

Clinical Studies in Infectious Diseases

The Current Paradigm and Moving Forward

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Introduction

- **History of clinical research in infectious diseases**
- **Regulatory science and criteria for evaluation**
- **Current issues with ID trials**
- **Moving forwards**

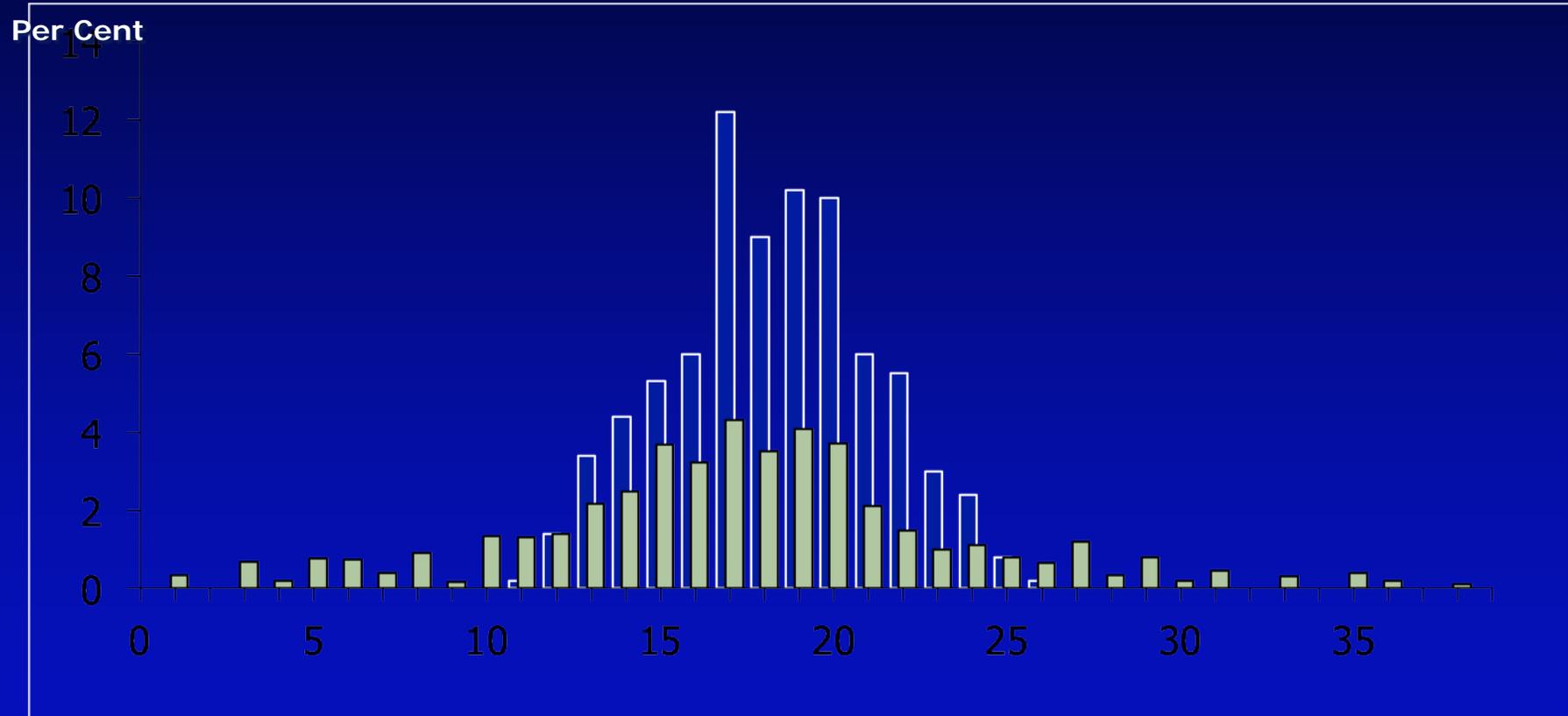
History

- **History of study of infectious diseases intertwined with advances in unbiased measurements of medical interventions**
- **1830 – Pierre Louis *controlled* trial on bloodletting in pneumonia with mortality**
- **1898 – Fibiger use of *alternation* attempt to control selection bias in trial of diphtheria toxin**
- **1920's – Cooperative Clinical Group in syphilis**
- **1928 - Commonwealth Fund serum therapy**
- **1938 – start of *randomized blinded placebo* controlled trial of streptomycin for TB1**

Science and Probability

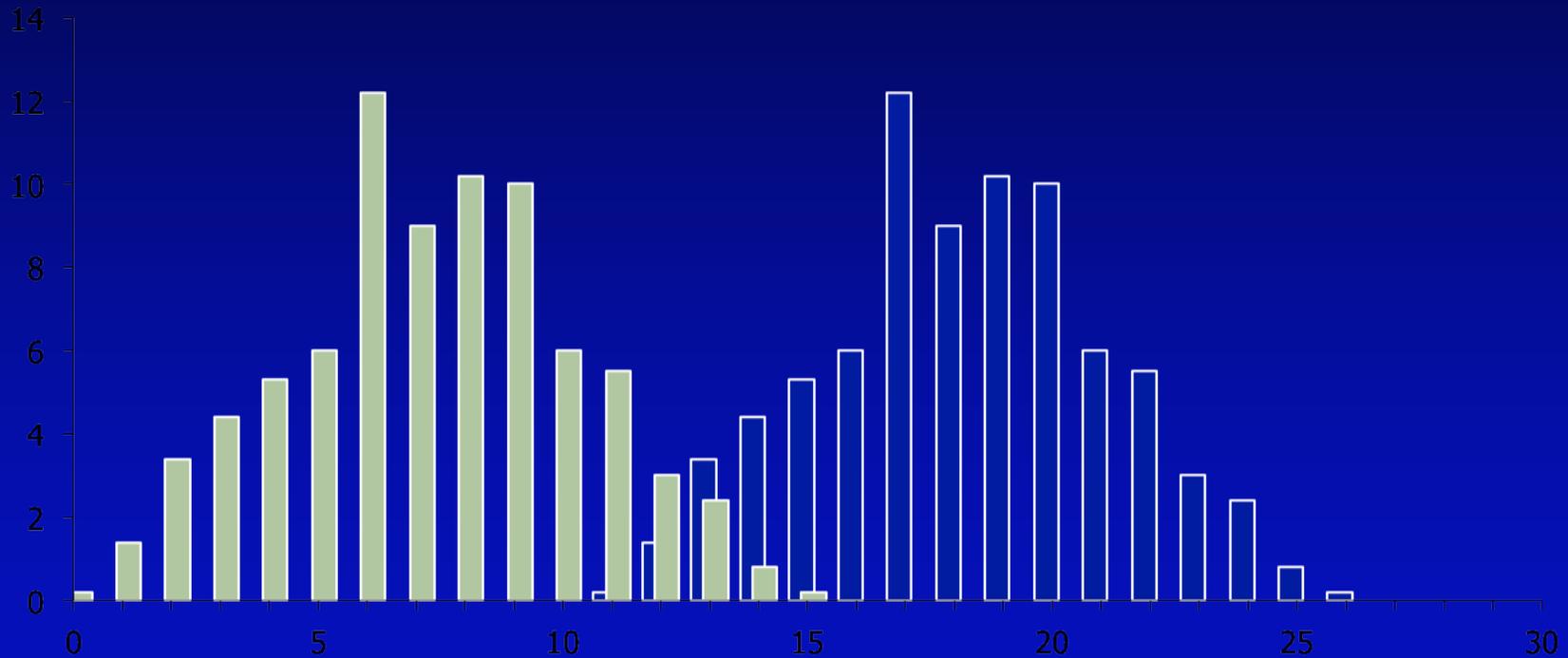
- **Science is basis for evaluating the greatest *probability* of making correct inferences that affect patients lives**
 - *“Given that certainty is impossible, there are three alternatives: belief, probability and criticism.....it [belief] may prevent us from making sincere attempts to test the cause as strenuously as possible and makes it somewhat easier to conceal error”.*
 - **Weed DL. Causal criteria and Popperian refutation. In Rothman KJ (ed) *Causal Inference*. 1988 p. 26.**
- **Scientific validity is basis for ethics of experimentation involving human beings**
 - **Belmont Report 1979**
- **Two types of error threaten validity of inferences from trials**

Random Error



Systematic Error / Bias

Per Cent



Size of induration (mm)

Unmet Medical Need

- **Unmet medical needs are reason to perform a trial**
- **Not a reason to accept lesser evidence of effectiveness**
- **Impact on overall assessment of harm vs benefit but need benefit first as spelled out in 1962 efficacy requirements in FD&C Act**

US v Rutherford 1979, Laetrile

- *“The Act makes no express exception for drugs used by the terminally ill and no implied exemption is necessary to attain congressional objectives or to avert an unreasonable reading of the terms ‘safe’ and ‘effective’. Nothing in the legislative history suggests that Congress intended protection only for persons suffering from curable diseases”*
 - **Thurgood Marshall**
- **Reaffirmed in Abigail Alliance v von Eschenbach 2007**

Adequate and Well-Controlled

1. **Clear statement of objectives**
2. **Study design permits valid quantitative comparison with a control**
3. **Select patients with disease (treatment) or at risk of disease (prevention)**
4. **Baseline comparability (randomization)**
5. **Minimize bias (blinding, etc.)**
6. **Appropriate methods of assessment of outcomes**
7. **Appropriate methods of analysis**

- **21 CFR 314.126**

Adequate and Well-Controlled

- “ These criteria for an adequate and well-controlled clinical investigation set forth in the...regulations are **minimal requirements** for any valid objective study...and...are in no sense unduly rigid and narrow. The regulations appear to be completely reasonable in describing the scientific content of a well-controlled and adequate investigation. In fact, compliance with these standards will not necessarily ensure that the investigation conducted is valid...[but] the criteria must be observed to give the study a chance to yield meaningful results” .
 - **Judge Latchum. US District Court, Pharmaceutical Manufacturers Association v Richardson (1970)**

Current Paradigm and Moving Forward

1. Clear objective

- Pressing question is where are new drugs superior in clinical setting where older drugs are less effective
- NI trials answer question of where is new drug somewhat less effective in setting where older drugs are still effective
- How can we address the right question?

2. Quantitative comparison with control group

- Is NI trial the only design that is possible?
- NI margin doesn't matter if we don't address biases in trial design
- Can we develop historical/concurrent external controls to evaluate superiority of new drugs?

Current Paradigm and Moving Forward

2. Quantitative comparison with control

- **Current regulations and guidance (ICH-E10, FDA NI guidance) do require evidence of effect size**
- **Requirement for evidence of effect of control (21CFR314.1269b)(iv))**
 - *“The analysis of the study should explain why the drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control drug”*

•Clinton Gore memo from 1995 states drugs cannot be too much less effective in setting of:

- **Serious and life threatening diseases**
- **Contagious diseases**

Current Paradigm and Moving Forward

3. Selecting subjects with the disease

- **Critical need for diagnostics not only for clinical trials but for clinical practice**
- **Ethical issue of enrolling subjects in trials who can obtain no benefit since don't have disease**

4. Baseline comparability

- **Randomization best way to avoid selection bias**
- **Can we develop detailed information from natural history studies to develop external controls with propensity scoring**

Current Paradigm and Moving Forward

5. Minimizing bias – need to develop clinical trials infrastructure

- **Prior effective antibiotics before randomization**
 - Six studies with single dose therapy for pneumonia from 1930s onwards
 - Studies show delay in antibiotics of few hours = increased mortality
 - Studies of thrombolytic therapy in MI/stroke, cardiac arrest and CPR all enroll within hours
- **Concomitant effective antibiotics during trial**
- **Removal of subjects from analysis**
 - subgroup analyses (especially when based on post-randomization variables like exposure) causes selection bias
 - Sounds “common sense” but studies show decreased mortality with increased adherence to placebo
- **Substantial amounts of missing data**

Current Paradigm and Moving Forward

6. Well-defined and reliable outcome measures

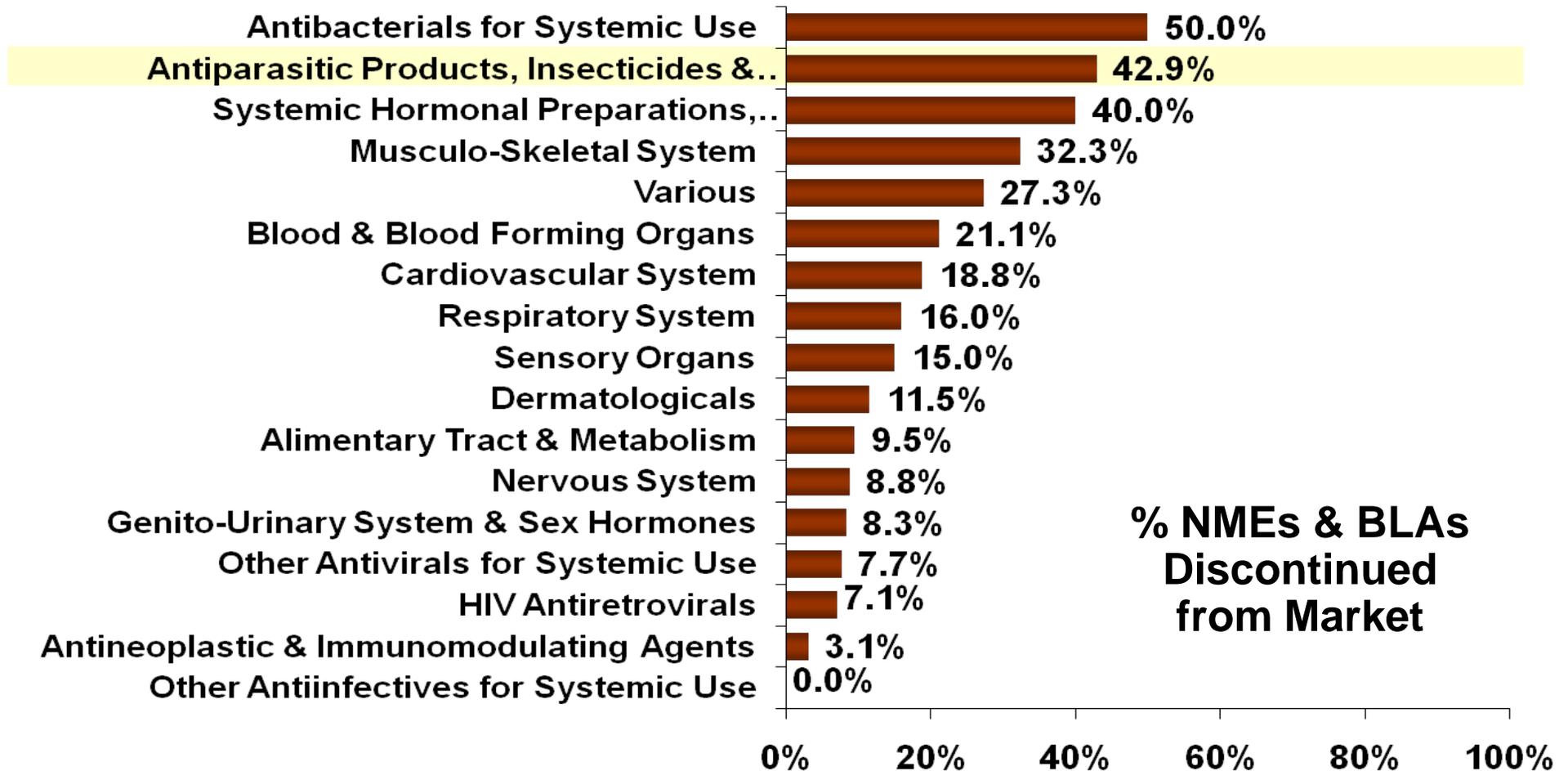
- **“Clinical response” composed of biomarkers and not well-defined, reliability unclear, not direct measure of patient benefit**
- **Does not reflect mortality (see tigecycline and doripenem) so what is it a surrogate for? Mortality does have assay sensitivity**
- **How can drugs be “life-saving” if we don’t evaluate whether they save lives? Doesn’t need to be superior, just no worse on mortality**
- **FNIH effort as one way forward to get unbiased evidence – others?**

7. Appropriate analysis

- **Source of bias addressed first**
- **Bayesian analysis – what are informative priors?**
- **Existence of animal models does not mean they are predictive**
- **Upjohn v Finch 1970 precedent**

Discontinued NMEs and BLAs. Approved by FDA (1980-1999)

Outterson K et al American Public Health Association Nov 2010



Conclusions

- **We can and will develop clinical trial methods to get the data to inform patients and clinicians choices**
- **Biased analyses are not a way forward, but a way backward**
- **Need to work together to get better information**
- **Develop better unbiased and reliable tools to make trials more efficient**
- **Our predecessors did it and we can too!**

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