Confirm & Learn?

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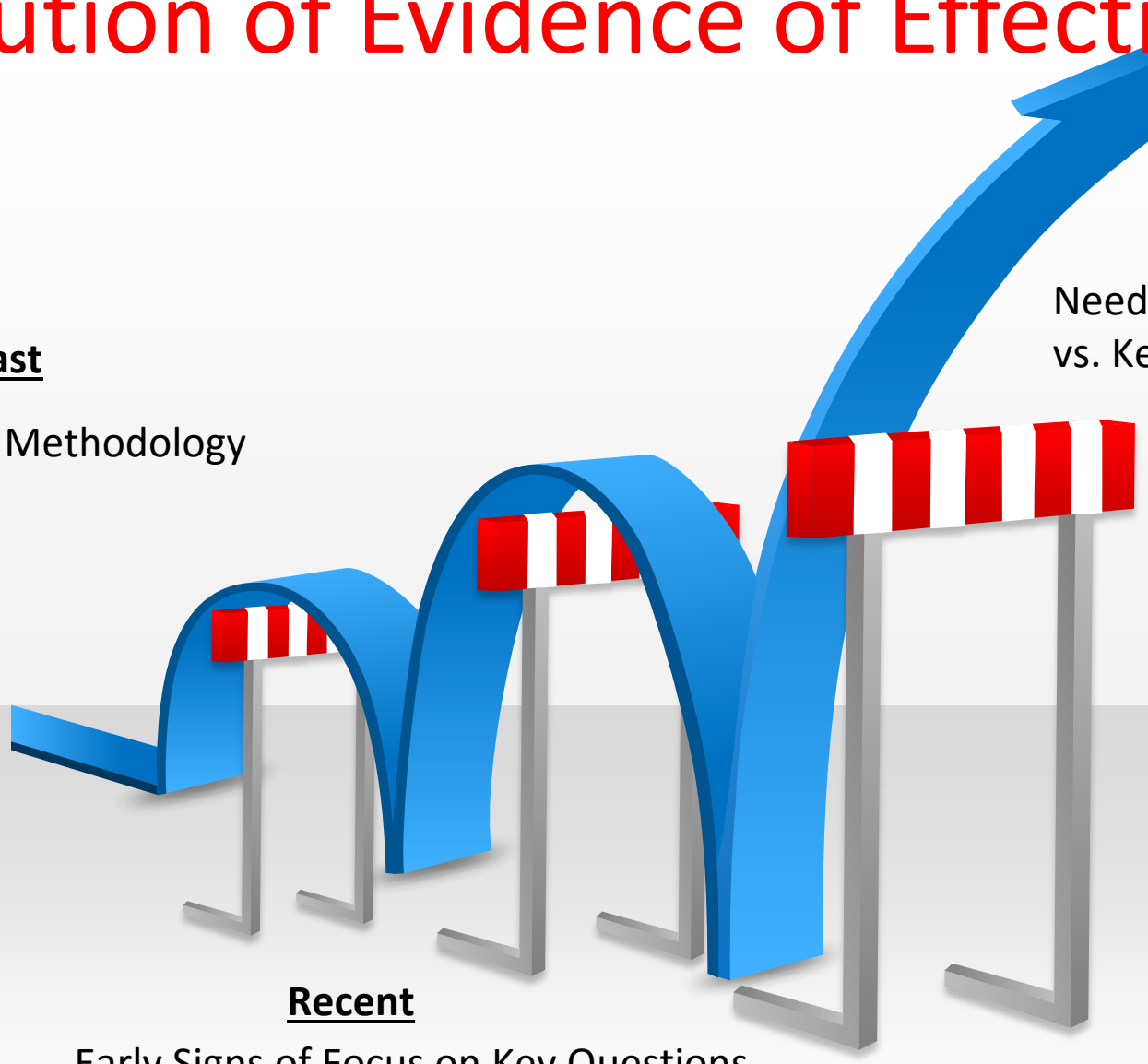
Evolution of Evidence of Effectiveness

Past

Focus on Methodology



Recent

Early Signs of Focus on Key Questions

Future

Need to choose between Methodology vs. Key Questions

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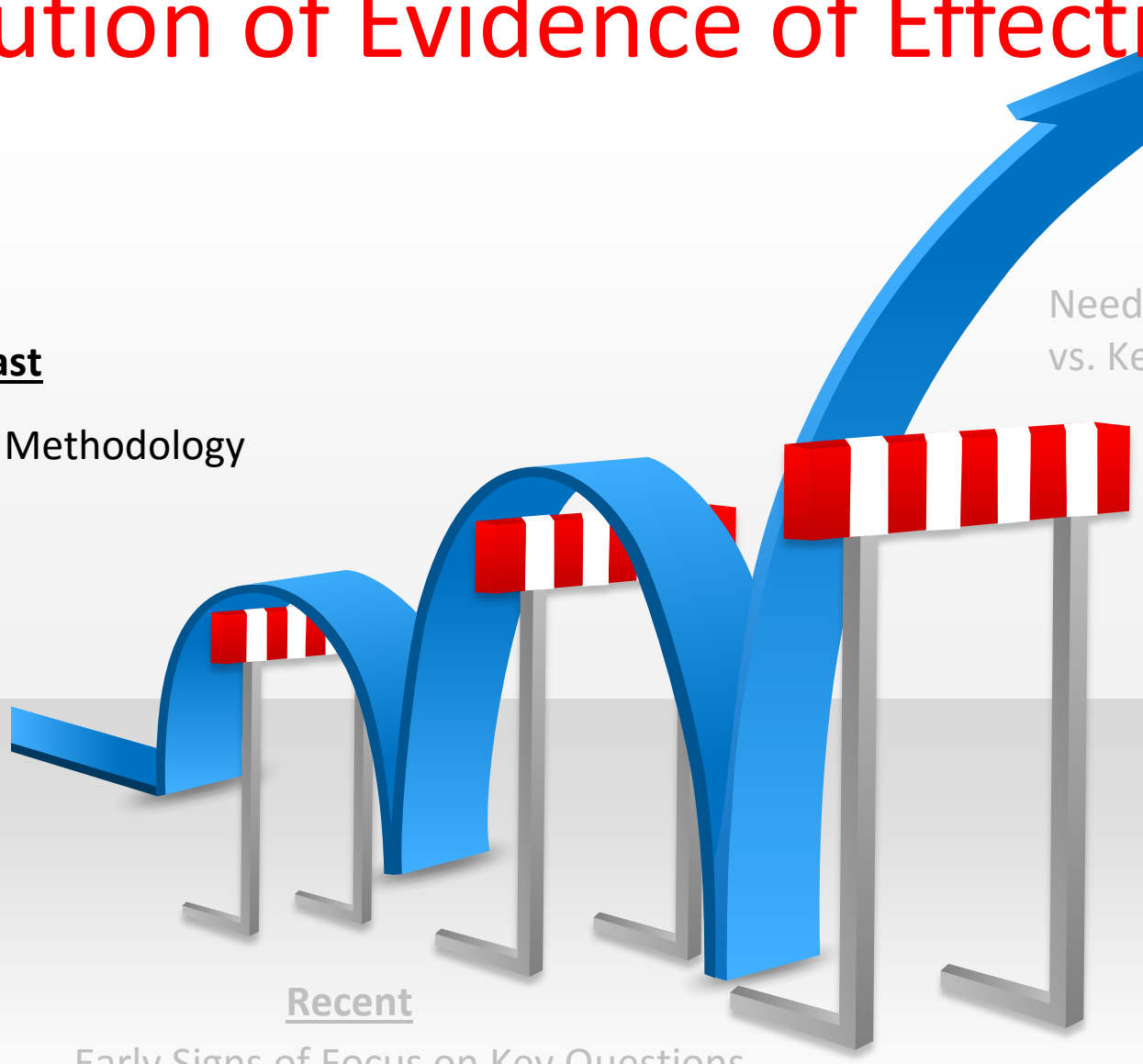

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Efficacy Requirement

Kefauver-Harris Drug Amendments (1962) passed to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers are **required** to prove to FDA the effectiveness of their products before marketing them.

Motivation to Focus on Methodology

- “In the Soule, Wasserman, and Burstein study of the effect of the OPE Chymoral (marketed by Armour) on symptoms associated with episiotomy, the investigators made 240 comparisons between the study and control group on factors such as edema (swelling), erythema (skin redness), bruising, and the subject's pain while resting, sitting, and walking. These were studied at **different time periods** after delivery. Of the 240 tests, statistically significant results were reached showing effectiveness of Chymoral for reduction of pain "on sitting on day four in subjects with labors over eight hours"; for reduction of pain "on sitting, on post-partum days two and three, in the 20 subjects less than 21 years old"

Warner-Lambert v Heckler **1986**. U.S. Court of Appeals, Third Circuit

2 AWC Trials (Substantial Evidence)

- With regard to quantity, it has been FDA's position that Congress generally intended to require at least **two adequate and well-controlled studies**, each convincing on its own, to establish effectiveness.
- *Warner-Lambert Co. V. Heckler,* 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence.

Replication of Evidence

- The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results.
- The inherent variability in biological systems may produce a positive trial result by chance alone.
- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet).

Replication of Evidence

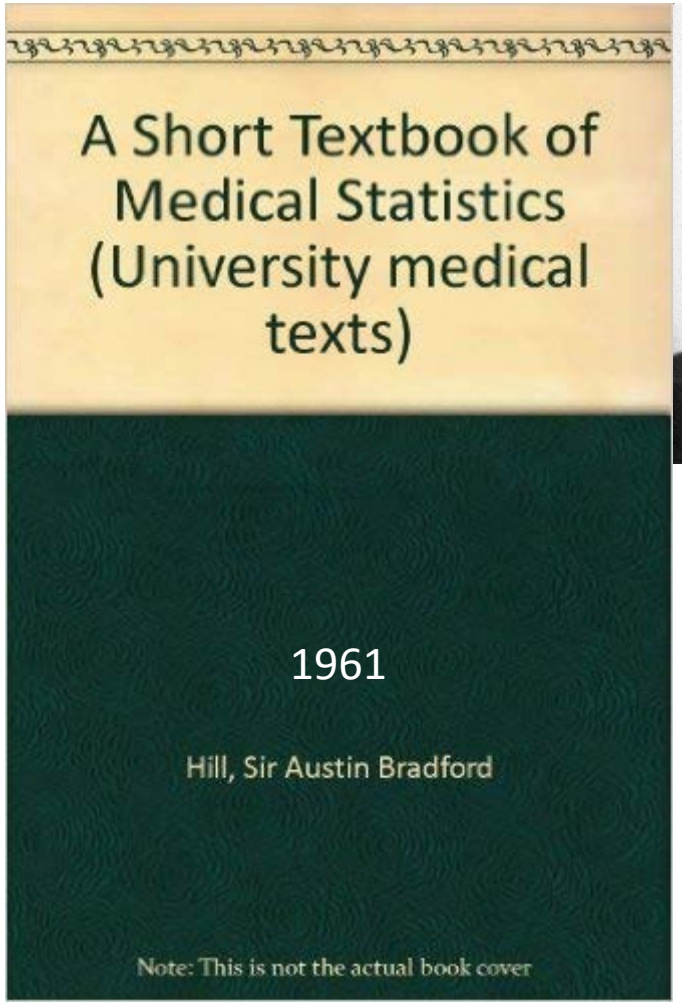
- The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. **Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.**

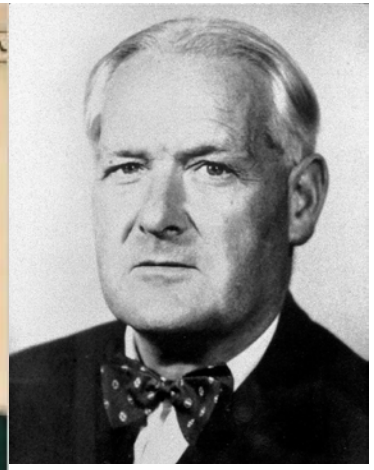
Totality of Evidence

- Evidence of effectiveness ought to be sought by establishing a **body of evidence** via multiple sources. A positive p-value by itself does not establish effectiveness.

- ***Internal consistency*** to demonstrate that the primary finding is consistent across different trials, sub-groups, endpoints is typically what drives approval. This is critical for **generalizability** of findings.

Once randomized, always analyzed!





Almighty P

Almighty P

Primary Goals of Registration Trials

- Establish substantial evidence of efficacy
- Support safety
- **Derive rational dosing based on benefit/risk**
- **Marketing claims**

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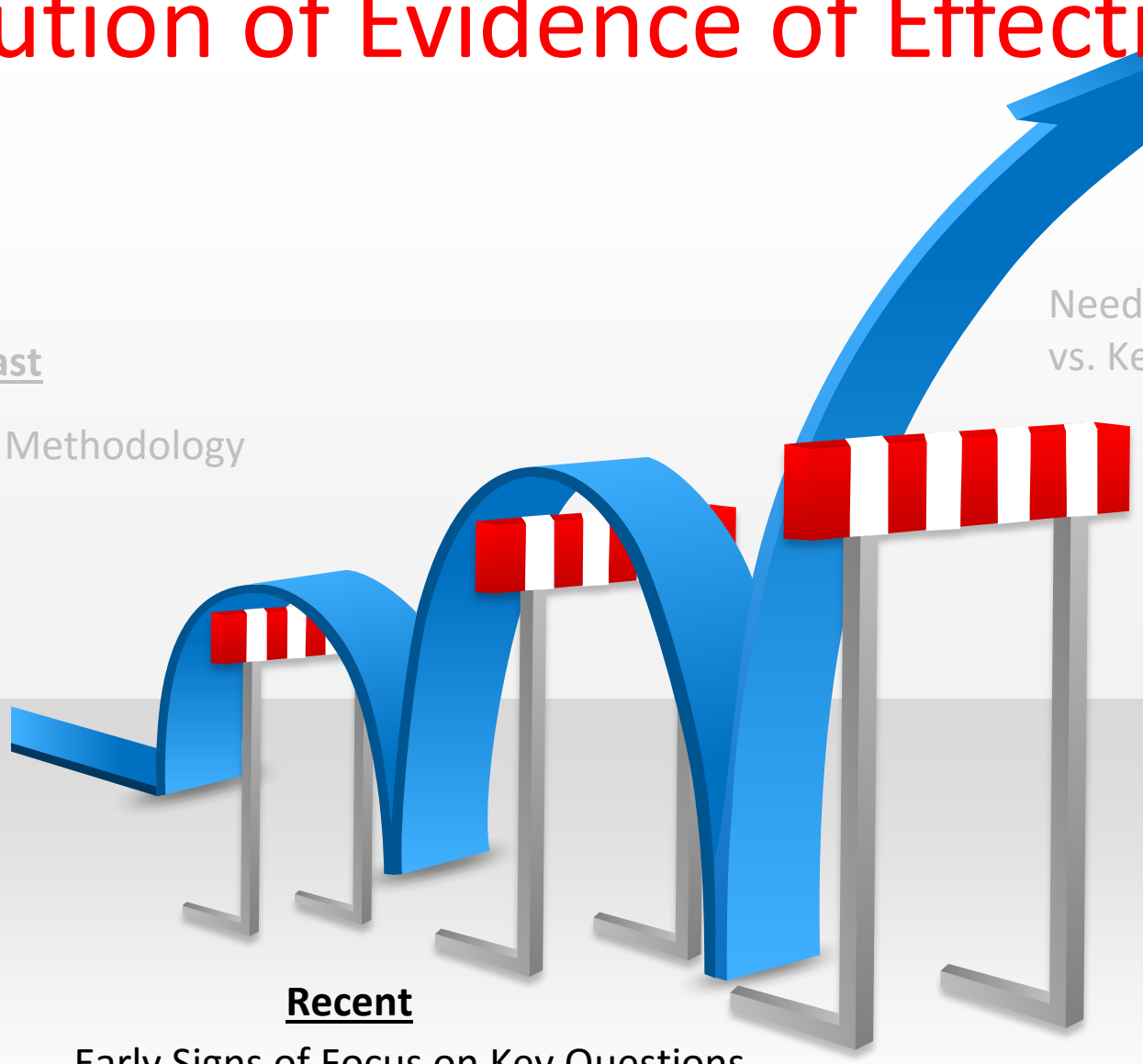


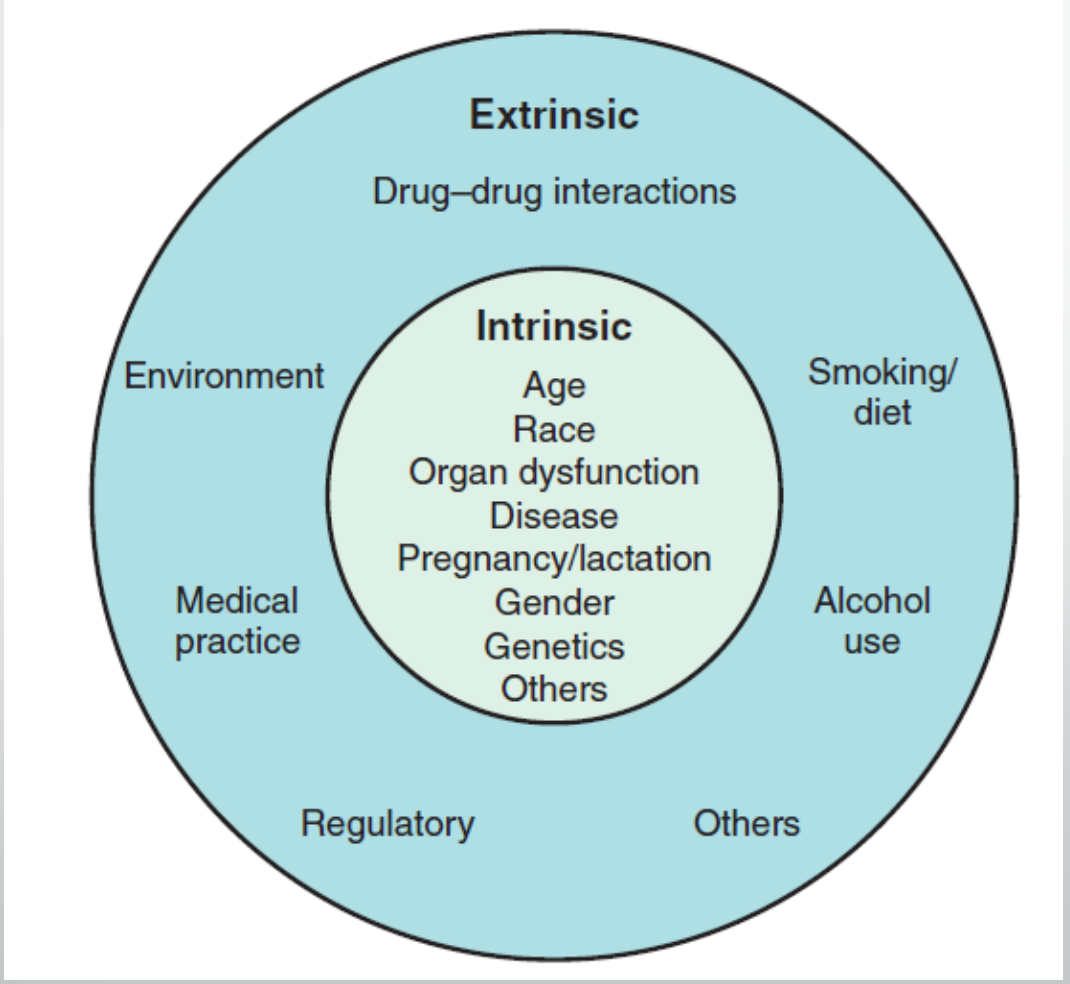
Carvedilol

Study	Selected Patient Eligibility Criteria	Primary End Point
U.S. Program		
220	LVEF ≤ 0.35 NYHA class II–IV CHF 6-min corridor walk distance 150–450 m	Change in exercise distance from baseline. Both 6-min corridor walk distance and 9-min treadmill test.
221	LVEF ≤ 0.35 NYHA class II–IV CHF 6-min corridor walk distance 150–450 m	Change in exercise distance from baseline. Both 6-min corridor walk distance and 9-min treadmill test.
239	LVEF ≤ 0.35 NYHA class II–IV CHF 6-min corridor walk distance < 150 m	Change in exercise distance from baseline and Minnesota quality of life score.
240	LVEF ≤ 0.35 NYHA class II–IV CHF 6-min corridor walk distance > 450–550 m	Clinical progression of heart failure, defined as death due to CHF, or hospitalization for CHF, or worsening CHF requiring increasing background medications by 50% for at least 30 days.
Australia New Zealand Study 223		
Early phase	History of dyspnea at rest or fatigue at rest with EF < 0.45 NYHA class IV was excluded	Maximal exercise tolerance on treadmill plus two hemodynamic measurements (LVEF and the LV internal dimensions).
Later phase	Same as above.	All cause death and all cause hospitalization. (This was only clarified later in the study.)

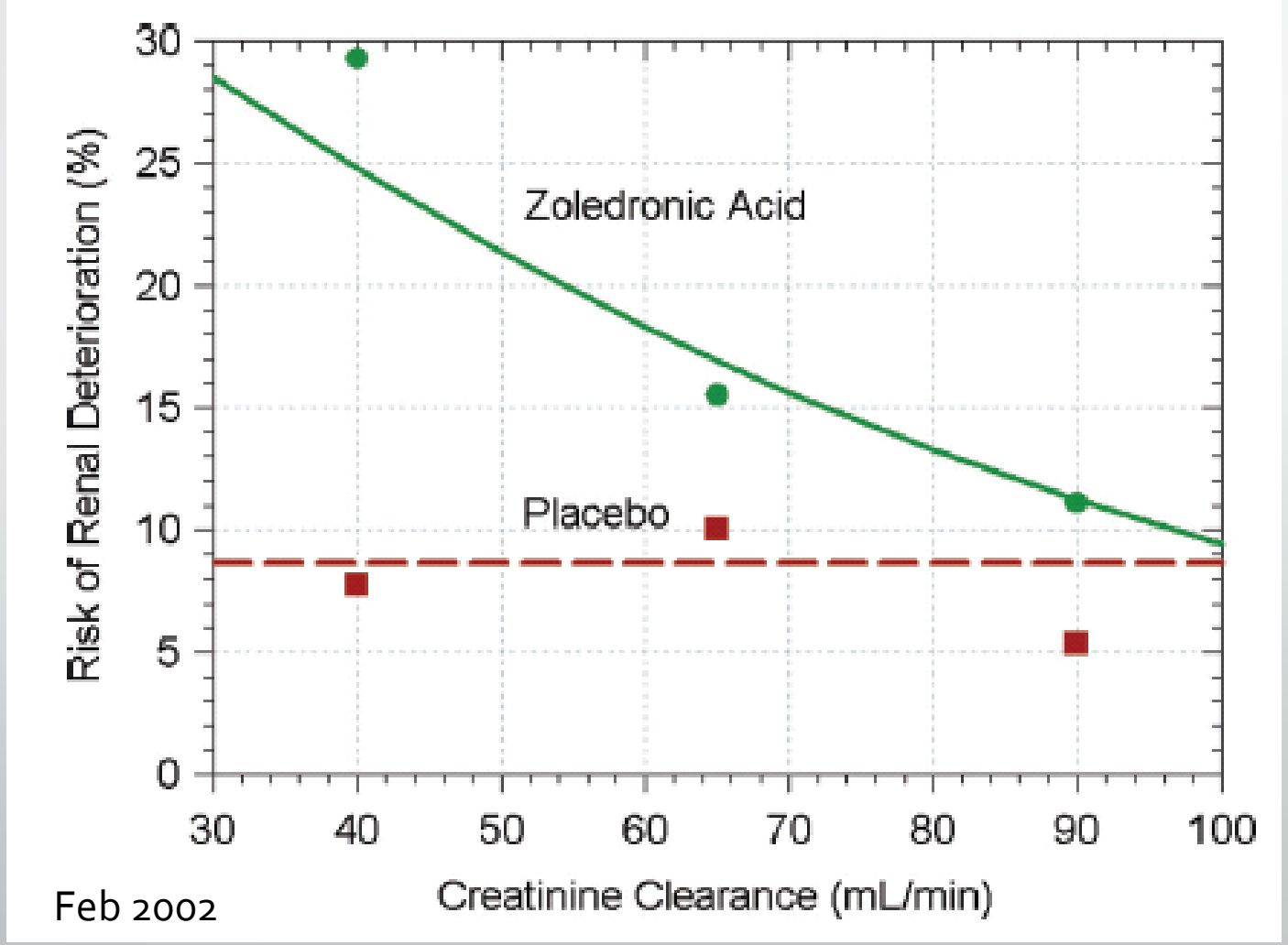
May 1996, Feb 1997

LEARN & APPLY

Bridging Efficacy & Safety to Other Populations



Zometa



Feb 2002

FDA Advisory Committee Meeting

FDA News – Certican

Nov 2005

Routine Discussion of ClinPharm Topics

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FDA Uses Computer Simulations to Guide Future Trial Design

Dosing proposed was tested for kidney transplant trial successfully

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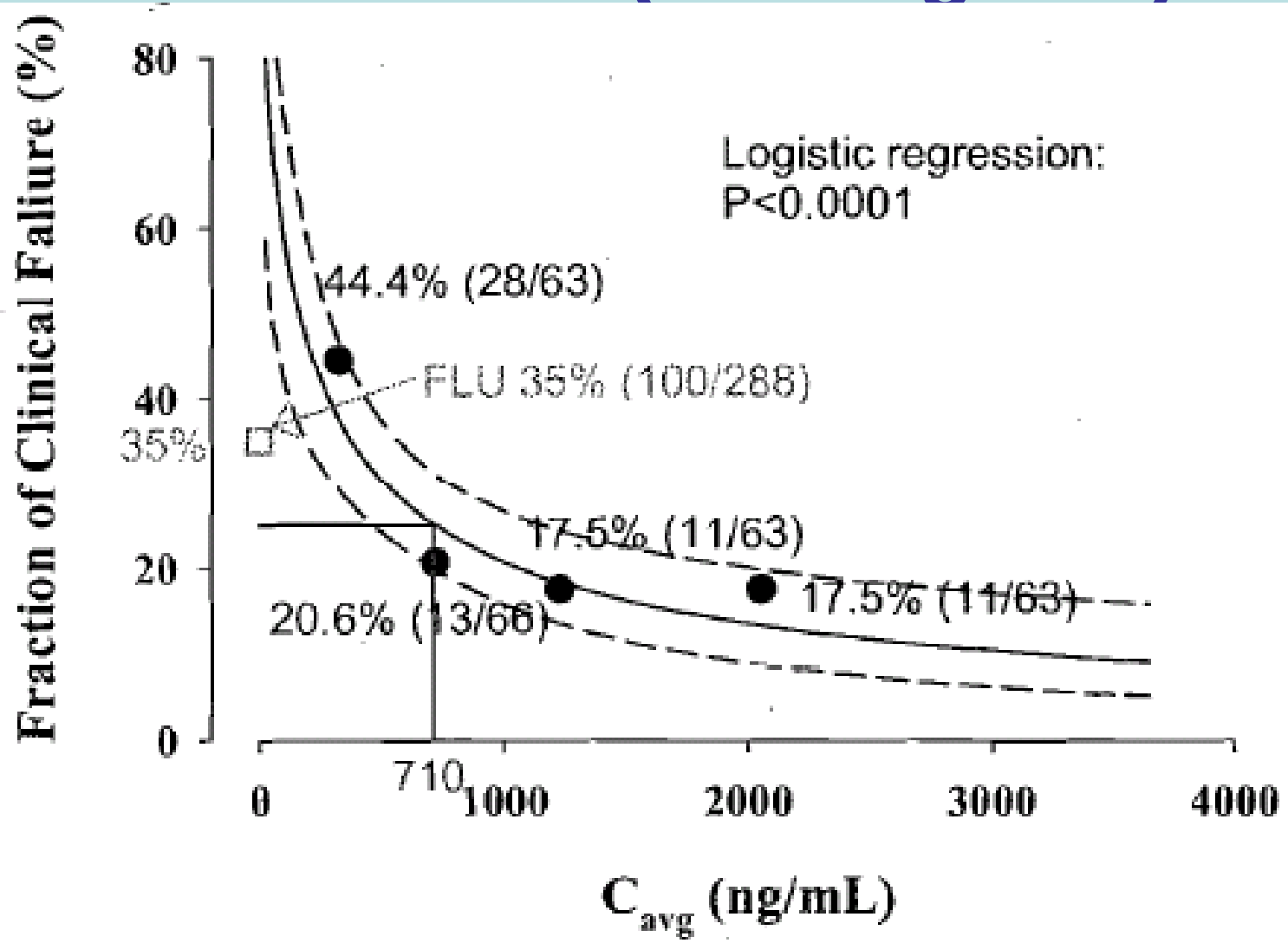
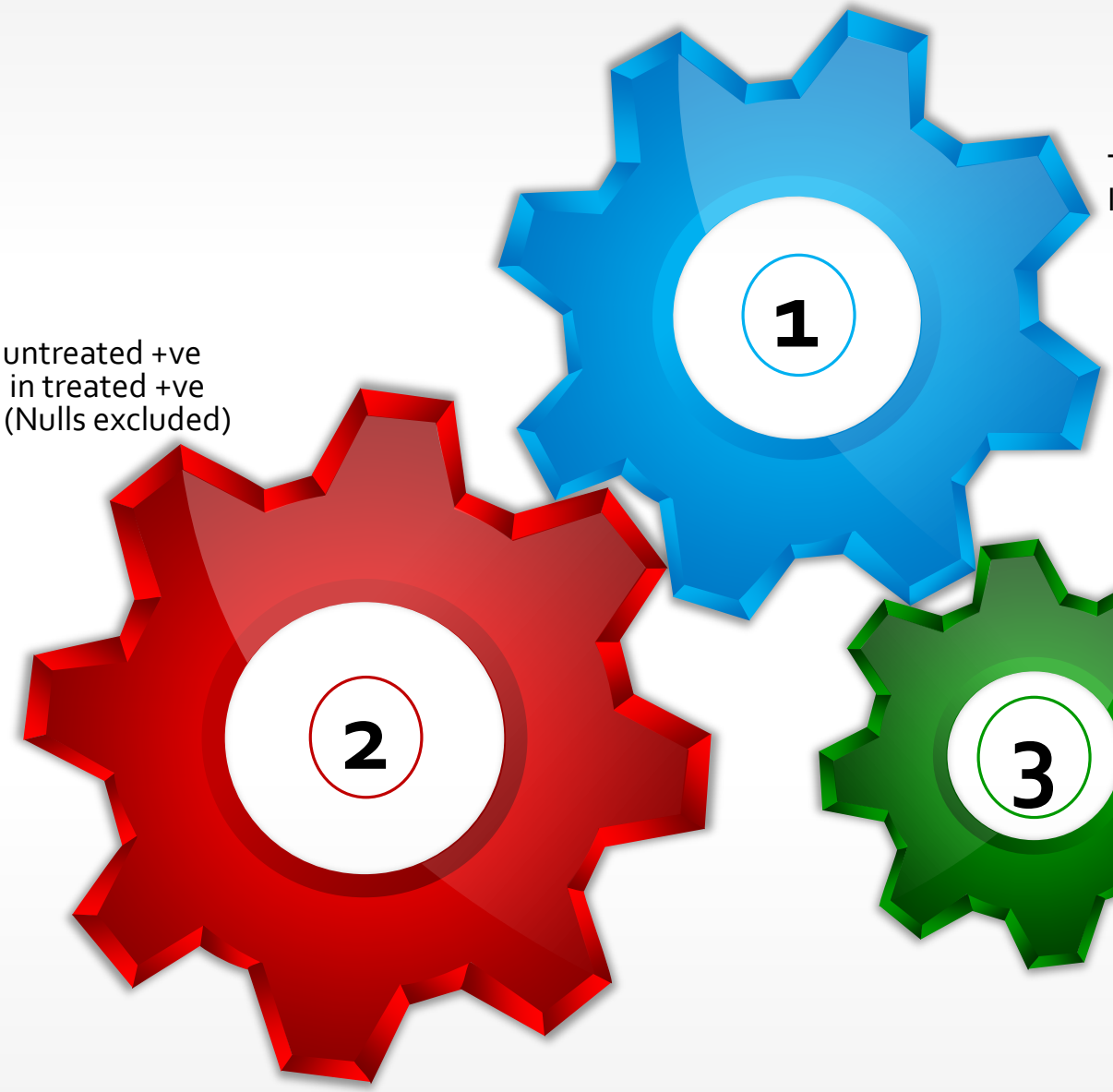
Posaconazole for Invasive Fungal Infections (200 mg TID)



http://www.fda.gov/cder/foi/nda/2006/022003s000_Noxafil_ClinPharmR.pdf

Decisions



Indication

Treatment of HepC + Peg Interferon + Ribavirin (PR)

Efficacy

SPRINT II in untreated +ve
RESPOND II in treated +ve
(Nulls excluded)

Approve Prior Null Responders?

More trials needed before approval?

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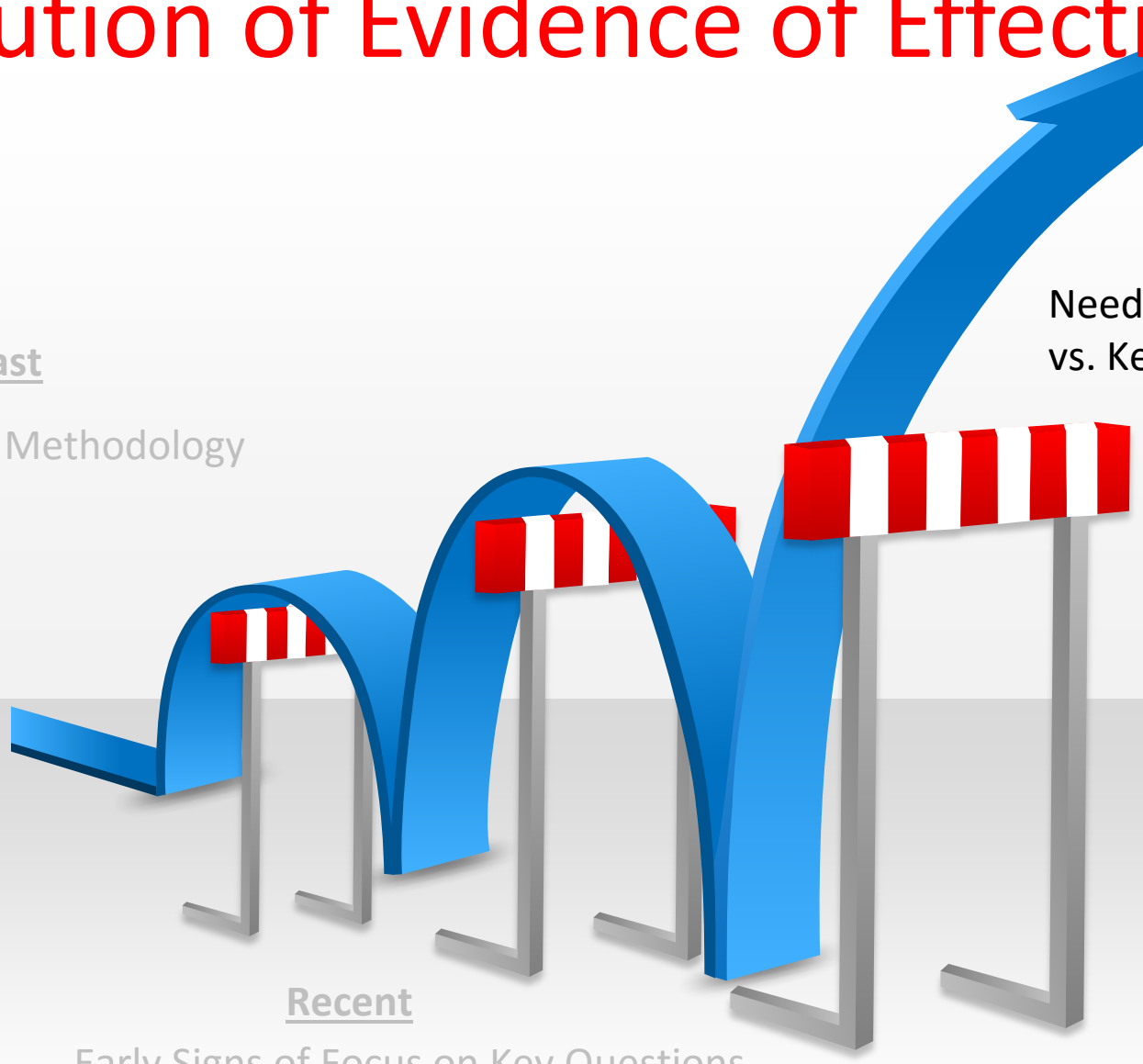

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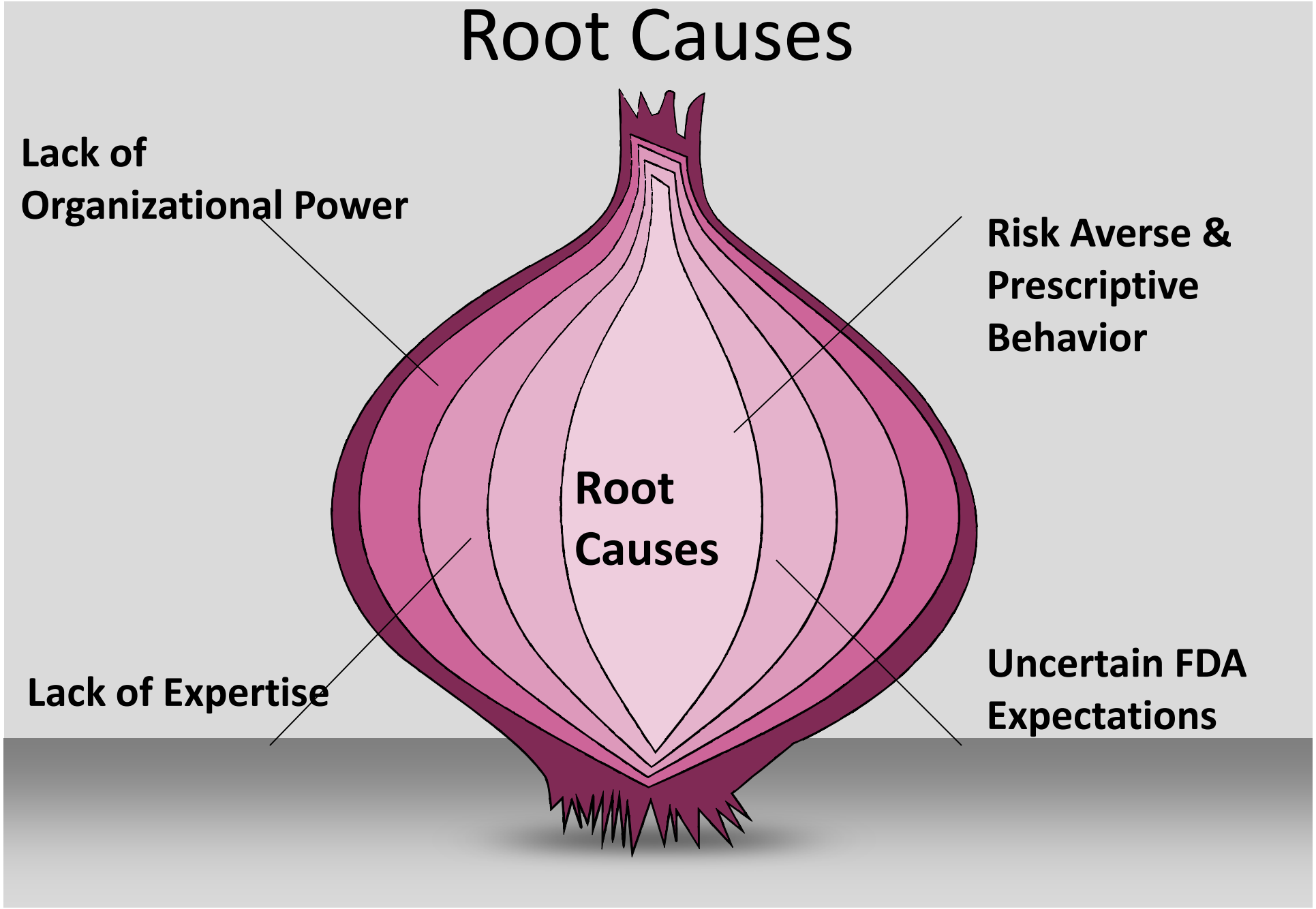
Root Causes


Lack of
Organizational Power
Risk Averse &
Prescriptive
Behavior
Root
Causes
Lack of Expertise
Uncertain FDA
Expectations

Learn & Apply Paradigm

- Disease
- Drug
- Trial

- Go, No-go
- Dose Selection
- Endpoint
- Approval
- Label
- Therapeutics

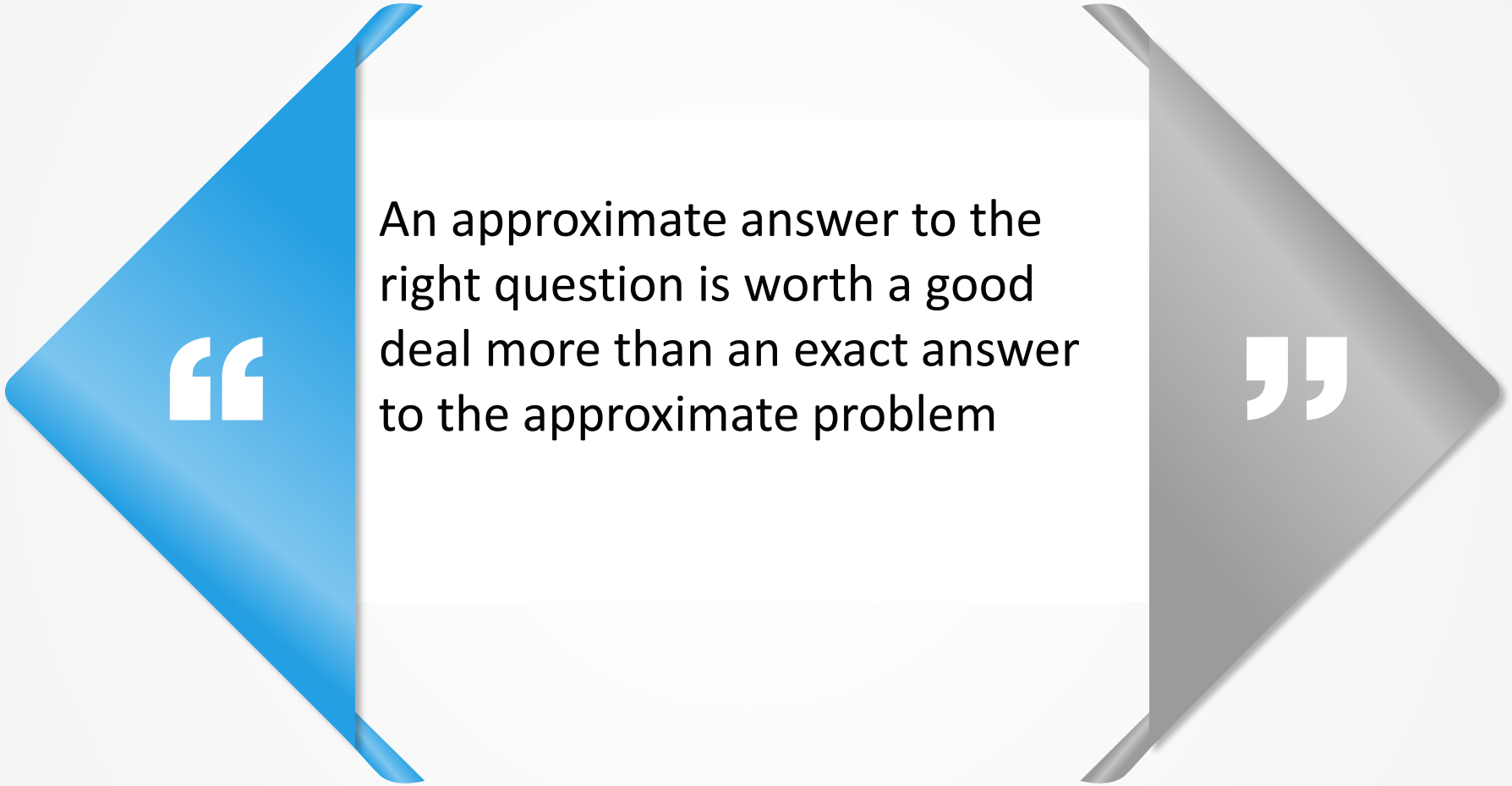
Knowledge is an important asset

Confirmation – Not important?

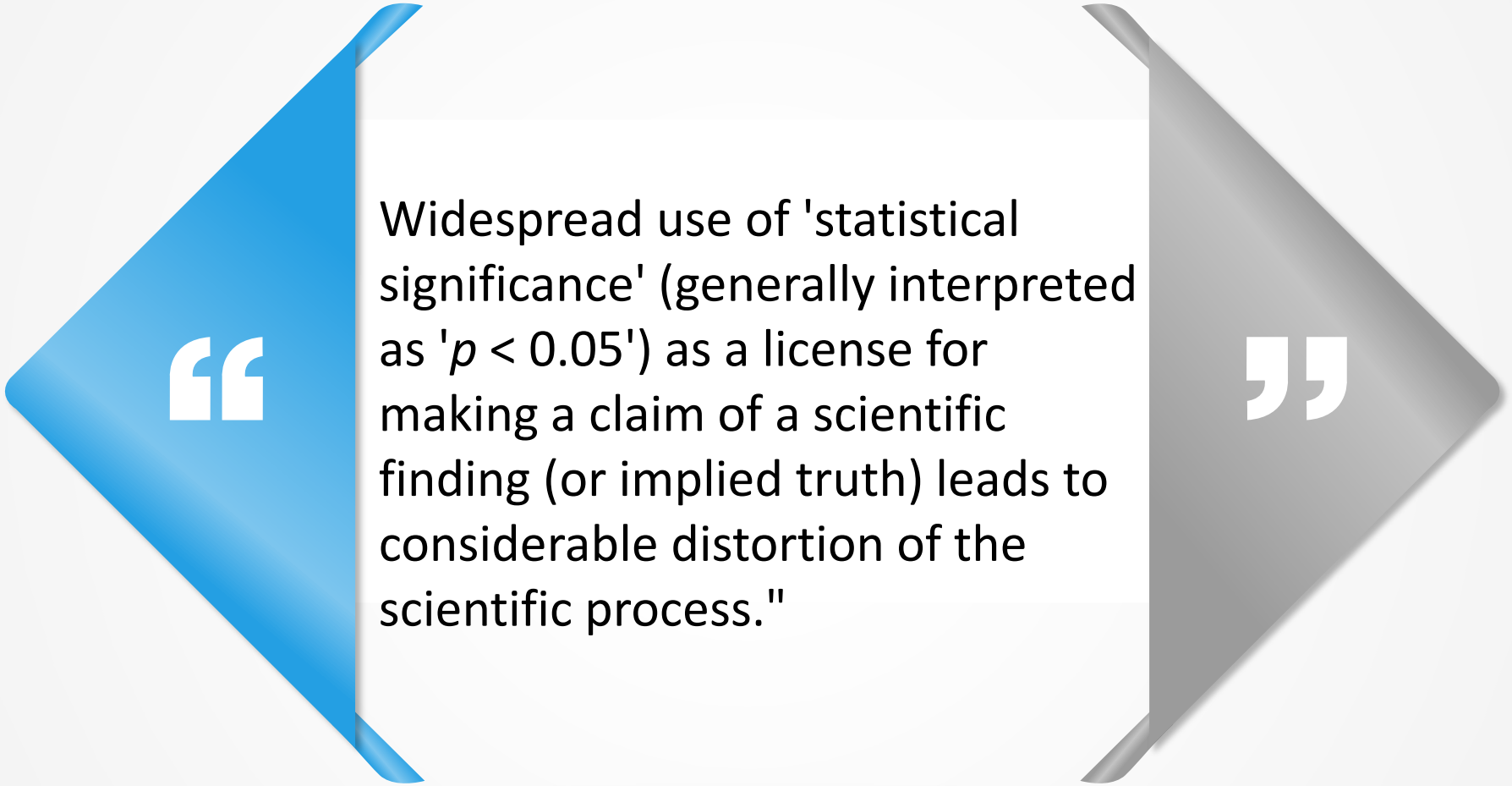
Confirm

- To confirm is important, but that cannot be the sole goal of drug development.
- Confirmation does not apply to safety, dose, biomarker-endpoint relationships…

John Tukey


An approximate answer to the right question is worth a good deal more than an exact answer to the approximate problem

ASA 2016


Widespread use of 'statistical significance' (generally interpreted as '$p < 0.05$') as a license for making a claim of a scientific finding (or implied truth) leads to considerable distortion of the scientific process."

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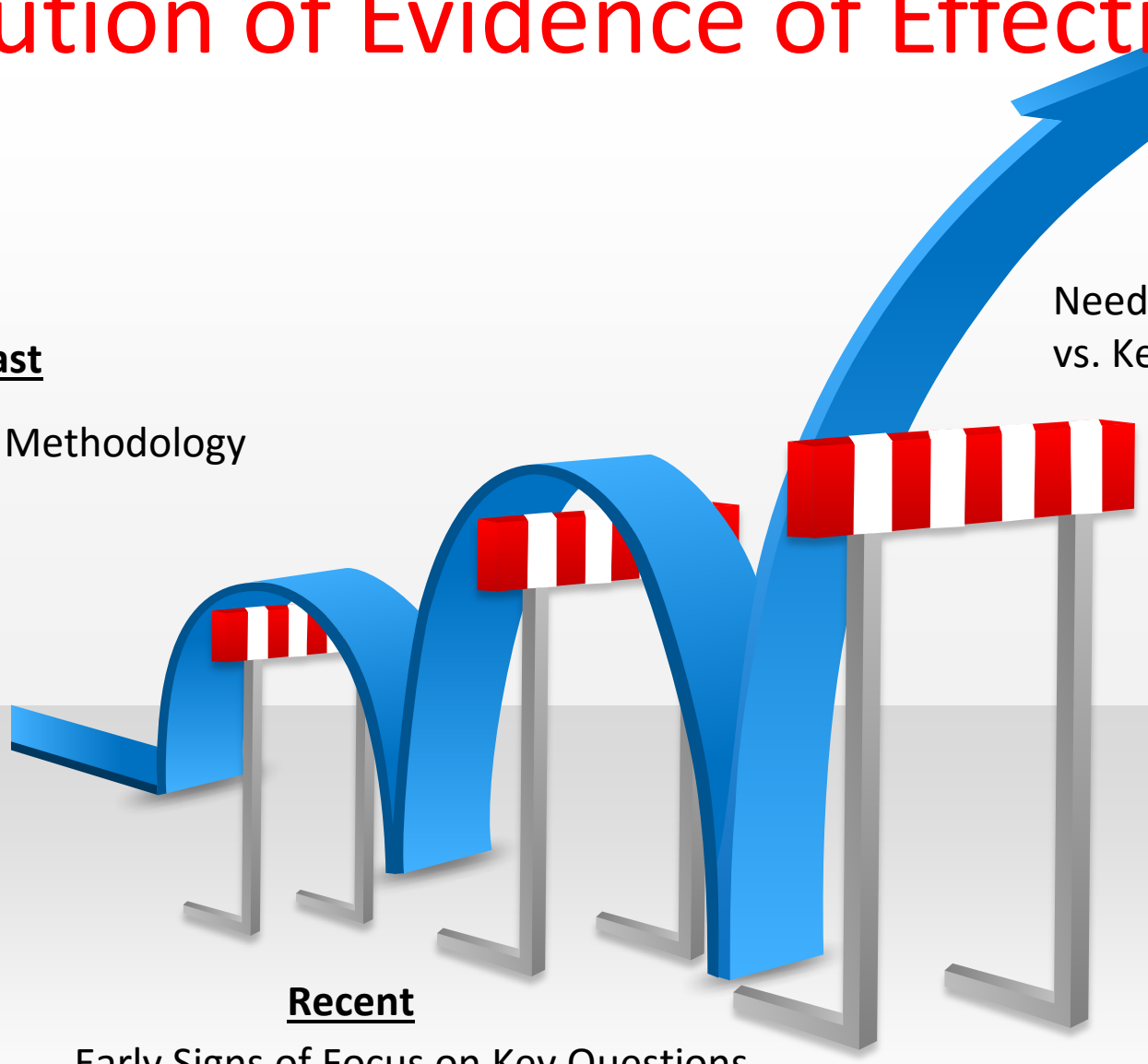

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