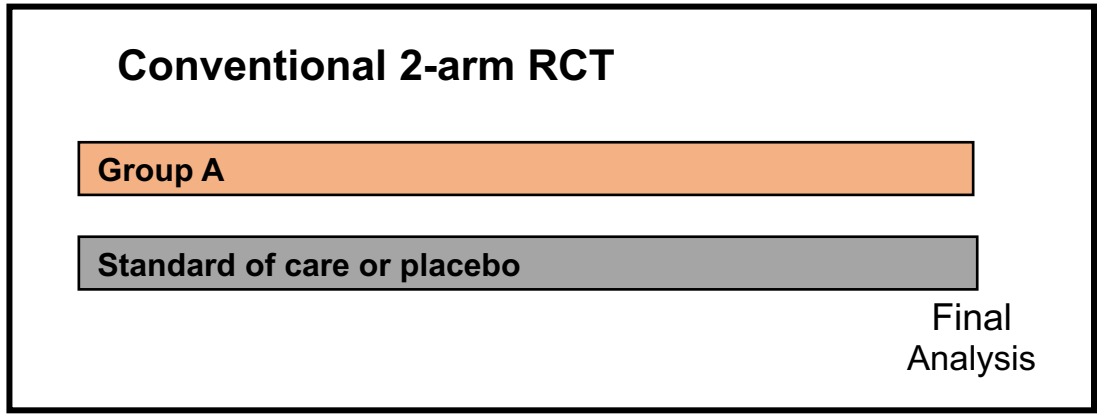
Improving efficiency and quality in clinical trials in global health research:

Adaptive trial designs and *master protocols*

Conventional trial designs and their problems

- Conventionally, randomized clinical trials (RCTs) are conducted with a **fixed sample size design** – e.g. two-arm parallel RCTs – that allow for one final analysis after a set number of participants finish follow-up



- Often, there are several areas with considerable degrees of uncertainty, so even if we come up with the optimal trial designs based on what we know in the planning stage, our assumptions may be shown to be inefficient or even wrong at the end

Adaptive trial designs

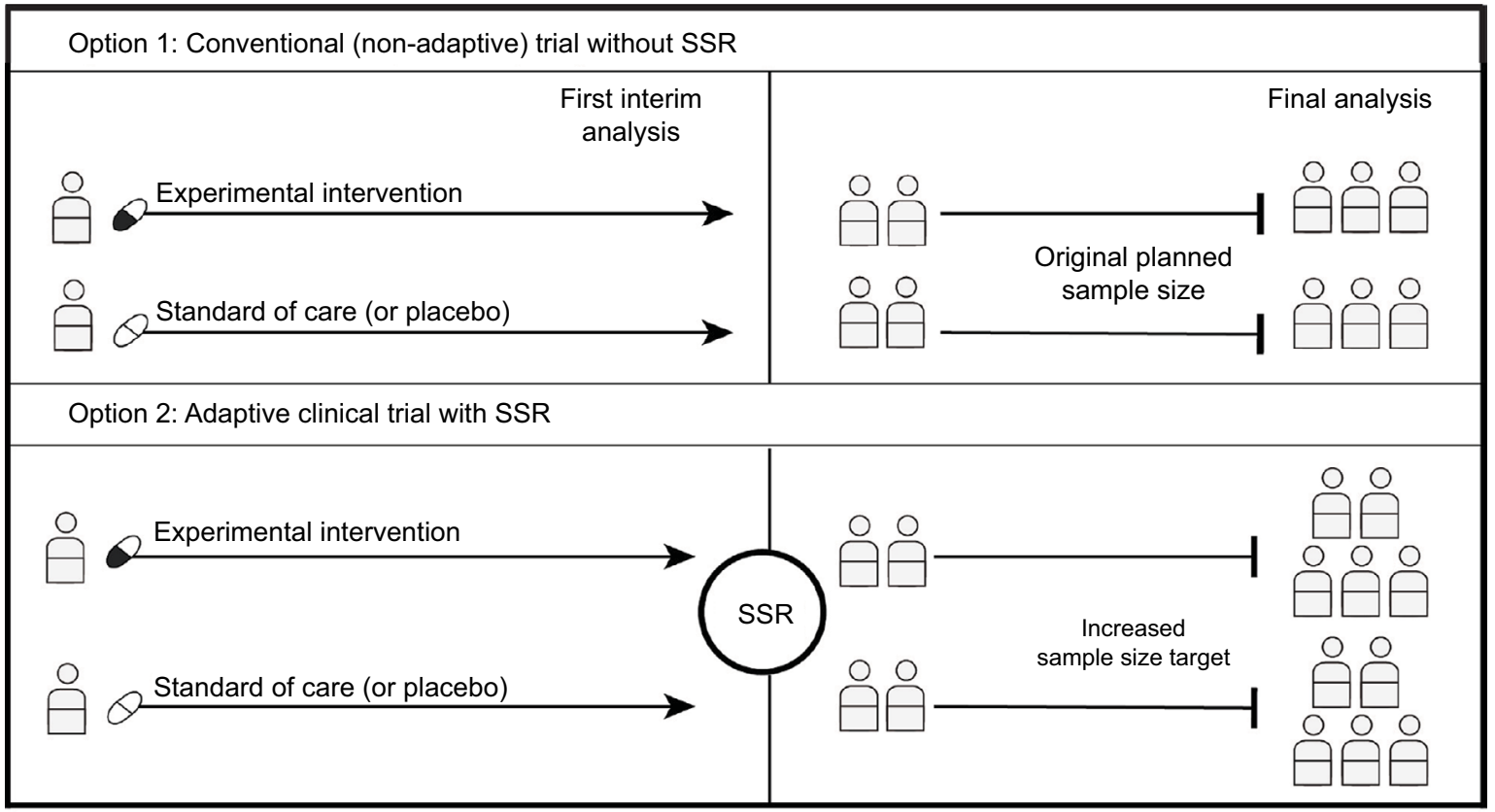
- They are an extension of conventional designs that allow for pre-specified modifications to the trial designs during the trial, with the decision for modifications being based on the interim data collected

- As data accumulates over time during the trial, the level of uncertainty we had initially will likely decrease. **Adaptive designs allow us to pre-specify adaptations in areas with uncertainty in the planning stage**

- This data-driven, adaptive learning nature allows the potential to reduce resource use, decrease time to trial completion, limit allocation of participants to inferior intervention(s), and/or improve the likelihood of success

Common types of adaptive trial designs:

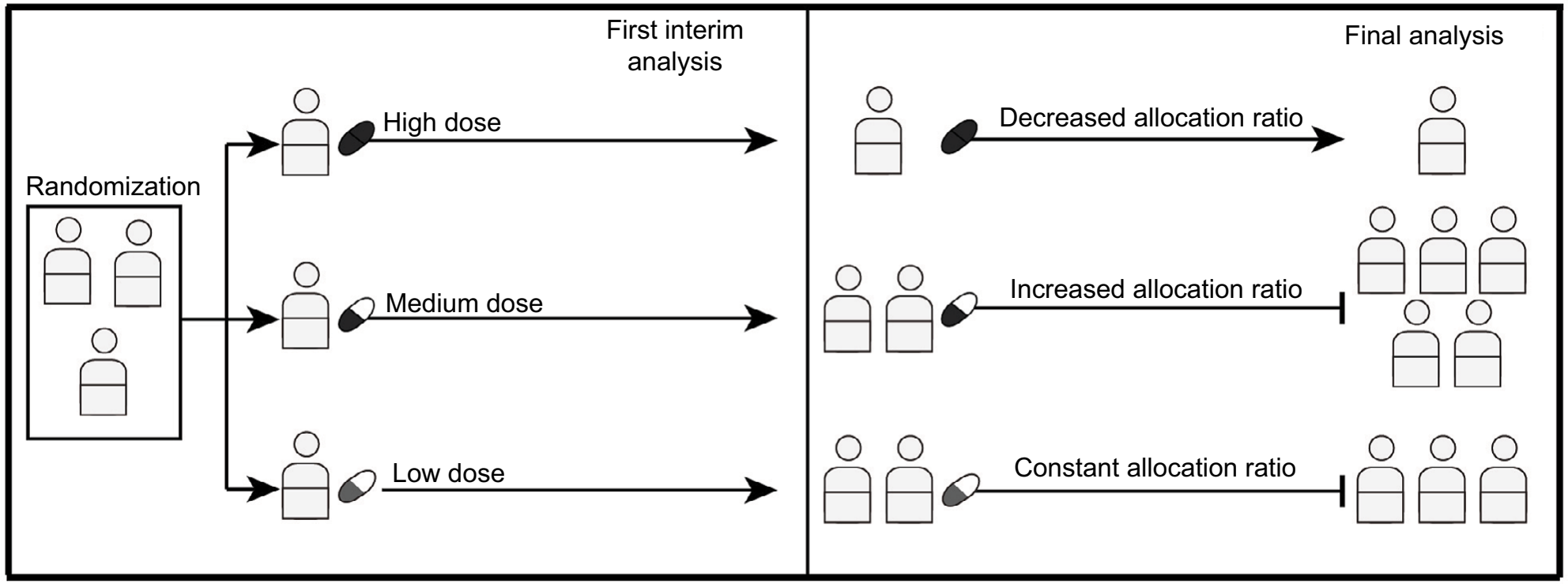
Sample size reassessment (SSR)



- Allows for changes sample target based on interim results

Common types of adaptive trial designs:

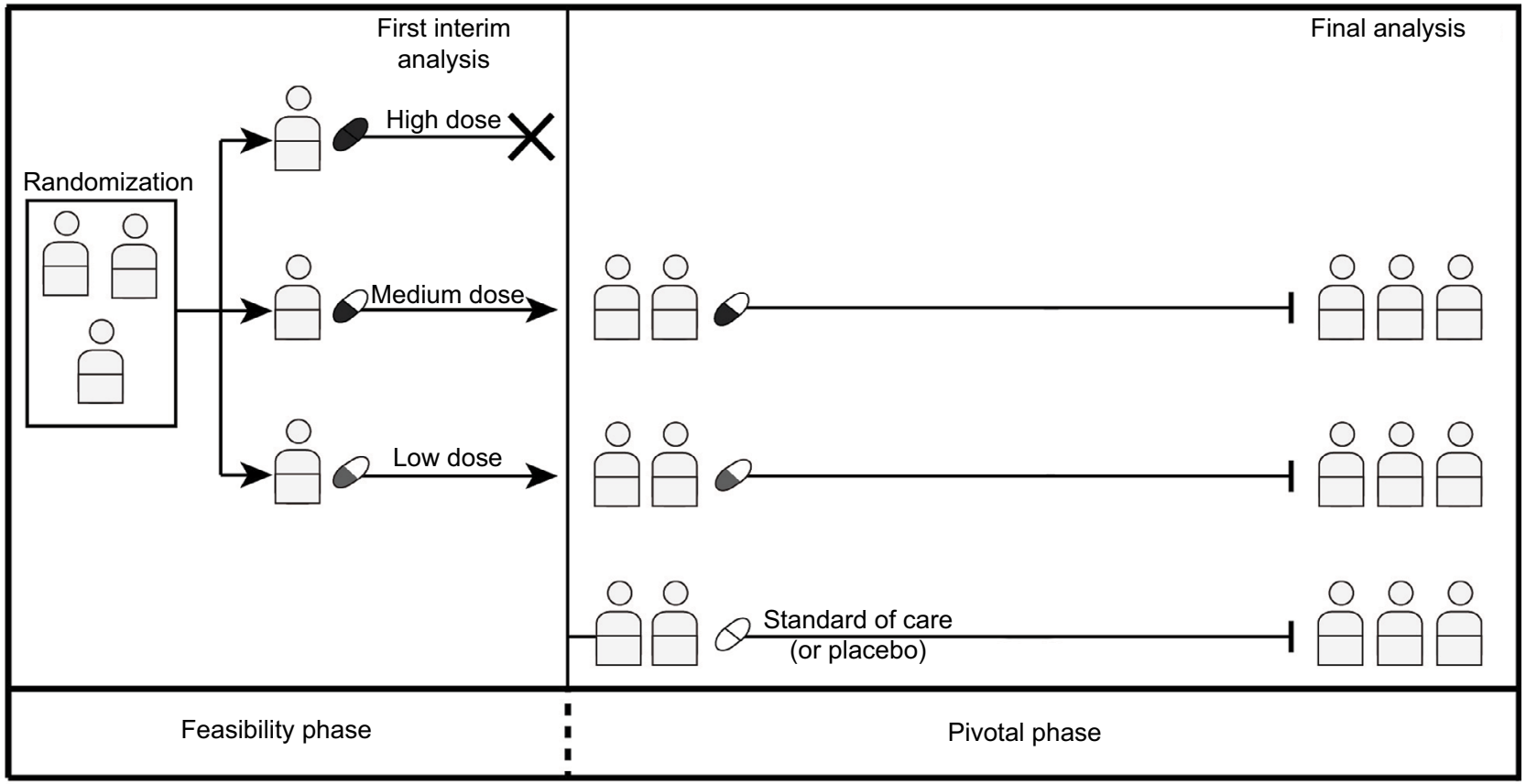
Responsive adaptive randomization



- Allows for changes in allocation ratio based on interim analyses in favor of intervention arm(s) with more favorable results

Common types of adaptive trial designs:

Seamless designs



- Allows for immediate continuation from one phase to a subsequent phase

Single-intervention hypothesis approaches in trial evaluation

- Instead of asking what the best intervention option is for a study population, single-intervention hypothesis approaches that ask whether a single intervention can offer benefits are commonly utilized in trial evaluation

- Even if they are adaptive, they can be inefficient and even problematic since the pace of scientific discovery can outpace the planned completion of the trials

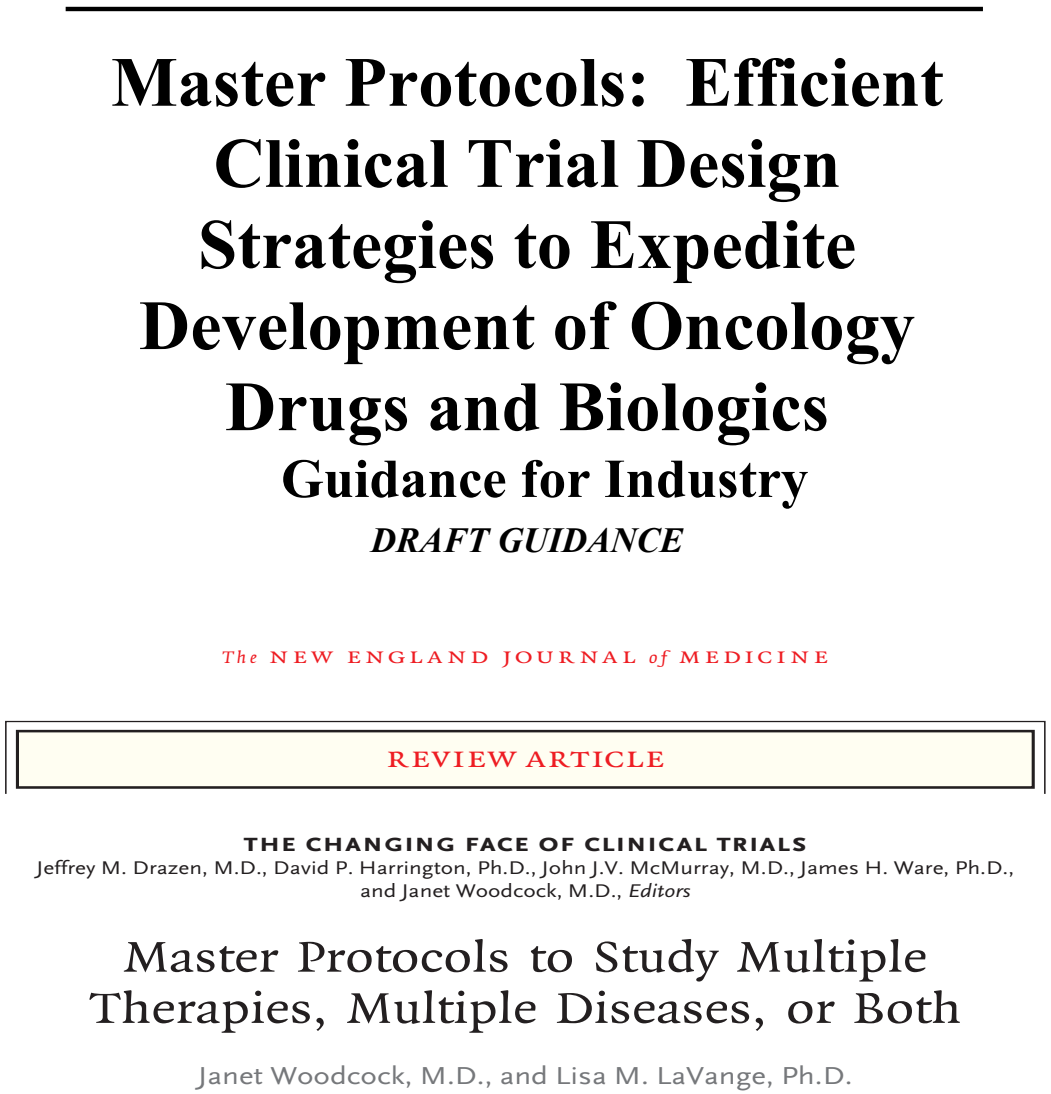
- Moving away from single-intervention hypothesis approach, a new concept of **master protocols** have emerged recently that have now been recognized by the FDA

Master protocols

- The term refers to **a single overarching design developed to evaluate multiple hypotheses**, with a goal of improving efficiency through standardized trial procedures

- Emerged from field of precision oncology that aims to find a targeted therapy based on their genetic mutation

- Often classified into three categories of 1) Basket trials; 2) Umbrella trials, and 3) **Platform trials**



Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics

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REVIEW ARTICLE

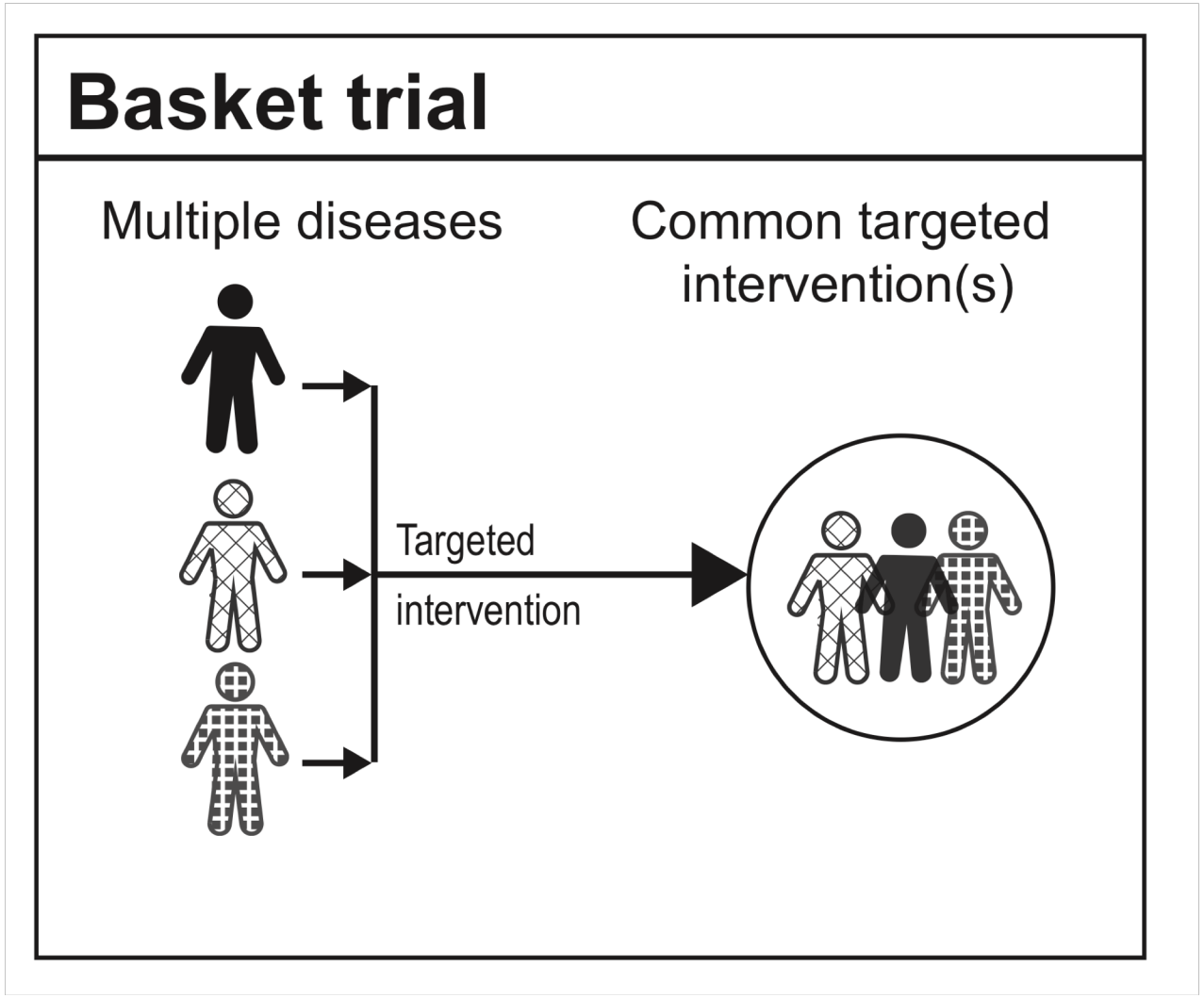
THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

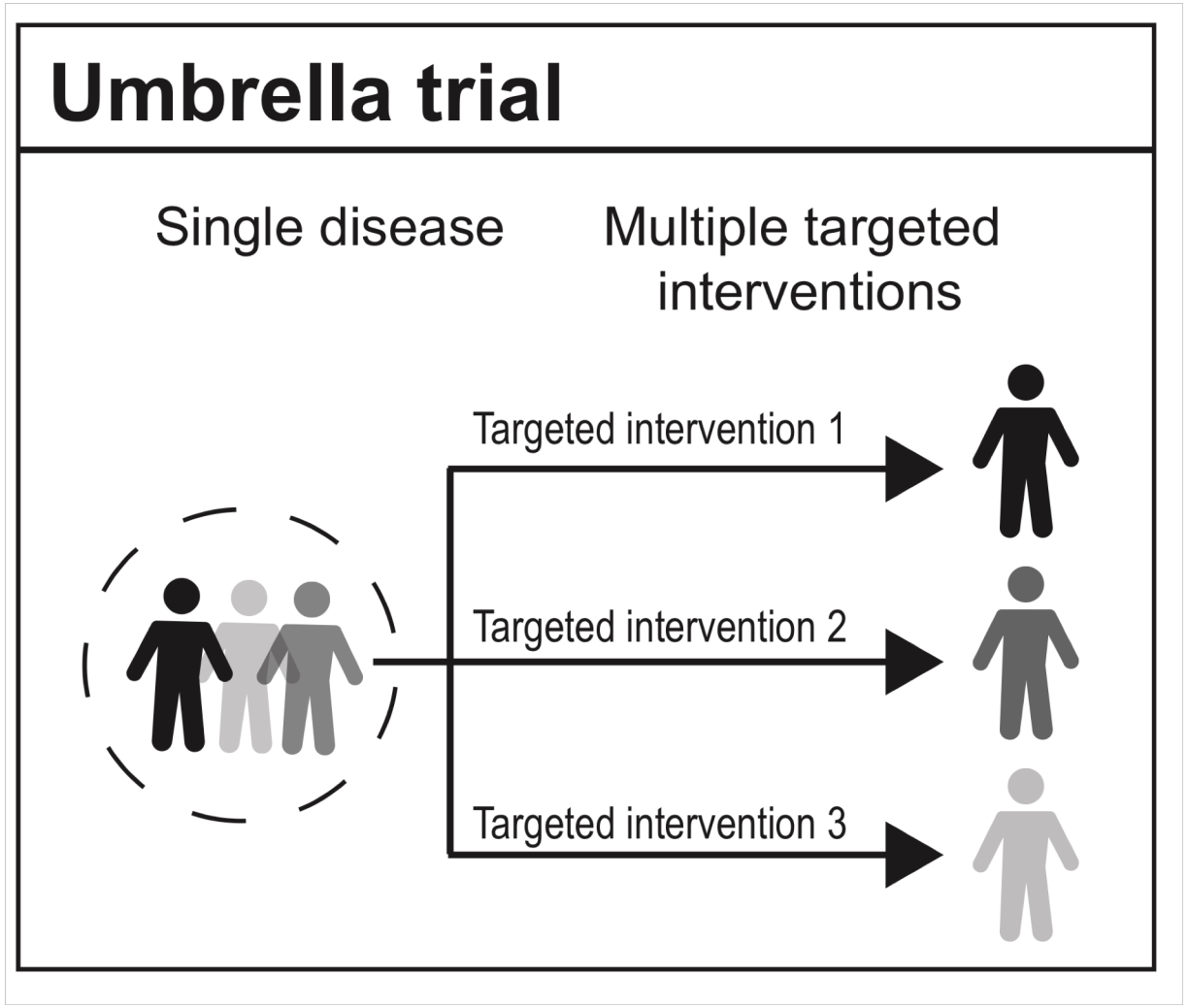
Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

An illustrative example of a basket trial



- Designs where a targeted therapy is evaluated on multiple diseases that share common genetic mutations

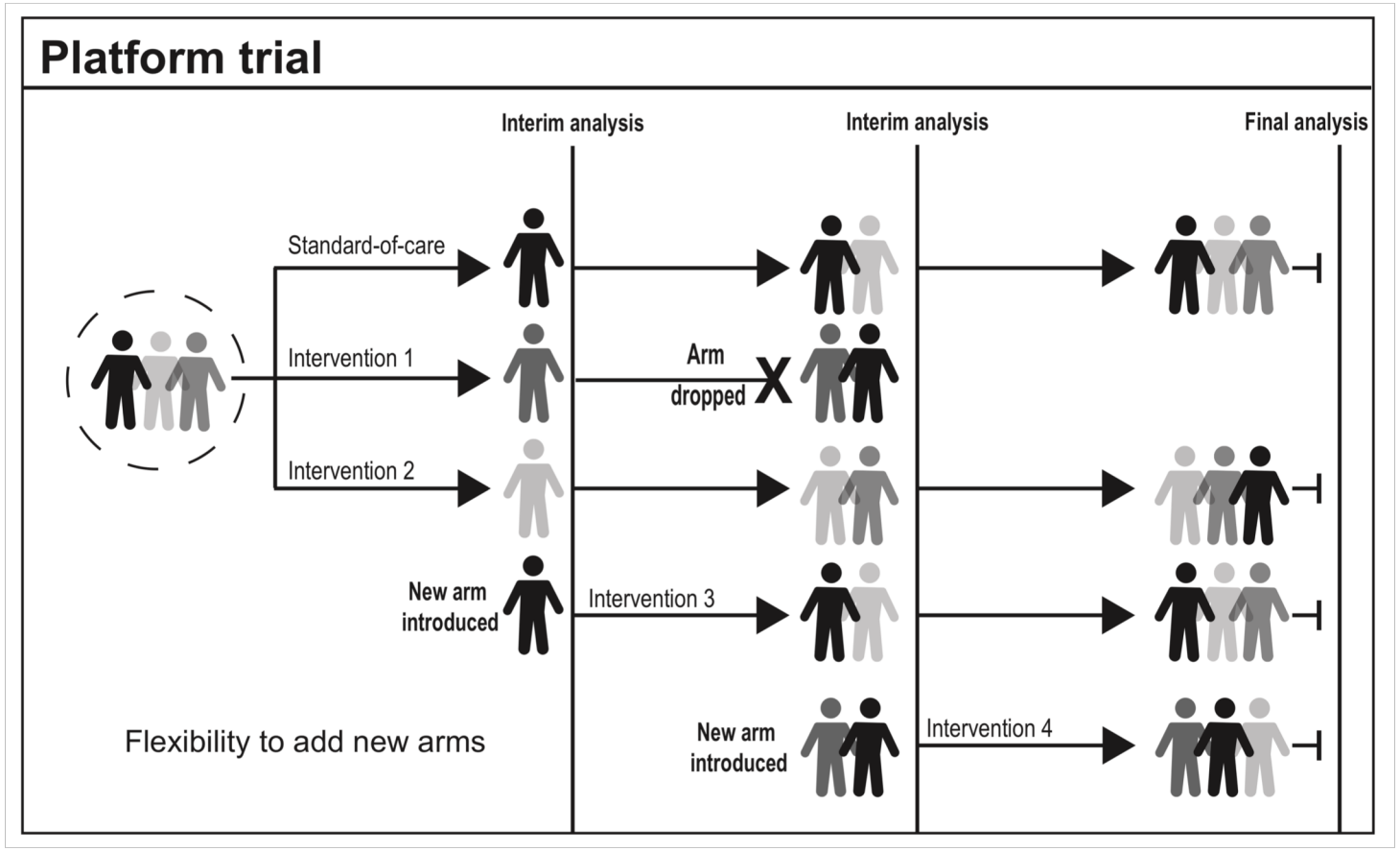
An illustrative example of an umbrella trial



- Multiple targeted therapies are evaluated for a single disease that is stratified into multiple subgroups by their genetic mutations
- Basket and umbrella trials employ a molecular screening protocol for their recruitment and differentiation

An illustrative example a platform trial

Also referred to as the multi-arm, multi-stage (MAMS) design



- Trials that evaluate several interventions against a common control group
- Has adaptation rules for dropping of ineffective interventions and flexibility of introducing new arms
- Can be perpetual in nature that allow for hypotheses to be updated over time

Landscape analysis on master protocols

- Our group's recent systematic review (search conducted on October 2018) found 59 master protocols

- The majority of current master protocols have taken place in the United States (n = 32/59)

- No master protocols have been conducted in low-income countries.

- Upper-middle income countries in Brazil, Mexico, and China were involved in master protocols, but these countries only accounted for a minority of study sites.

A quick summary of adaptive designs and master protocols

	Conventional designs	Adaptive designs	Master protocols
Definitions	Fixed sample size designs	Designs that allow for pre-specified modifications	Single overarching design developed to evaluate multiple hypotheses
Characteristics	One final analysis at the end of the trial	Multiple analyses with pre-specified adaptations and rules	Standardized operational structures, data collection/analyses, etc
Protocol driven	Yes	Yes	Yes
Examples	• 2-arm parallel randomized clinical trial	Common examples include: • SSR • RAR • Seamless II/III designs	Three classifications: • Basket trials • Umbrella trials • Platform trials

Summary

- Adaptive trial design are protocol driven clinical trials with pre-specified modifications and rules.

- Master protocols, particularly platform trials, aim to move away from single-intervention hypothesis approach onto disease and asks the question of what the best intervention option is for a study population.

- We believe these methodological advancements can be applied to improve the efficiency and quality of clinical trial research in global health

Key references

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