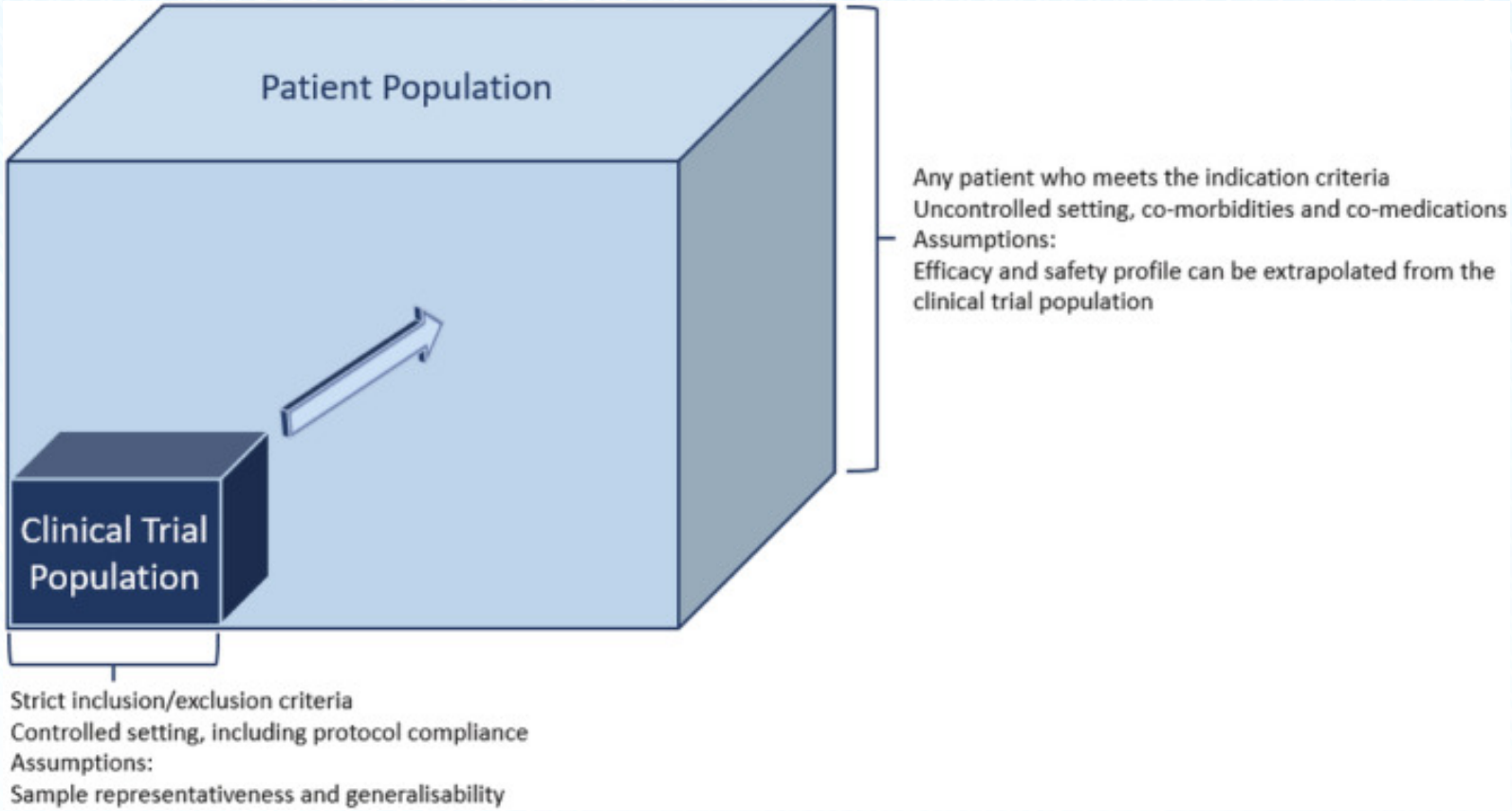
Objectives

- Consider reasons for revamping clinical trial designs to reflect wider representation of the population and more settings of real-world conditions.
- Outline the differences between classical and novel clinical trial designs and explain how they relate to established clinical trials.
- Explain the impact that innovative clinical trial design has on patients and how modern clinical trial designs include a diverse, patient-centered approach.

Clinical Trials Perspectives/Experience

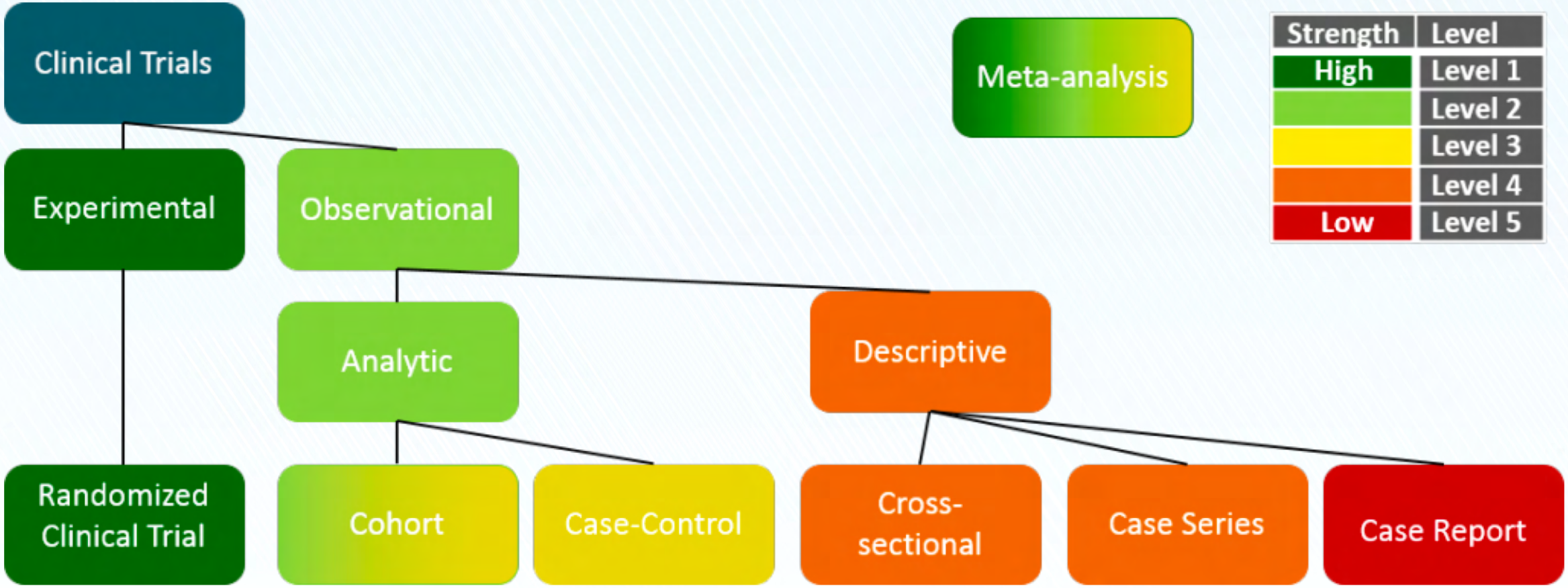
- Recruitment?
- Retention?
- Diversity?

Clinical Trial Populations



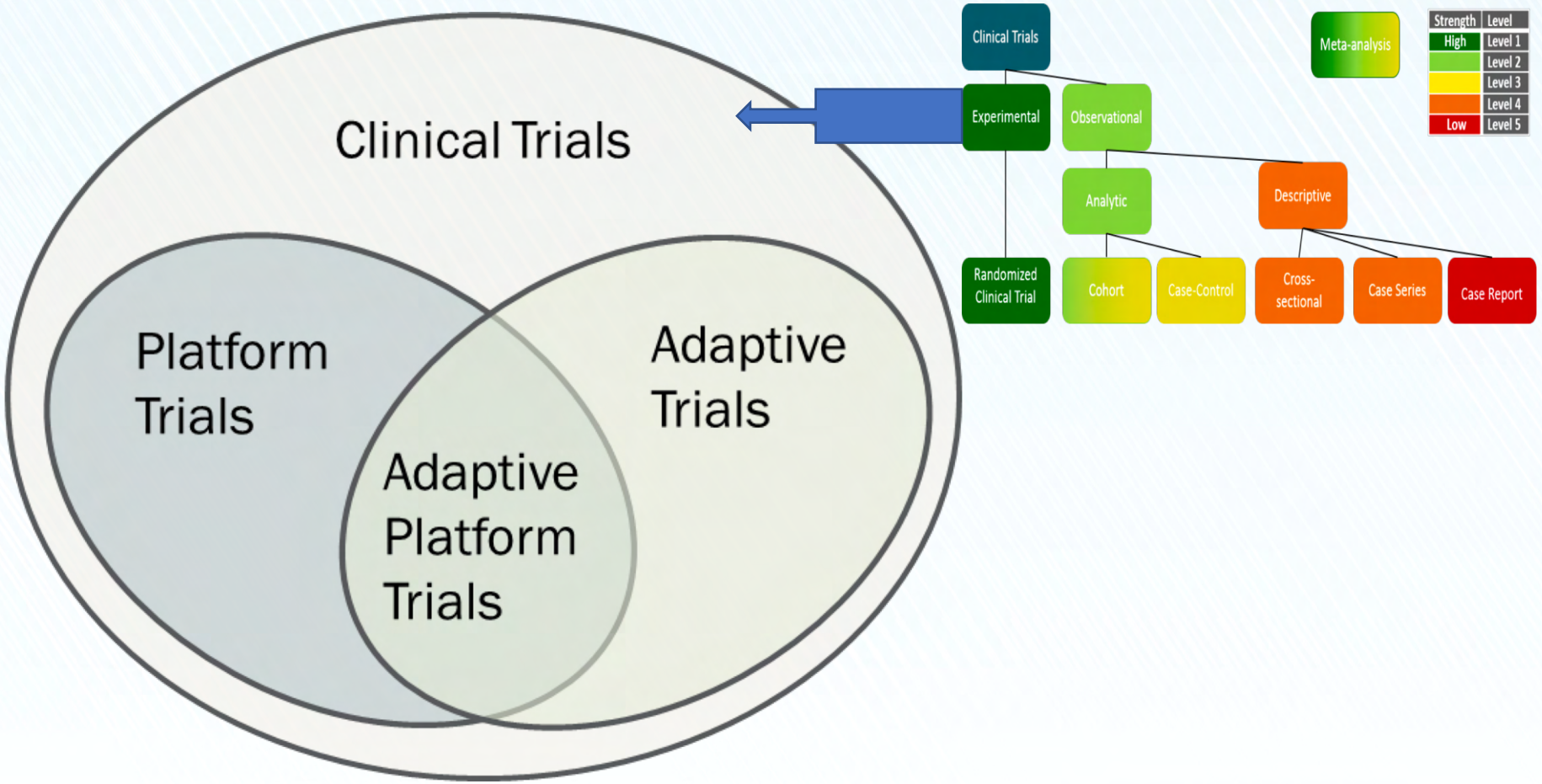
Gross, A. S., Harry, A. C., Clifton, C. S., & Della Pasqua, O. (2022). Clinical trial diversity: An opportunity for improved insight into the determinants of variability in drug response. *British journal of clinical pharmacology*, *88*(6), 2700–2717. https://doi.org/10.1111/bcp.15242

Overview of Classical Clinical Trial Designs

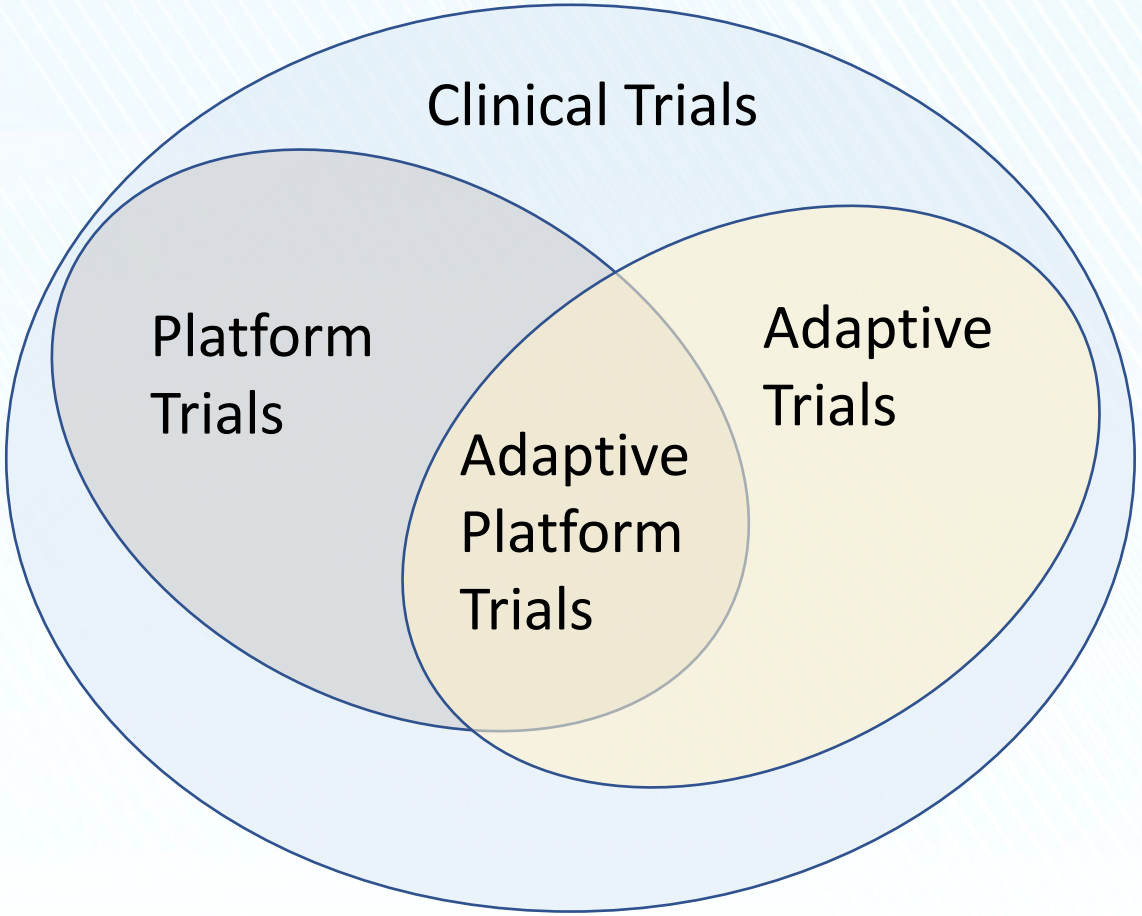


Hydrocephalus Association. Website: https://www.hydroassoc.org/research-101-an-explanation-of-clinical-trials-design Accessed: 11/8/2023

Classical versus Novel Clinical Trial Designs



Master Protocol Trial Designs



- **Platform trial design:** A trial design in which multiple interventions can be evaluated over time.
  - Master protocol with subprotocol appendices
  - Basket trials, umbrella trials, and platform trials
    - Basket trial: a targeted therapy is evaluated for multiple diseases with a common factor.
    - Umbrella trials: multiple targeted therapies in a single disease that is stratified into multiple sub-studies based on specific factors.
- **Adaptive trial design**: Trial design evolves as information accrues according to prespecified rules and interim analyses based upon prespecified schedules.
- **Master protocol:** Main protocol designed to evaluate multiple interventional hypotheses with standardized elements (supplemented with intervention-specific appendices, other protocol-related appendices).

The Adaptive Platform Trials Coalition Nat Rev Drug Discovery 2019

Types of Master Protocols

Type of Trial	Objective
Umbrella	To study multiple targeted therapies in the context of a single disease
Basket	To study a single targeted therapy in the context of multiple diseases or disease subtypes
Platform	To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm

Woodcock, J., & LaVange, L. M. (2017). Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *The New England journal of medicine*, *377*(1), 62–70. https://doi.org/10.1056/NEJMra1510062

Master Protocols

Basket Trials

- One basket (genetic mutation) can contain multiple items (cancer types)

Umbrella Trials

- An umbrella (cancer type) can have multiple ribs (genetic mutations)

Platform Trials

- Multiple trains can (drugs) come and leave a platform (cancer type)

Ravi, R., & Kesari, H. V. (2022). Novel Study Designs in Precision Medicine - Basket, Umbrella and Platform Trials. *Current reviews in clinical and experimental pharmacology*, *17*(2), 114–121. https://doi.org/10.2174/1574884716666210316114157

Platform Trial Design

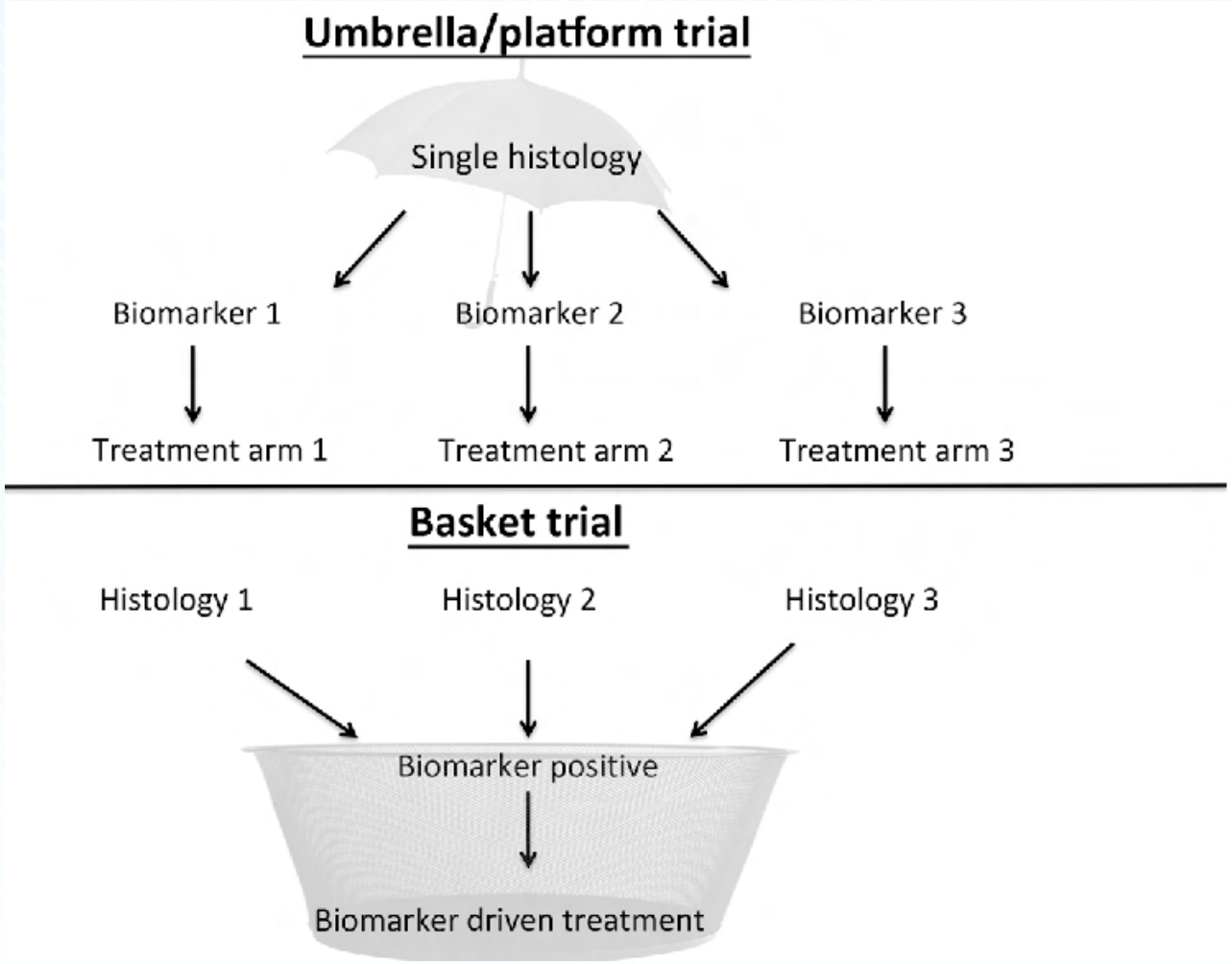
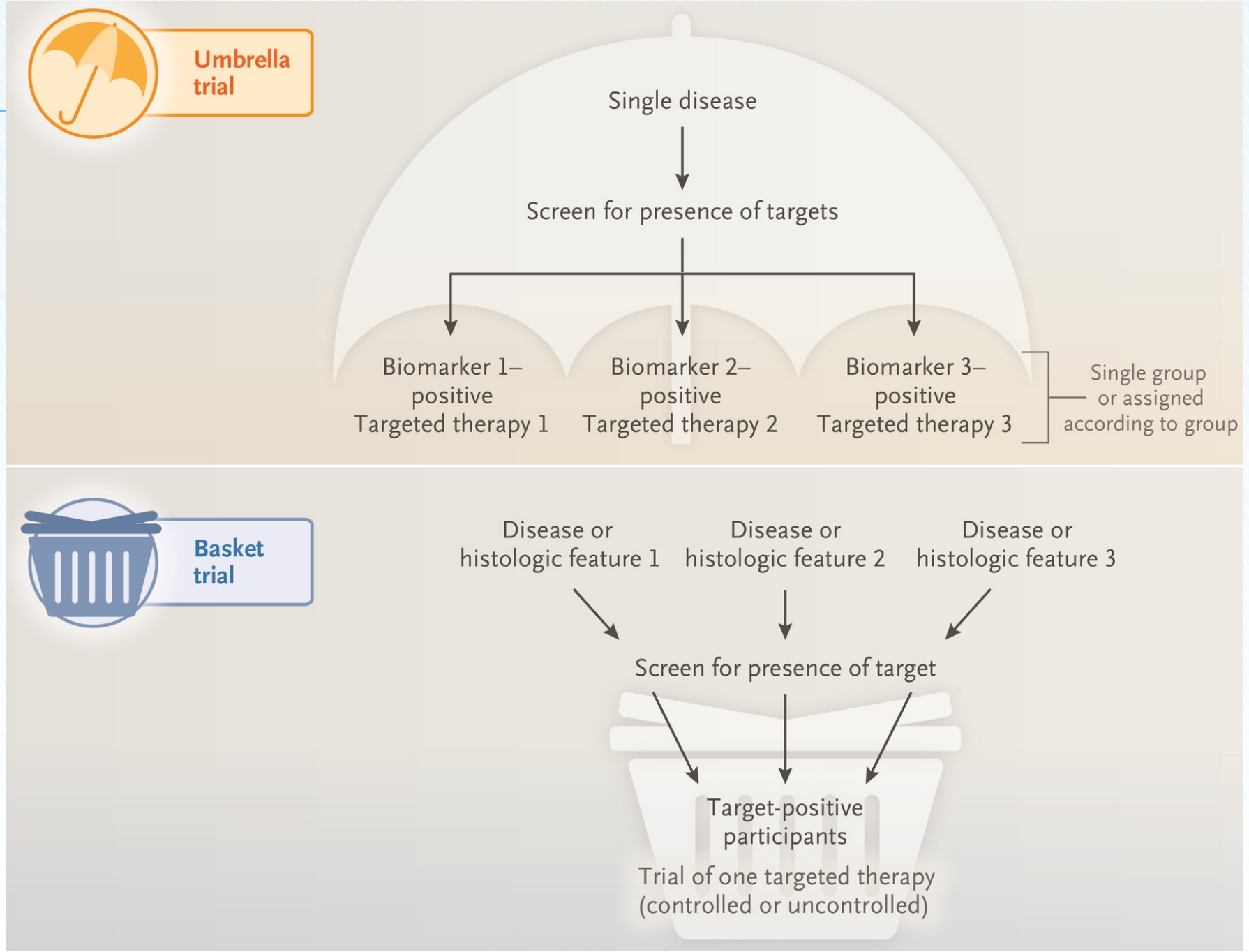


Figure 1.
A, Study schema for an umbrella or platform trial.
B, Study schema for a basket trial.

Woodcock, J., & LaVange, L. M. (2017). Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *The New England journal of medicine*, *377*(1), 62–70. https://doi.org/10.1056/NEJMra1510062

Platform Trial Design

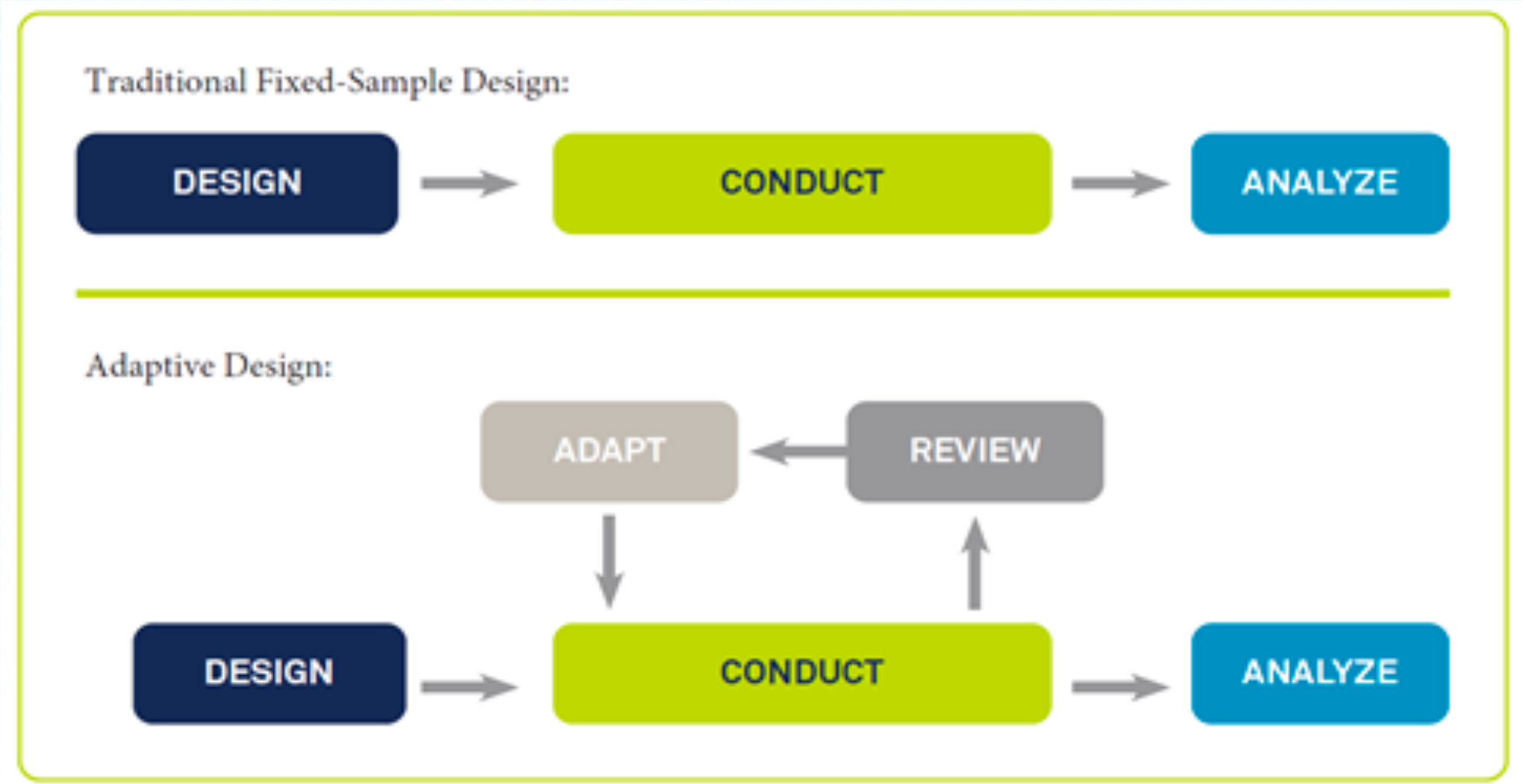


Woodcock, J., & LaVange, L. M. (2017). Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both. *The New England journal of medicine*, *377*(1), 62–70. https://doi.org/10.1056/NEJMra1510062

Adaptive Platform Trials

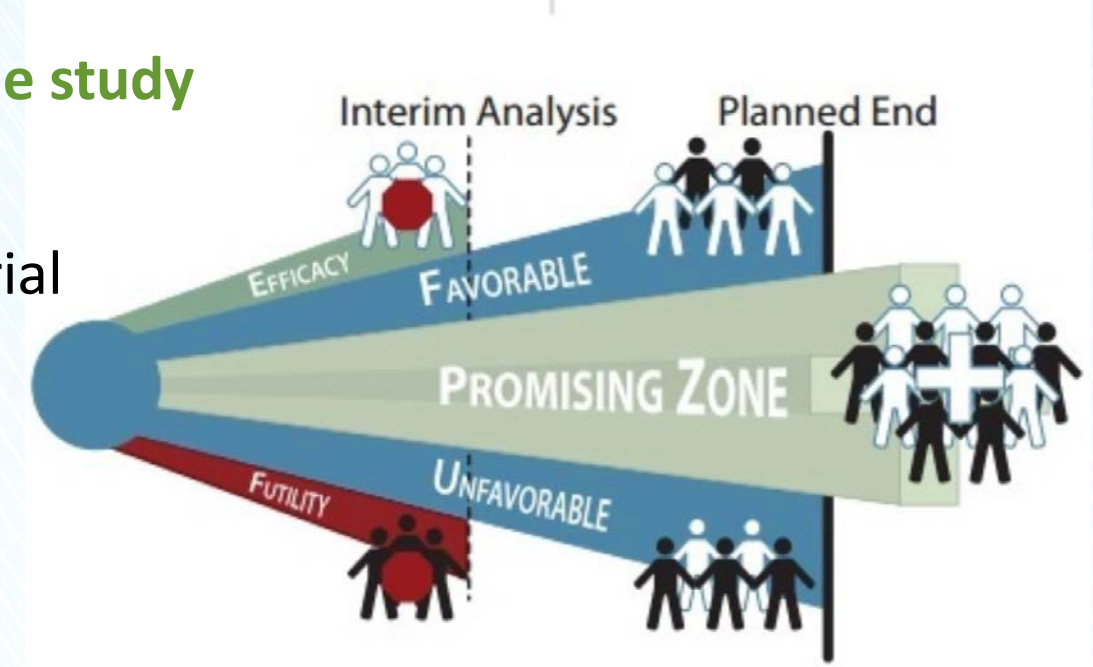
- Need efficient trial strategies to evaluate multiple treatments and combinations of treatments, in patient populations over time.
- Efficiencies:
  - Concurrent control arm with multiple investigational interventions
  - Regulatory, ethical, operational
- Challenges: long-term commitment of resources, personnel

Comparison between Trial Designs



Adaptive Trial Design – What Adaptations?

- Allows assessment of response to **treatment while the study is running**
- Can incorporate findings from within or outside the trial
  - Eligibility
  - Biomarker information
  - Treatments
  - Endpoints
  - Randomization
- This allows the trial to stay current with the latest updates and potentially increase recruitment and retention.

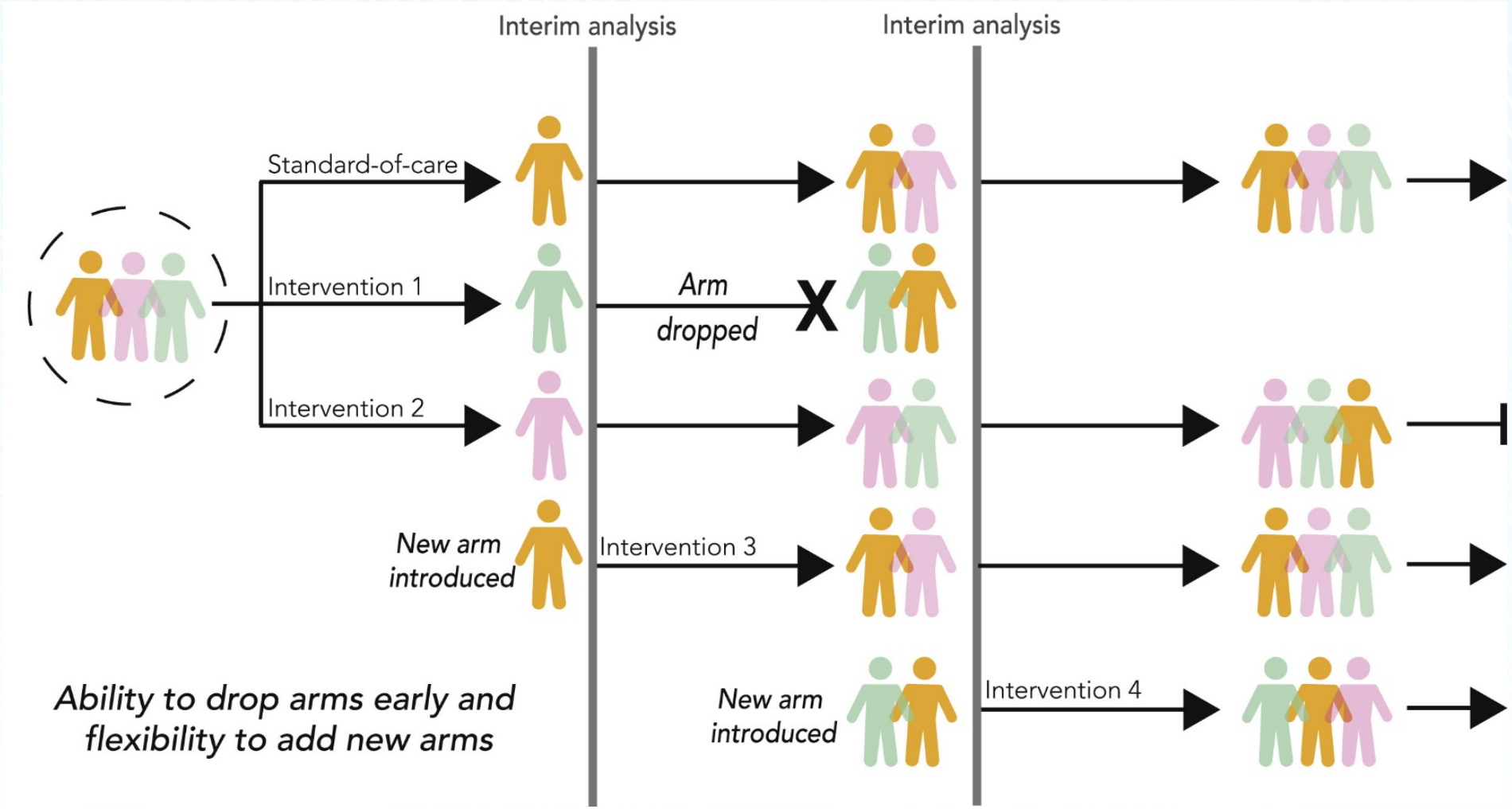


Adaptive Designs (reference slide examples)

Trial adaption, and cited examples of use	Type of adaptive design (AD) and example statistical methods
Changing the predetermined sample size in response to inaccurate assumptions of study design parameters to achieve the desired statistical power.	Sample size re-estimation (SSR) using aggregated interim data from all participants or interim data separated according to allocated treatment.
Stopping the trial early for efficacy, futility, or safety when there is sufficient evidence	Group sequential design futility assessment using stochastic curtailment.
Evaluating multiple treatments in one trial allowing for early selection of promising treatments or dropping futile or unsafe treatments and add to ongoing trial.	Multi-arm multi-stage (MAMS), dose/treatment-selection, drop-the-loser, or pick-the-winner, or add arm.
Changing the treatment allocation ratio to favor treatments indicating beneficial effects.	Response-adaptive randomization.
Multiple trial phases, in one trial under a single protocol.	Operationally or inferentially seamless AD.
Adjusting the trial population or selecting patients with certain characteristics that are most likely to benefit from investigative treatments.	Population or patient enrichment or biomarker AD.
Changing the primary research hypotheses or objectives or primary endpoints. For example, switching from non-inferiority to superiority.	Adaptive hypotheses.
Switching the allocated treatment of patients to an alternative treatment influenced by ethical considerations, for instance, due to lack of benefit or safety issues.	Adaptive treatment-switching.
Combination of at least two types of adaptations.	Multiple; inferentially seamless phase 2/3 or population enrichment; biomarker-stratified with RAR; adaptive platform trials.

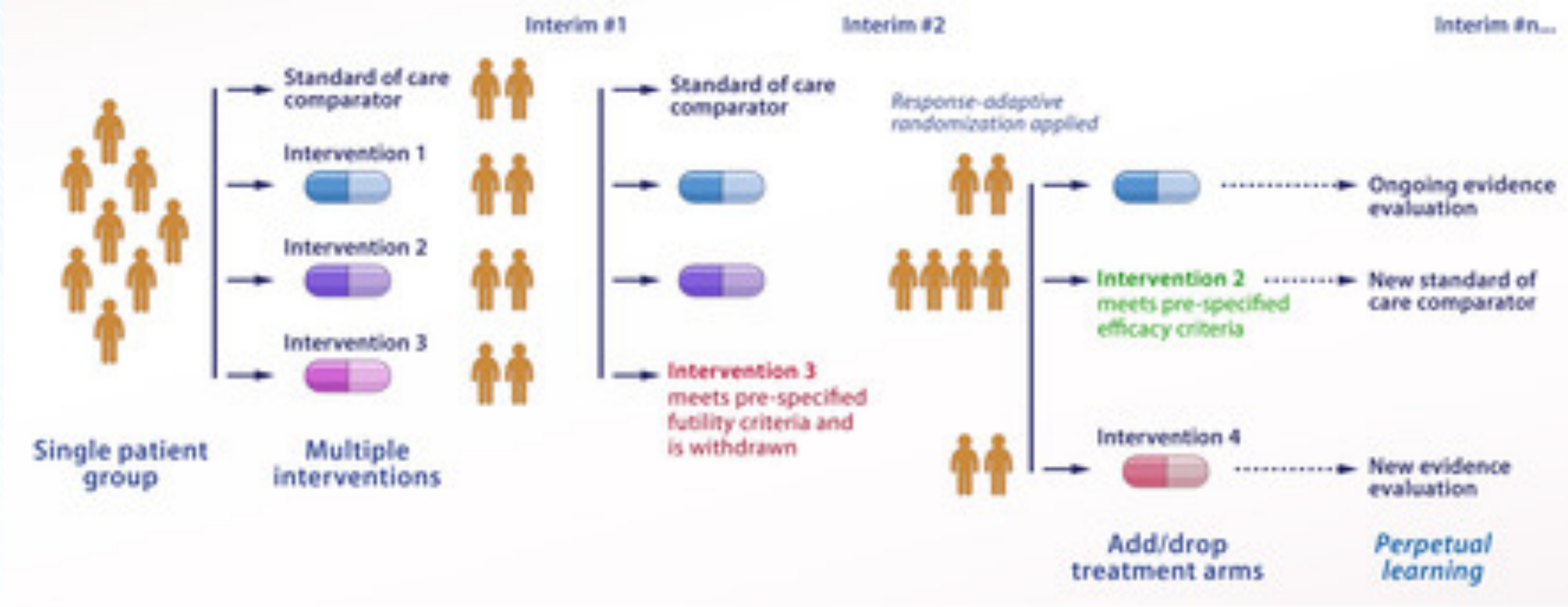
Adapted from: Dimairo, M., et al. Trials 21, 528 (2020). https://doi.org/10.1186/s13063-020-04334-x

Platform Trial - Randomized



Park JHJ et al. J Clin Epi 125: 1-8, 2020. https://doi.org/10.1016/j.jclinepi.2020.04.025

Platform Design – Randomized Response Adaptive



Patrick R. Lawler. Circulation. 145, Issue: 9, Pages: 629-632, DOI: (10.1161/CIRCULATIONAHA.121.058113)

Risk of Bias in Platform Trials

- Prespecified plans for interim and statistical analyses used in the trial
  - Prespecified plans applied equally to all interventions
- Concurrent/nonconcurrent randomized participants for statistical comparisons
- Information flow/results
  - Investigational Drug Steering Committee (IDSC), Trial Committee, Participants
- Follow reporting guidelines in publications

Summary - Traditional and Platform Trials

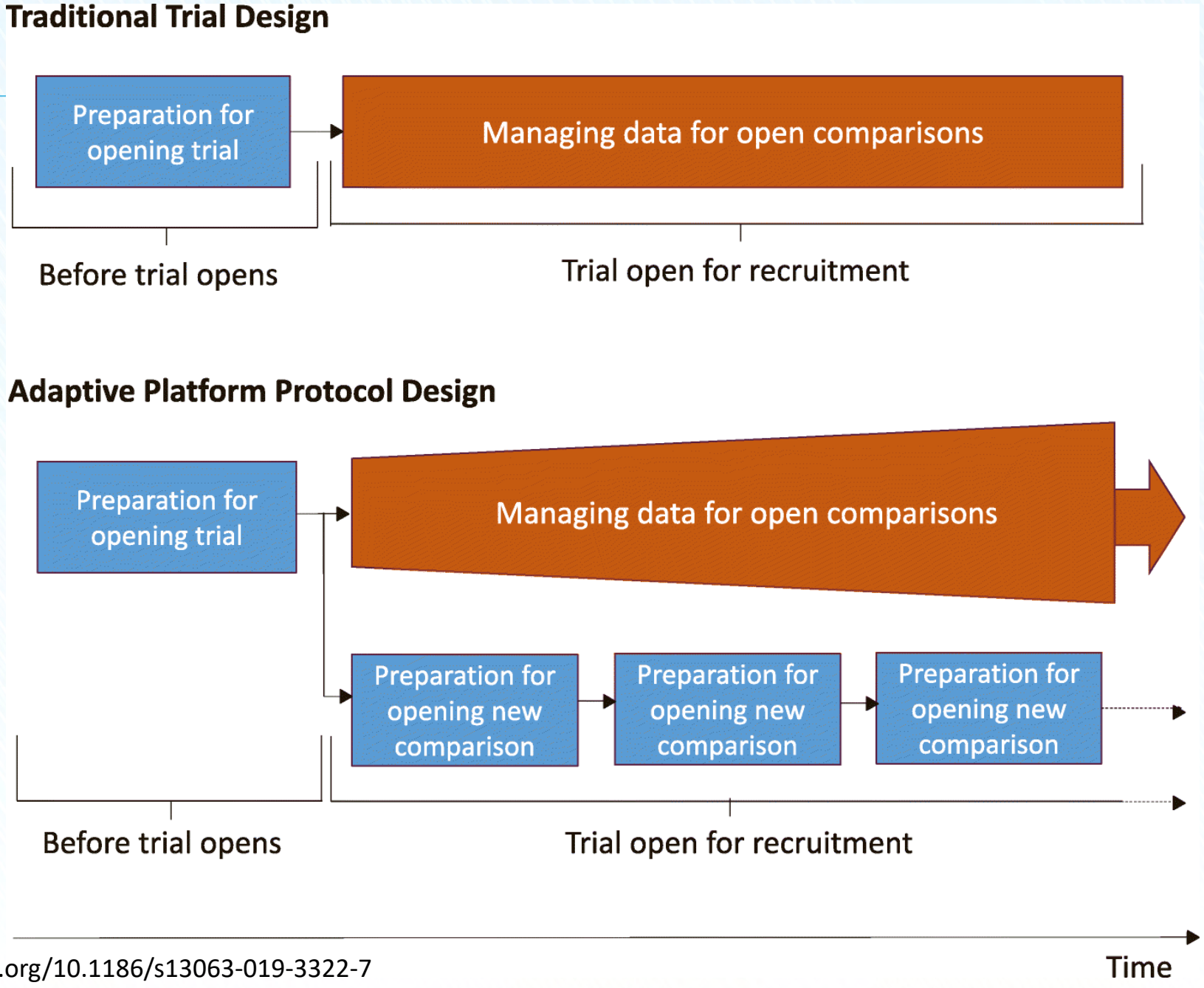
Table. General Characteristics of Traditional and Platform Trials[a]

Characteristic	Traditional Trial	Platform Trial
Scope	Efficacy of a single agent in a homogeneous population	Evaluating efficacy of multiple agents in a heterogeneous population; explicitly assumes treatment effects may be heterogeneous
Duration	Finite, based on time required to answer the single primary question	Potentially long-term, as long as there are suitable treatments requiring evaluation
No. of treatment groups	Prespecified and generally limited	Multiple treatment groups; the number of treatment groups and the specific treatments may change over time
Stopping rules	The entire trial may be stopped early for success or futility or harm, based on the apparent efficacy of the single experimental treatment	Individual treatment groups may be removed from the trial, based on demonstrated efficacy or futility or harm, but the trial continues, perhaps with the addition of new experimental treatment(s)
Allocation strategy	Fixed randomization	Response-adaptive randomization
Sponsor support	Supported by a single federal or industrial sponsor	The trial infrastructure may be supported by multiple federal or industrial sponsors or a combination

[a] Platform trials and similar trials may also be called basket, bucket, umbrella, or standing trials.

Berry SM et al. JAMA. 2015;313(16):1619-1620. doi:10.1001/jama.2015.2316

Trial Management



Hague, D., et al. Trials 20, 294 (2019). https://doi.org/10.1186/s13063-019-3322-7

Key Considerations: Preplan and Prespecify

- Selection criteria of new research questions & interventions
- Clinical leadership
- Scientific peer review
- Funding/sustainability
- Biomarker development and cohort selection
- Investigator/site engagement & feasibility of accrual
- Protocol development
- Ethics and regulatory assessment and version control
- Clear terminology
- Contracts and drug supply
- CRFs and database changes
- Site implementation
- Trial management priorities
  - New, ongoing, IA

Revamping clinical trial designs to reflect wider representation of the population

- Adaptive clinical trial designs allow for pre-specified trial design changes during the trial when data becomes available.
  - The adaptive design may begin with a narrow population if there are concerns about safety, then expand to a broader population based on interim safety data from the trial that provide support for increasing inclusion.
  - Broadening the inclusion criteria based upon interim assessments
  - As the trial progresses, data may reveal the need to decrease the frequency of study visits, thus allowing more flexibility in visit windows and potentially supplementing with electronic communication as appropriate.
    - Thus, easing the burden on the trial participants and potentially increasing recruitment and retention.

New clinical trial design allows for more representative settings of real-world conditions

- Adaptive designs allow for more **flexibility** to the clinical trials and for **modifications during the course** of the trial in order to streamline and optimize the process.
- This innovative approach has the potential to:
  - Reduce resource use
  - Decrease time to trial completion
  - Limit allocation of participants to inferior interventions, and
  - Improve the likelihood that trial results will be scientifically or clinically relevant

Pragmatic Clinical Trial Design

- The idea was actually introduced in 1967 by Schwartz and Lellouch
- Pragmatic trials are designed to evaluate the ***effectiveness*** of interventions in real-life routine practice
- Pragmatic trials produce results that can be ***generalized*** and ***applied*** in routine practice settings.
- Pragmatic trials may test the same intervention as an explanatory trial, but they are conducted in real-world clinical practice settings, with typical patients and by qualified clinicians.

"If we want more evidence-based practice, we need more practice-based evidence."

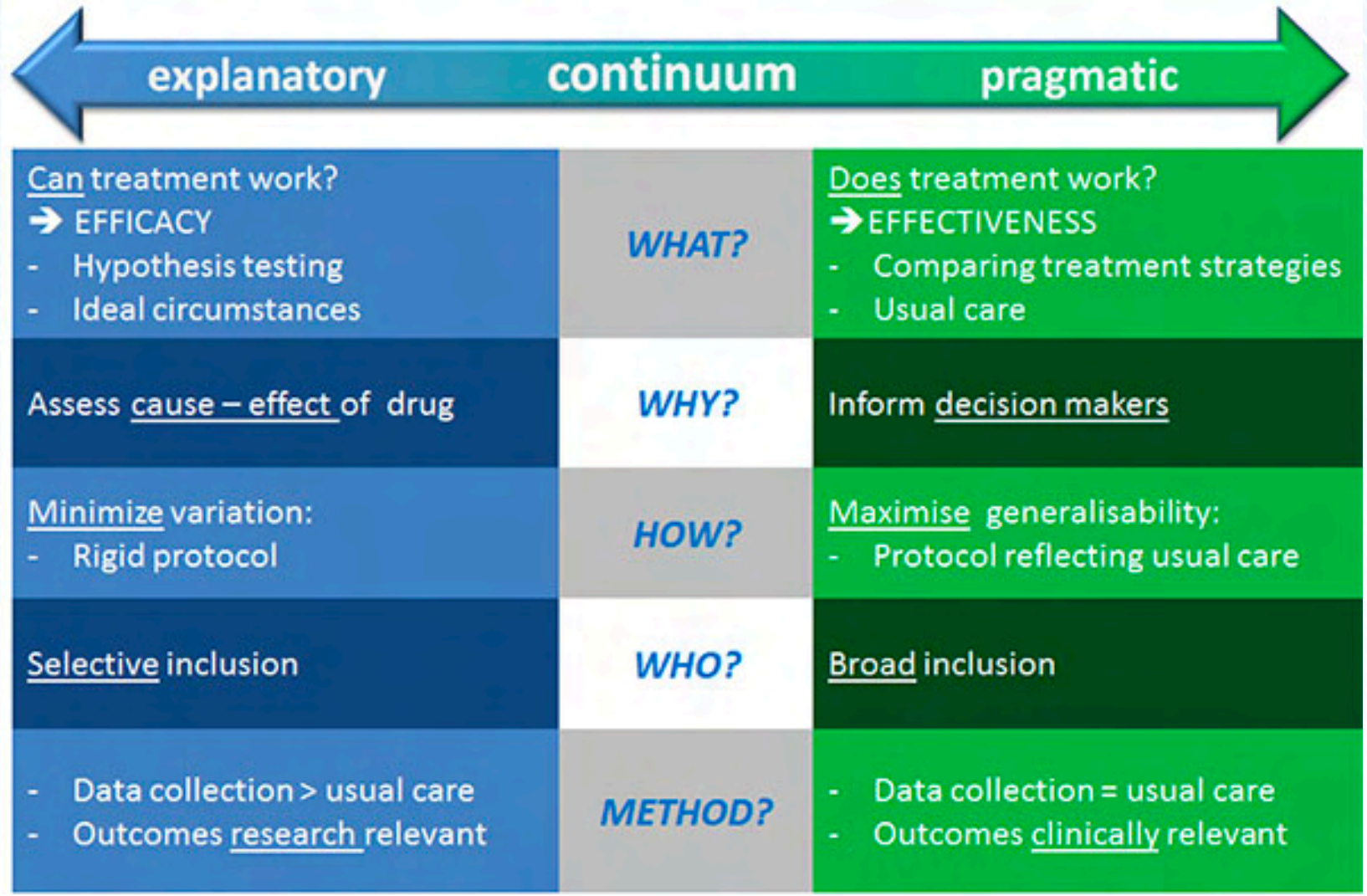
Green, LW. American Journal of Public Health, 2006.

Le-Rademacher, J., Gunn, H., Yao, X., & Schaid, D. J. (2023). Clinical Trials Overview: From Explanatory to Pragmatic Clinical Trials. *Mayo Clinic proceedings*, *98*(8), 1241–1253. https://doi.org/10.1016/j.mayocp.2023.04.013

Key Differences

Explanatory	versus	Pragmatic
Can the intervention work?	Question	Does the intervention work when used in real world practice?
Well-resourced, ideal	Setting	Real world practice
Highly selective, excludes many, poor adherence, homogenous	Participants	Little or no selection beyond the clinical indication of interest, heterogenous
Strictly enforced, adherence is closely monitored	Intervention	Applied flexibly
Short-term surrogates, process measurements	Outcomes	Directly relevant to participants, funders, communities, and healthcare providers
Indirect: little effort made to match the design of the trial to the decision-making needs of those in the usual setting in which the intervention will be implemented	Relevance to Practice	Direct: the trial is designed to meet the needs of those making decisions about treatment options in the setting in which the intervention will be implemented

Explanatory versus Pragmatic Trials



REACHING *Underserved* POPULATIONS

Why do we need Pragmatic Trials?

- We are not reaching patients with complex, comorbid conditions and those most in need.
- Traditional research rarely happens in typical clinical settings, thus findings often aren't feasible for real-world uptake.
- We are not asking questions important to providers, patients, administrators, or policymakers.

Key Messages: IMPACT

- Modern clinical trial designs offer several practicable and desirable benefits which facilitate faster answers and allow clinical trials to serve as a tool to move treatment on for patients much more quickly.
- The use of shared resources across multiple comparisons must be cost-saving compared to separate two-arm non-adaptive trials to address the same questions.
- There are notable design, operational and logistical challenges which require careful attention.

References/Additional Sources

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THANK YOU …

- For your time and attention today

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Question Time

Extra Slides

Area	Proposed Approach
Research question	Define criteria for review of new interventions
Trial Management Group	Collaborative Group Study chair/principal investigator: overall trial oversight Co-chairs/PIs: clinical and scientific leadership for addition of new trial interventions
Scientific peer review	Ongoing discussion with key funding stakeholders/partners Planning for adequate support of central and site resources Addition of new comparison discussed in early stages to assess feasibility of funding
Biomarker	Clearly define cohort and identify biomarkers, assure feasibility and laboratory QC
Protocol	Consider futureproof changes in trial design (e.g. modular)
Ethics/Regulatory approval	Rationale for addition of new interventions discussed early with regulatory bodies
CRF and database	Timelines for implementing changes are key for timely implementation
Site implementation	Engage early (e.g. via survey) to gauge interest in new research question Discuss activation criteria with centers Pre-set timelines for local approval of new comparison (if control arm is shared)
Other	Constant assessment of priorities and competing tasks (e.g. new, ongoing versus interim analysis tasks) Importance of adequate resourcing for trial management team

Adapted Schiavone, F, et al. Trials 20, 264 (2019). https://doi.org/10.1186/s13063-019-3216-8