

Obscuring Intervention Allocation (OIA) in Pragmatic Trials: Ethical Issues

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Scientific & Social Value

- I. Trials are tools for answering questions.
 - a. Nature and source of uncertainty is critical to ethical evaluation of trial designs.
- II. Design features have to be justified by:
 - a. Contribution to evidence quality vs alternative designs.
 - b. Relative risks/costs vs alternative designs.



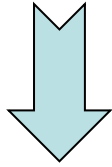
Frustrating Preferences

- I. OIA can frustrate provider and participant preferences.
 - a. Has efficacy been established?
 - b. Does honoring preferences confound efficacy?
 - c. Which component is best target for improving outcomes?

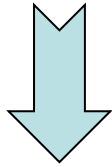


Real World Effectiveness

Ensemble Efficacy



Utilization Factors

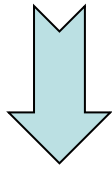


Real World Effectiveness

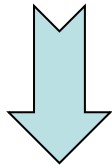


Real World Effectiveness

Ensemble Efficacy¹



Utilization Factors



Real World Effectiveness

- a. Drug
- b. Dosage
- c. Schedule
- d. Population
- e. Co-interventions
- f. Diagnostic requirements

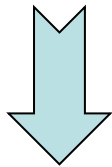
¹Kimmelman & London (2015) The Structure of Clinical Translation. Hastings Cent Rep. Mar-Apr;45(2):27-39. doi: 10.1002/hast.433. Epub 2015 Jan 27

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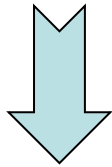


Real World Effectiveness

Ensemble Efficacy¹



Utilization Factors



Real World Effectiveness

- Provider or Patient Preferences
- Cost
- Tolerance/Adherence
- Clinical capacity
- Awareness

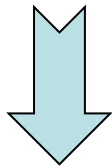
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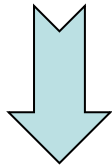


Real World Effectiveness

Ensemble Efficacy¹



Utilization Factors



Real World Effectiveness

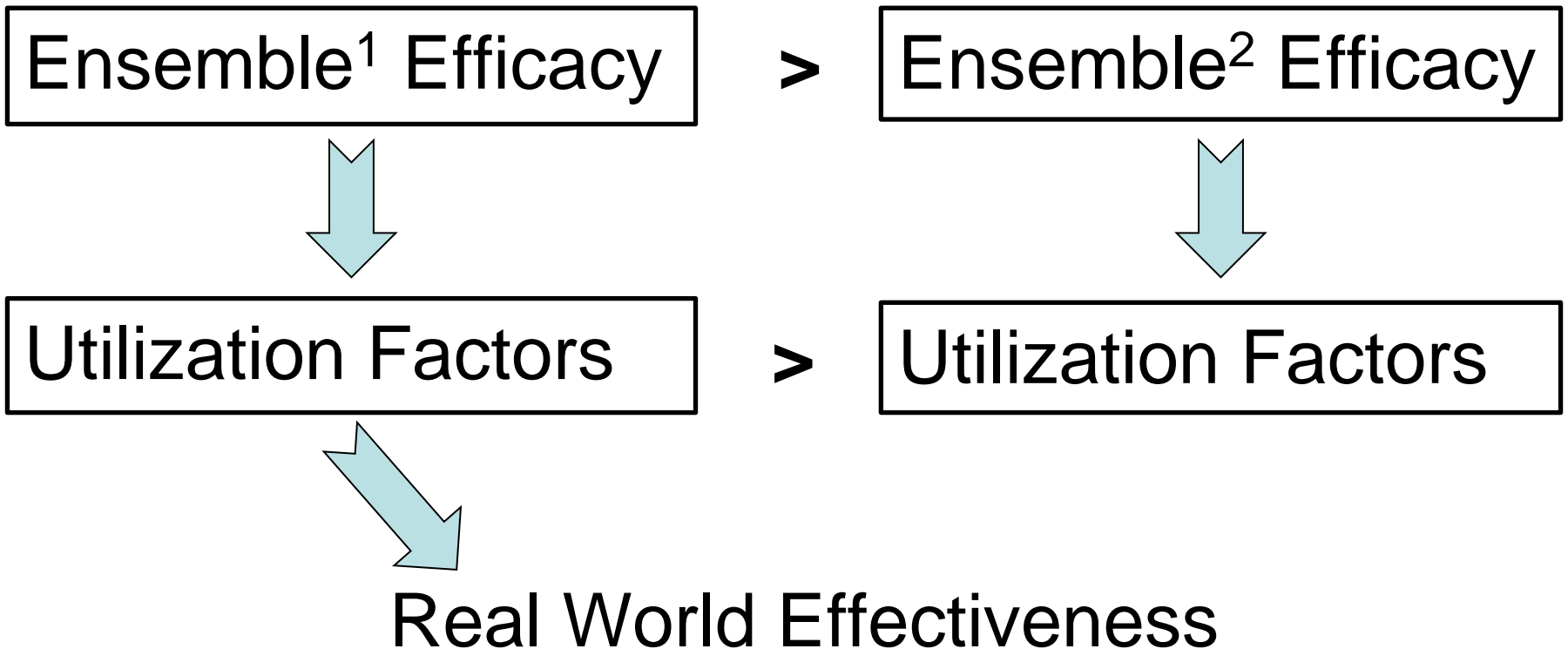
- Single dose vs multiple
- Oral vs injection
- Medical vs surgical
- Less testing
- Better tolerated

¹Kimmelman & London (2015) The Structure of Clinical Translation. Hastings Cent Rep. Mar-Apr;45(2):27-39. doi: 10.1002/hast.433. Epub 2015 Jan 27

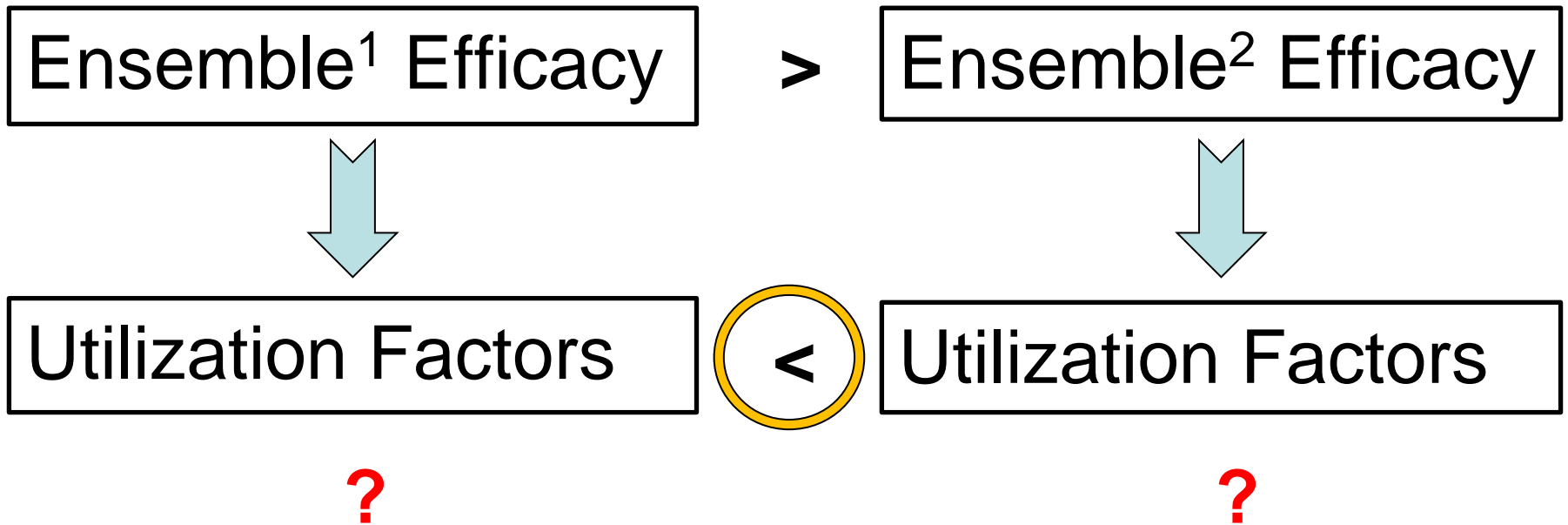
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Least Uncertainty



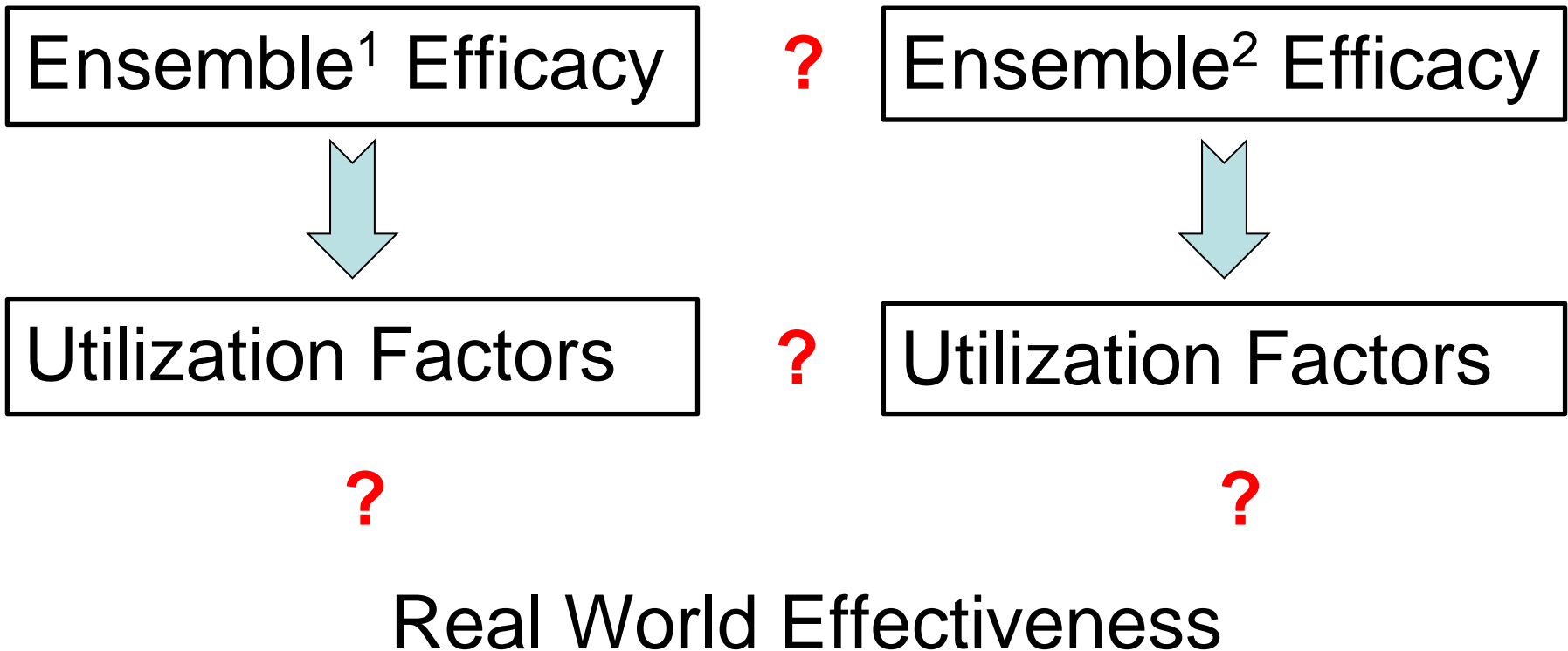
OIA Not Warranted



Real World Effectiveness



OIA May Not Be Warranted

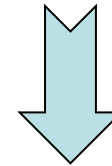
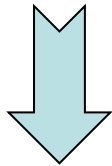


Policy Question

Ensemble¹ Efficacy



Ensemble² Efficacy



Utilization Factors



Utilization Factors



- I. Identify most efficacious and change practice?

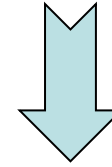
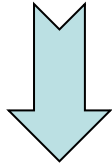


Policy Question

Ensemble¹ Efficacy

?

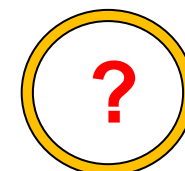
Ensemble² Efficacy



Utilization Factors

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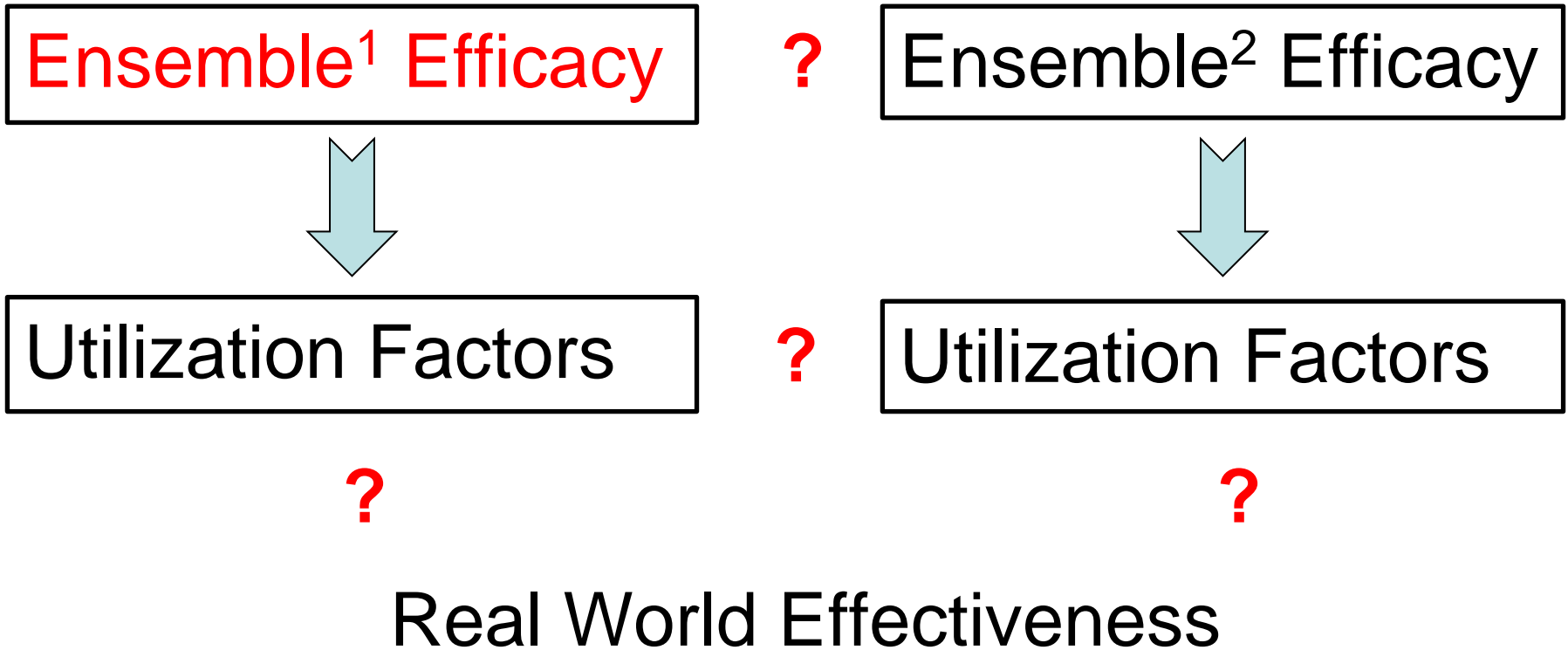
Utilization Factors



II. Allow preferences to vary and identify most effective?



Presumption Favoring OIA



Frustrating Preferences

- I. Expectations of efficacy without sound evidence are often **false**.
 - a. Myriad stakeholders rely on evidence from trials for decisions affecting health, welfare, use of scarce resources.
 1. Guideline 1, CIOMS International Ethical Guidelines for Health-related Research Involving Humans



Sham Knee Surgery

- I. Arthroscopic surgery for osteoarthritis of the knee: 650,000 procedures at cost of \$3.25 Billion annually.
- II. Sham surgery vs arthroscopic surgery showed no benefit to the real surgery².
 - a. Sham essential for OIA.
 - b. OIA essential for a clear picture of intervention efficacy.
 - c. Efficacy data necessary to weigh net clinical merit.

²Moseley, J. Bruce, Kimberly O'Malley, Nancy J. Petersen, Terri J. Menke, Baruch A. Brody, David H. Kuykendall, John C. Hollingsworth, Carol M. Ashton, and Nelda P. Wray. 2002. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *New England Journal of Medicine* 347 (2): 81–88.



Double Sham Surgery

- I. Chronic migraine prevention: “double placebo”³
 - a. Acupuncture + placebo medicine or
 - b. Sham acupuncture + topiramate
- II. Compares interventions of different modality while controlling for patient perception.

³Liu L, Zhao L, Zhang CS, et al. Acupuncture as prophylaxis for chronic migraine: a protocol for a single-blinded, double-dummy randomised controlled trial. *BMJ Open* 2018;8:e020653. doi:10.1136/bmjopen-2017-020653



Risks from OIA

- I. “Sham” can range from mere theater to invasive surgical procedures.
- II. Some placebos may have a positive risk profile.
 - a. Risks need to be offset by the value of evidence.⁴
- III. Risks from sham & from receiving a potentially *ineffective* active intervention should be communicated to participants.

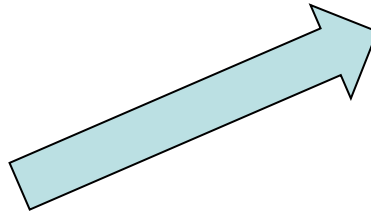
⁴London AJ. 2006. “Sham Surgery and Reasonable Risks” in David Benatar ed. *Cutting to the Core: Exploring The Ethics of Contested Surgeries* (New York: Rowman & Littlefield) 211-228.



OIA and Extending Label

Ensemble Efficacy

- a. Drug
- b. Dosage
- c. Schedule
- d. Population
- e. Co-interventions
- f. Diagnostic requirements



INVESTED Trial⁵

d. medically stable adults over 65 years.



d'. acute myocardial infarction or heart failure hospitalization over 18 years old.

⁵O. Vardeny et al. / American Heart Journal 202 (2018) 97–103



Example: INVESTED trial⁵

Established Effective Intervention Ensembles

A. High-dose tri-valent inactivated influenza vaccine
Approved for medically stable adults over 65 years.



Study Arms

A'. High-dose tri-valent inactivated influenza vaccine
Patients with acute myocardial infarction or heart failure hospitalization over 18 years old

B. Standard-dose quadrivalent inactivated influenza vaccine
Approved for patients over 6 months.

⁵O. Vardeny et al. / American Heart Journal 202 (2018)

97–103



Uncertainty Matters

- I. Nature of the uncertainty should influence trial design.
- II. Uncertainty about relative risks / potential benefits should be clearly communicated to participants.
 1. Uncertainty vs disagreement⁶
- III. Role of design in addressing uncertainty should be explained.

⁶London AJ. (2018) Learning health systems, clinical equipoise and the ethics of response adaptive randomization. *J Med Ethics* **44**:409–415.



Thank you

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