Statistical Approaches for Antibiotic Trials: Are we Answering the Wrong Questions?

FDA-IDSA-NIH-Pew Public Workshop: Enhancing the Clinical Trial Enterprise for Antibacterial Drug Development in the United States
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Berry Consultants
Statistical Innovation

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  - County of Los Angeles, Department of Health Services, Harbor-UCLA Medical Center
  - David Geffen School of Medicine at UCLA
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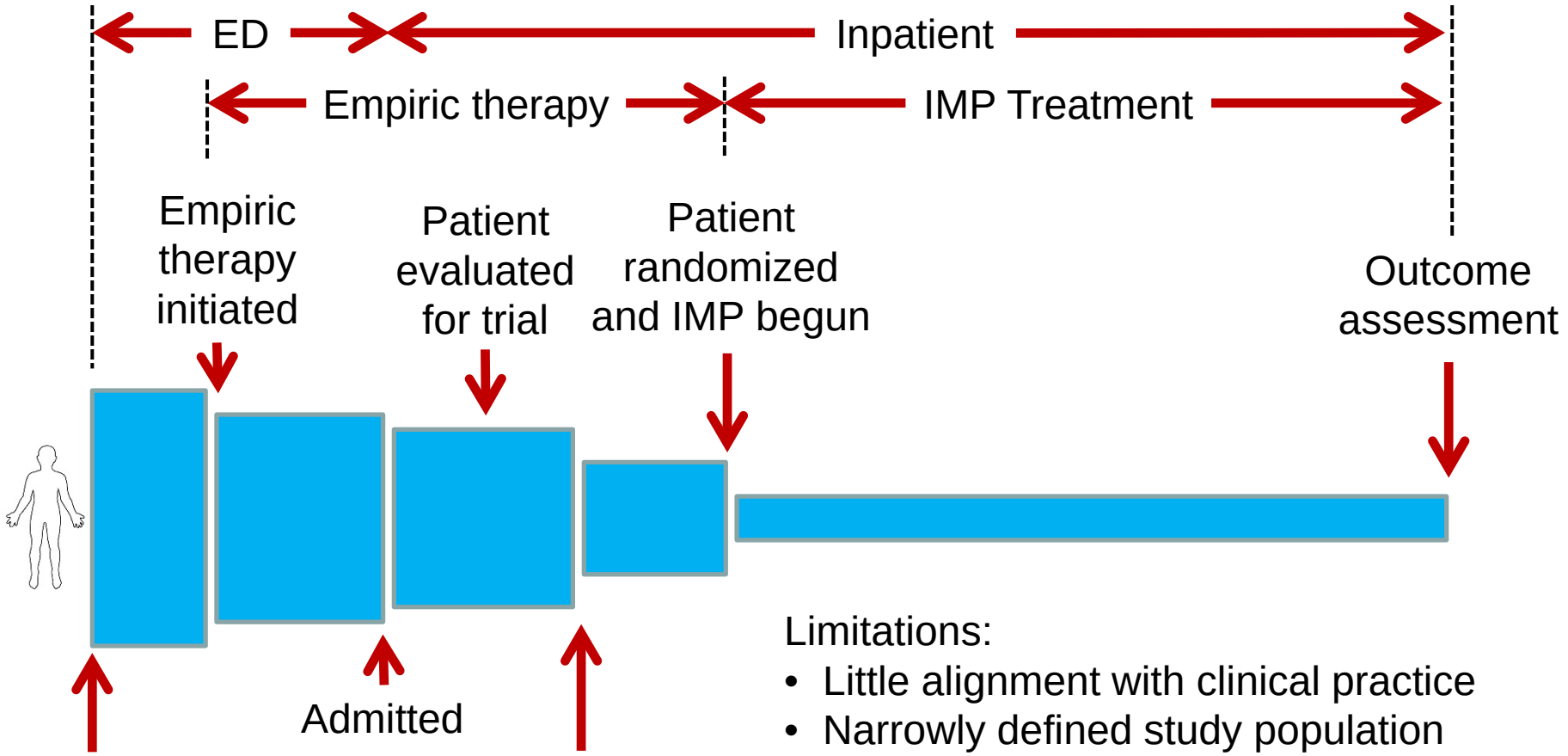
Take Home Points

- The statistical and overall design strategy for antibiotic trials should
  - Directly inform clinical use of products, in light of how antimicrobials are actually used
  - Support antibiotic stewardship
  - Inform regulatory approvals and labeling
- As currently designed, many trials of antibiotics do not meet these goals
  - Overly narrowly focused (eligible population, infection site)
  - Predictably undermine stewardship efforts
  - Risk missing benefits due to delayed initiation of agents
- But they could

Anatomy of an Antibiotic Trial



Limitations:

- Little alignment with clinical practice
- Narrowly defined study population
- Late initiation of investigational agent
- Evidence and labeling address a single infection site

Typical Trial versus Clinical Use

Characteristic	Clinical Use of Broad Spectrum Agents	Clinical Trials of Broad Spectrum Agents
Timing of treatment	Often empiric or based on poor clinical response	After empiric therapy or based on culture results
Populations	Across multiple sites or types of infections	Single defined site or type of infection
Motivation for selection of or change in treatment	Presentation and risk for MDR pathogens Clinical deterioration	Based on culture and sensitivity results
Types of infections treated with agent(s)	Multiple sites and multiple pathogens	Single site and limited list of or single pathogen
Non-inferiority and superiority	Desire NI in empiric treatment and superiority against MDR organisms	Typically designed to demonstrate NI or superiority alone

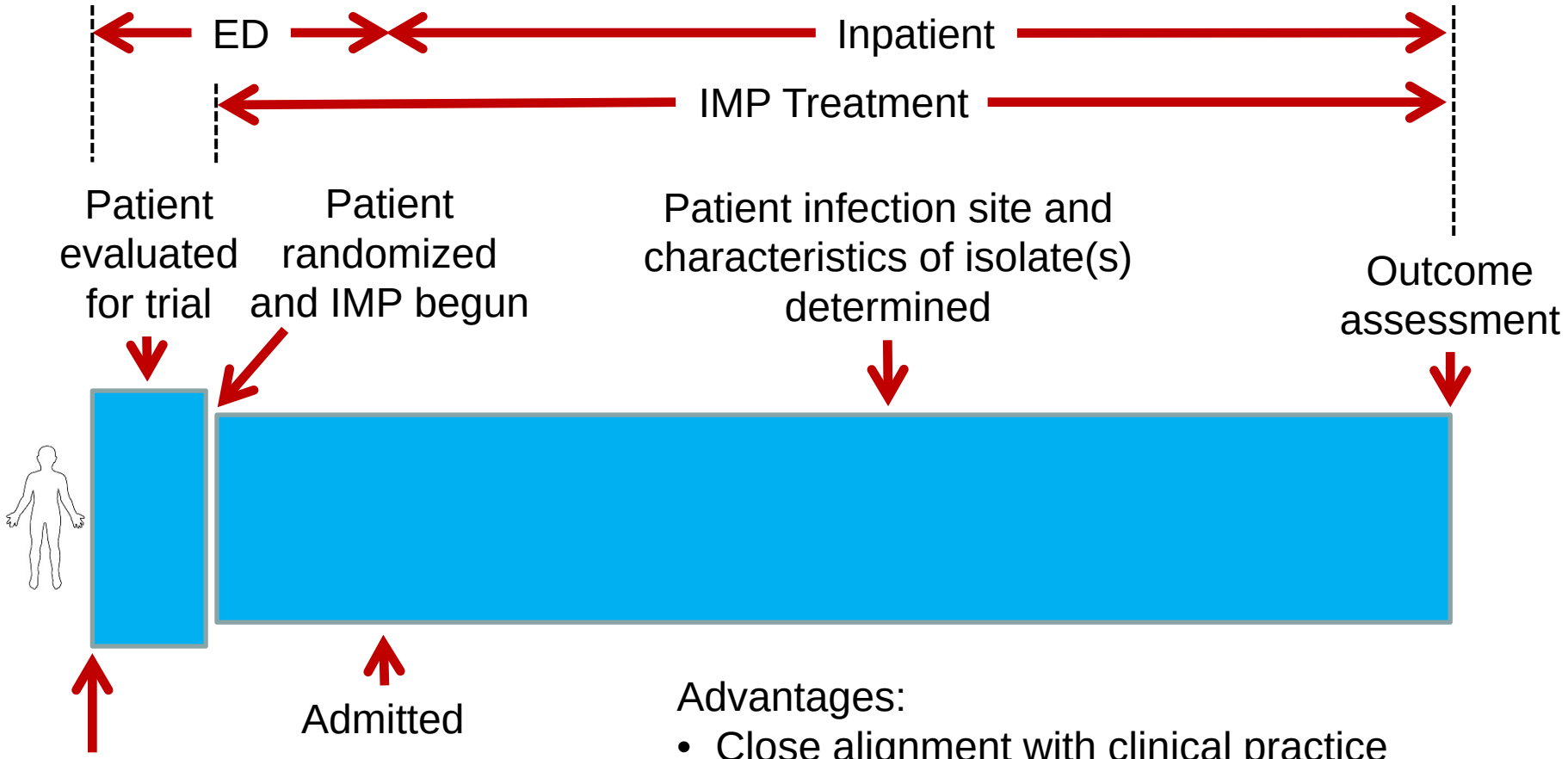
Sites of Infection

- New agents are needed to treat challenging organisms across multiple sites of infection
- In clinical practice, antibiotics with demonstrated penetration into infected sites and appropriate coverage are routinely used for infections at those sites, independent of specific supporting data or labeling
- Problems with surprising lack of antibiotic efficacy at specific sites (e.g., lung) have generated concern regarding sharing efficacy data across anatomic sites

Proposed Strategy

- Platform trial
- Enrollment timing and antibiotic initiation designed to match likely clinical use
- Careful integration of information across body sites to improve clinical and statistical efficiency
- Address both non-inferiority and superiority
- Additional efficiencies
  - Early enrollment and randomization to maximize treatment effect
  - Potential to share control arms
  - Avoid cost/time lost during implementation and “tear down”

Proposed Antibiotic Trial



Advantages:

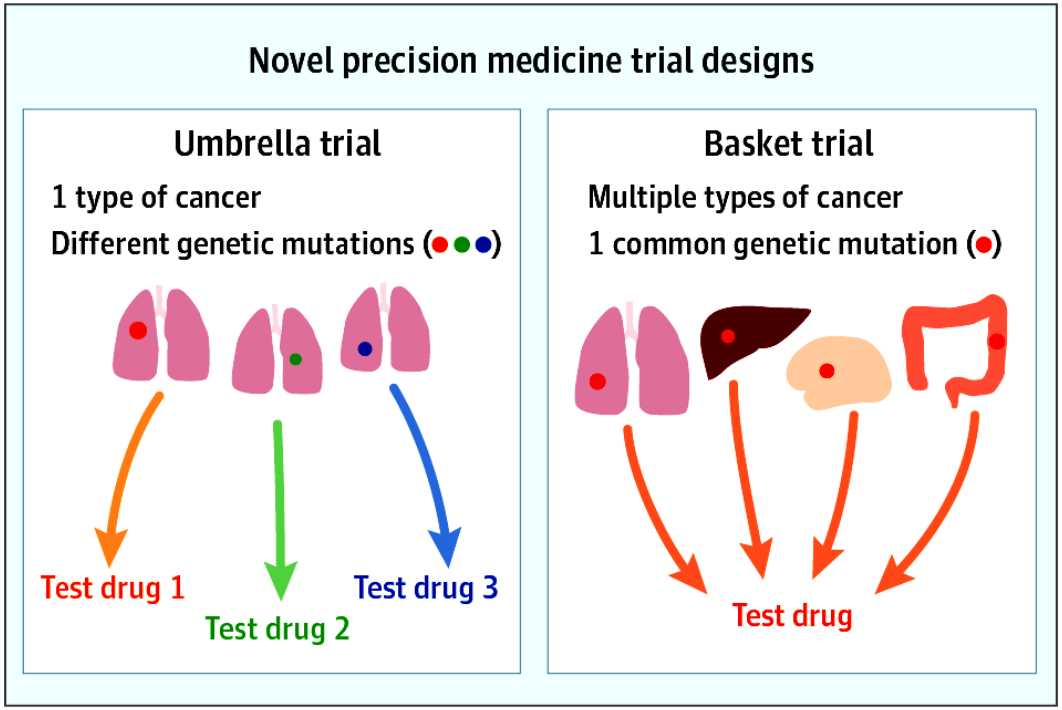
- Close alignment with clinical practice
- Broad study population
- Early initiation of investigational agent
- Evidence across resistance patterns and sites of infection

Platform Trial

- An experimental infrastructure to evaluate multiple treatments, often for a group of diseases, intended to continue beyond the evaluation of any individual treatment
  - Multiple treatments and often combinations
  - Often a group of related diseases or subgroups
  - Dynamic list of available treatments, potentially assigned with response-adaptive randomization
  - Preferred treatments may depend on health system, patient, or disease-level characteristics
  - Focus is on effective treatment of disease

Terminology

- Master Protocol versus Platform Trial
- Other Terms
  - Master protocol
  - Umbrella trial
  - Basket trial
  - Perpetual trial



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REVIEW ARTICLE

THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

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N Engl J Med 2017;377:62-70.
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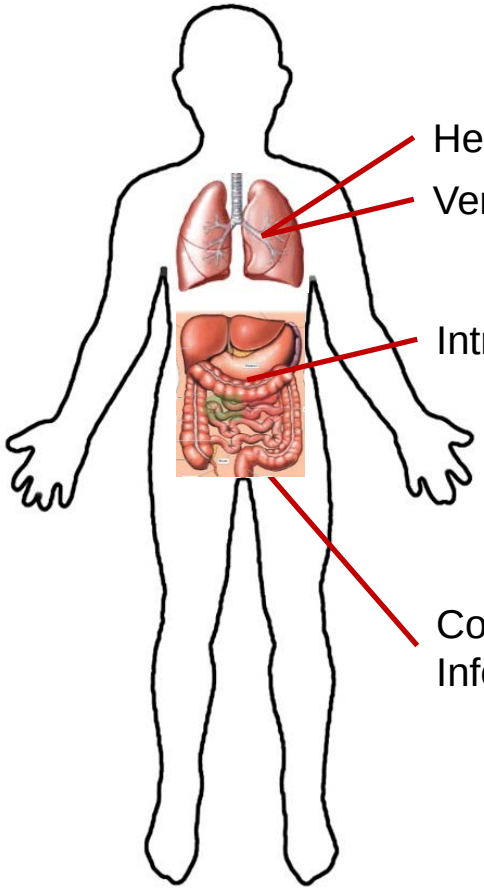
HIGH-QUALITY EVIDENCE IS WHAT WE USE TO GUIDE MEDICAL PRACTICE. The standard approach to generating this evidence — a series of clinical trials, each investigating one or two interventions in a single disease — has become ever more expensive and challenging to execute. As a result, important clinical questions go unanswered. The conduct of "precision medicine" trials to evaluate targeted therapies creates challenges in recruiting patients with rare genetic subtypes of a disease. There is also increasing interest in performing mechanism-based trials in which eligibility is based on criteria other than traditional disease definitions. The common denominator is a need to answer more questions more efficiently and in less time.

A methodologic innovation responsive to this need involves coordinated efforts to evaluate more than one or two treatments in more than one patient type or disease within the same overall trial structure.[1-4] Such efforts are referred to as master protocols, defined as one overarching protocol designed to answer multiple questions. Master protocols may involve one or more interventions in multiple diseases or a

NEJM 2017;377:62-70

Proposed Strategy



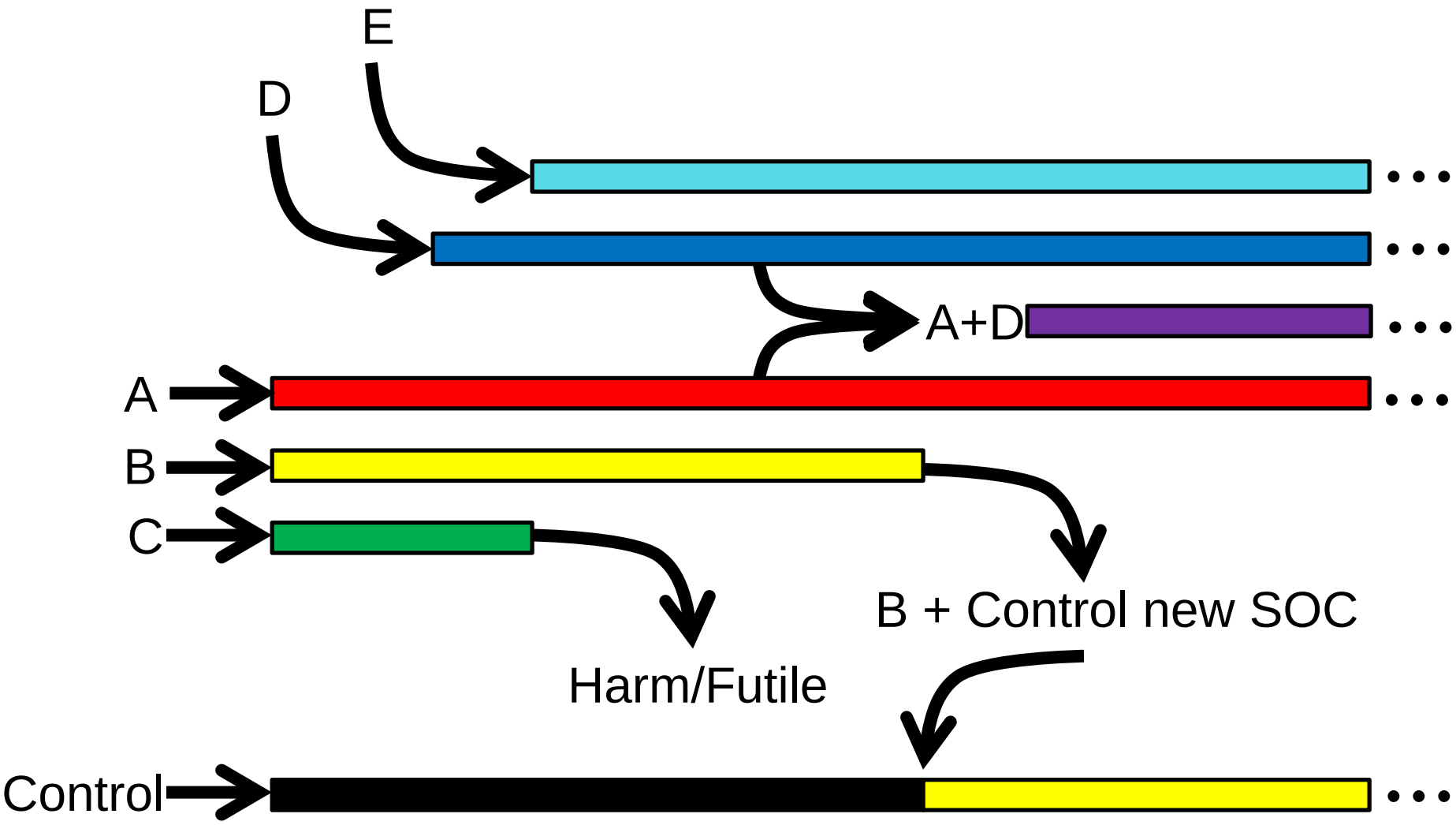
Healthcare Associated Pneumonia (HABP)
Ventilator Associated Pneumonia (VABP)
} HABP/VABP

Intra-abdominal Infection (cIA)

Complex Urinary Tract Infection (cUTI)

- Bacterial isolates
  - Sensitive to SOC
  - Resistant to SOC
  - None isolated/missing
- Want to demonstrate
  - Superiority to SOC in resistant
  - Non-inferiority to SOC in sensitive ± missing
- Take advantage
  - Multiple body sites
  - Multiple active arms/shared control

Proposed Strategy



Platform Trial Efficiencies in Antibiotics

- Three innovations with savings of 45 to 60% compared to individual, traditional phase III trials
  - Platform—shared control
  - Sharing of information between body sites ←
  - Early stopping of drugs in each body site for success or futility
  - Savings quantified over sequential evaluation of multiple agents

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Heterogeneity of Treatment Effect

- A given antimicrobial is likely to have variation in treatment effects
  - Disease subtypes (e.g, sites of infection, severity of illness)
  - Infecting organism
  - Differences in background therapies
- How can we efficiently and intelligently integrate information across heterogeneous situations?
  - "Integration" does not imply pooling of data, neither "splitting" nor "lumping"
  - Need prespecified strategies that address the possibilities that (1) treatment effects will be largely similar; and (2) treatment effects will be highly disparate

Informal Borrowing of Information

- Clinicians “borrow” information all the time
  - Similar but distinct patient classes
  - Similar but distinct treatments
  - Non-quantitative or documented
- Examples
  - Use of medications in patients not meeting strict inclusion criteria for pivotal trials
  - Off label use
  - Interchangeable use of drugs within classes

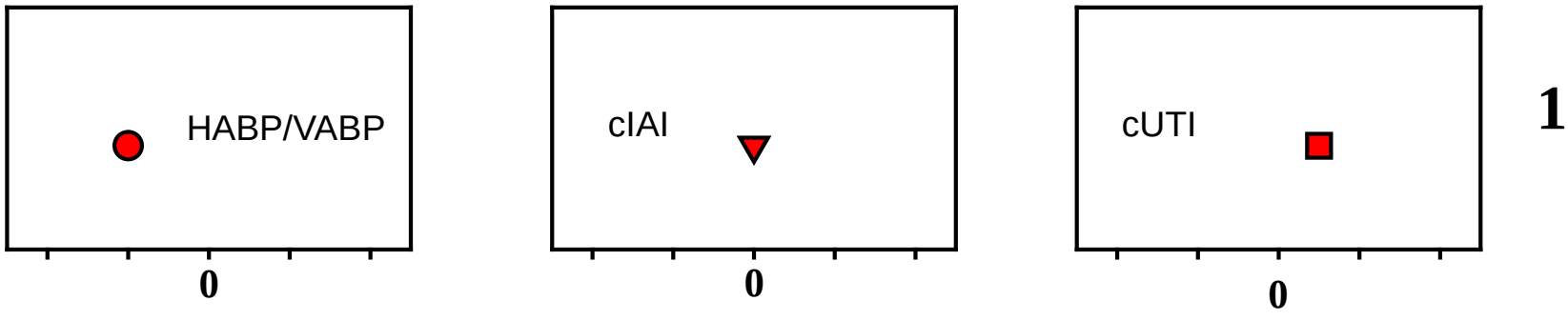
Heterogeneity and Information

- The common “all or none” approach to integrating information across heterogeneous patient populations, disease categories, or treatments may
  - Fail to identify subgroups that experience different treatment effects or complications
  - Fail to recognize compelling “circumstantial” evidence of treatment efficacy
  - Lead to overestimation of heterogeneity in treatment effect

Hierarchical Models

- Provide a flexible method for sharing information from potentially heterogeneous infection types to the degree justified by the consistency of information across infection types and by limitations in the amount of information available from each group

Hierarchical Model



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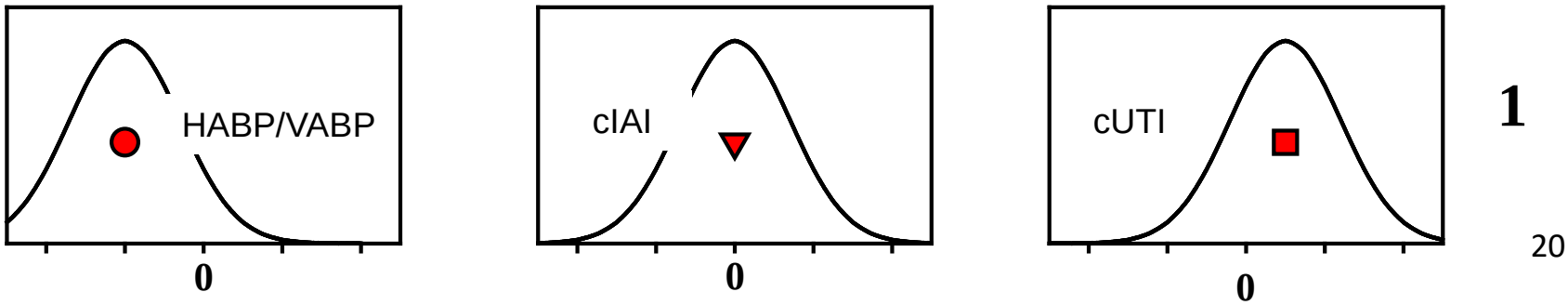

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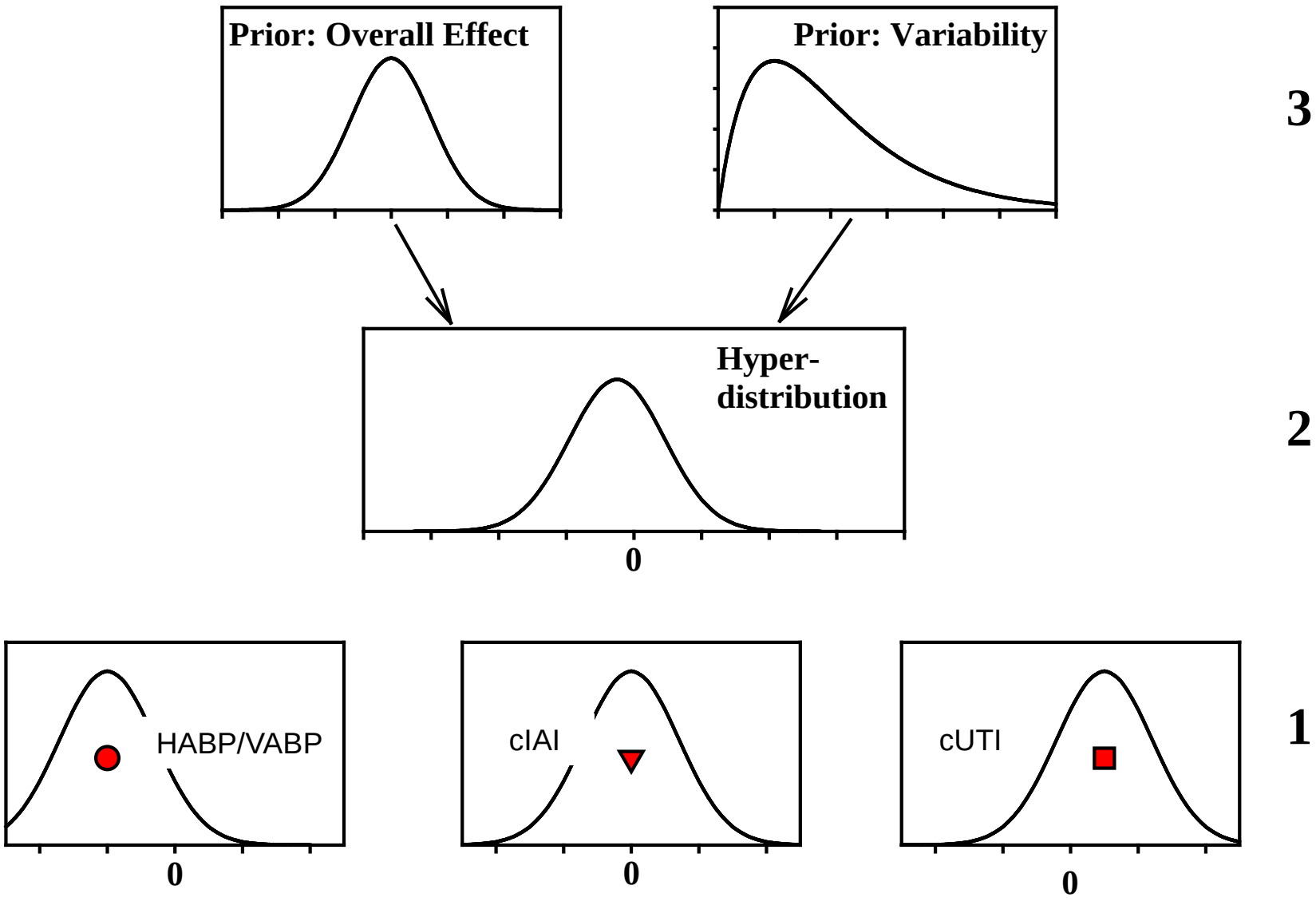

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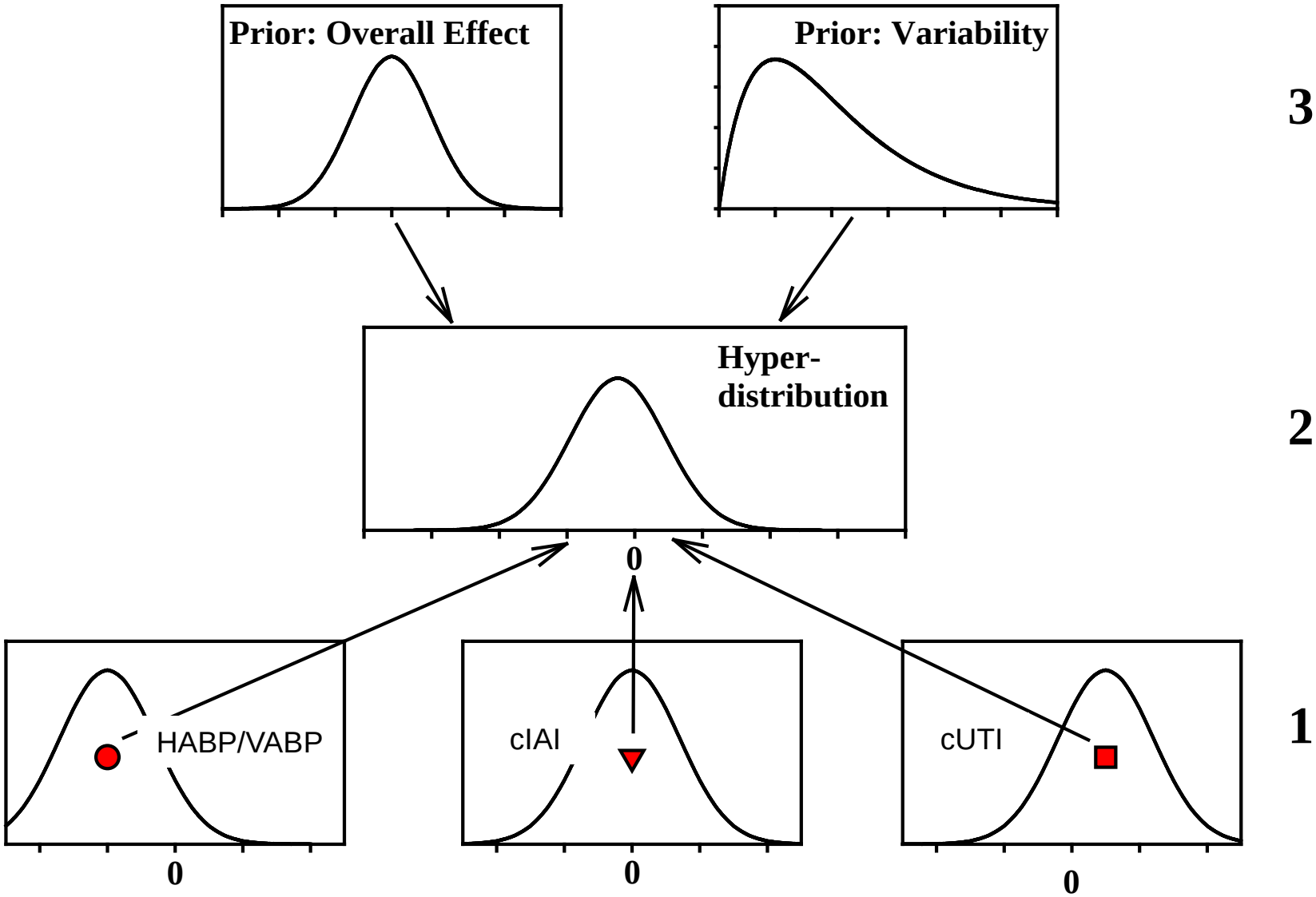

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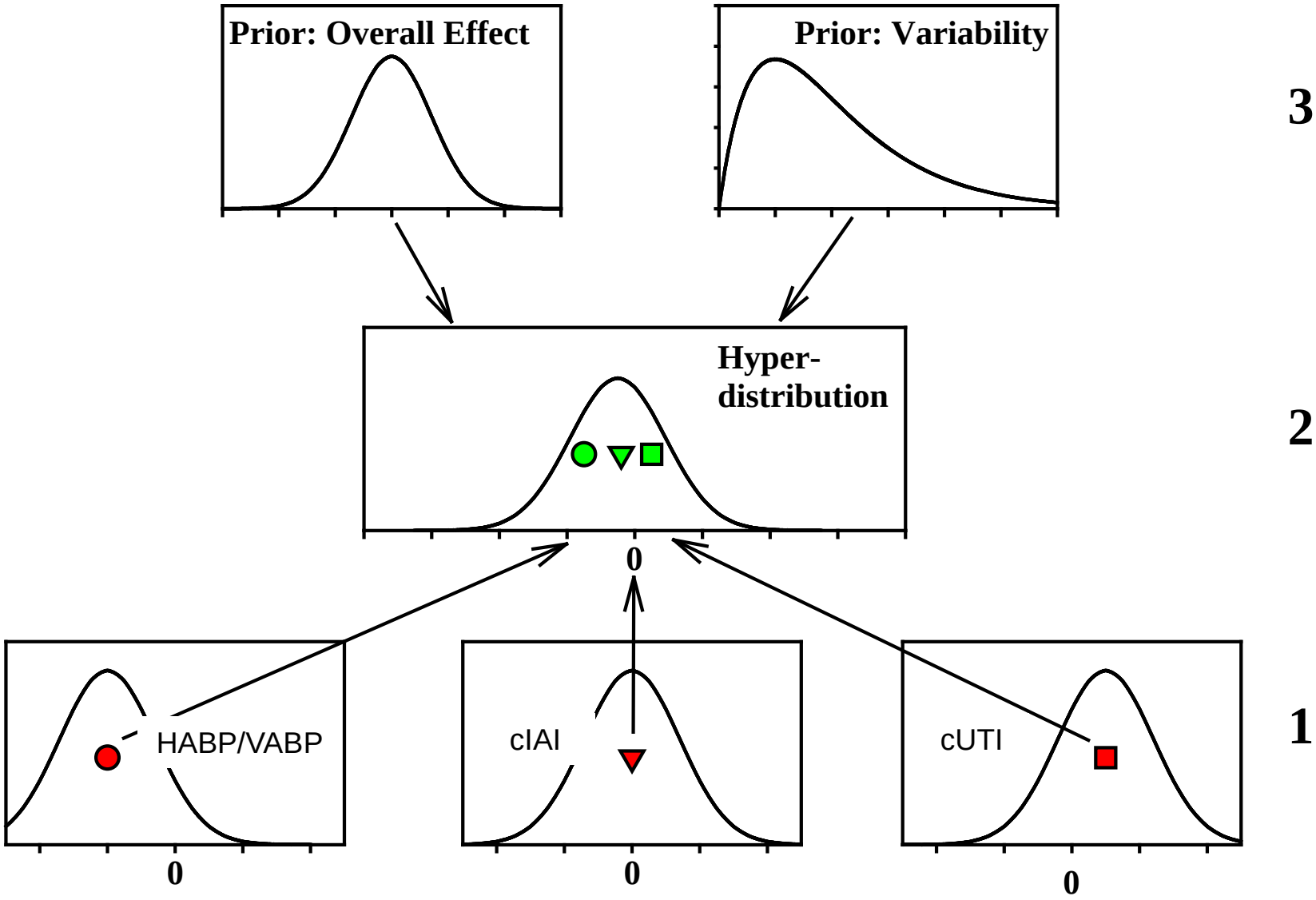
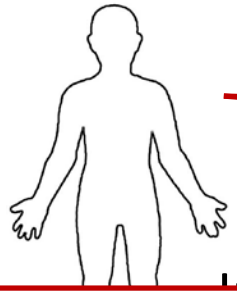


Treatment Estimates in Subgroups

- The best estimate of the true treatment effect in a subgroup is not the treatment effect observed in that subgroup, if there are 3 or more subgroups
- This is the James Stein effect

James W, Stein C. Estimation with quadratic loss. *Proc. Fourth Berkeley Symp. Math. Statist. Probab.* 1961;1:361-380. [Univ. California Press.]

Non-inferiority and Superiority



Infe… organism

isol… lated

to b…

1° u… d to

sup… inferiority

…depending

2° u…

non-inferiority hypothesis

Might be used to address safety, PK, and other goals

Might be used to address safety, PK, and other goals

Advantages

- Based on pretreatment assessment (culture) so valid subgroups
- Allows early initiation of IMP, reflecting clinical usage
- More of the patients contribute data informing clinically important questions

Additional Comments

- Agents should only be tested for infections at sites for which there is strong learn-phase rationale (e.g., demonstrated penetration, PK, lack of inactivation)
- Each enrolling site can contribute a larger number of patients per month since multiple infection types and resistance patterns are included, decreasing per-patient cost
- The efficiency of the platform trial is increased when more than one investigational agent is available
- Current environment, with multiple smaller companies may be conducive to platform strategy

Trial Design, Labeling and Stewardship

- Antibiotics targeting highly resistant pathogens are a class of drugs for which on-label use is often clinically inappropriate and off-label use is often appropriate
- Generally approved by body site, not organism, so labeling seems to support use of precious new antibiotics when less-precious options are available
- Indication should match need
  - Only use these new agents when a highly-resistant organism is isolated or likely (stewardship)
  - Consider use of new agent when a highly-resistant organism is isolated from anatomic sites at which penetration is known to be adequate

Trial Design, Labeling and Stewardship

- Examples (thanks to Brad Spellberg, MD)
  - Ceftazidime-avibactam: cUTI, cIAI
  - Meropenem-vaborbactam: cUTI, cIAI
  - Plazomicin: cUTI
  - Eravacycline: cIAI
  - Imipenem-relebactam: cUTI, cIAI
  - Cefedericol: cUTI
- These agents should likely be reserved for CRE but they are not approved for the pathogen but for the common infections listed
- The design drives labeling, labeling drives marketing, and both may undermine stewardship

Spellberg B, Nielsen TB, Gilbert DN, et al. Ensuring Sustainability of Needed Antibiotics: Aiming for the DART Board. Ann Intern Med. 2019;171:580–582.

Conclusions

- The most common structure and statistical design of confirmatory trials of antimicrobials targeting highly resistant organism risks
  - Failing to answer the questions of most direct clinical urgency and impact
  - Failing to address the likely use across multiple infection sites, based on demonstrated presence, or risk of, highly resistant pathogens and PK data
  - Inefficiency due to highly selected populations, and blunted treatment effects from interval empiric therapy
- A multi-infection-site, multidrug, platform trial addressing both non-inferiority and superiority could efficiently address these challenges