Pursuing the Truth: To Random or not to Random.

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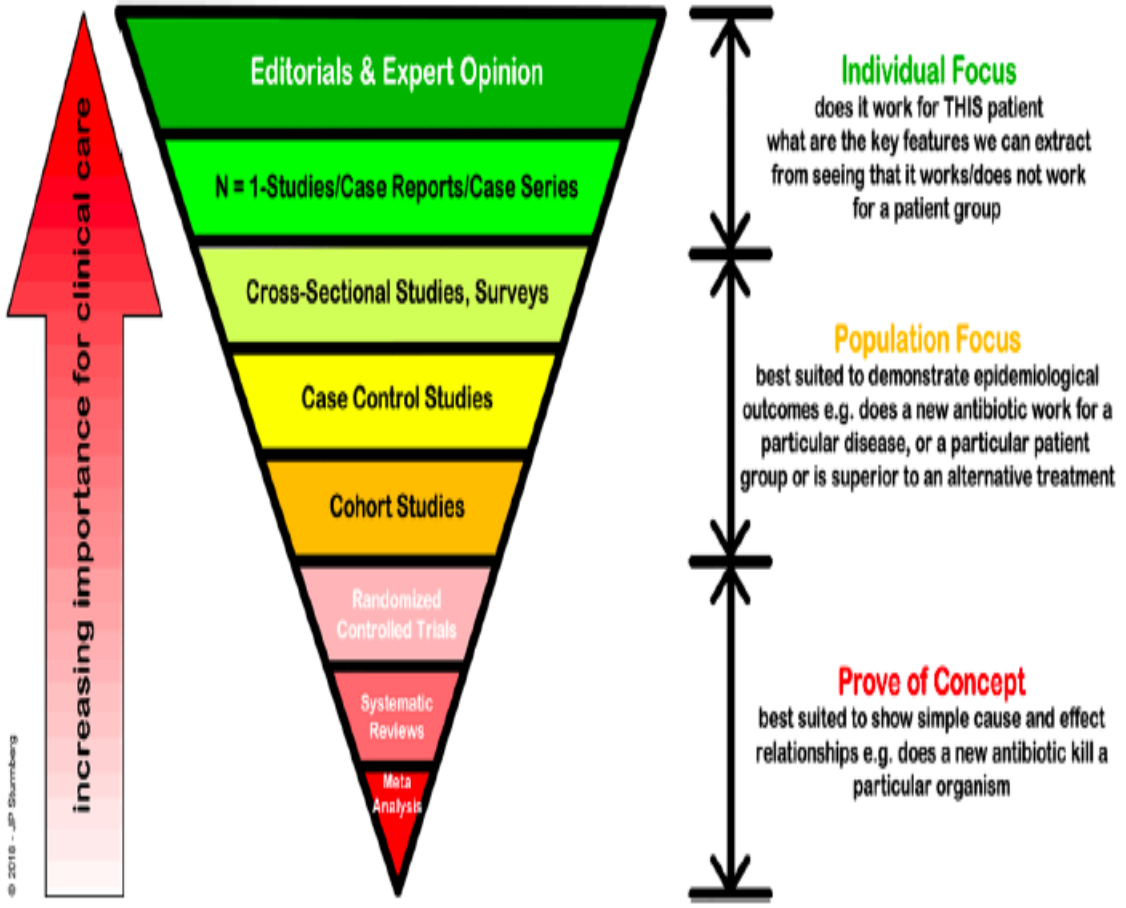

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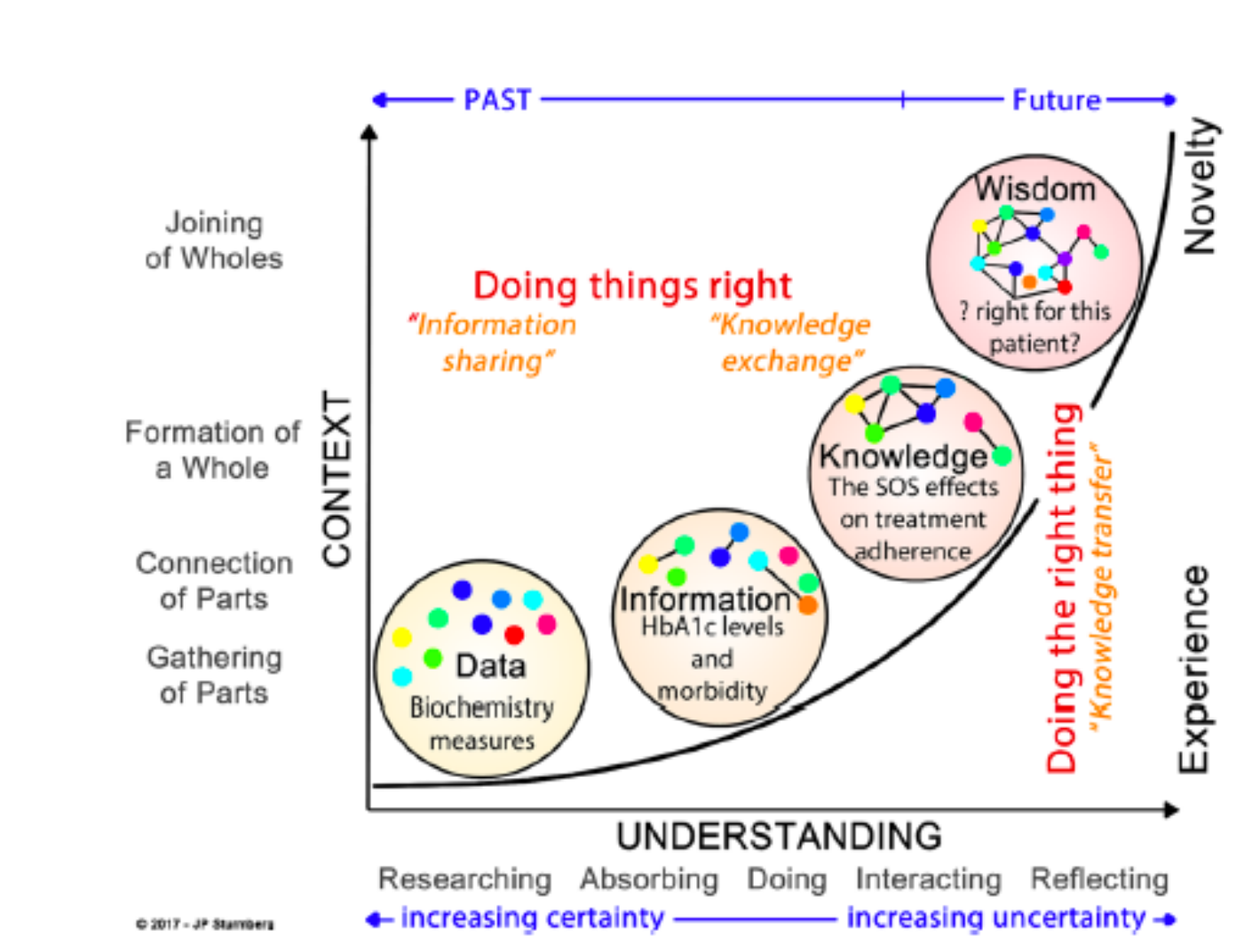

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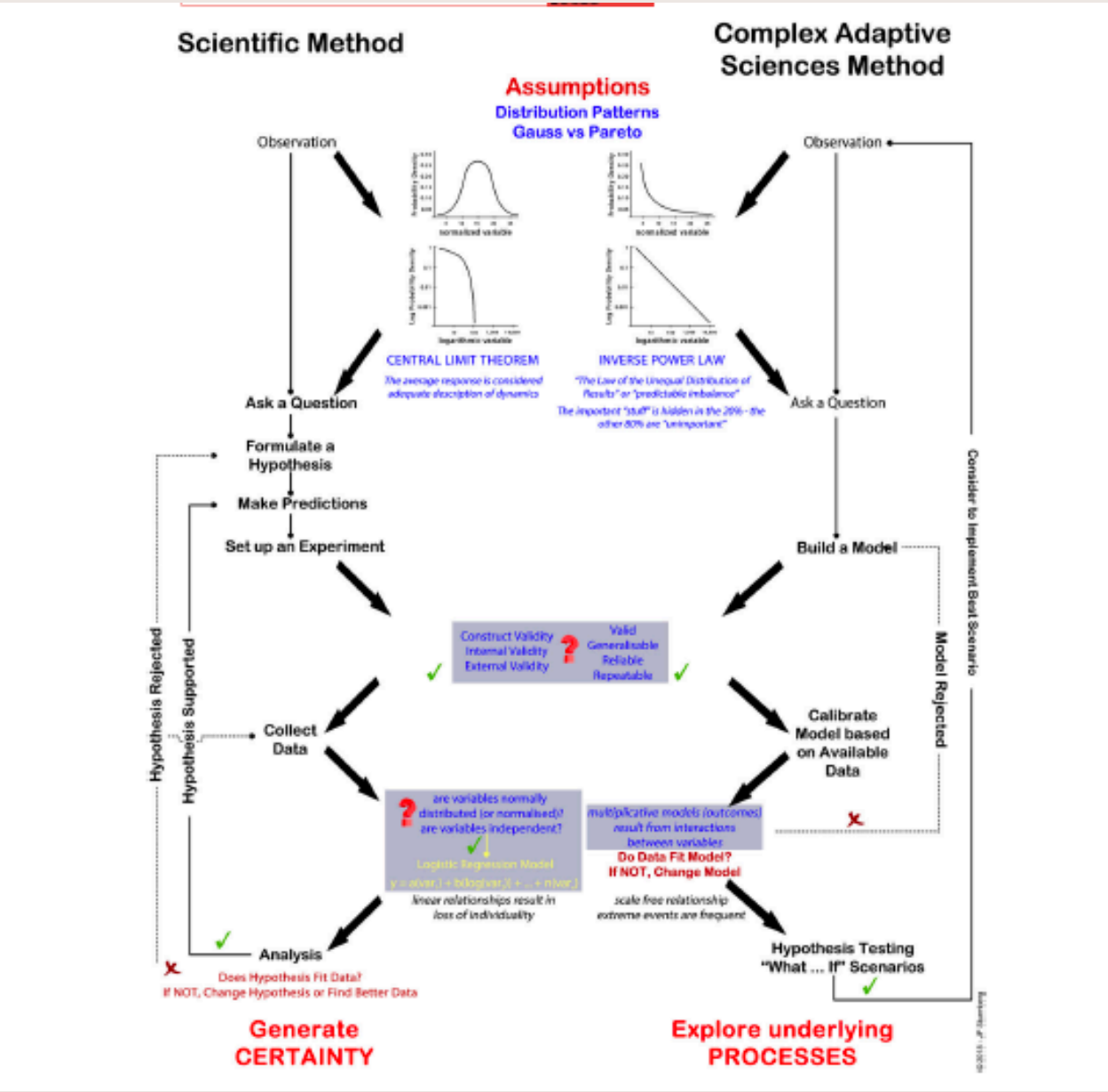

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TABLE 1 Comparing different study designs and their contribution to knowledge for clinical practice

	Purpose	Examples	Aims
Editorial and expert opinion			Critical reflection ± critical review of an intervention on clinical care
N = 1 studies/case reports/case series	Effectiveness for THIS person	Drug/intervention response if more than one option for a condition is available	
Cross-sectional studies, surveys[a]	Prevalence of a condition at one point in time within a population		
Case control studies[b]	Comparative effectiveness studies Identifying causal reasons for differences in outcomes	Intervention response	
Cohort studies[c]	Effectiveness of intervention/risk response in a defined group/ setting over a longer time period	Drug/intervention outcomes or exposure consequences for a particular condition	
Randomized controlled trial[d]	Simple cause-and-effect relationship studies	Drug discovery studies	
Systematic reviews[e]			Critical description of findings in relation to a condition in different contexts
Meta analysis[f]			Quantitative summary of findings from individual studies

[a]Cross-sectional study. Studies in which the presence or absence of disease or other health-related variables is determined in each member of a population at one particular time.

[b]Case-control study. Studies that start by identifying persons with and without a disease of interest (cases and controls, respectively) and then look back in time to find differences in exposure to risk factors.

[c]Cohort study. In cohort studies, groups of individuals, who are initially free of disease, are classified according to exposure or non-exposure to a risk factor and followed over time to determine the incidence of an outcome of interest. In a prospective cohort study, the exposure information for the study subjects is collected at the start of the study, and the new cases of disease are identified from that point on. In a retrospective cohort study, the exposure status was measured in the past, and disease identification has already begun.

[d]Randomized controlled trial (RCT). A clinical trial involving one or more new treatments and at least one control treatment with specified outcome measures for evaluating the intervention. The treatment may be a drug, device, or procedure. Controls are either placebo or an active treatment that is currently considered the "gold standard." If patients are randomized via mathematical techniques, then the trial is designated as a randomized controlled trial.

[e]Systematic review. A review which endeavours to consider all published and unpublished material on a specific question. Studies that are judged methodologically sound are then combined quantitatively or qualitatively depending on their similarity.

[f]Meta-analysis. A quantitative method of combining the results of independent studies, which are drawn from the published literature, and synthesizing summaries and conclusions to arrive at one overall measure of the effect of a treatment.

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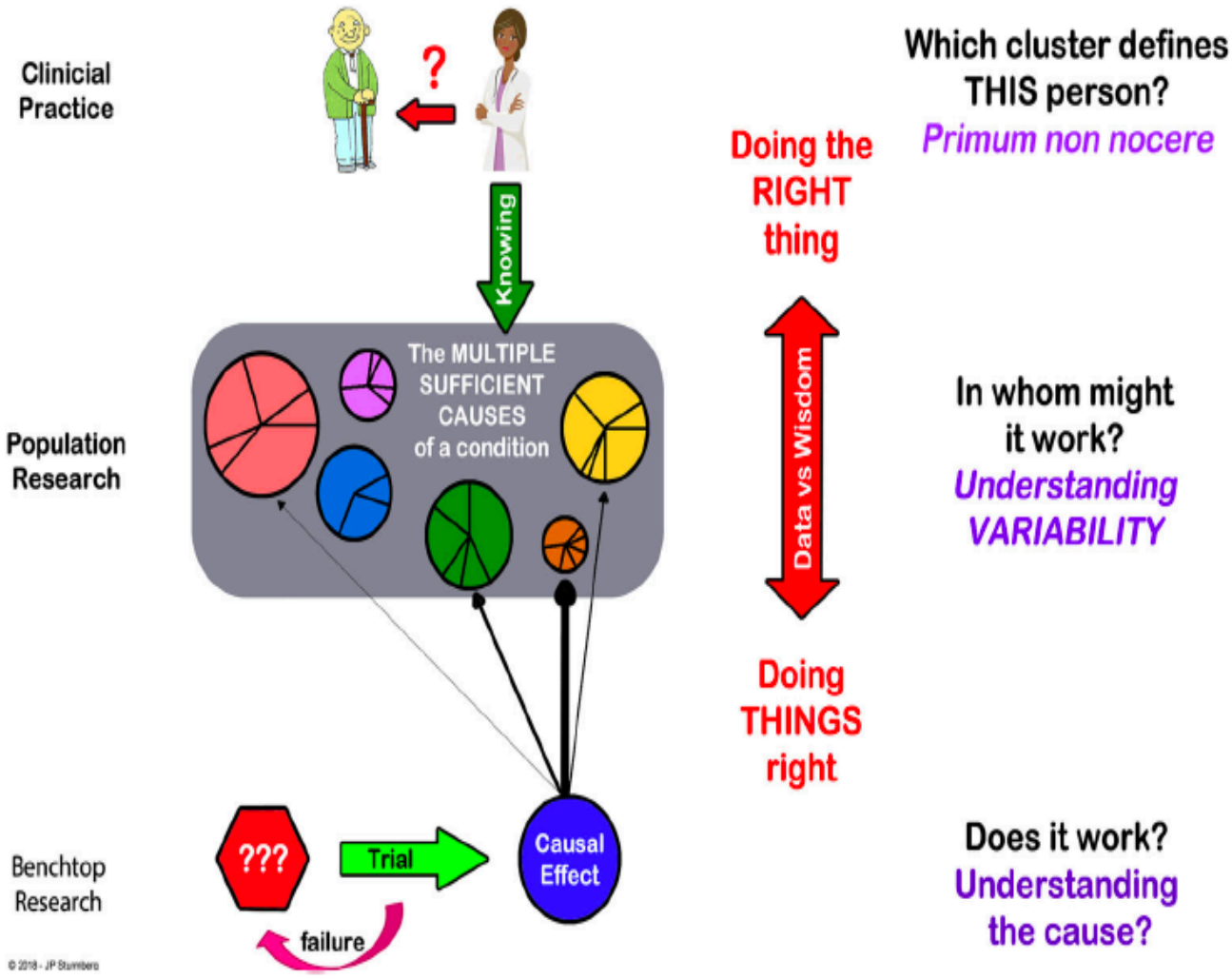

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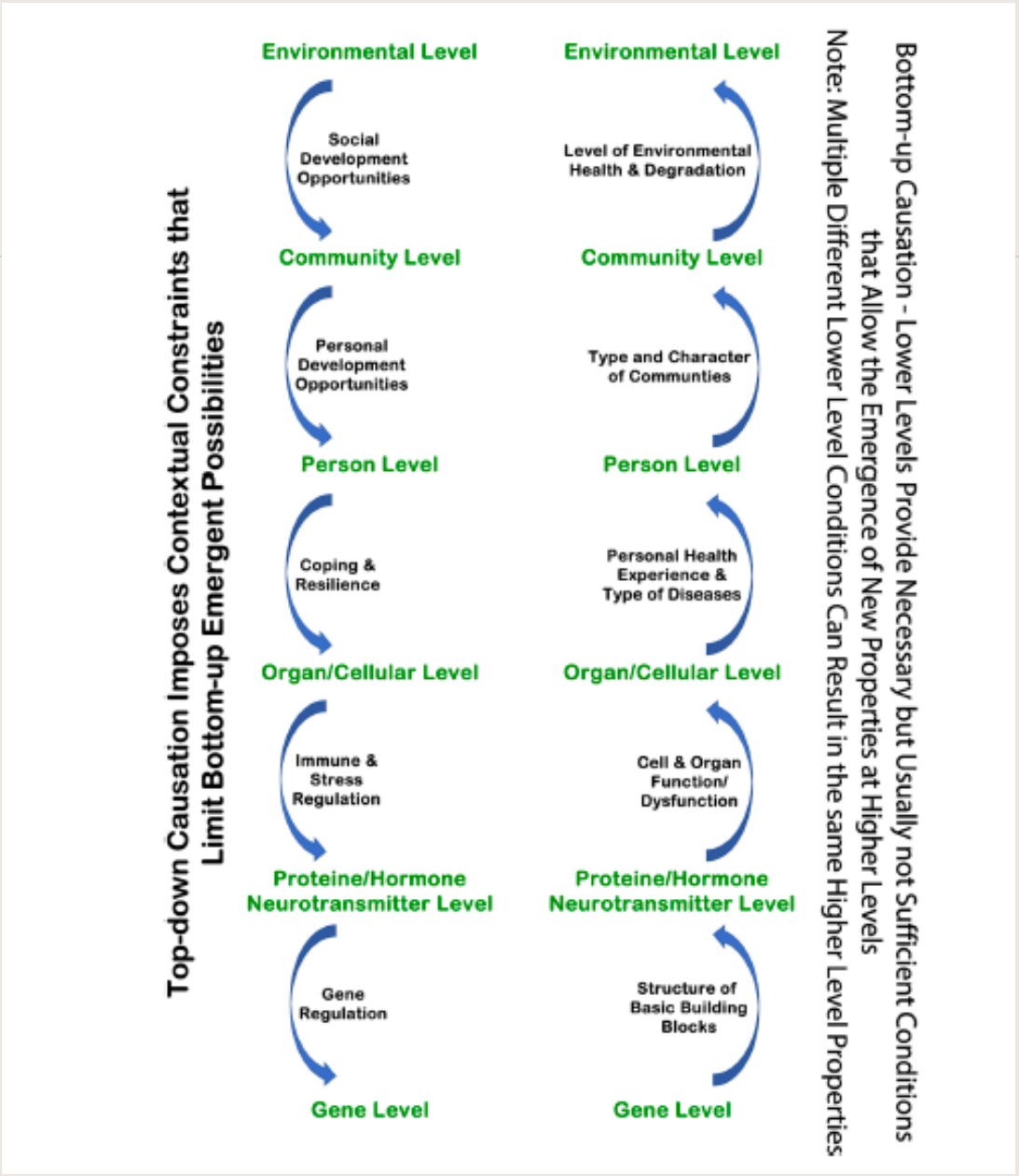

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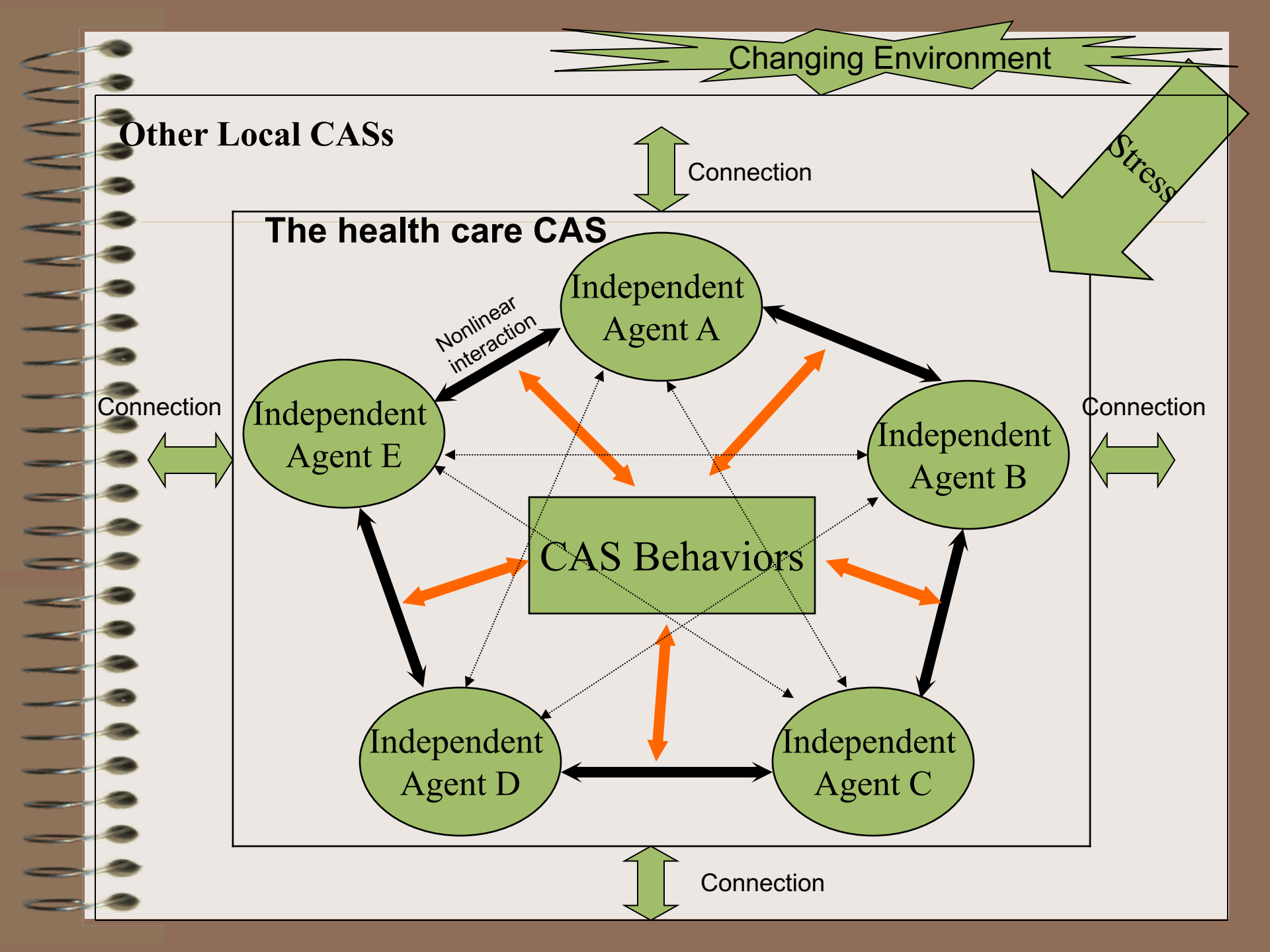
Outlines

- Open interactive discussion
- Introduction to Chaos and CAS
- Appraising RCT or experimental study
- Appraising observational study
- The difference between them
- Their Pros and Cons
- References

Research Questions

- Can we trust observational and/or RCT study in a CAS?
- To random or not to random?
- To conceal allocation or not to conceal?
- Observational studies are they alternative approach to RCT or a complimentary one?


Changing Environment
Other Local CASs
Connection
Stress
The health care CAS
Independent Agent A
Nonlinear interaction
Connection
Independent Agent E
Independent Agent B
Connection
CAS Behaviors
Independent Agent D
Independent Agent C
Connection

Complex Adaptive System

- A number of independent diversified agents
- Local nonlinear dynamic interaction among these agents
- These interactions lead to the emergent behaviors of the CAS
- No centralized control
- Self-organization (distributed control).

Complex Adaptive System (CAS)

- A diverse system composed of multiple interconnected elements (COMPLEX)
- An adaptive system capable of changing and learning from experience (ADAPTIVE).
- The CAS term was coined at the interdisciplinary Santa Fe Institute (SFI), by John H. Holland, Murray Gell-Mann and others.
    - John H. Holland is one of the inventors of evolutionary computation and genetic algorithms.
    - Murray Gell-Mann is a Nobel Prize laureate.
- The science of CAS is seeking the answers to some fundamental questions about living, adaptable, changeable systems.

CAS: John H. Holland

- "A dynamic network of many agents (which may represent cells, species, individuals, firms, nations) acting in parallel, constantly acting and reacting to what the other agents are doing.
- The control of a CAS tends to be highly dispersed and decentralized. If there is to be any coherent behavior in the system, it has to arise from competition and cooperation among the agents themselves.
- The overall behavior of the system is the result of a huge number of decisions made every moment by many individual agents."

Complexity: The Emerging Science at the Edge of Order and Chaos by M. Mitchell Waldrop)

CAS: Kevin Dooley

- A CAS behaves/evolves according to three key principles:
  - Order is emergent as opposed to predetermined
  - The system's history is irreversible
  - The system's future is often unpredictable.
- The basic building blocks of the CAS are agents. Agents scan their environment and develop schema representing interpretive and action rules. These schema are subject to change and evolution.

K. Dooley, AZ State University

Methodological Quality

- "Extent to which a study's design,conduct, and analysis has minimized **selection**, *measurement*, and confounding biases"

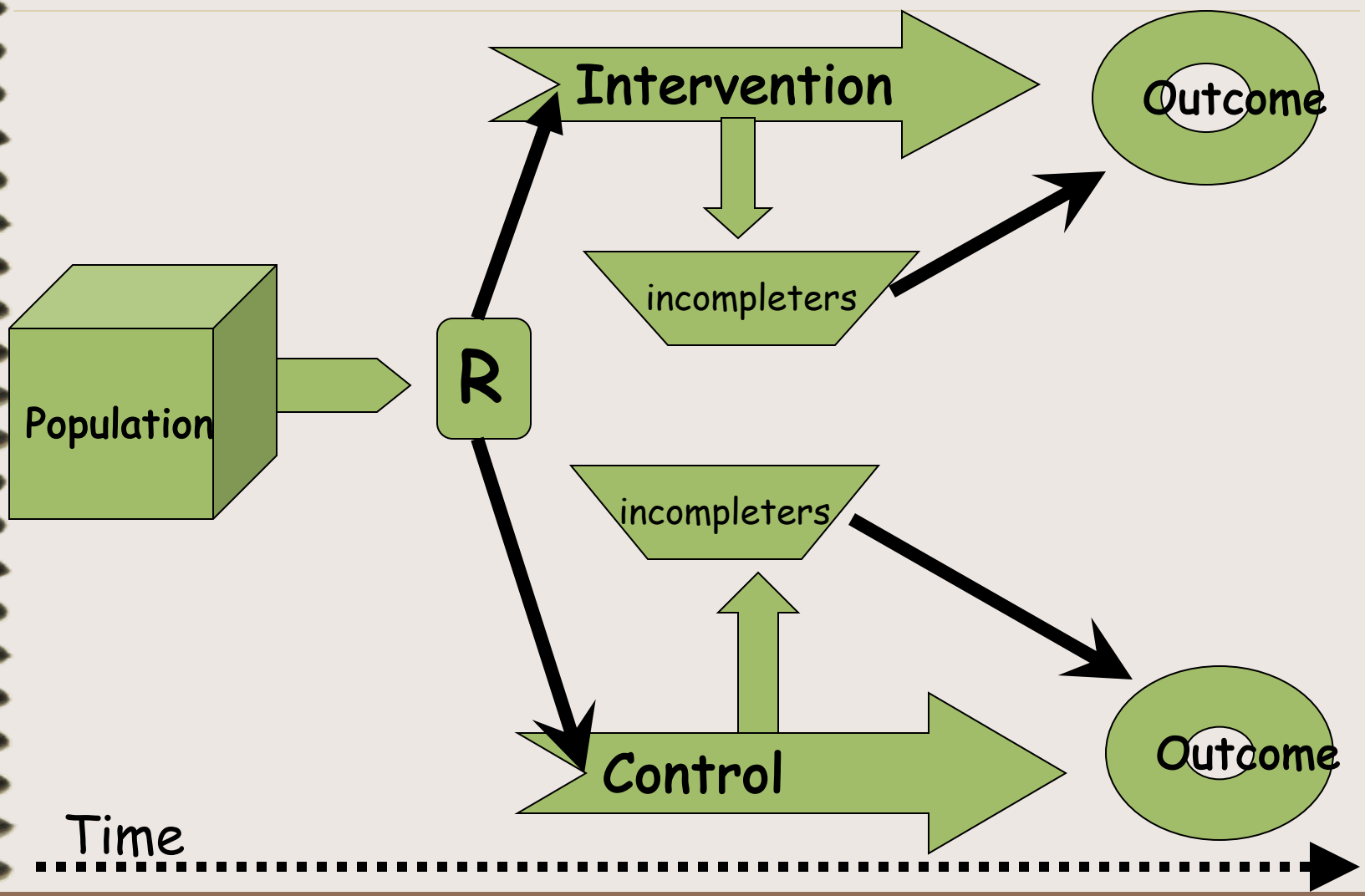
- good quality study = unbiased true results

West et al, Rating the strength of scientific evidence.2002

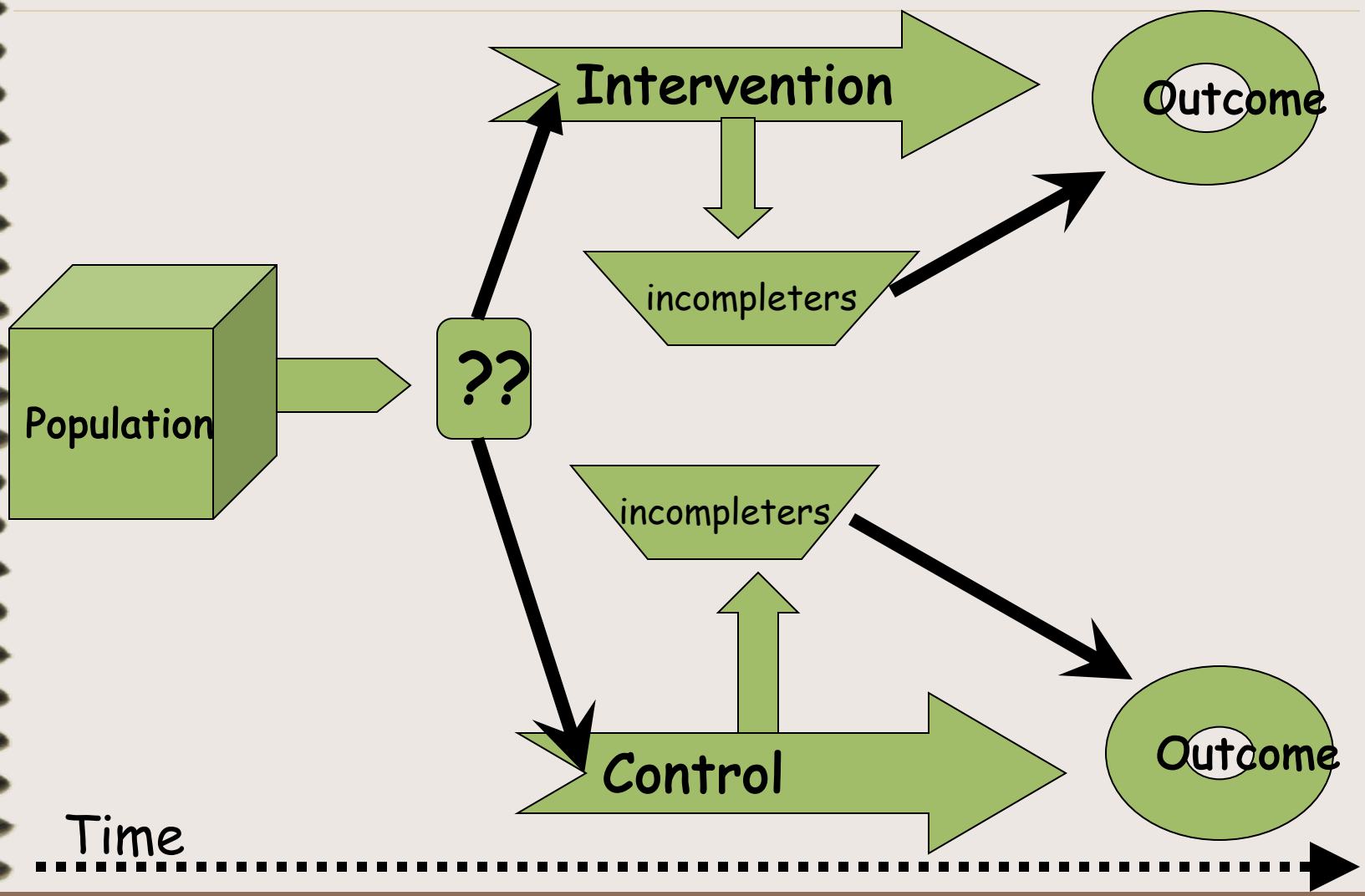
Hierarchical Structure of Evidence?

- A: systematic review of RCTs
- B: single RCT
- C: unrandomized clinical trial
- D: case-control/ cohort/ quasi-experimental studies.
- E: Descriptive studies
- F: experts opinions.

RCT Structure



Observational study Structure



Sources of Bias in RCT or Observational study

Source	Definition
Selection of subjects	Inclusion & exclusion criteria
Comparability of groups	Randomization and allocation of patient. Similarity at baseline.
Blinding	Masking pts, investigators, care providers, outcome assessors, biostatician
Adequate sample size	Power to detect a difference
Therapeutic regimen Or Exposure	Detailed information on the trx Information on co-trx Information on unplanned trx

West et al 2002

Sources of Bias in RCT or Observational study

Source	Definition
Outcomes	Reliable and valid measurement
Handling withdrawal after eligibility determination	Withdrawals, drop-outs, or other losses from the study, by patients group
Threat to validity	Confounders and bias and how they are accounted for
Statistical analysis	Appropriateness of model Adequate description and reporting of the analysis "Intention-to-treat" analysis
Sponsorship	

West et al 2002

The Crucial Steps?

- **R:** randomized & concealed allocation of Subjects.
- Attrition
- Outcome Measure
- Analysis
- Sponsorship

RCT is better than Observational study: what are the evidence.

The "safeguards" evidence

- Random assignment aim to eliminate both unconscious and deliberate human influence on the assignment of subjects to different groups.
- Blind assessment ensures that treatment and analysis of outcomes are not colored by prejudice.

RCT is better than Observational study: what are the evidence.

The discrepancy Argument

- Three SERs found that
  - poor methodology could either overestimate or underestimate treatment effects
  - the variation between random and nonrandom evidence may not be greater than those between different RCTs.

RCT is better than Observational study: what are the evidence.

- Currently the ***random assignment*** and masked outcome measure offered the best protection against unpredictability of bias.
- Randomization produce comparable groups with respect to known and unknown prognostic factors at baseline.

Is the double-blind, masked RCT objective?

- Can unbiased method produce bias?
- Is the outcome in RCT is similar to the outcome in ordinary clinical practice?
- Knowledge that one has a chance of receiving placebo may introduce in a patient's perceptions uncertainty sufficient to decrease the magnitude of the response to either drug or placebo.

Kaptchuk, 2001

Is the double-blind, masked RCT objective?

- Participation in RCT may increase the detection of beneficial or adverse responses.
- Participation in RCT may create ambivalence, confusion, passivity, or absence of commitment among subjects (resentful demoralization and voluntary submission) that can lead to unpredictable reactions.
- The assumption in RCT of that the placebo affect in the treatment arm equals the placebo effects of the placebo arm.

Kaptchuk, 2001

The Real Question

- "What should we do when randomized, controlled trials and observational studies disagree, and which type of study design is more likely to give the truth?"
- How do we in fact determine the truth in clinical medicine?
- Are the conclusions of randomized clinical trials replicable when the outcomes are examined in everyday practice?
- **Can unrecognized confounding factors distort the results of observational study?**

Sacket, 2000

So: The General limitations of observational studies

1. The inability to take unknown confounders into account.
2. Non-blinding of practionners and patients
3. The inclusion of practitioners' and patients' treatment preferences.

Black, 1999

So: When should we use observational study instead of RCT?

- The RCT is
  - Unnecessary
  - Inappropriate
  - Inadequate
  - impossible

Black, 1999

When RCT is inappropriate?

1. The RCT is not large enough to accumulate infrequent adverse outcomes. (post-marketing surveillance for drug side effects).
2. Evaluating the impact of intervention in preventing rare outcomes.
3. The outcome lies far in the future
4. The random allocation itself might reduce the effectiveness of the intervention. An intervention in which clinicians and / or patients have a preference (despite agreeing to random allocation) and where active participation in the intervention by the patients is necessary. (intervention promote health or prevent disease)

Black, 1999

Last point

- People who are prepared to have their treatment allocated on a random basis have
  - a more serious illness
  - are less educated
  - are less affluent

  than those who decline to participate.

Black, 1999

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