Quality Based Drug Development - Traditional versus – Non-Traditional Clinical Trials in the context of 21st century novel clinical research.

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DISCLAIMER

The Views expressed here are of our own and are not related to my employer

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Example of Differences in How Data from Conventional Randomized Controlled Trials (RCTs) & Real-World Evidence (RWE) are Utilized

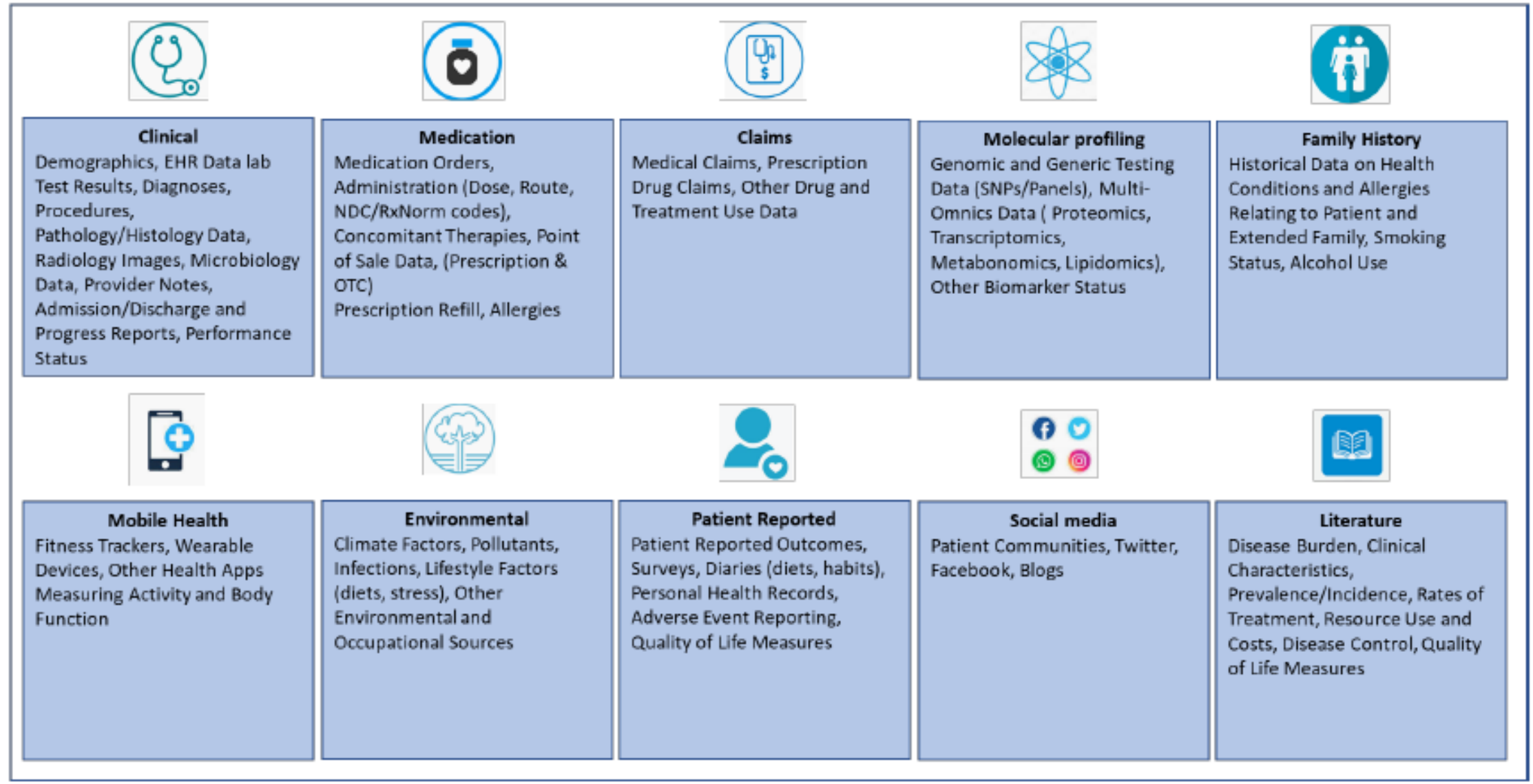
Characteristics	RCTs	RWE
Standard of evidence	Gold standard	Complementary to RCTs
Cost	Costly to develop	Less Costly
Patient Population	Well-defined within constraints of specific inclusion criteria Results reflect outcomes in limited population	Broader and promotes evaluation of patients populations less often studied in clinical trials Patient data derived from other sources, including insurance claims
Sample size	Limited Requires sample size calculation to be performed in advance	Orders of magnitude larger
Efficacy	Randomized and blinding lead to minimized risk of data bias and confounding	Randomization and blinding may not be feasible Risk of unrecognized data bias and confounding greater
Adverse events	Only more frequently occurring adverse events revealed	Can reveal adverse events with much lower frequency and those requiring longer exposure to occur
Approval or Clearance of new medical products	Considered the gold standard necessary for new drug approval, and when feasible for new device approval	Not generally accepted for approving new drugs but can complement RCT findings, accepted for new device indications
Role in diabetes	Define efficacy and provide a preliminary safety profile in a well-defined and controlled population	Allows estimation of more realistic treatment effects of a wide range of diabetes interactions such as social determinants of heath and comorbidities
Other issues	May be less useful when strong signals are available form RWE or early-phase trials	Facilitates post marketing surveillance of adverse events and assessment of the product effectiveness Results may be less credible due when a control group is not included

INTRODUCTION

It is well evident that safety and efficacy data collected from randomized controlled trials (RCT) provide high quality data on restricted patient populations and has been standard for determining market authorization. There are reasonable benefits in using RWE:

- Less time and cost to produce meaningful data
- Ability to capture additional information
- Social determinants of health that can impact health outcomes
- Detection of uncommon adverse events
- Better utilization of innovative technologies such as AI, ML and Block Chain
- Data articulation to achieve 21st century novel clinical research objectives.
- Helpful in the generation of subjects pharmacogenomic information and pharmacokinetic differences between individual subjects.

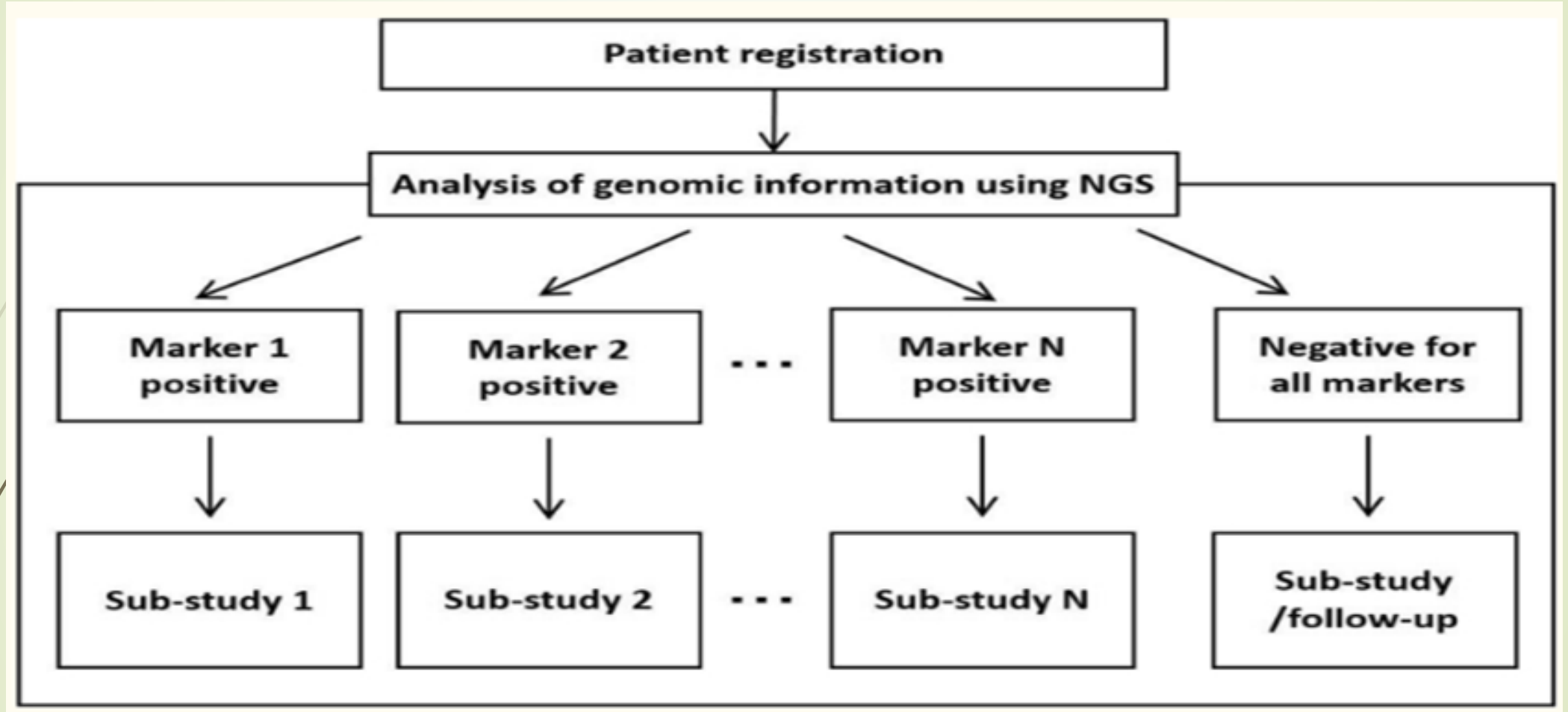
Some Examples of Real-world data



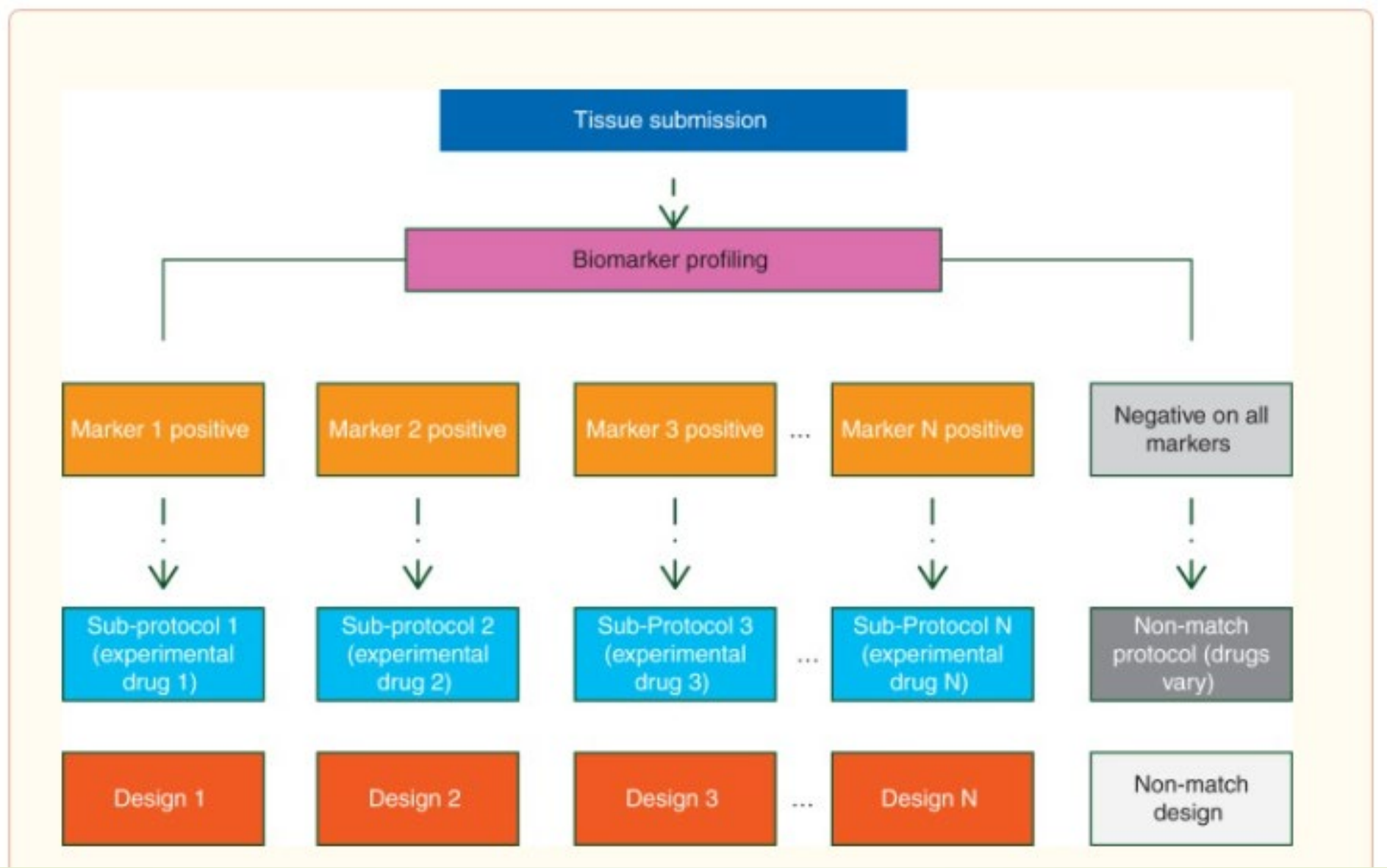
Categorizing Modern Oncology Clinical Trial Designs

Name	Description
Platform trial	Evaluates many therapies in a particular disease or group of diseases. Therapies usually have different sponsors and may be combinations or sequences.
Standing trial	Platform trial in which therapies enter and leave over time.
Master protocol	A trial with multiple treatment options requiring separate protocols but under the same aegis. Informed consent is usually required for both the master protocol and the respective individual protocol.
Indication finder	Evaluates a particular therapy across multiple cancers that are defined by organ type, or across subtypes within a specific organ type. The goal is to determine which diseases or which biomarker subtypes are appropriate for further development.
Basket (or bucket) trial	Evaluates the effect of a particular targeted therapy on a particular genetic or molecular aberration across cancer organ types. Variant of indication finder but the therapy is not evaluated for its off-target effects.
Umbrella trial	This term may be useless because it is used for very different designs by different researchers and reporters. I use it for platform trials (many therapies) that are indication finders for each therapy.
Adaptive trial	Trials in which unblinded data are monitored and used to determine the future course of the trial based on prospectively defined decision rules.
Seamless phases[a]	A particular kind of adaptive trial that moves from one phase of drug development to another without pausing accrual. Decisions at the phase switch usually involve greater focus. Examples include dropping arms, dropping doses or schedules, dropping patient subsets, changing randomization proportions, estimating the sample size for the next phase, and there are many other possibilities. (I do not include changing primary endpoint for reasons indicated in the text.)

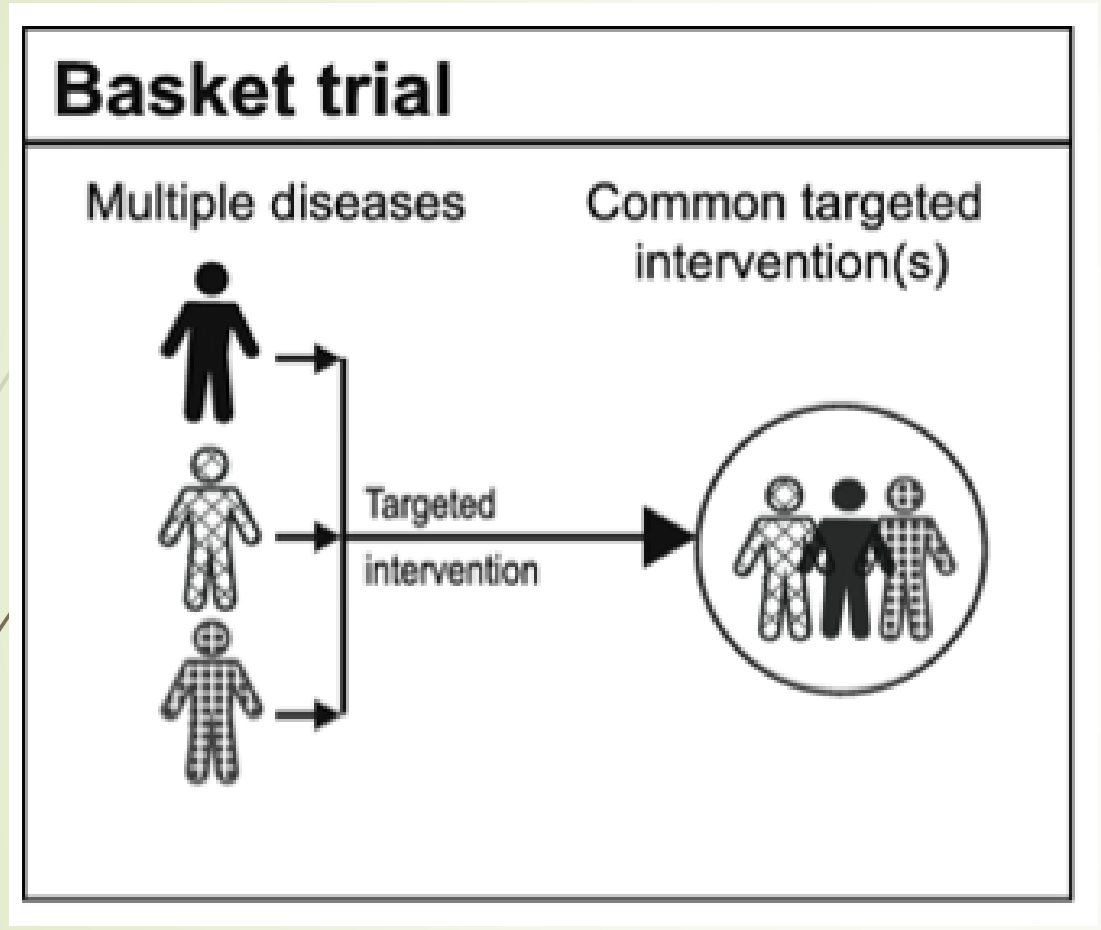
Master Protocol Trial

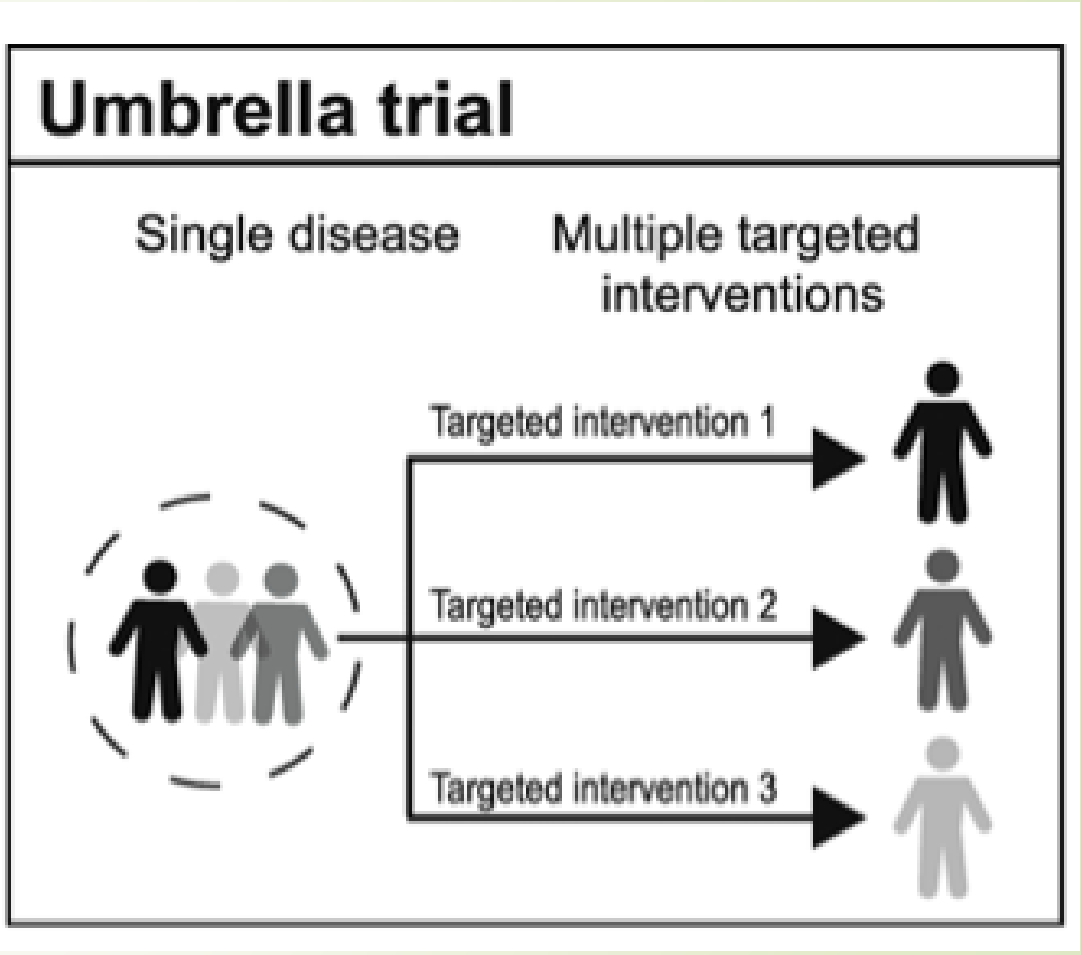


General Schema of a Master Protocol



Basket Trial & Umbrella Trial





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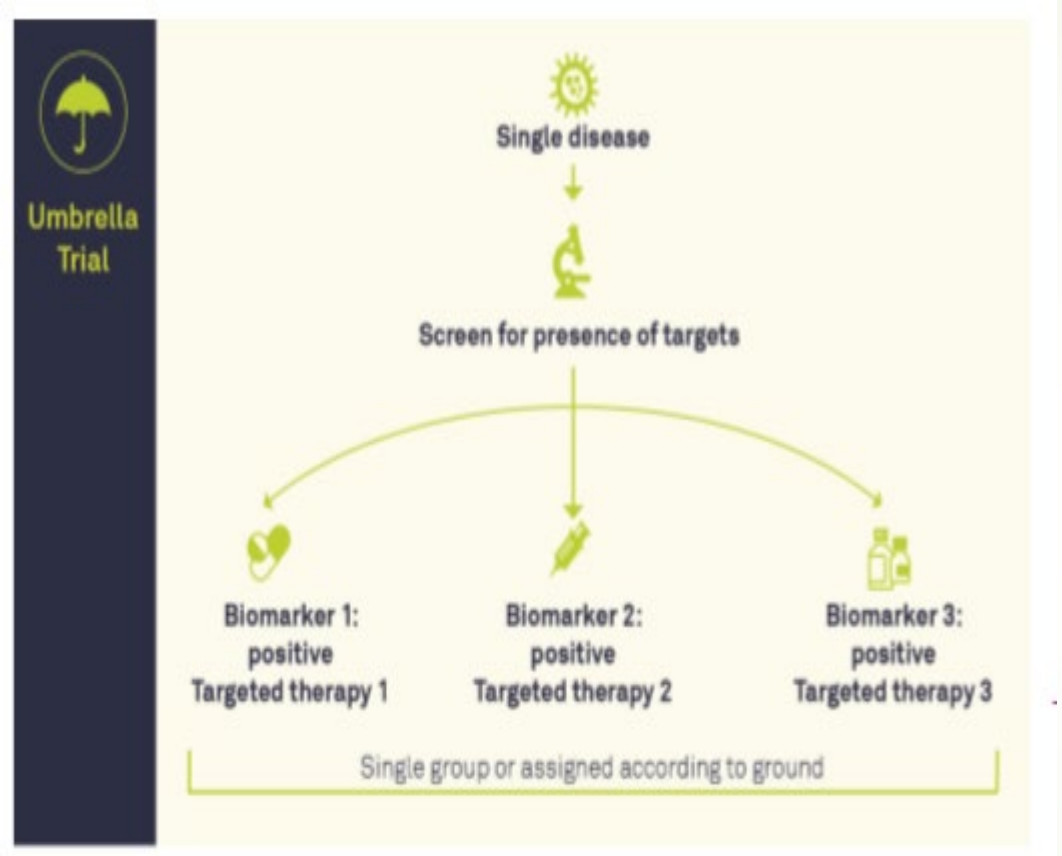
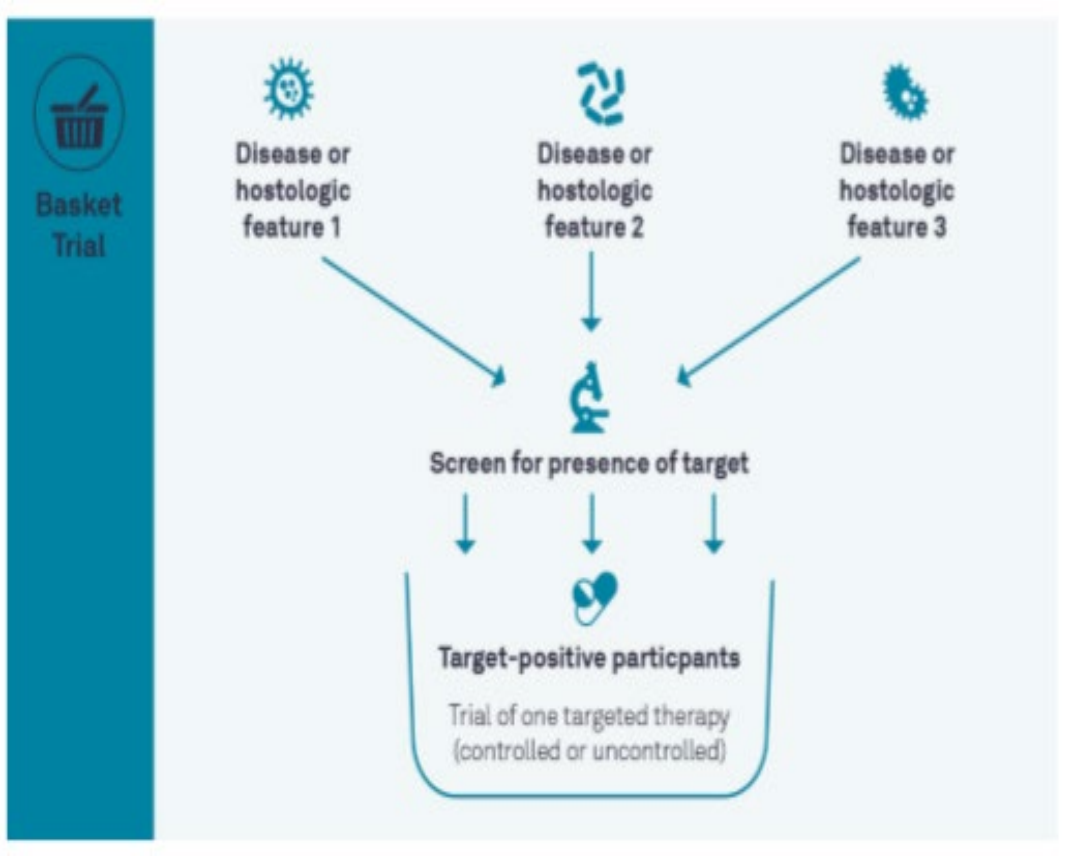
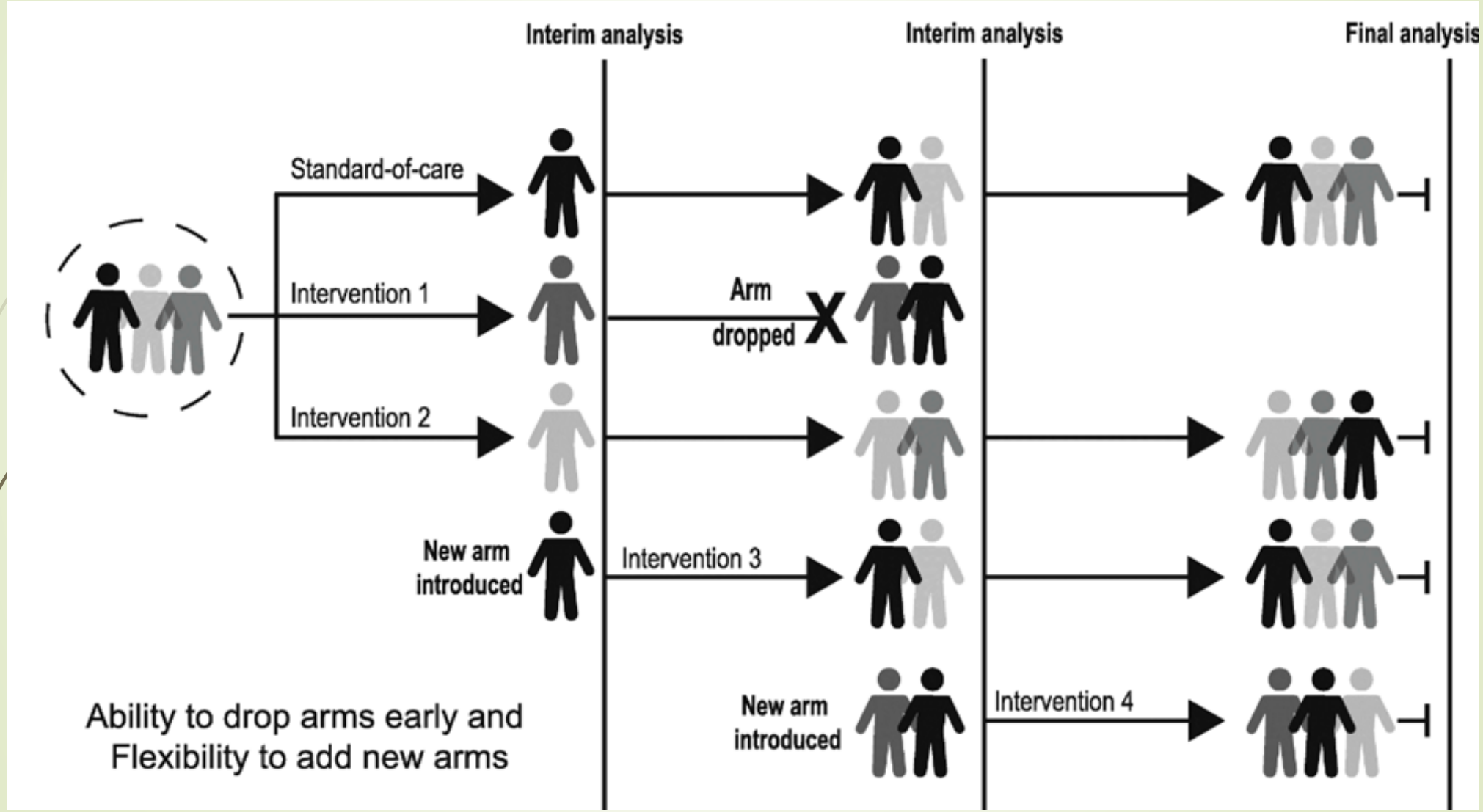
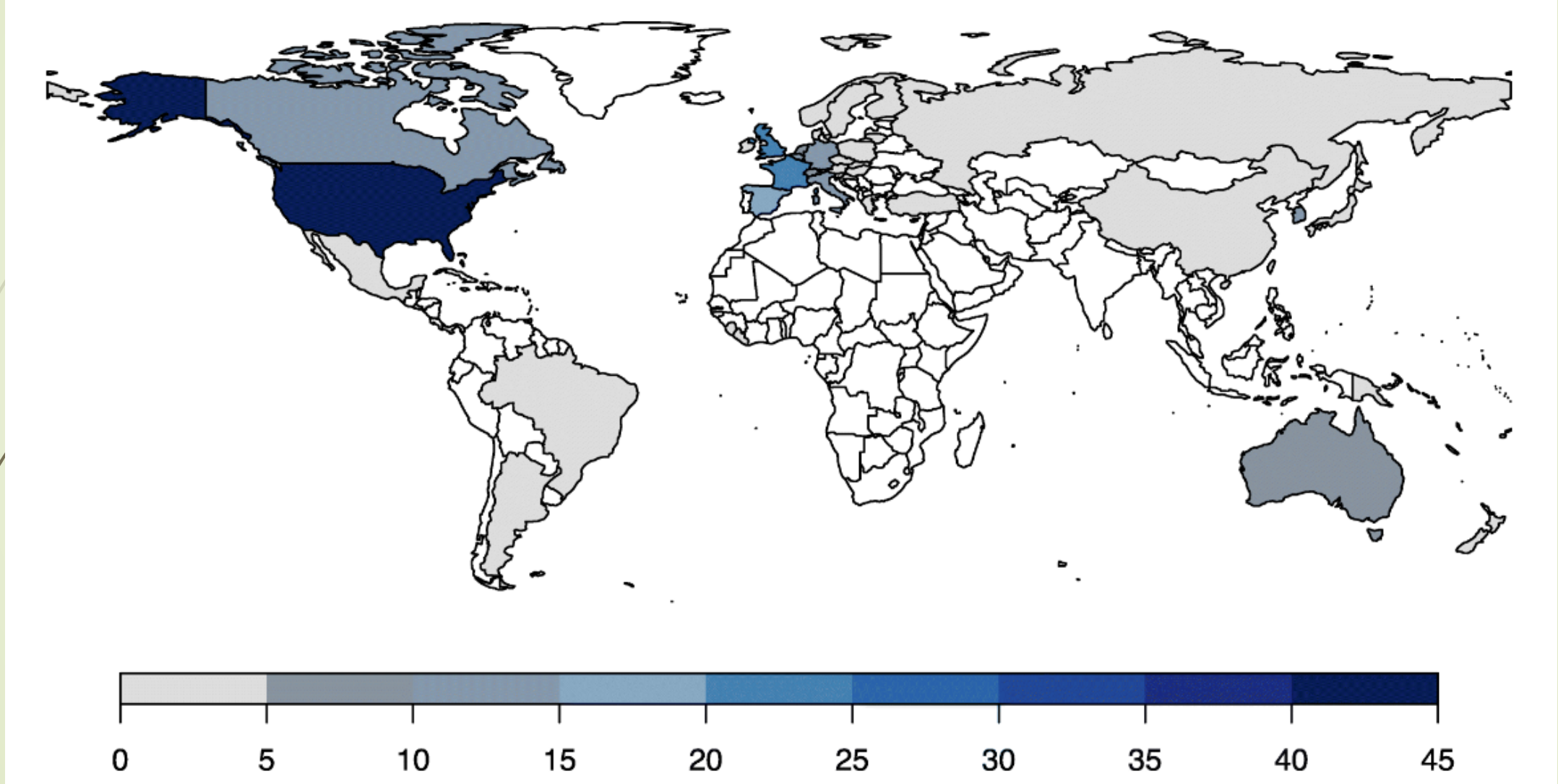




Platform Trial

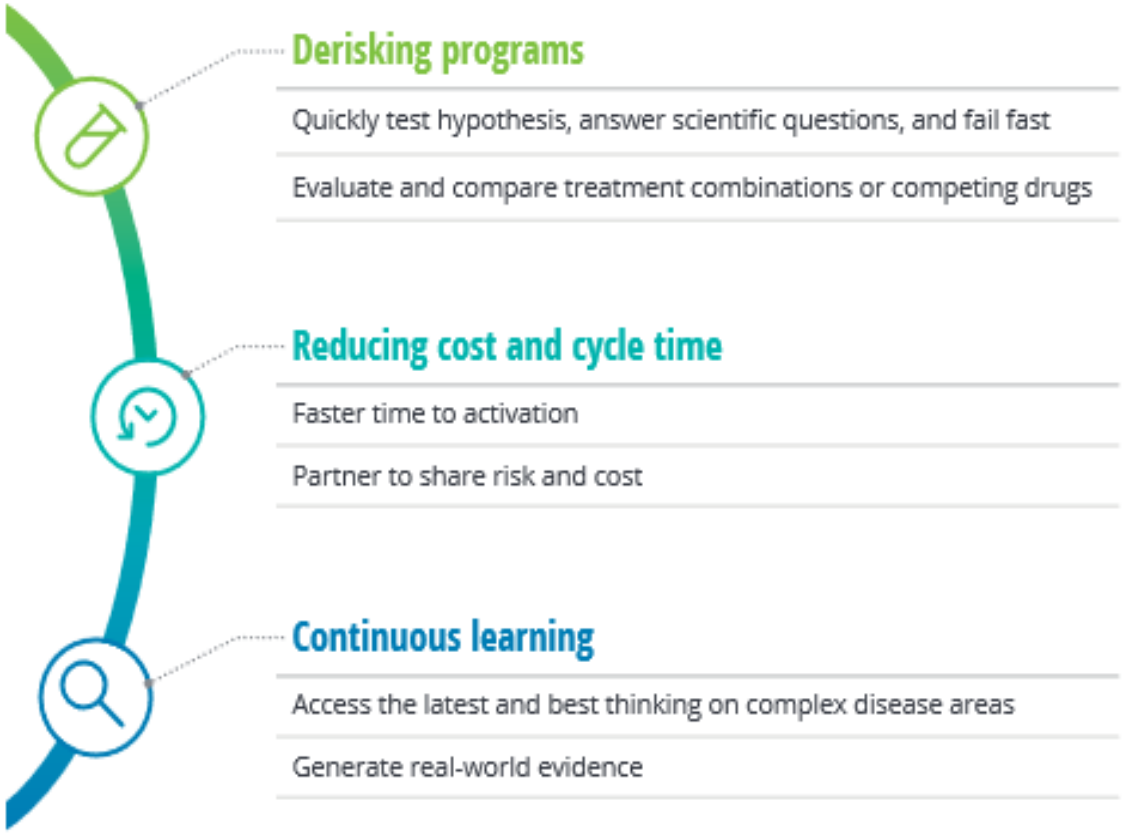


Countries Conducting Adaptive Trials



Benefits

Benefits of master protocols



Derisking programs

- Quickly test hypothesis, answer scientific questions, and fail fast
- Evaluate and compare treatment combinations or competing drugs

Reducing cost and cycle time

- Faster time to activation
- Partner to share risk and cost

Continuous learning

- Access the latest and best thinking on complex disease areas
- Generate real-world evidence

Cost-savings assumptions

Cost component	Estimated reduction in cost (percentage)*
Source data verification costs	10–20%
Site recruitment costs	20–25%
Site monitoring costs	20–25%
Administrative costs	20–25%
Shared cost of control arms	30–35%
Overhead costs	30–35%
Aggregate savings across entire trial	12%–15%

Savings – Time & Cost

Impact of cycle time savings

Traditional patient enrollment and site-startup time:
117 weeks

Master protocol patient enrollment and site-startup time:
96–102 weeks

Savings: 13%–18% (15–21 weeks)

Impact of cost savings

Traditional cost:
$11.2M

Master protocol cost:
$9.5–$9.8M

Savings: $1.3–$1.6M (12–15%)

Thank You

Q & A