Pragmatic Trials
&
SMART Design

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- https://youtu.be/FWSxSQsspiQ
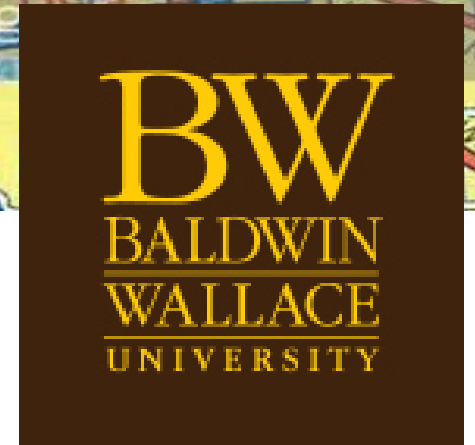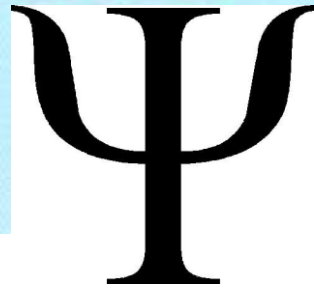
- https://www.youtube.com/watch?v=6JONMYxaZ_s

- https://www.youtube.com/watch?v=IGQmdoK_ZfY

Agenda

- Clinical Trails Research

- Randomized Control Trials (RCT)

- Pragmatic Control Trials (PCT)

- Adaptive Treatment Strategies (ATS)

- Sequential Multiple Assignment Randomized Trial (SMART)

The evidence-based medicine movement encourages consideration of relevant research findings when making clinical decisions (Hotopf, 2002).

This results is a need for medical practitioners to be research literate (Alford, 2007)

Polio Caused by Ice Cream?

- 1952 pandemic, 58,000 American children were infected

- Researchers found rates of polio infections seemed to rise and fall in lock step with the consumption of ice cream

- Dr. Benjamin Sandler - The excess sugar in ice cream was the cause.

- Researchers ultimately found out that polio outbreaks due to improved sanitation.

- As cities and towns became cleaner, children lost early exposure to the polio virus and the valuable immunity it conferred

What is research?

- Scientifically, exploring a question of interest
  - *May* include the use of the scientific method
    - Observation
    - Hypothesis
    - Prediction
    - Experimentation
    - Conclusion

Clinical Research

- Branch of healthcare science

- Determines the **safety** and **efficacy** of medications, devices, and treatments intended for human use

- May be used for prevention, treatment, diagnosis, or for relieving symptoms of a disease

- Often times the precursor to clinical practice

- Refers to most any test article from inception in the lab to the consumer market

Clinical Research (cont.)

- Helps doctors and researchers find new and better ways to understand, detect, control, and treat illness.

    - Identify the genes associated with the opioid use disorder.

    - Explore the influence of patients wearing hearing aids, eye glasses, access to calendars, items from home, on prevalence of delirium
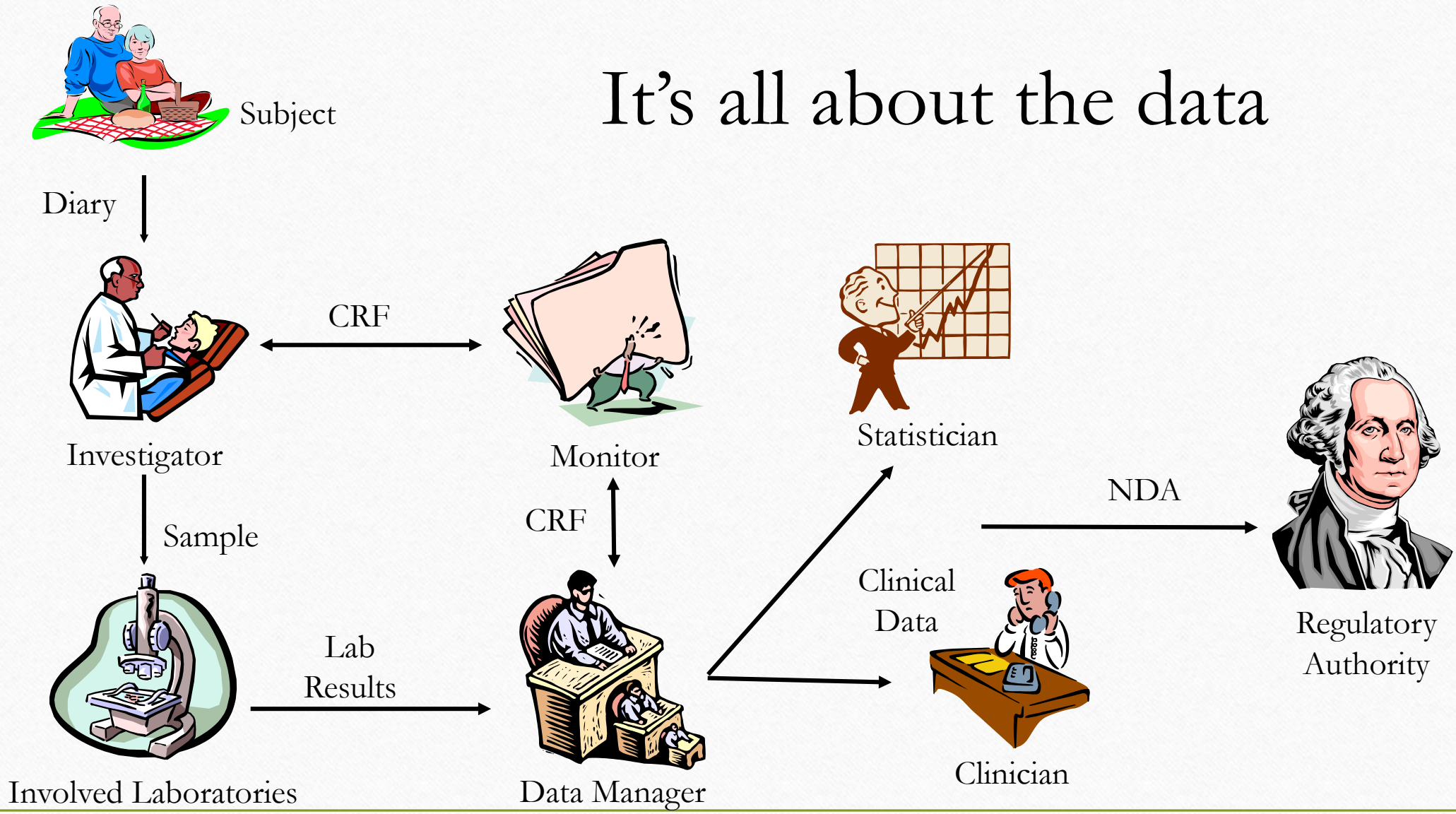
What is a protocol?

- All clinical studies are based on a set of rules or directions called a protocol.

- A protocol describes:

  - Types of people eligible to participate

  - Determines the schedule of tests, procedures, medications, and dosages; and sets the length of the study.

What is a Clinical Trial?

- If a clinical research study involves testing or studying a drug or medical device to see if it's a safe and effective treatment for people, it's called a "trial."
  - A clinical trial may test the effectiveness of a new drug for treating Parkinson's disease

It's all about the data

Subject → Diary → Investigator → Sample → Involved Laboratories → Lab Results → Data Manager

Investigator ↔ CRF ↔ Monitor ↔ CRF ↔ Data Manager

Data Manager → Clinical Data → Statistician / Clinician

Statistician → NDA → Regulatory Authority

What are Clinical Trial Phases?

- Clinical trials are conducted in a series of steps:
  - Phase I - Small sample, determine safe dosage range, evaluate safety, and identify side effects
  - Phase II - Larger sample, evaluate effectiveness & safety
  - Phase III - Large sample, confirm effectiveness, monitor side effects, compare to other treatments, collect data on usage requirements
  - Phase IV - Post production, explore effect in various populations and side effects associated with long term-use

Ensuring quality and ethical clinical trials

- Good Clinical Practice (GCP)

  - A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials or studies

- Why is GCP important?

  - Provides public assurance that the rights, safety and well-being of human subjects involved in research are protected
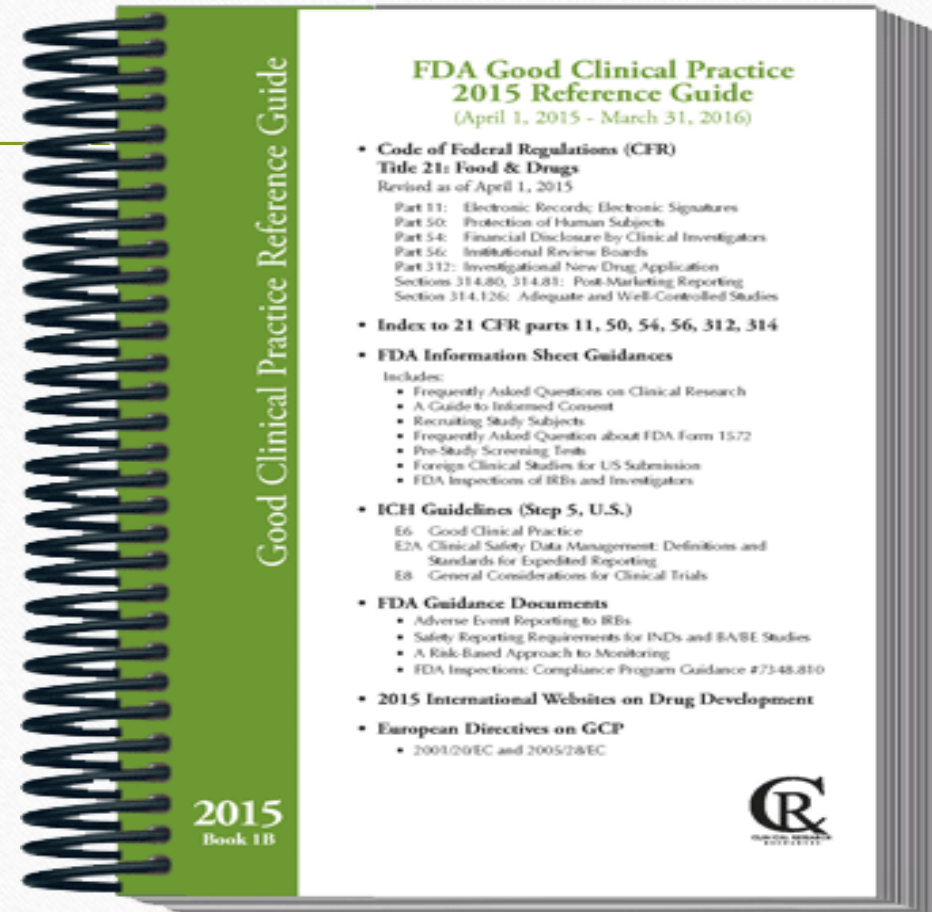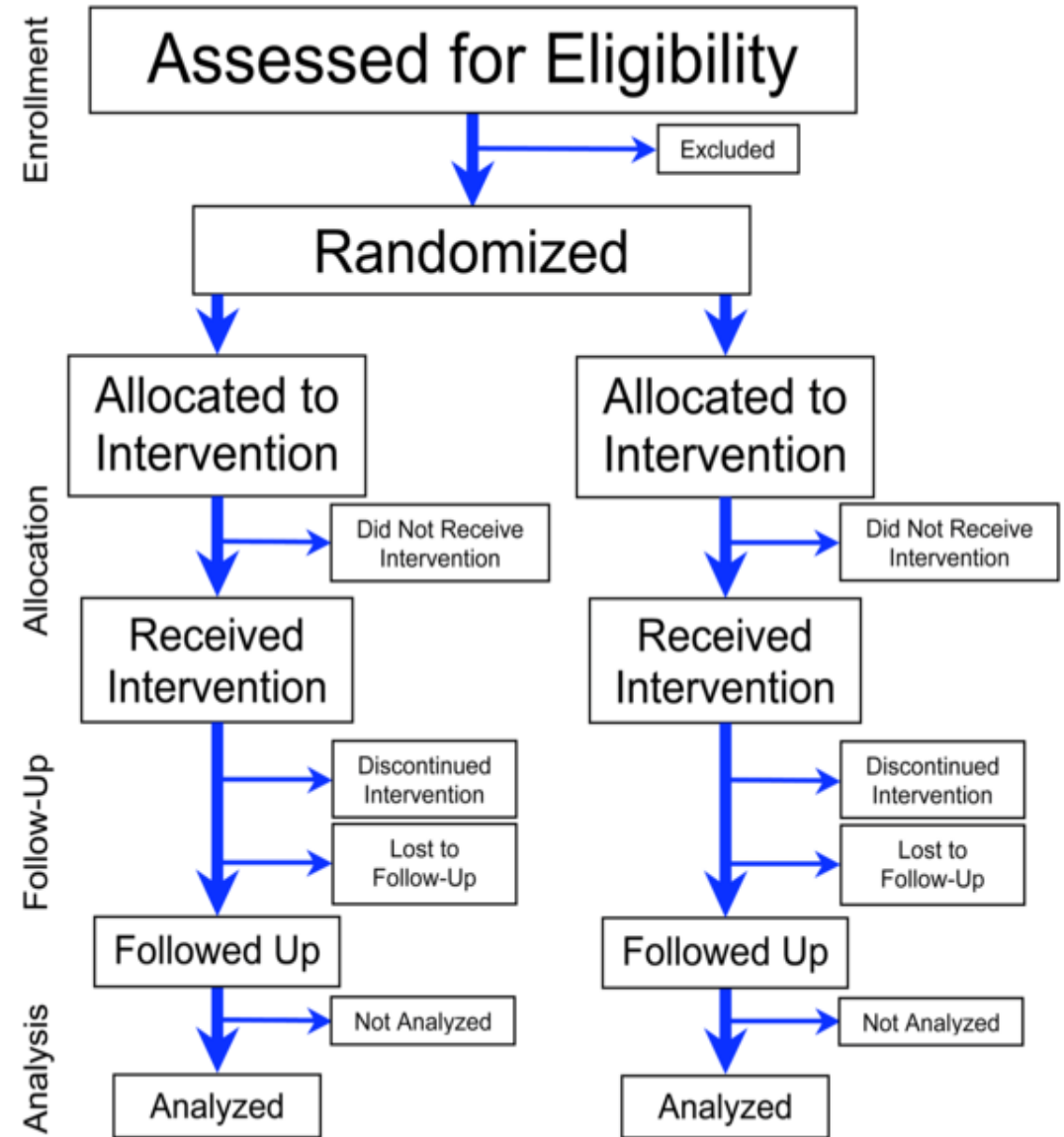
Randomized Control Trials (RCTs)

- A study in which people are allocated at random to receive one of several clinical interventions.
  - The control may be a standard practice, a placebo, or no intervention
  - In behavioral research, need to ensure control group is not ignored
    - Evening back massage on patient sleep quality
      - Treatment gets back massage, Control ignored
      - Results could be due to back massage, or maybe the opportunity for the patient to talk (express concerns, feelings, etc.) before going to bed.

Gold Standard for Clinical Trials

- Randomized Control Trials (RCTs)

  - Participants randomly allocated to one, two, or more treatments

    - Random assignment performed after participants have been assessed for eligibility – but before intervention begins

  - After randomization the groups are:

    - Followed in EXACT same way

    - ONLY difference is treatment being compared

Randomized Clinical Trials (RCTs)

- Designed as experiments with high internal validity – ability to determine cause/effect relationships

- Typically employ comprehensive designs to control for most, if not all, sources of bias (systematic error)

- Usually, **extensive inclusion and exclusion criteria** are used to identify optimal target sample

- However, characteristics that contribute to high internal validity, can hamper external validity – generalizing results to extended population

The Typical Medical Drug Trial

- Random allocation of participants to groups

- Blinding of participants to group allocation

- Blinding of the practitioner delivering the intervention and/or the researcher assessing the outcome

- The use of a placebo control group

- Tight monitoring of the experimental conditions and interventions
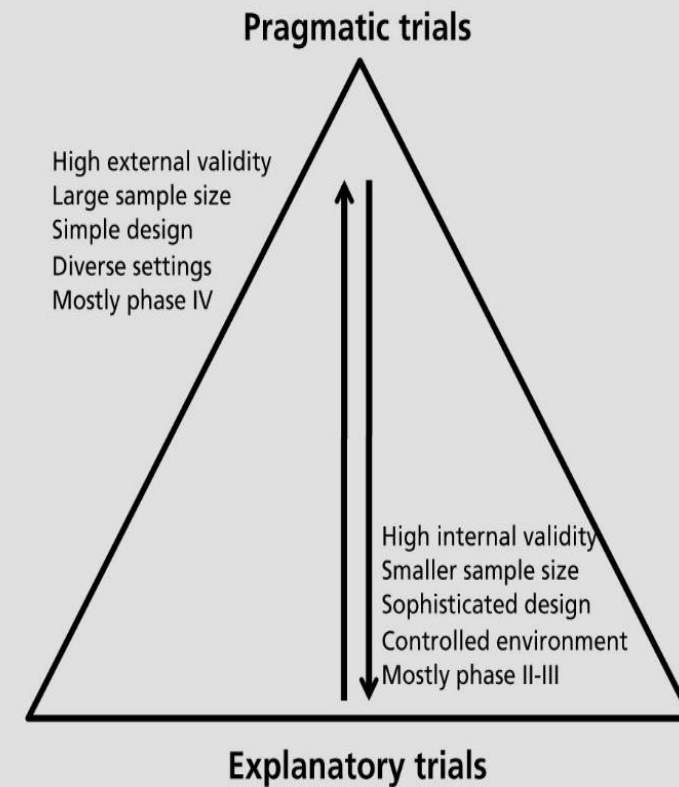
The Typical Medical Drug Trial

However, real-life is seldom tightly monitored – behaviors, attitudes, experiences, perceptions and motivations drive human behavior

As a result, there is a need for real-life research
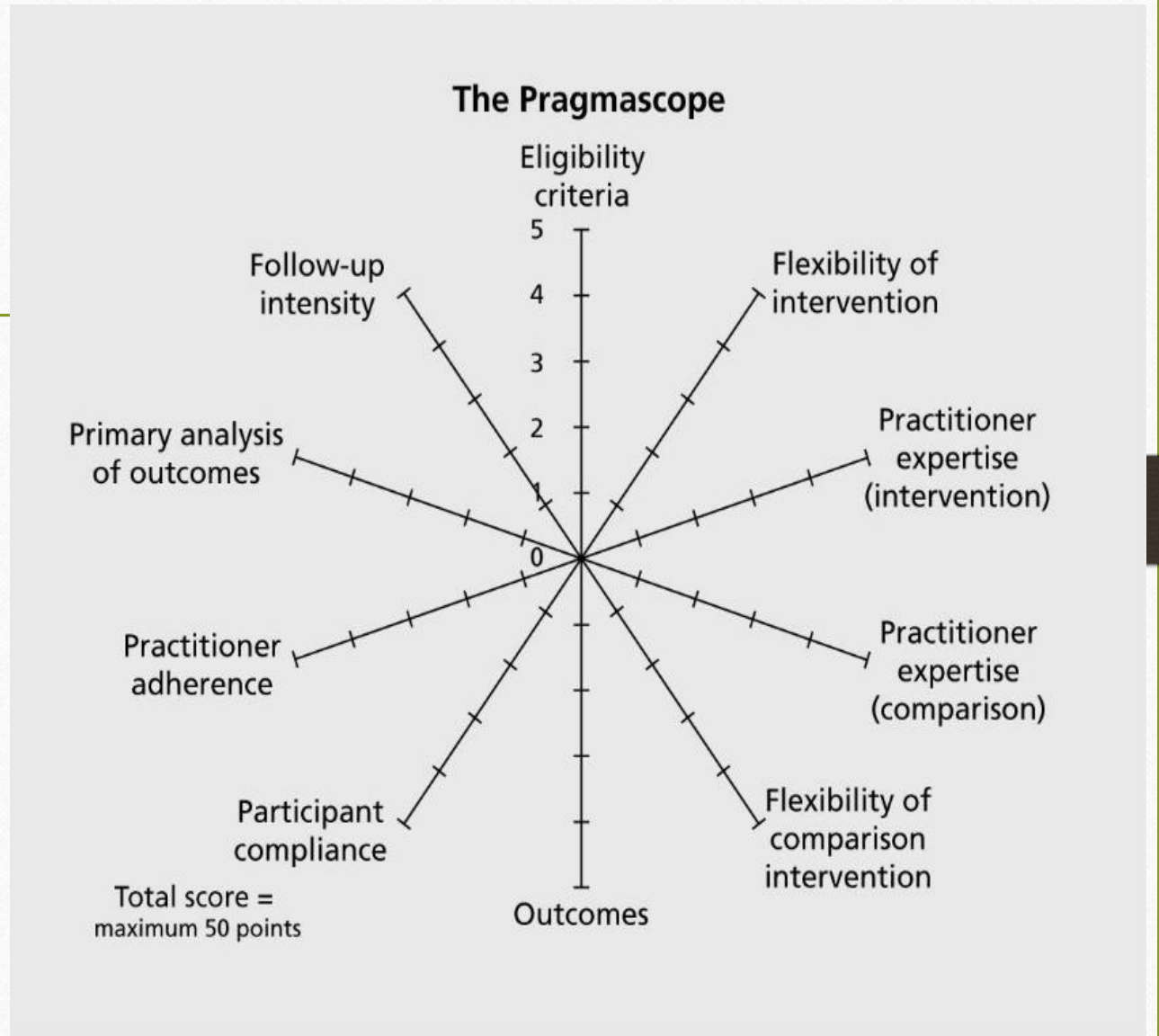
"Explanatory" & "Pragmatic" trials

(Schwartz & Lellouch,1967)

- **Explanatory** – Evaluate the efficacy of intervention in controlled setting
  - if and how an intervention works

- **Pragmatic** – Test the effectiveness of intervention in a broad routine clinical practice
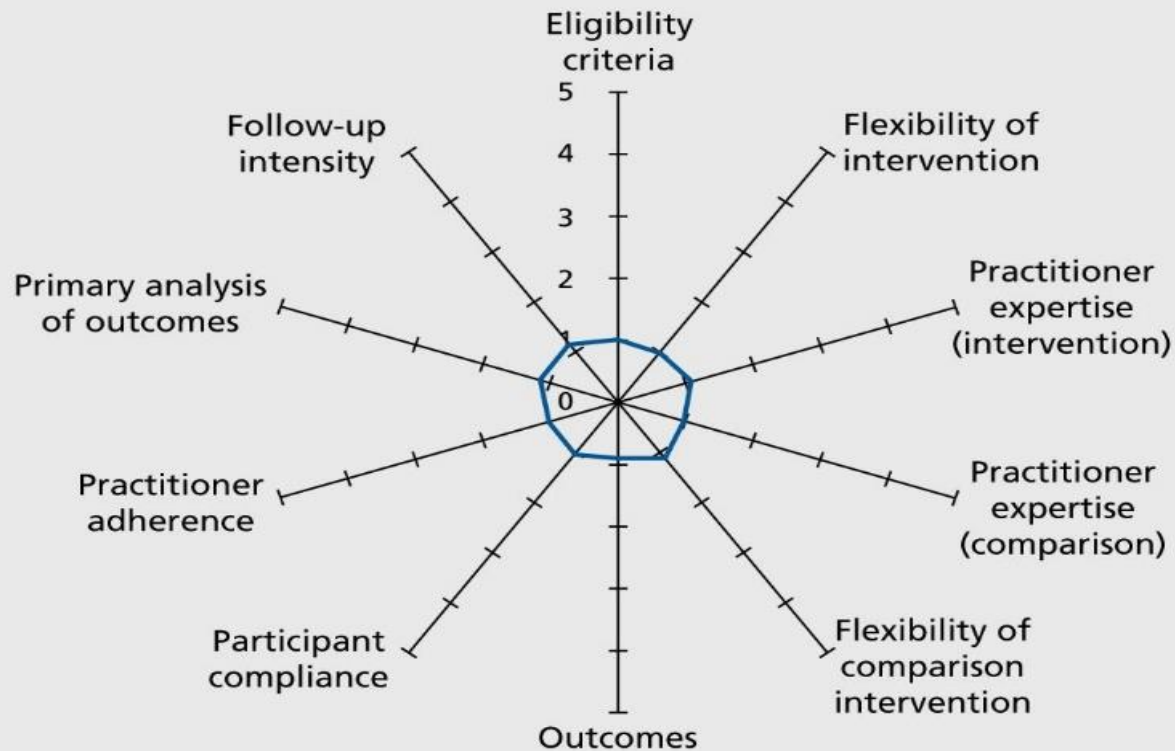 - whether an intervention works in real life

Pragmatic trials

High external validity
Large sample size
Simple design
Diverse settings
Mostly phase IV

High internal validity
Smaller sample size
Sophisticated design
Controlled environment
Mostly phase II-III

Explanatory trials

Distinguishing Between Explanatory & Pragmatic Trials

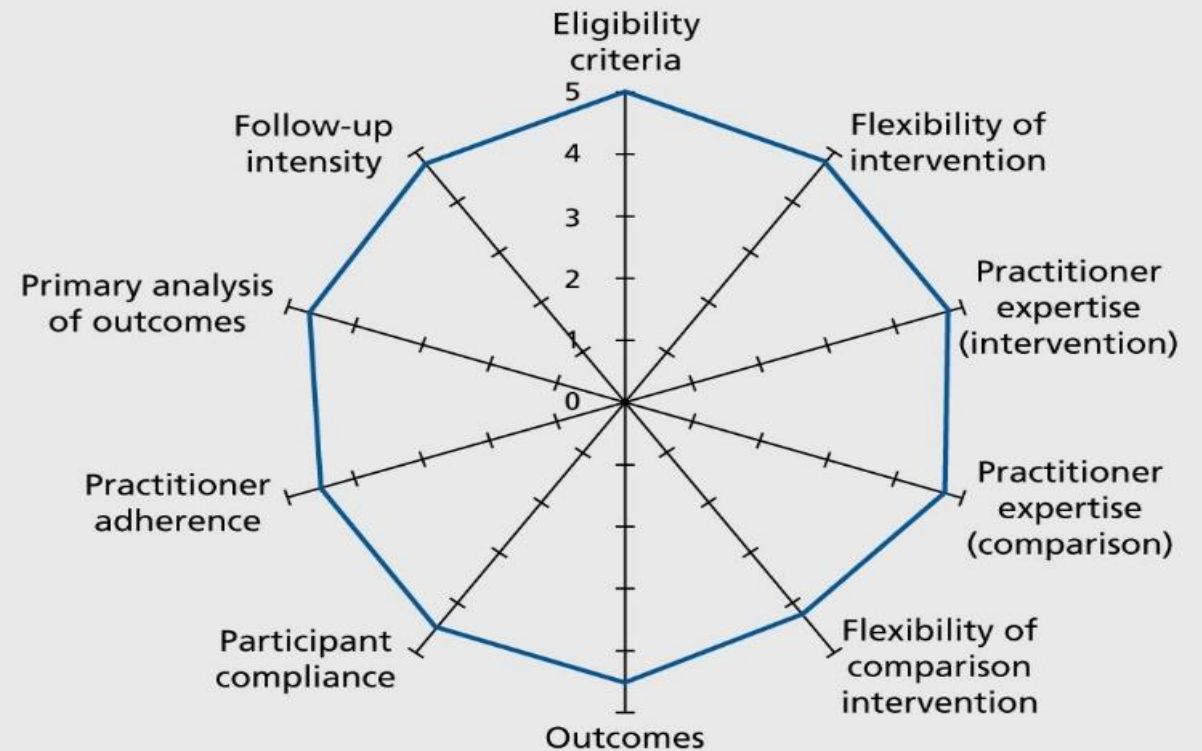- The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) (Thorpe et al., 2009)

The Pragmascope

Eligibility criteria

Follow-up intensity

Flexibility of intervention

Primary analysis of outcomes

Practitioner expertise (intervention)

Practitioner adherence

Practitioner expertise (comparison)

Participant compliance

Flexibility of comparison intervention

Total score = maximum 50 points

Outcomes

Distinguishing Between Explanatory & Pragmatic Trials (cont.)

Pragmatic (PCT) vs. Explanatory (ECT or RCT)

| PCT	RCT (ECT)
No inclusion or exclusion criteria	Significant inclusion and exclusion criteria
Practitioners are not constricted by guidelines on how to apply experimental intervention	Experimental intervention strict application guidelines
Experimental intervention applied by all practitioners	Experimental intervention applied by highly trained practitioners
Best alternative treatments are used for comparison with no restrictions on their application	Typically placebo, significant restrictions on application

Pragmatic (PCT) vs. Explanatory (ECT or RCT) cont.

| PCT	RCT (ECT)
No formal follow-up sections	Formal follow-up sessions
Primary outcome does not require extensive training to assess	Significant training to assess outcome(s) Medically and Statistically
No special strategy to motivate practitioners adherence to the trials protocol	Commitment to adherence
Analysis includes all participants in an intention-to-treat (ITT) fashion	Inclusion of participants who appropriately completed the trial

Pragmatic Clinical Trial Examples

- Little et al., 1997; Antibiotics for sore throats
  - 3 groups; Immediate antibiotics, Delayed antibiotics, and No antibiotics
  - No Placebo group
  - Setting – Primary care facility
  - Outcome – Clinical severity from patient (not microbial swabs)

Prevalence of Sore Throat (Little et al., 1997)
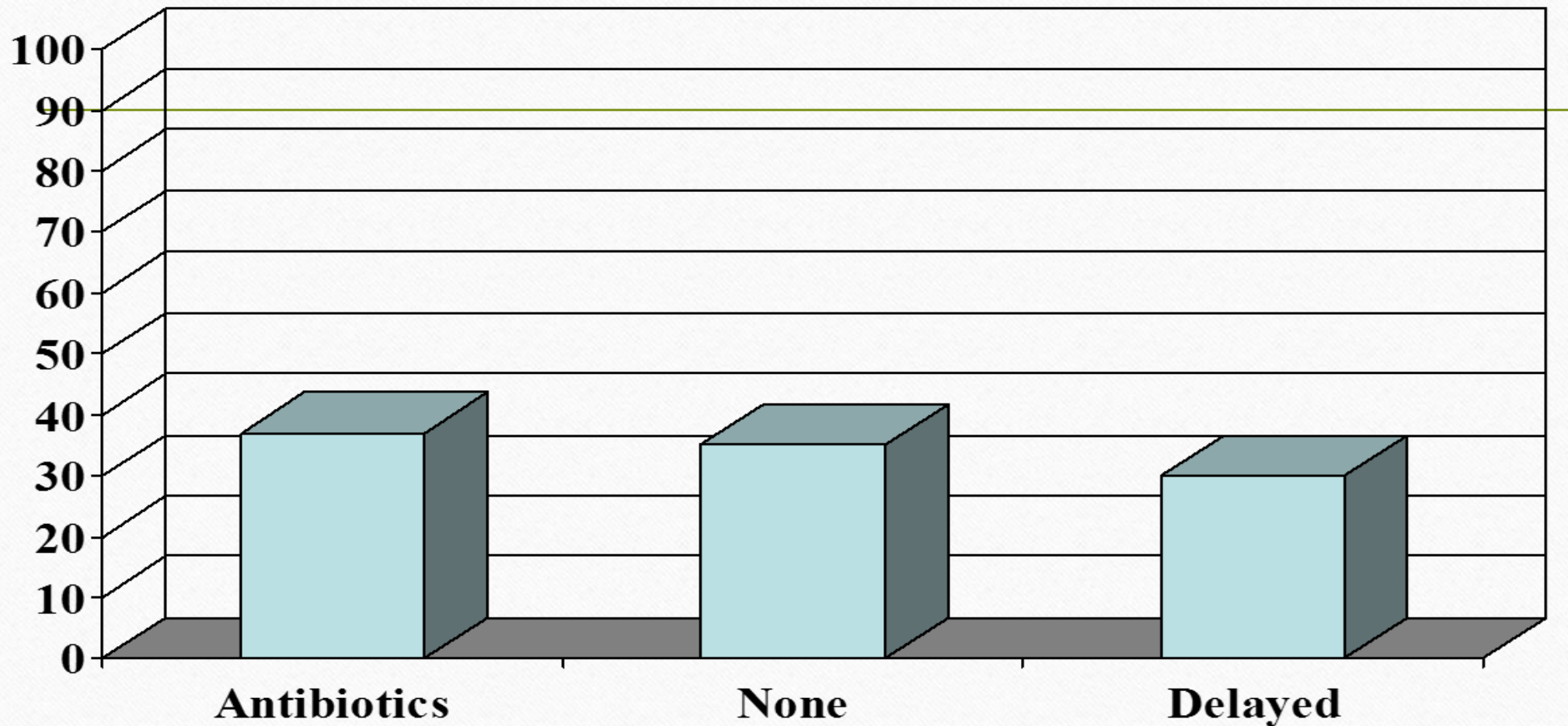
Re-attendance within 12 months (Little et al., 1997)
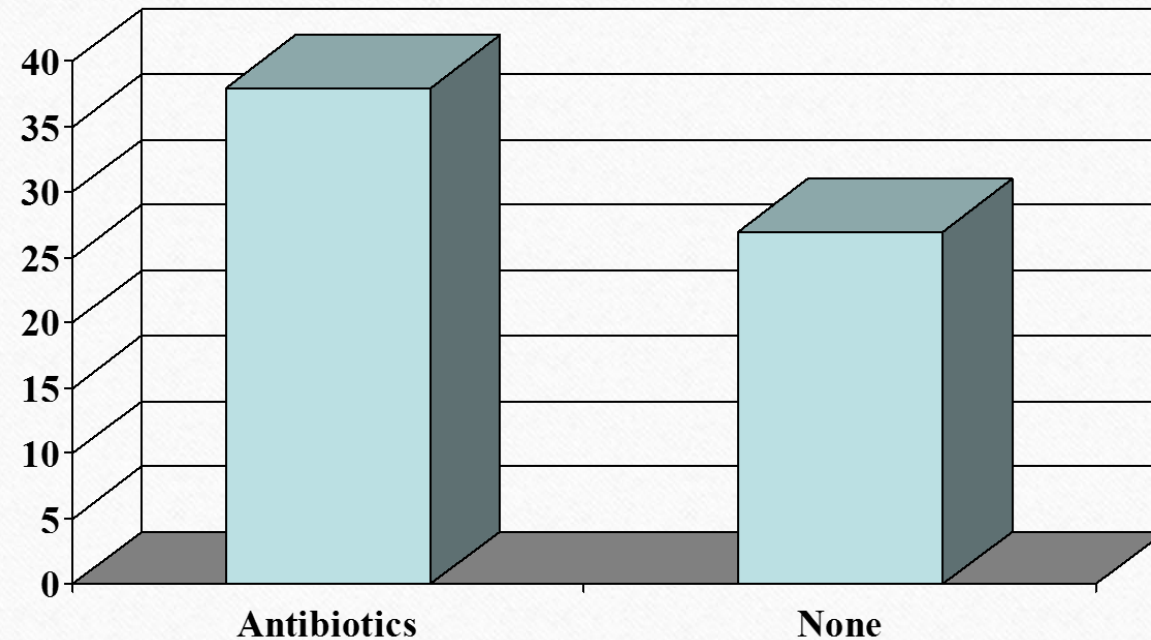
Pragmatic Information

- GPs prescribing antibiotics for uncomplicated sore throats has very little, if any, effect

- Patients prescribed antibiotics are more likely to re-attend when they next have a sore throat compared with giving no antibiotics
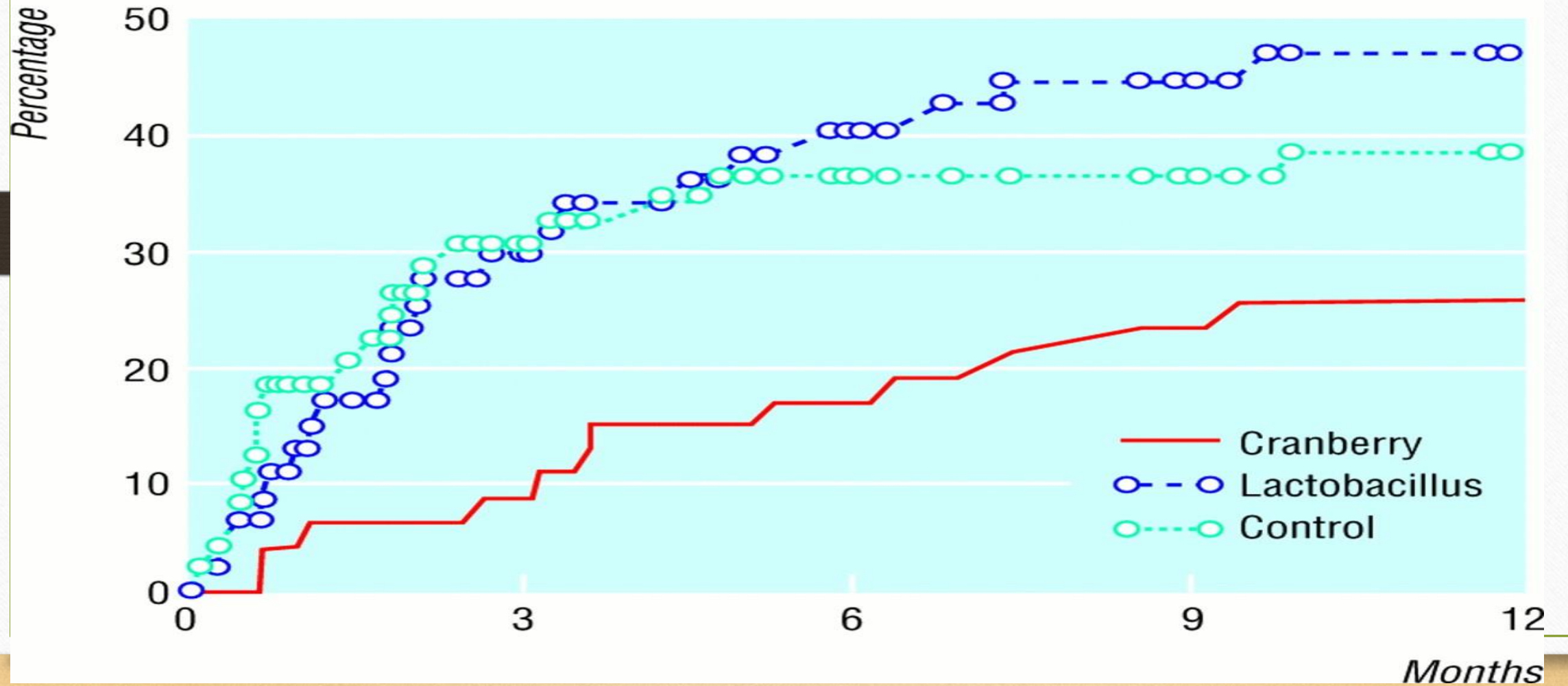
Pragmatic Clinical Trial example 2

- Avorn et al. (1994) – (RCT example) Cranberry juice for urinary tract infection
- 2 groups; cranberry juice, placebo
- Outcome – bacterial count in urine samples
- Result Cranberry juice significantly reduced bacteria in the urine
- Practically, does it reduce the symptoms?
  - Conduct a PCT

Pragmatic Clinical Trial example 2

- Kontiokari et al. (2001) – (PCT example) Cranberry juice and relief from symptoms

  - 3 groups; cranberry juice, yakult drink (probiotic dairy product), open control

  - Outcome – time to recurrent of urinary tract symptoms (e.g., pain on passing urine, flank pain)

  - Infection confirmed with swabs

Pragmatic Clinical Trial example 2

Pragmatic Clinical Trial example 2

- Cranberry Conclusion

- Avorn et al. (1994) - (RCT trial) Suggests that cranberry juice reduces bacteria in the urine.

- Kontiokari et al. (2001) – (PCT trial) Suggests cranberry supplementation reduces probability of recurrent symptoms of urinary tract infection in young women.

Summary RCT & PCT

- RCT
  - Designed with high internal validity – ability to determine cause/effect relationships
  - Extensive inclusion and exclusion criteria
  - Remember, characteristics that contribute to high internal validity, can hamper external validity – generalizing results to extended population
- PCT
  - Designed with high external validity
  - Reduced inclusion and exclusion criteria

Dynamic Treatment Regimes (DTR)

aka

Adaptive Treatment Strategies (ATS)

Adaptive Treatment Strategies (ATS)

- Why should we care about DTRs / ATSs?

  - The single-decision setting

    - A patient with a disease, and we need to decide on a treatment based on a list of choices.

    - We want to make the best decision (treatment regimen) based on baseline data

  - The multi-decision setting:

    - We wish to treat a patient for a disease with multiple treatment decisions spread over time

    - We want to make the best decision based on data from each decision time (dynamic treatment regimen)

Adaptive Treatment Strategies (ATS)

- Sequential decision rules that adapt over time to the changing status of each patient
  - Ongoing state of patient serves as input for decision rule, then outputs individualized treatment recommendation
  - Treatment individualization and _adaption over time_

Adaptive Treatment Strategy (ATS)

- The basic ATS:
  - Select study sample
  - Provide treatment A
  - Document response (r) or no response (nr)
  - Adaptive treatment decision
    - If response, then continue A
   - If no response, then A + B

ATS example
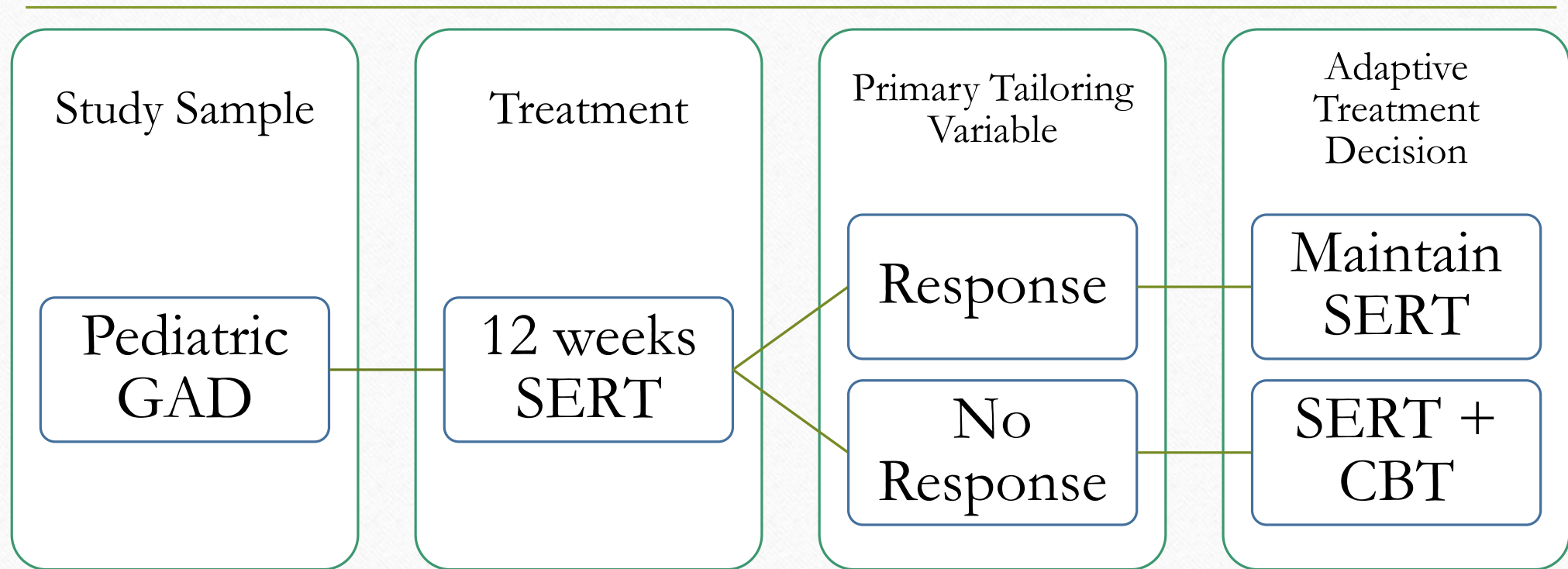
Primary goal of ATS

- Identify an optimal ATS, defined as the rule that will maximize expected long term benefit

- Comparing ATSs provides additional data for quality decision making

  - Often in chronic diseases, there are delayed effects where a treatment that produces the best initial response rate, may end up being too toxic for further treatment and result in lower overall response.
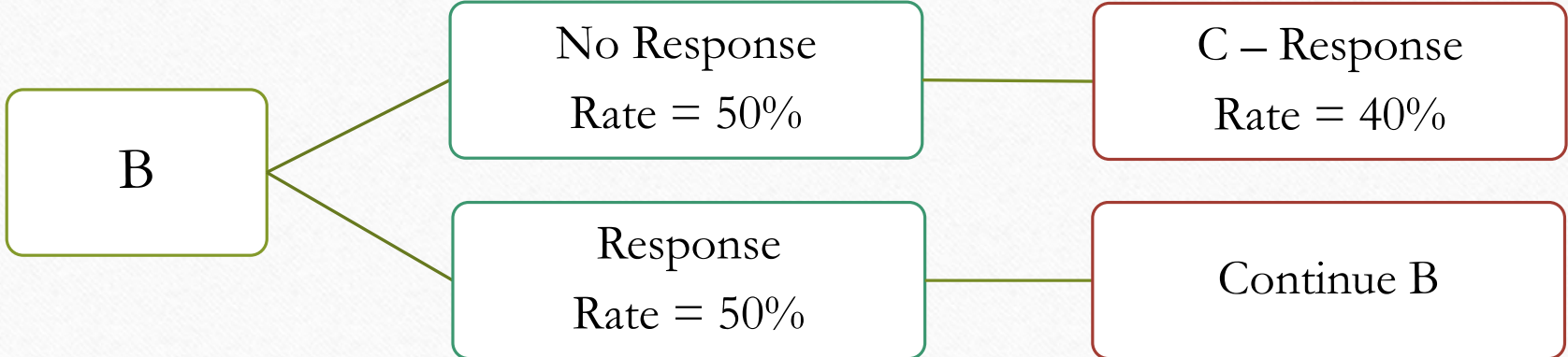
Comparing two ATS

ATS (A, C)

A
- No Response Rate = 40% → C – Response Rate = 10%
- Response Rate = 60% → Continue A
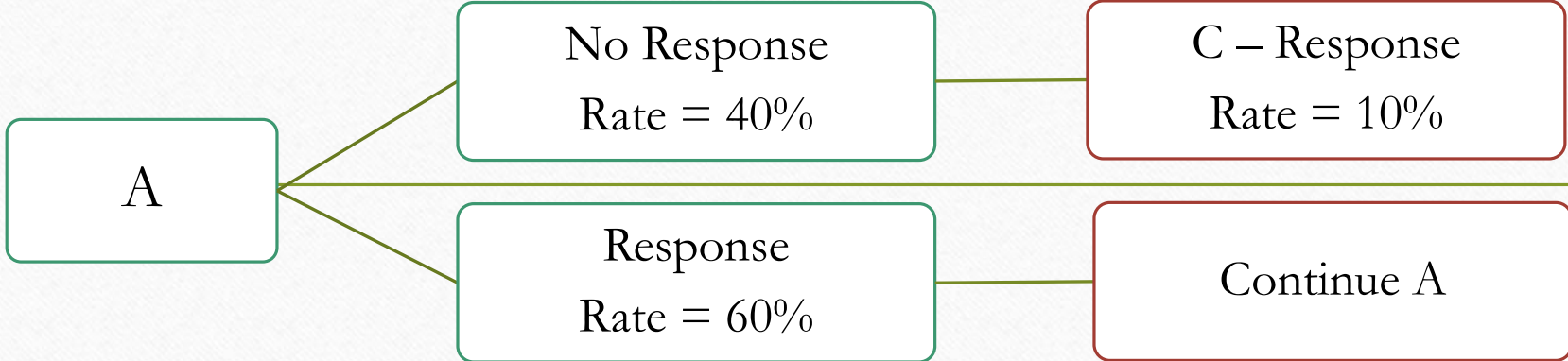
Overall Response Rate
60% + 40% * 10% = 64%

ATS (B, C)

B
- No Response Rate = 50% → C – Response Rate = 40%
- Response Rate = 50% → Continue B

Overall Response Rate
50% + 50% * 40% = 70%

# Sequential Multiple Assignment Randomized Trial (SMART)

- Growing interest in how best to adapt treatments to maximize clinical benefits
- Adaptive Treatment Strategies (ATS) developed to aid in maximizing treatment benefits

"To improve outcomes we will need to [develop treatments which] … personalize care based on individual responses" (NIMH)

Sequential Multiple Assignment Randomized Trial (SMART)

- Facilitate the development of ATSs

- Develop the sequence of treatments that lead to optimal outcomes long-term – multiple ATSs

- Key feature of a SMART:

  - Evaluate the timing, sequencing, and adaptive selection of treatments

  - Participants move through multiple stages of treatment

    - Each stage includes a critical decision

    - Participants are randomized at each stage/critical decision

SMART example
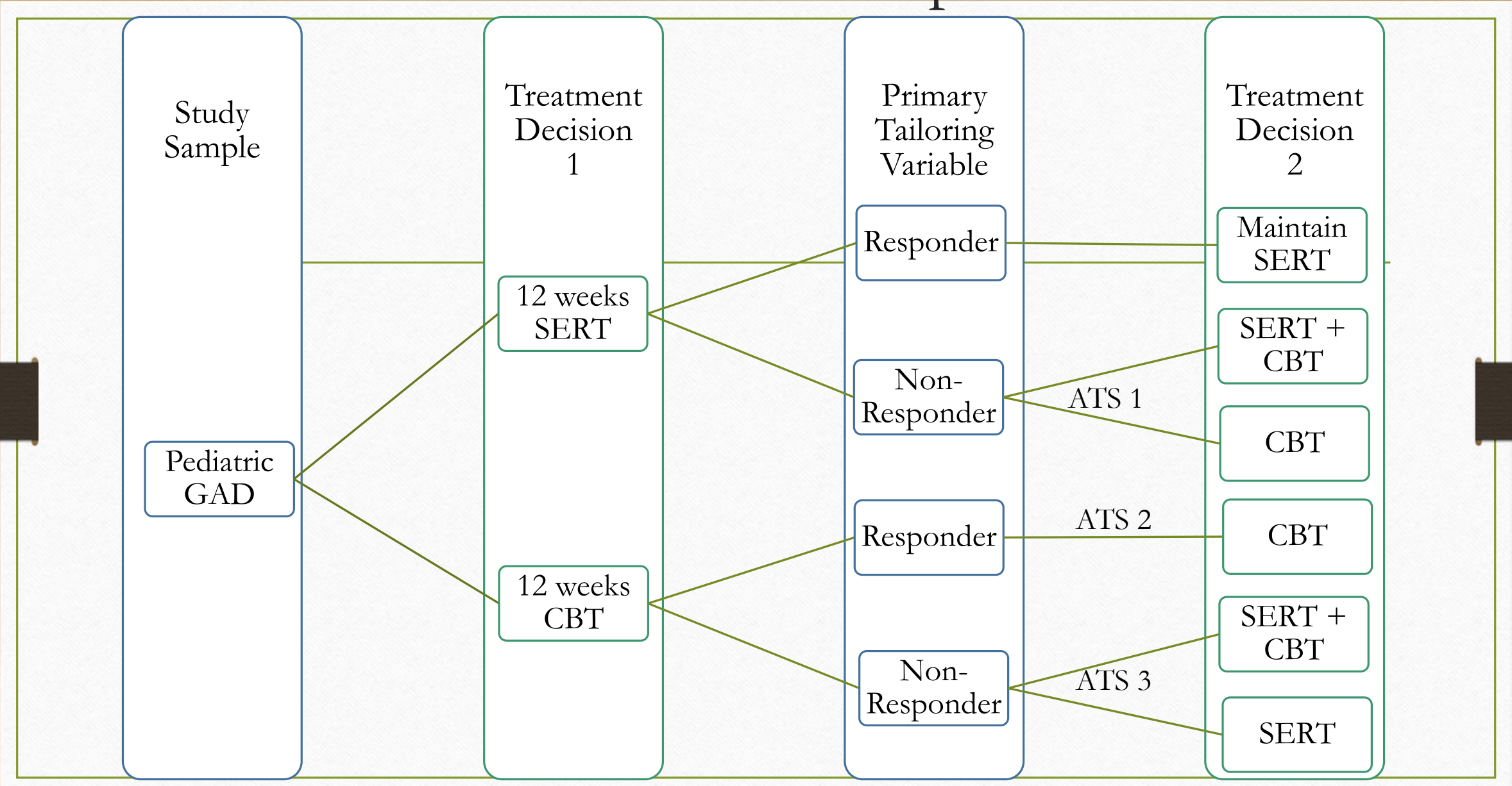
Statistical Complexity of SMARTs

- Single –decision setting:

  - Linear, logistics regression, variance analyses

- Multiple-decision setting:

  - Added complexity – interactions of treatment, timing of treatment, dosage level

  - Need to account for delayed effects

  - Q-Learning, backward outcome weighted learning (BOWL), and simultaneous outcome weighted learning (SOWL) are popular choices

  - Fundamentally based on Markov Decision Process (MDP)

Markov Decision Process (MDP)

- A mathematical framework for modeling decision making in situations where outcomes are partly random and partly under the control of a decision maker.

    - A set of possible states S

    - A set of possible actions A

    - A real valued reward (response) function $R(s,a)$

   - A description T of each action's effects in each state.

Markov Decision Process (MDP)
(Clinical Example)

1. Patient is in some state **S**,

2. Clinician chooses action **A** available in state **S**,

3. Process responds at the next time step by moving into a new state and giving the clinician a corresponding response **R(s,a)**

S (LDL Cholesterol) → **A** (Prescribe statins) → **R** (Change in LDL) →

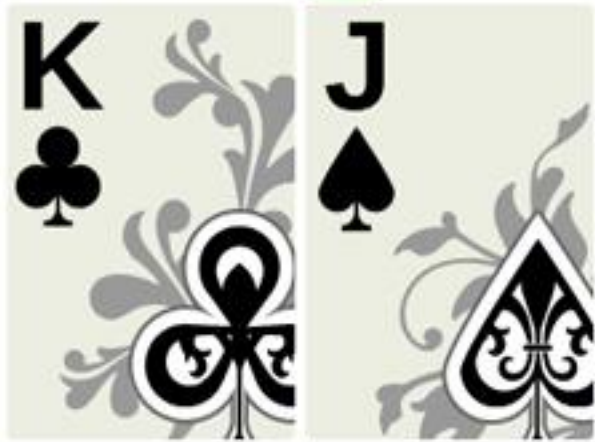**A** (Maintain /revise) → **R** (Change in LDL)

MDP – Decisions based on new information
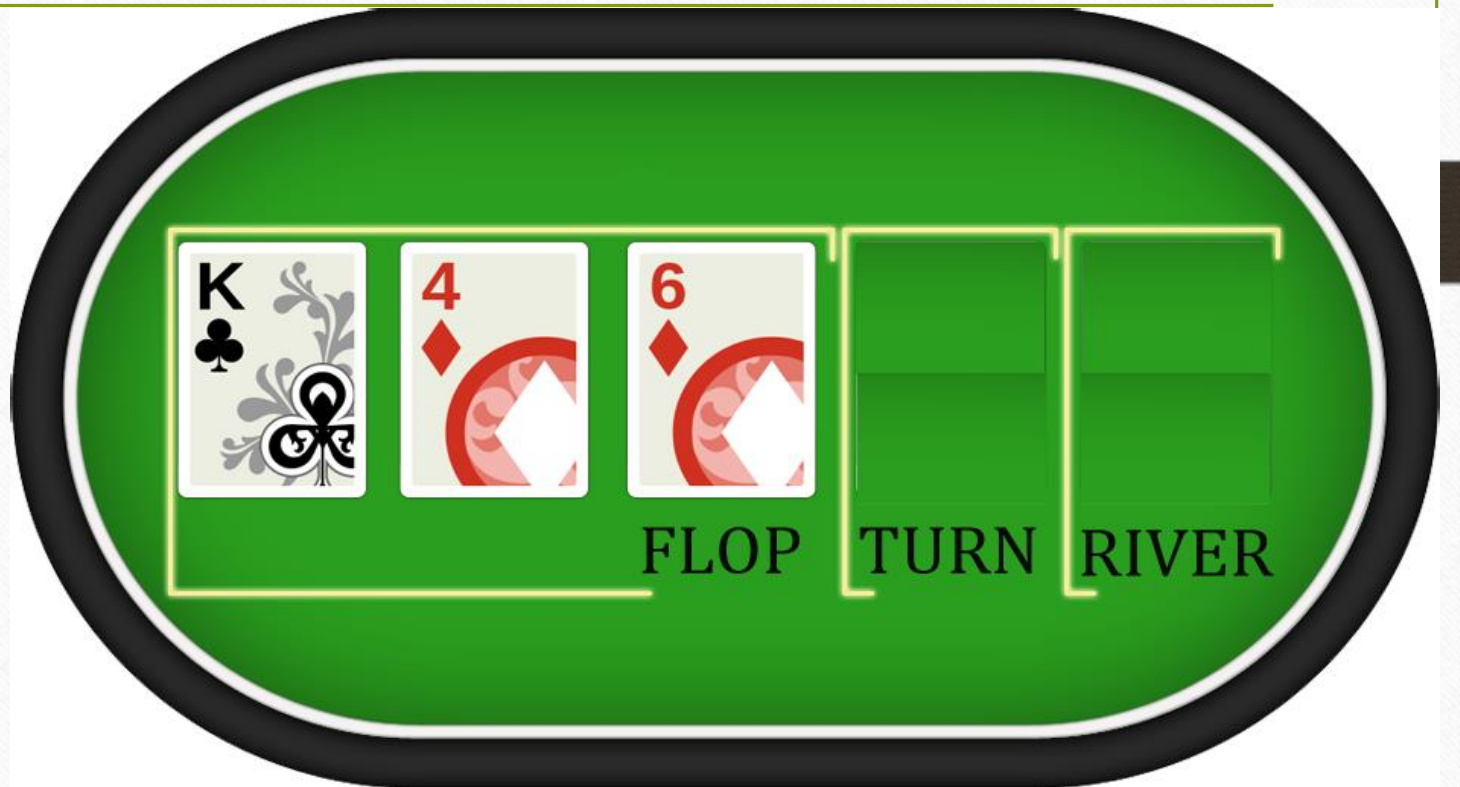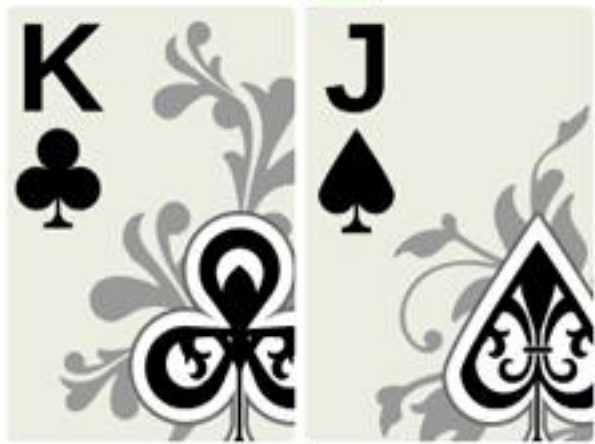
MDP – Decisions based on new information
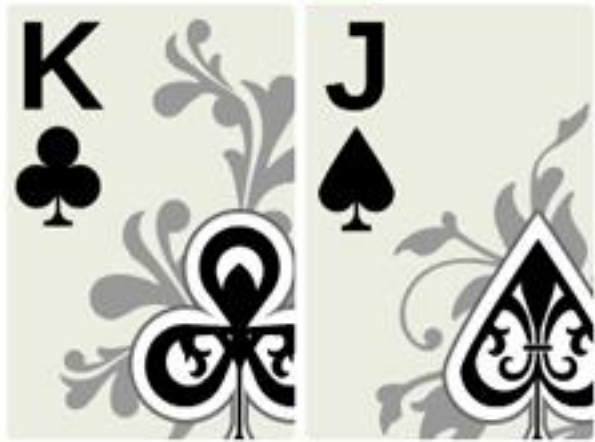
MDP – Decisions based on new information

Reinforcement Learning Techniques based on MDPs and used in DTRs

- Q-Learning – Similar to MDPs but factors in **weights w relating to response time, and anticipated maximum future response of action**

  - Variance between response times is an important factor in clinical research

  - Estimating maximum future response is also important.

- O-Learning – Outcome Weighted Learning (OWL), more recently Backward Outcome Weighted Learning (BOWL), and Sequential Outcome Weighted Learning

  - Weighted factors to best predict and identify optimal DTR

SMART Summary

- Develop the sequence of treatments that lead to optimal outcomes for the long-term – multiple ATSs

- Participants move through multiple stages of treatment

  - Each stage includes a critical decision

  - Participants are randomized at each stage/critical decision

- Following successful completion of a SMART, the design can be tested against a usual care treatment in a standard RCT

Summary for Today

- **Randomized Control Trial (RCT)** - Quantitative, comparative, controlled experiments

- **Explanatory** – Evaluate efficacy of intervention in controlled setting – internal validity

- **Pragmatic** – Test effectiveness of intervention in broad routine clinical practice – external validity

- **Adaptive Treatment Strategies** - Sequential decision rules that adapt over time to the changing status of each patient

- **SMART:** Develop the sequence of treatments that lead to optimal outcomes long-term – multiple ATSs

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