Adaptive Trial Designs

Ross Upshur

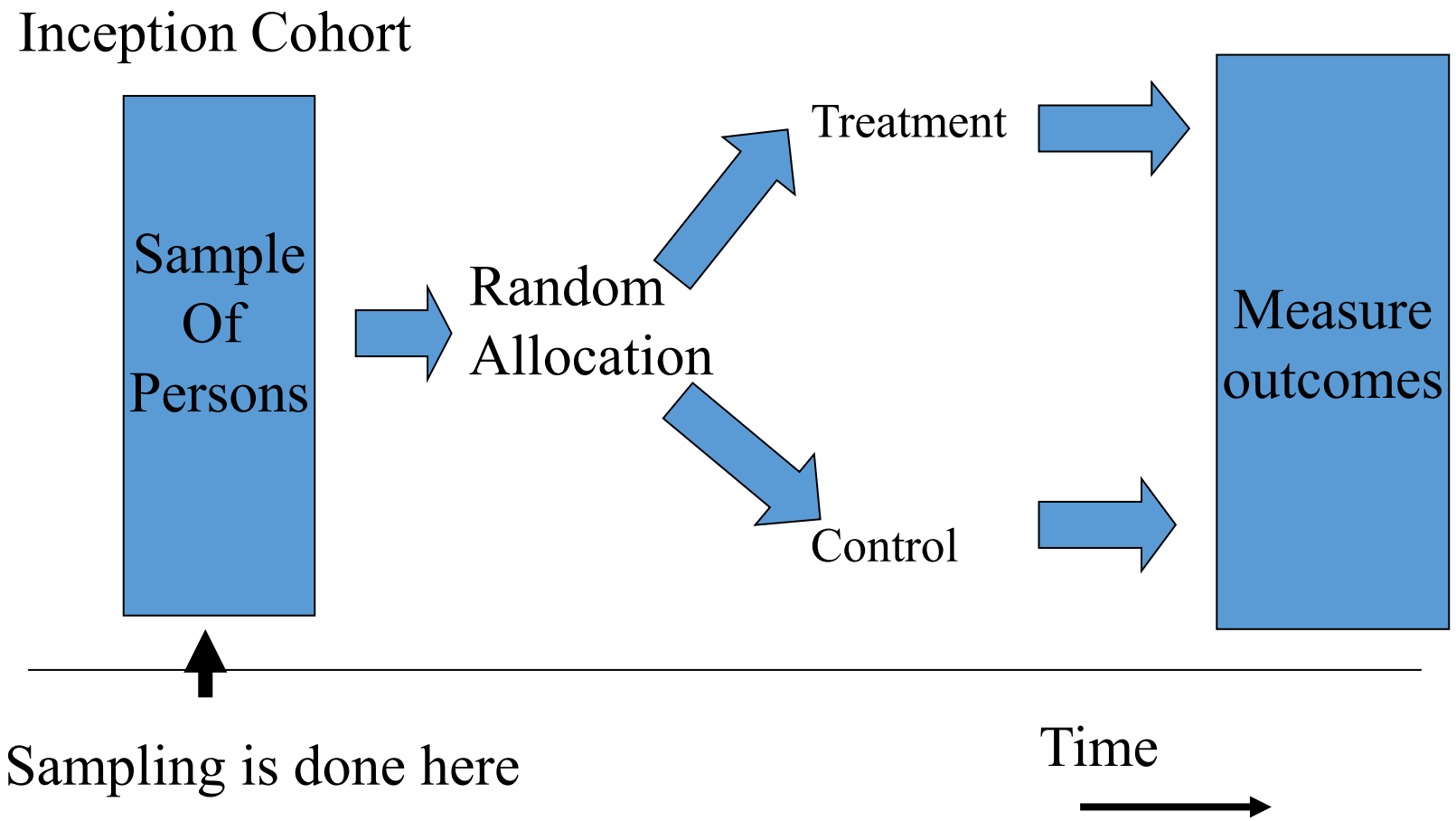

ALL THE FACTS OF SCIENCE AREN'T ENOUGH TO UNDERSTAND THE WORLD'S MEANING. FOR THIS, YOU MUST STEP OUTSIDE THE WORLD!
WITHOUT LANGUAGE OR THOUGHT, HOW CAN YOU UNDERSTAND ANYTHING?

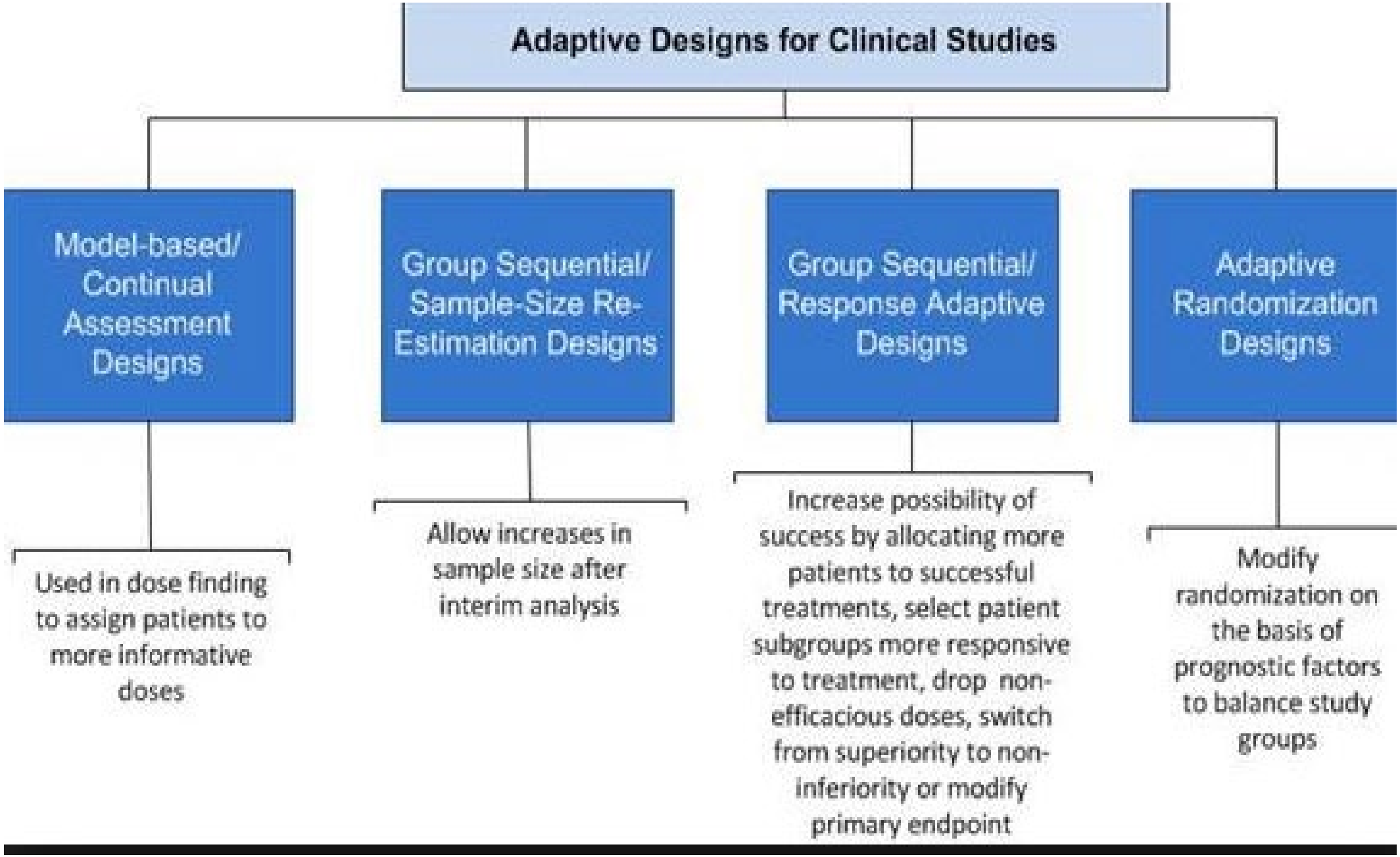
Truth

- The truth cannot be told so as to be understood but not believed.

William Blake

Randomized Control Trial




Adaptive Designs for Clinical Studies
Model-based/ Continual Assessment Designs
Group Sequential/ Sample-Size Re-Estimation Designs
Group Sequential/ Response Adaptive Designs
Adaptive Randomization Designs
Used in dose finding to assign patients to more informative doses
Allow increases in sample size after interim analysis
Increase possibility of success by allocating more patients to successful treatments, select patient subgroups more responsive to treatment, drop non-efficacious doses, switch from superiority to non-inferiority or modify primary endpoint
Modify randomization on the basis of prognostic factors to balance study groups

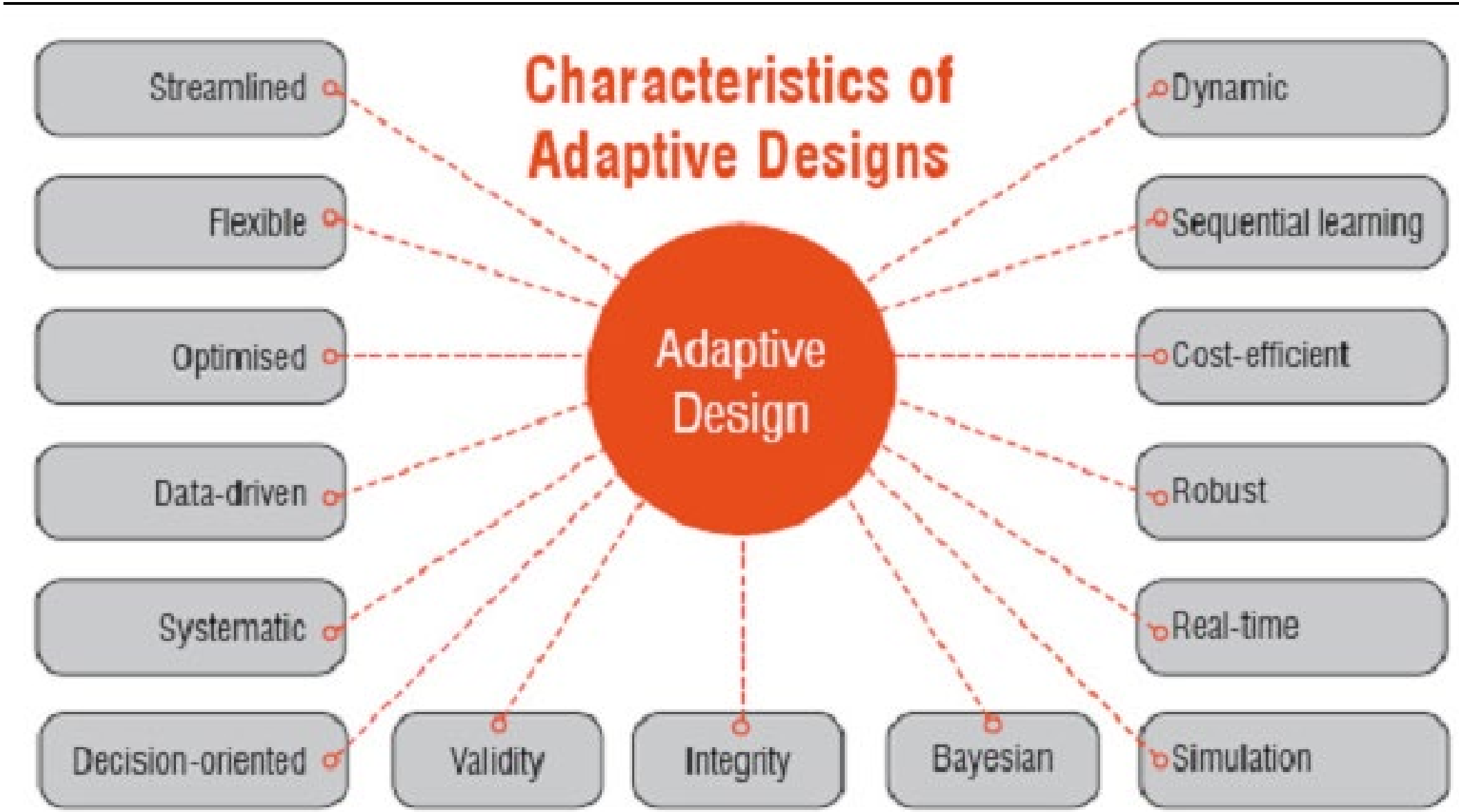
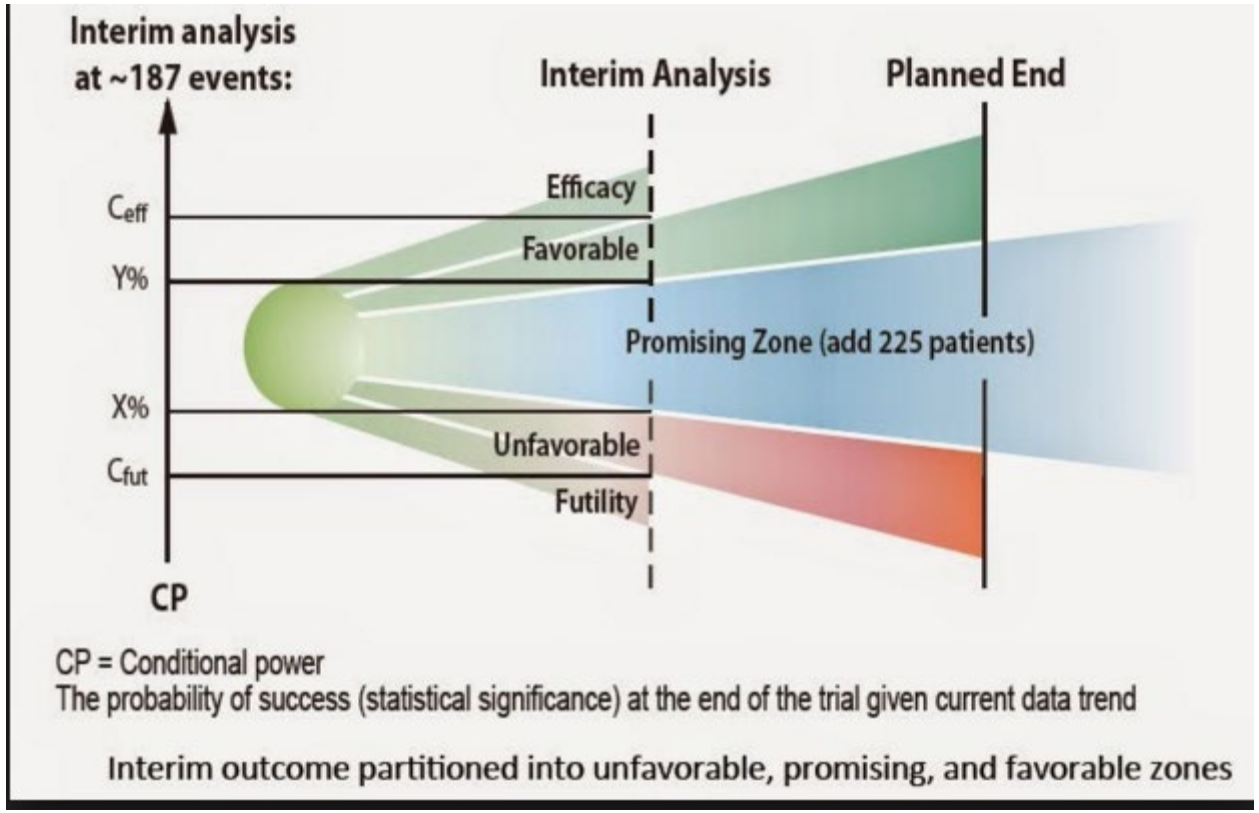

Characteristics of Adaptive Designs
Adaptive Design
Streamlined
Flexible
Optimised
Data-driven
Systematic
Decision-oriented
Validity
Integrity
Bayesian
Simulation
Real-time
Robust
Cost-efficient
Sequential learning
Dynamic

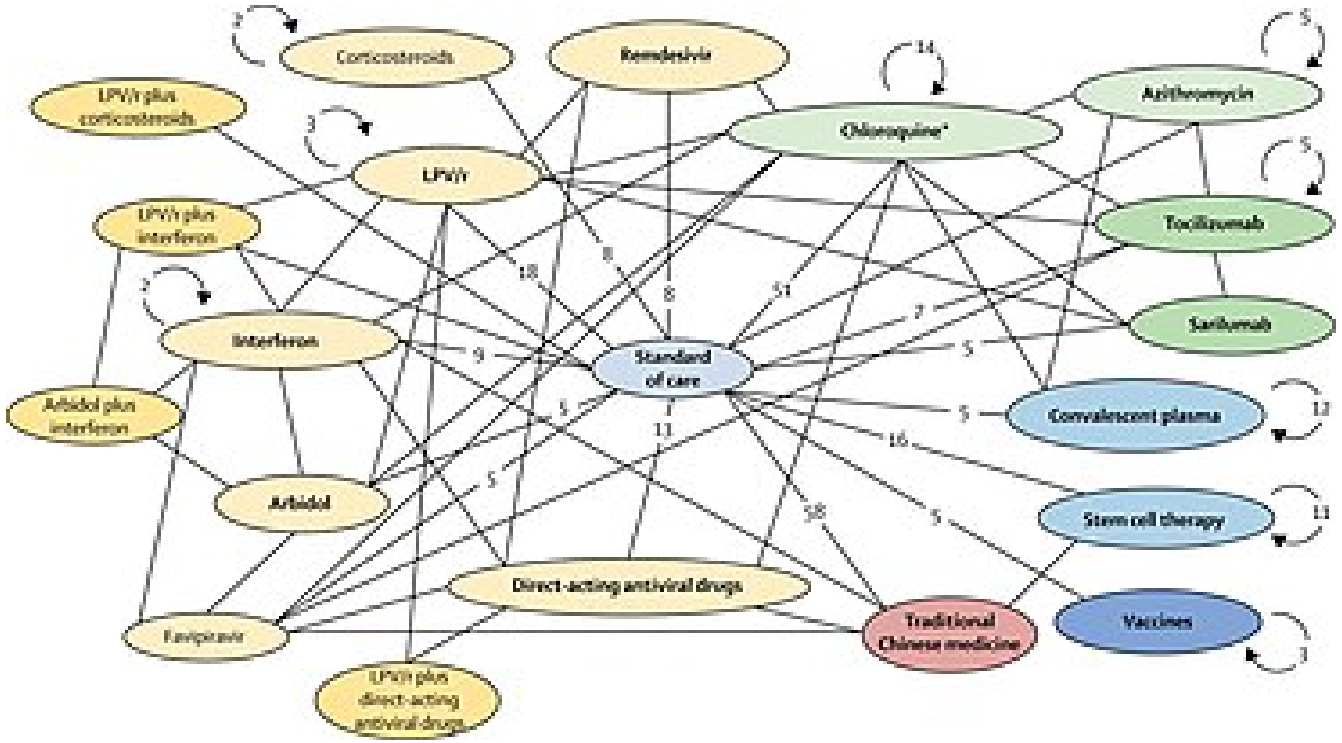
Figure 3

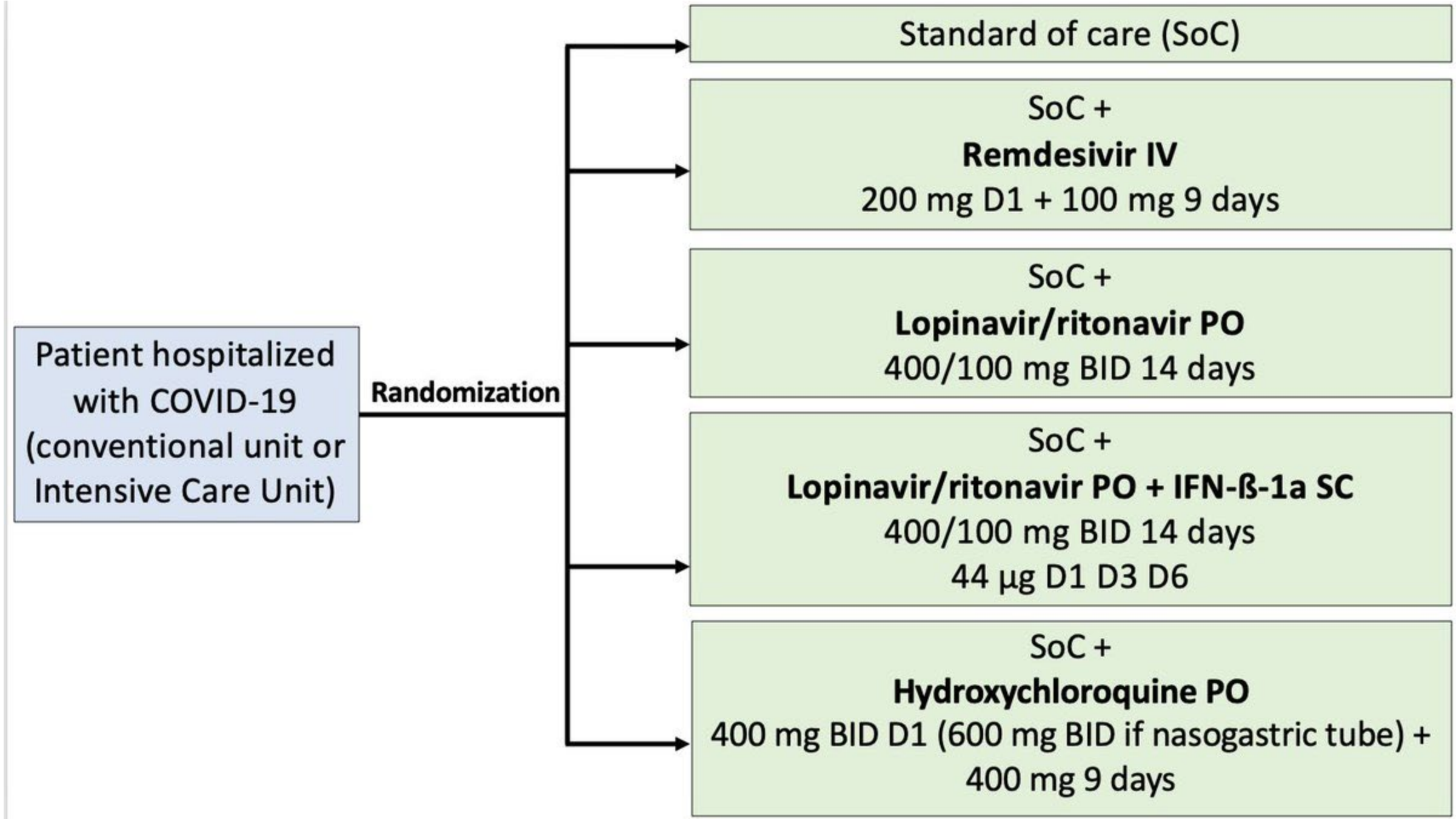
Table 2. Eight Common Types of Adaptations

- Stopping early (or late, i.e., extending accrual) with a conclusion of superiority or futility
- Adaptively assigning doses to more efficiently assess the dose-outcome relationship
- Adding or dropping arms or doses
- Seamless phases of drug development within a single trial
- Changing the proportion of patients randomized to each arm
- Adaptively identifying in on an indication or responder population
- Changing accrual rate

Used with permission from Berry D., Nat Rev Clin Oncol 2012; 9: 199-207.


Interim analysis
at ~187 events:
Interim Analysis
Planned End
Efficacy
Favorable
Ceff
Y%
Promising Zone (add 225 patients)
X%
Unfavorable
Cfut
Futility
CP
CP = Conditional power
The probability of success (statistical significance) at the end of the trial given current data trend
Interim outcome partitioned into unfavorable, promising, and favorable zones


Corticosteroids
Remdesivir
Azithromycin
LPV/r plus corticosteroids
Chloroquine*
LPV/r
Tocilizumab
LPV/r plus interferon
Sarilumab
Interferon
Standard of care
Arbidol plus interferon
Convalescent plasma
Arbidol
Stem cell therapy
Direct-acting antiviral drugs
Traditional Chinese medicine
Vaccines
Favipiravir
LPV/r plus direct-acting antiviral drugs


Patient hospitalized with COVID-19 (conventional unit or Intensive Care Unit)
Randomization
Standard of care (SoC)
SoC +
Remdesivir IV
200 mg D1 + 100 mg 9 days
SoC +
Lopinavir/ritonavir PO
400/100 mg BID 14 days
SoC +
Lopinavir/ritonavir PO + IFN-ß-1a SC
400/100 mg BID 14 days
44 µg D1 D3 D6
SoC +
Hydroxychloroquine PO
400 mg BID D1 (600 mg BID if nasogastric tube) +
400 mg 9 days

Component	Traditional	Flexible
Interim Analyses	Limited (1 to 2)	Frequent
Randomization	Fixed (1:1, 2:1)	Variable
Number of Arms	Limited (2 to 3)	Few to Many
Use of Incomplete Data	Imputation at Final Analysis	Imputation at All Stages
Philosophy	Frequentist	Bayesian or Frequentist
Control of Error Rates	Via Theoretical Calculation	Via Extensive Simulation

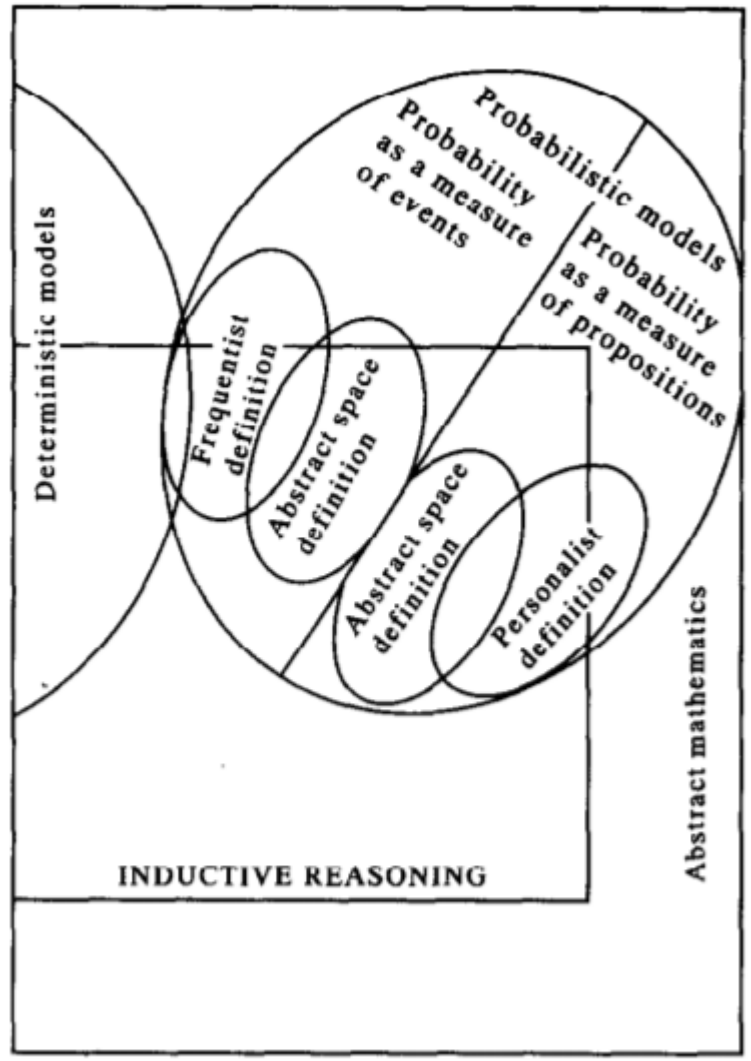


Fig. 2. Probabilistic models further refined.

Cartwright's Causal Criterion

- C causes E if and only if P (E/C) +/- $\{F_1 + F_2 \ldots F_N\}$ > P(E/-C} +/- { F_1+ $F_2 \ldots F_N$} where $F_1 \ldots F_N$ are a complete set of covariates
- An idealized model that sets out precise *ceteris paribus* conditions