Interplay of Good Science and Ethics in Clinical Trials During Epidemics

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Outline

- The challenges that epidemics present
- Therapies and state of development
- Factors to consider when planning for and selecting a clinical trial design
- Some lessons learned from Ebola virus disease
- Sound clinical trial science is the foundation for sound research ethics

Therapies State of Development -& Production / Supply

- Investigational therapies in early stages of development
  - Clinical studies for emerging/epidemic disease not yet conducted
  - Supply and short term ramp-up capacity often limited

- Approved for another use - therapies not yet studied for the emerging disease
  - Safety may differ in setting of disease
    - drug-disease interactions
  - Supply for clinical trials likely available

State of Therapies – Preclinical and Clinical Data

What is known about the drug? & What is known about the drug for treating the epidemic infection?

- Available preclinical data can provide valuable information on
  - Toxicity in animals
  - Activity – In vitro, cell culture, animal models of infection
- Possible insights from what is known about the class of the therapeutic
- Any available clinical data? What is it relevance to the epidemic disease? Efficacy? Safety?

  Are drug-disease interactions likely?
- Available information important to consider as one factor when considering and selecting clinical trial designs

Knowledge of the Disease

- Clinical characteristics / pathophysiology / biology of the disease
- Diagnosis – clinical & diagnostic tests
- Major manifestations, course over time, major morbidity / complications of disease, mortality rate, sequelae – informs endpoints for clinical trials
- Role of supportive measures in treating patients
- Is there a spectrum of disease severity? – are outcomes highly predictable or do outcomes vary?

Purpose of Clinical Trials

- The purpose of conducting clinical trials is to distinguish the effect of the drug from other influences, such as spontaneous change, placebo effect, or biased observation
- Clinical trials continue to teach us things we don't expect to occur for both efficacy and safety
- Some estimates are that only 1 out of 9 drugs that enter phase 1 human testing will be shown to be safe and effective.

Trial Designs

- Concurrent controlled trials - randomized
  - Inactive control with other supportive care
  - Active control
    - Superiority
    - Non-inferiority if treatment effect of active control established – importance of assay sensitivity
  - Dose comparison
- Historical / External control trials
- Elements of flexibility in trial to facilitate the studying therapies -- adaptive designs, group sequential designs, Bayesian analytic techniques, other

Some Factors to Consider when Selecting a Trial Design

- Critically important to consider a number of factors when selecting a trial design(s) including:
  - Disease - its characteristics, course over time, spectrum of severity, variability in outcomes, potential for other interventions to affect outcomes
  - Investigational drug
    - toxicity data
    - activity data
    - supply issues
  - Clinical trial environment
  - Acceptability to those in the affected areas
  - Many other factors

Selecting a Trial Design

- Acceptability to the affected people is essential and necessary but not sufficient and should not be used as a justification for doing
  - Trials that are unlikely to be informative
  - Trials that don't protect patient welfare
    - Trials that lack the capacity to provide reasonable means to detect harm and/or have little reason to expect benefit from the investigational compound and are associated with risk of harm
- Essential that leaders in the field work together with leaders in the affected locations in pursuit of appropriate trials
- To extent those relationships are already in place that may help

Some lessons regarding clinical trial design from the Ebola epidemic

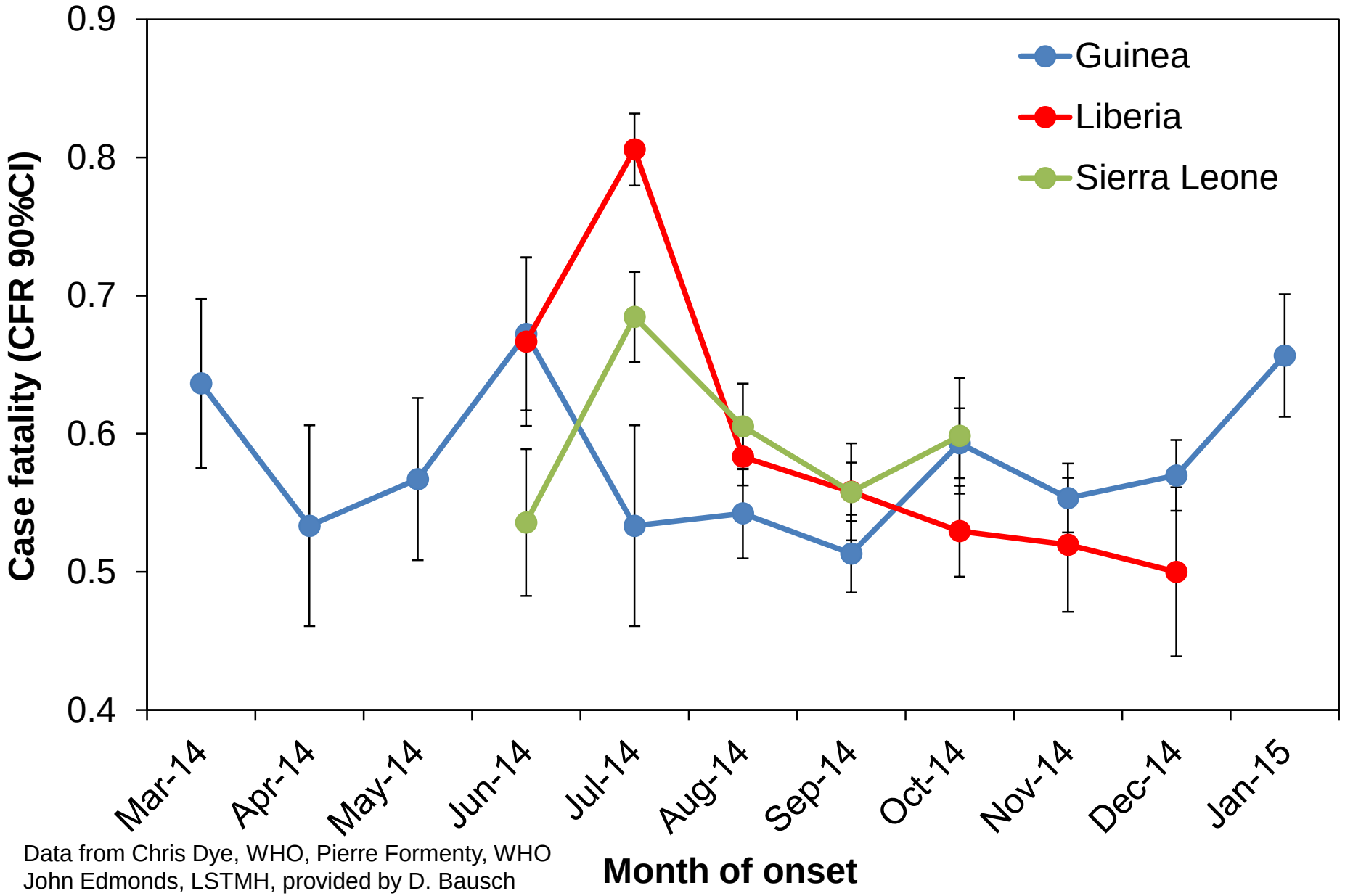
Background - 1

- Candidate therapies generally in early stages of development for EVD
- Available data varies for each product
  - Differing preclinical and clinical data
  - Some agents have shown activity against certain Ebola strains in animals
- Some have also raised toxicity concerns
- None shown safe and effective for treatment of patients with EVD

Background - 2

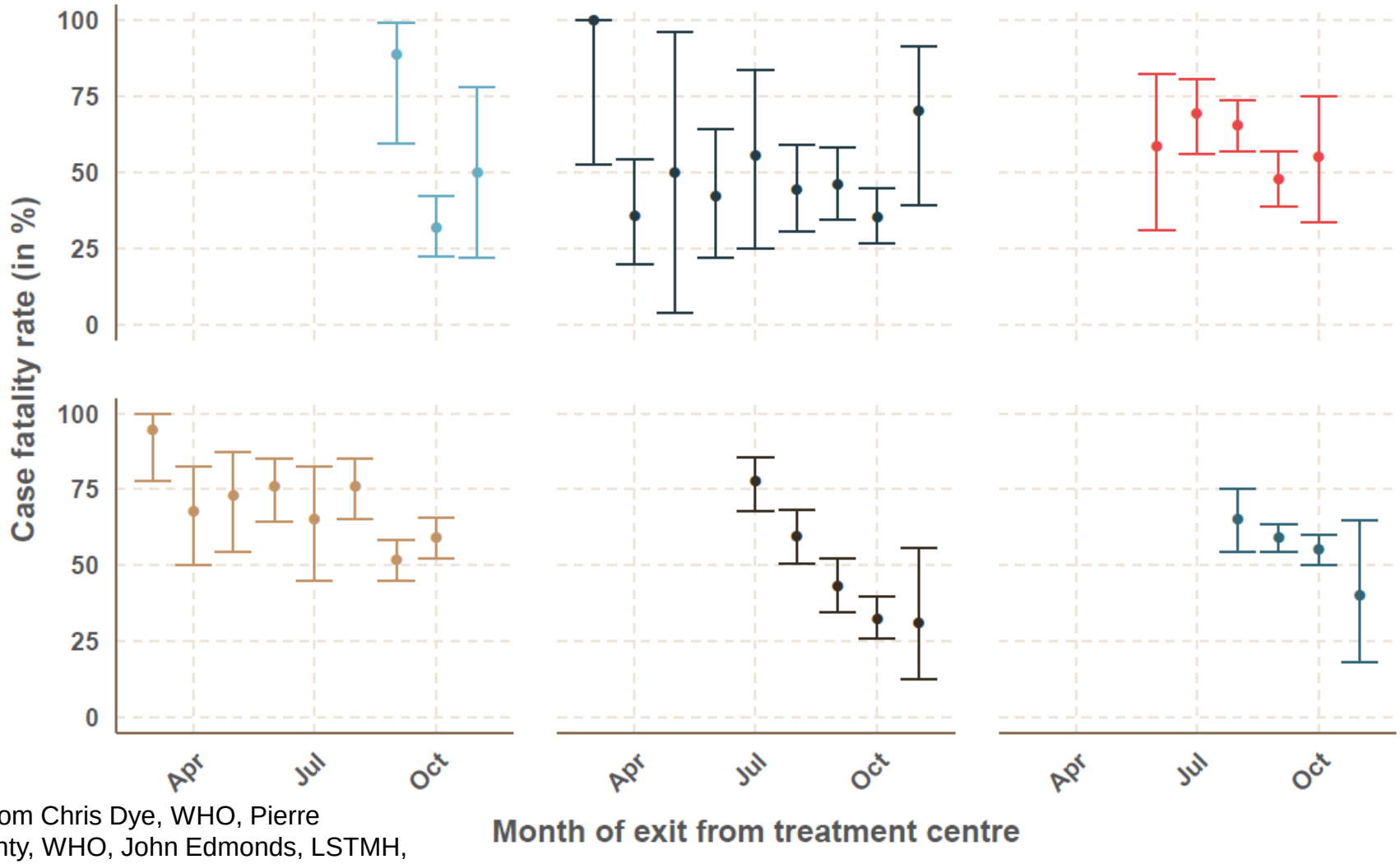
- Some disease factors to consider when selecting a trial design
  - Outcomes for patients with EVD vary across different treatment units
  - Level of supportive care appears to have an impact on outcomes and also may vary across study centers or may improve in setting of a clinical trial
  - Underlying patient/host factors appear to impact outcomes

No systematic trend in case fatality during the course of the epidemic



Data from Chris Dye, WHO, Pierre Formenty, WHO
John Edmonds, LSTMH, provided by D. Bausch

Variable CFR by centre and time



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Evaluating Therapies for Patients with EVD

- Critically important to get this right and figure out whether the investigational drugs being developed for the treatment of patients with EVD are, overall
  - helping patients
  - having little effect
  - harming patients
- Finding out what works (and what does not work) as quickly as possible in order to get effective therapies to patients
- Will form foundation for future drug development for EVD
- Erroneous conclusions of benefit can harm many patients

Trial Design Considerations - 2

- What may be an appropriate trial design for studying a drug therapy for one disease may not be an appropriate trial design for studying a drug therapy for a different disease because of differing drug or disease characteristics

Trial Design Considerations - 3

- Example: External / Historical controlled trial *ICH E-10*
  - *The inability to control bias restricts use of the external control design to situations in which the **effect of treatment is dramatic** and the **usual course of the disease highly predictable**.*
  - *It is well documented that **untreated historical control groups tend to have worse outcomes** than an apparently similarly chosen control group in a randomized study, possibly reflecting a selection bias.*
- Whether a particular trial design is appropriate depends on the characteristics of the disease under study and the drug being studied
  - External control may be an informative design for some oncologic diseases where treatment effect is dramatic and disease course without treatment is highly predictable
  - Characteristics and variability of EVD generally make an external control design in an overall population unreliable for studying EVD therapeutics

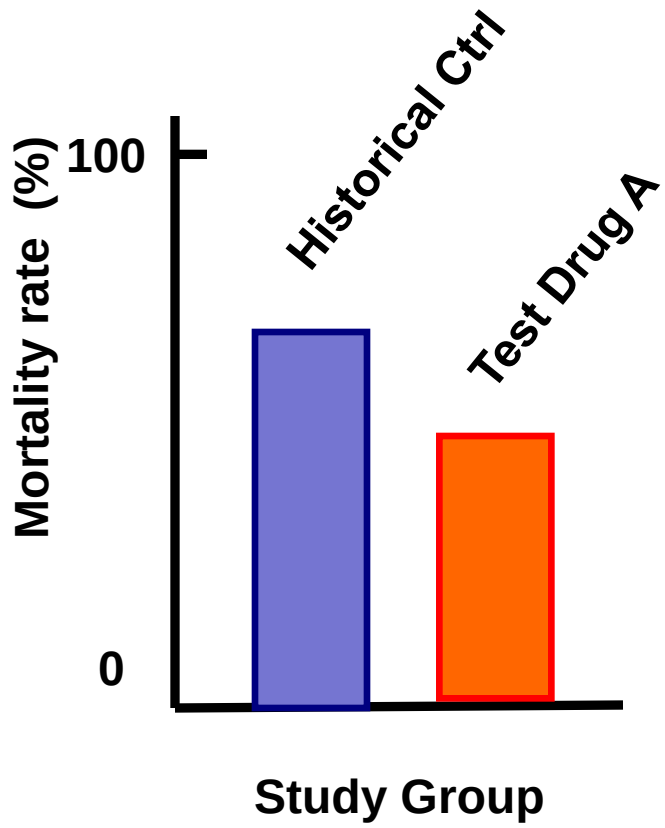
Randomized Concurrent Controlled Trials of an EVD Therapy

- An innovative trial designs with a concurrent standard of care control has been implemented
- Open to enrollment to
  - Returning health care workers – U.S.
  - Patients in W. Africa
  - Same trial design in the U.S. and W. Africa
- Group sequential design using Bayesian analysis with frequent looks to determine “a winner” as soon as possible
- Appropriate design for EVD, for the therapy under study, under the current circumstances
- Seeking to get to a valid answer as soon as possible in order to benefit patients

Why Utilize a Randomized Concurrent Control Group?

- Obtaining a truly comparable historical control group is difficult
- Historical control groups generally have worse outcomes than randomized controls
  - Selection bias – who actually gets in a trial
  - "Trial effect" – care/supportive care in the trial may be better
- Variability in outcomes for patients with EVD – historical outbreak mortality ranges from under 50% to greater than 80% and may be further improved with more aggressive supportive care
  - Greater variability possible across study sites depending on level of supportive care
- Temporal differences – improvements in supportive care over time
- Interpretable **safety data** in acutely ill patient population with drugs with potential toxicities critically important to protect patient welfare

Historical vs Randomized Concurrent Ctrl (RCC) Possible Implications



Study Group	Mortality Rate % (n/N)
Historical Control	70 %
Test Drug A	50 %
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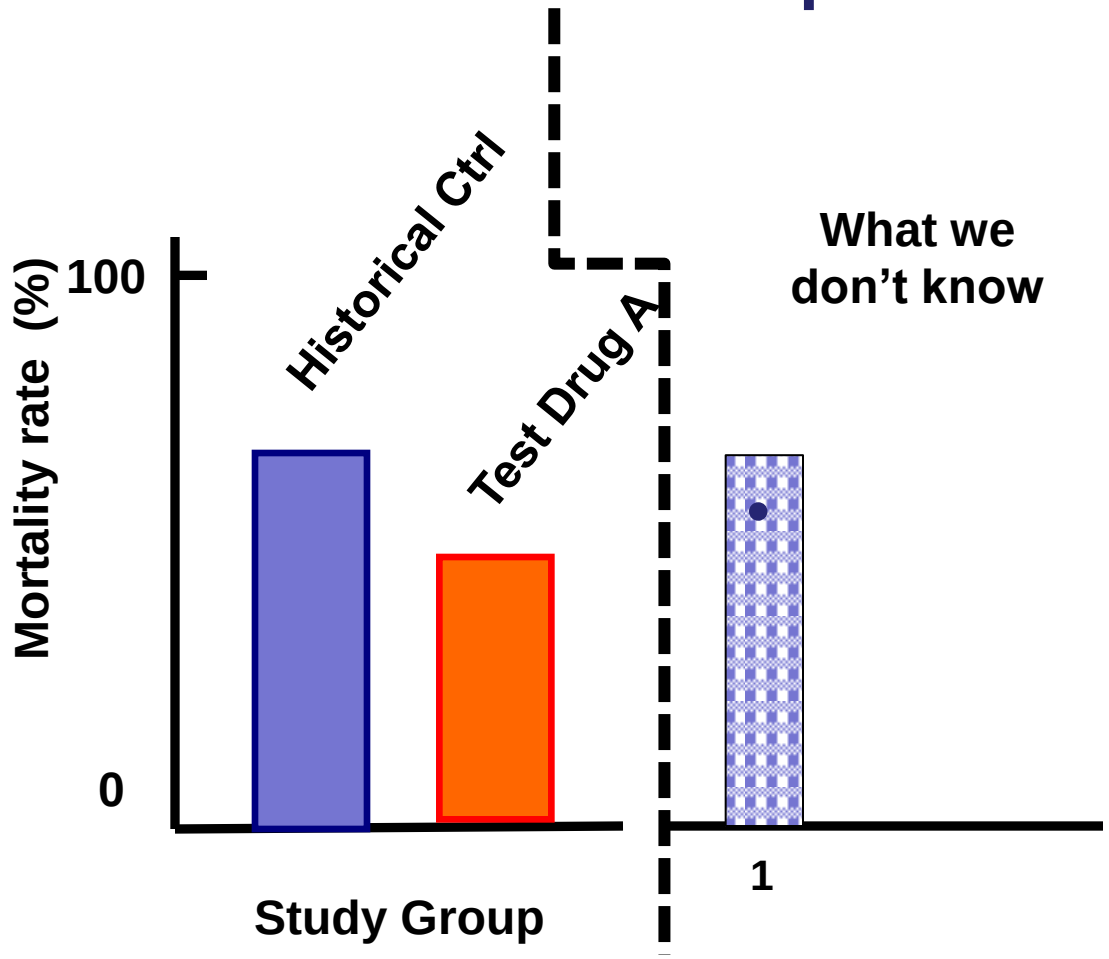
Historical vs Randomized Concurrent Ctrl (RCC) Possible Implications



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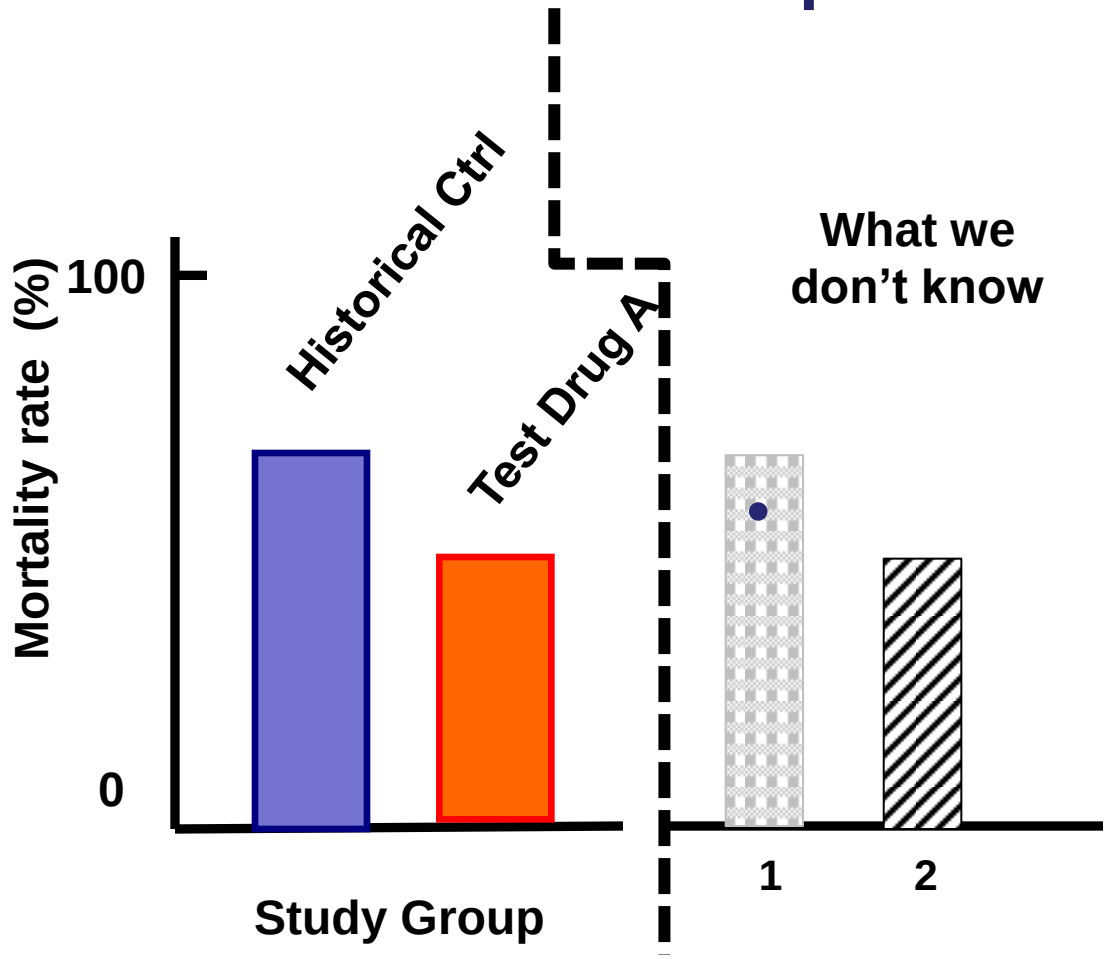
"True" Control Rate	
Case 1	70%

Historical vs Randomized Concurrent Ctrl (RCC) Possible Implications



Study Group	Mortality Rate % (n/N)
Historical Control	70 %
Test Drug A	50 %
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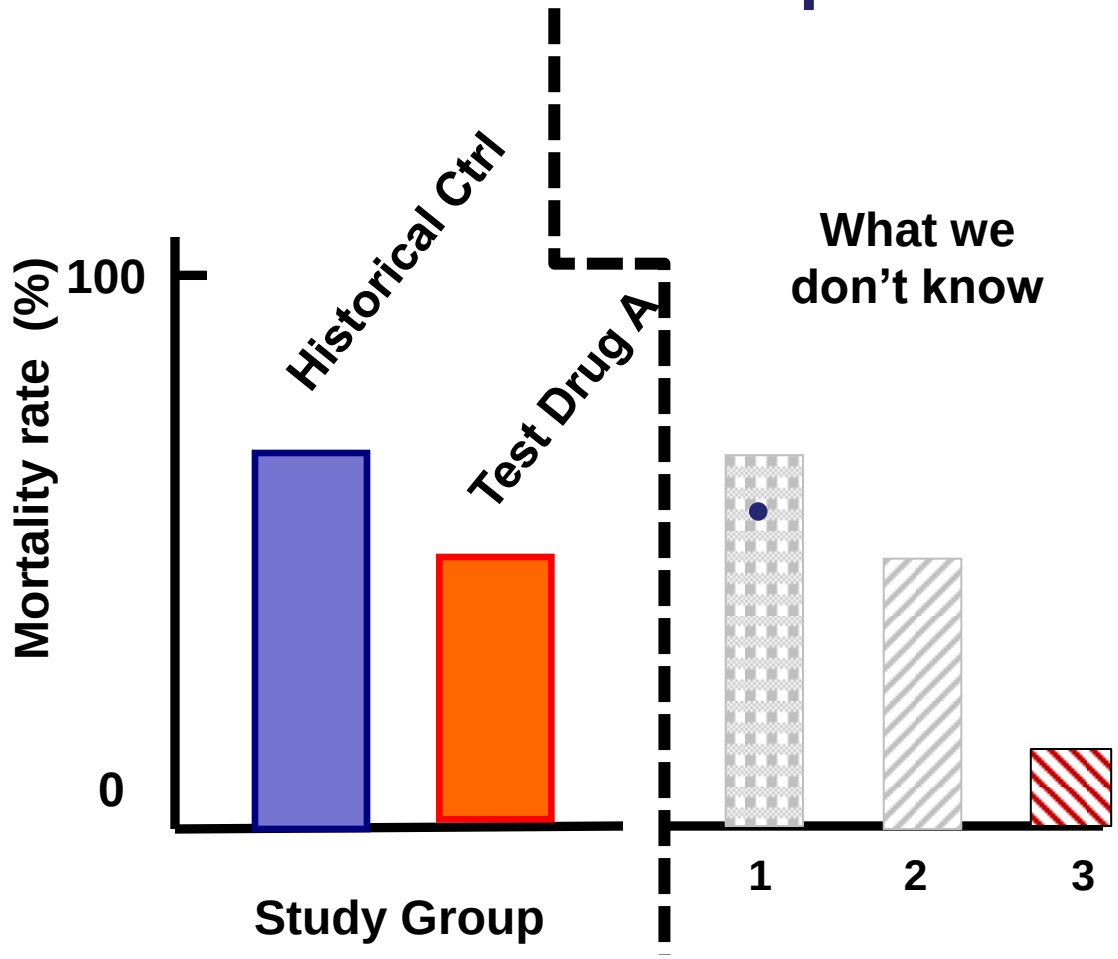
"True" Control Rate	
Case 1	70%
Case 2	50%

Historical vs Randomized Concurrent Ctrl (RCC) Possible Implications



Study Group	Mortality Rate % (n/N)
Historical Control	70 %
Test Drug A	50 %
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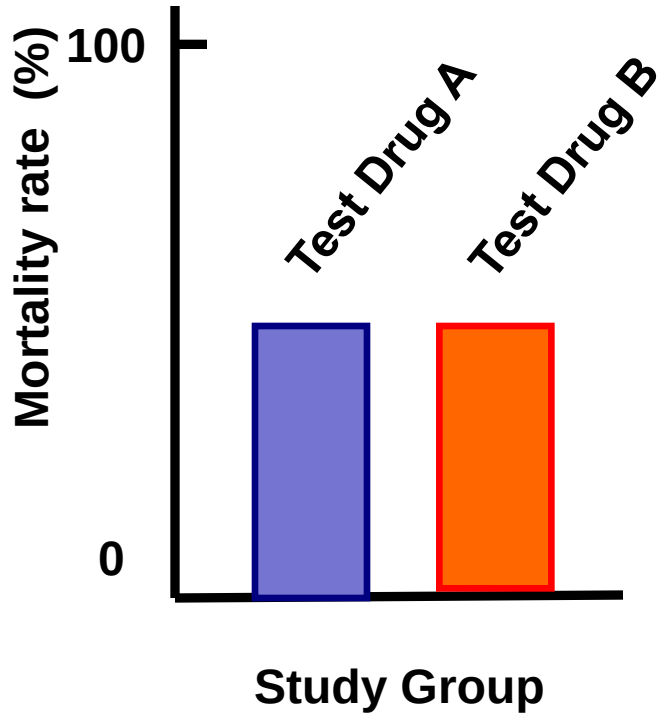
"True" Control Rate	
Case 1	70%
Case 2	50%
Case 3	20%

Why Utilize a Supportive Care Control Arm?

- Therapies to date have not demonstrated clinical benefit
- Provide best available supportive care for all – this should provide benefit for all
- Trial comparing two putative actives – without a supportive care control arm – possible outcomes
  - If two putative active agents look the same can't discern if both are beneficial, ineffective, or harmful
  - If one putative active agent looks better than the other
    - One may be helpful
    - One may be harmful
    - Both beneficial, but one more so
    - Both harmful, but one less so

Role of a Supportive Care Control Arm
Possible Implications



Study Group	Mortality Rate % (n/N)
Test Drug A	50 %
Test Drug B	50 %
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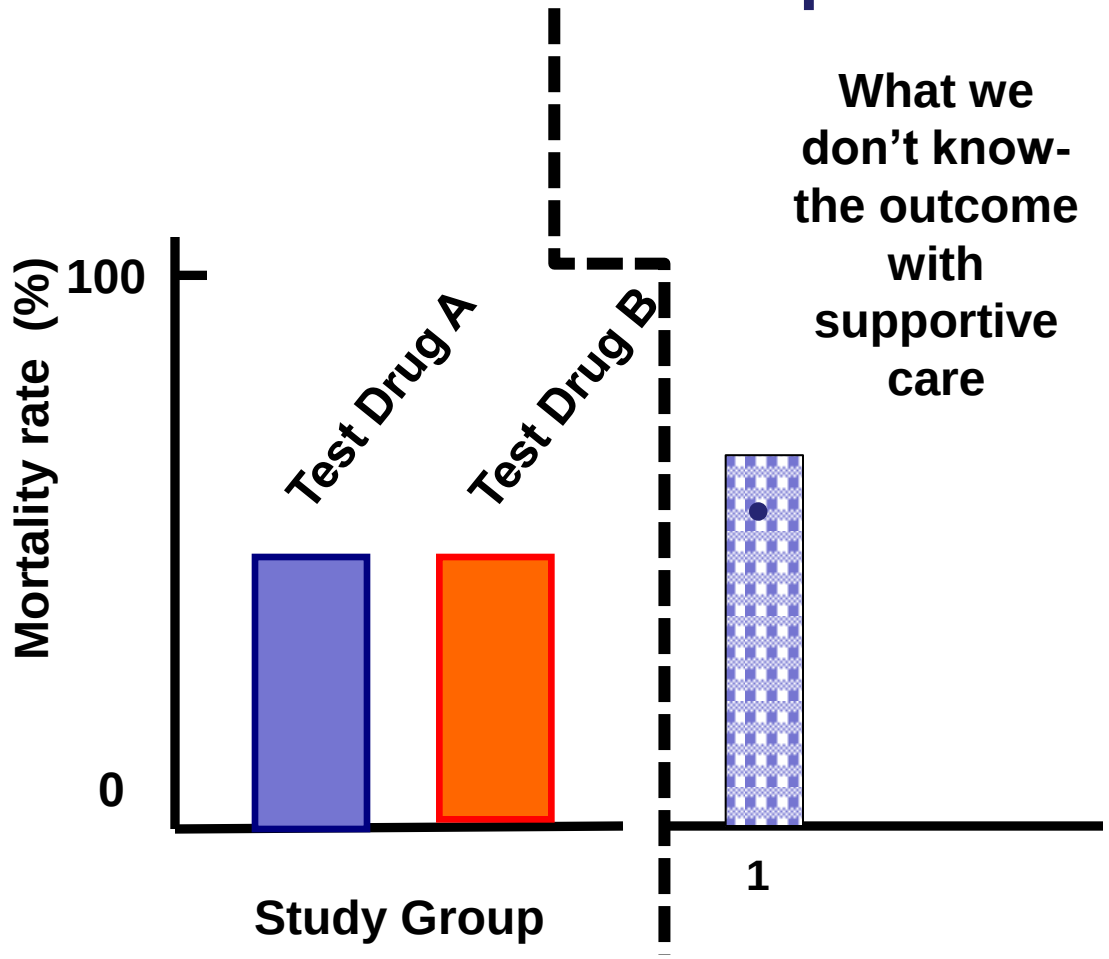
Historical vs Randomized Concurrent Ctrl (RCC) Possible Implications



Study Group	Mortality Rate % (n/N)
Test Drug A	50 %
Test Drug B	50 %
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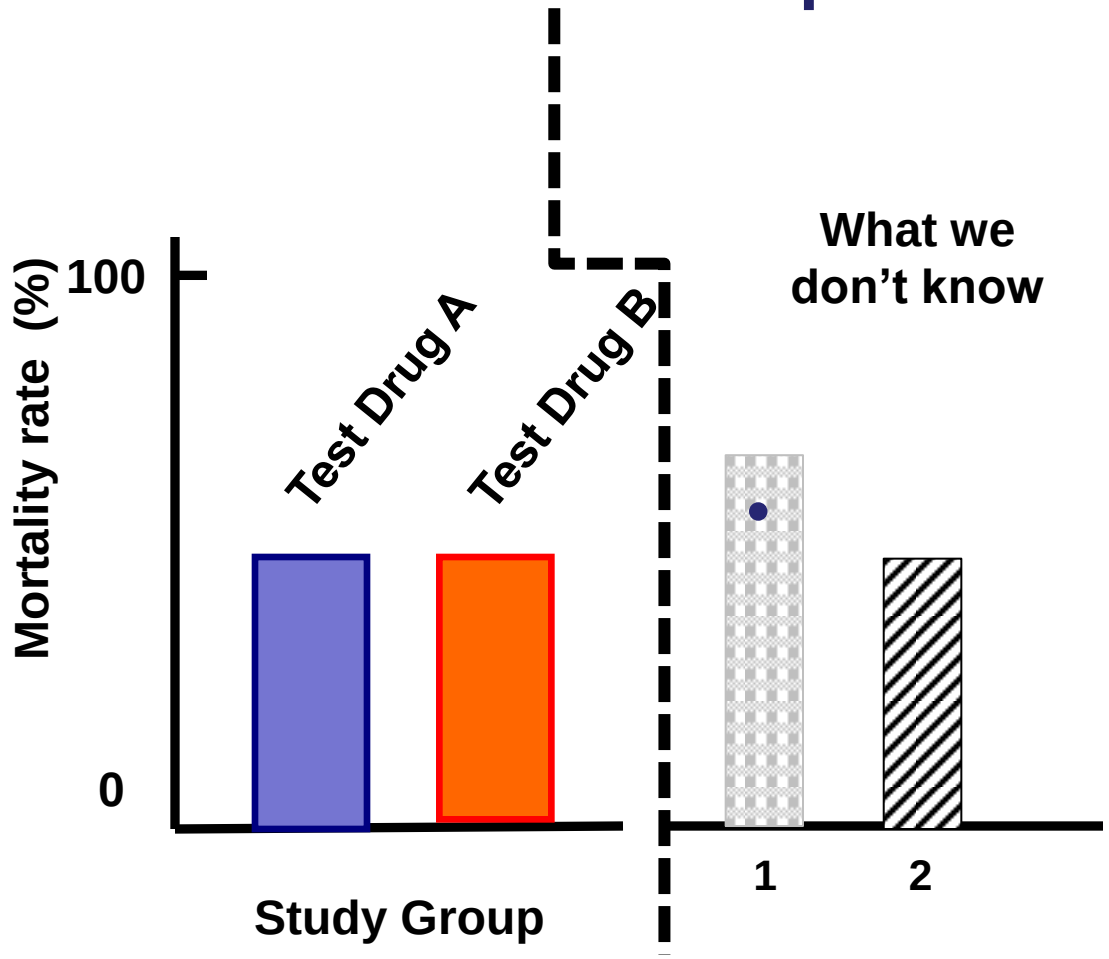
Supportive Care in RCT	
Case 1	70%

Historical vs Randomized Concurrent Ctrl (RCC) Possible Implications



Study Group	Mortality Rate % (n/N)
Test Drug A	50 %
Test Drug B	50 %
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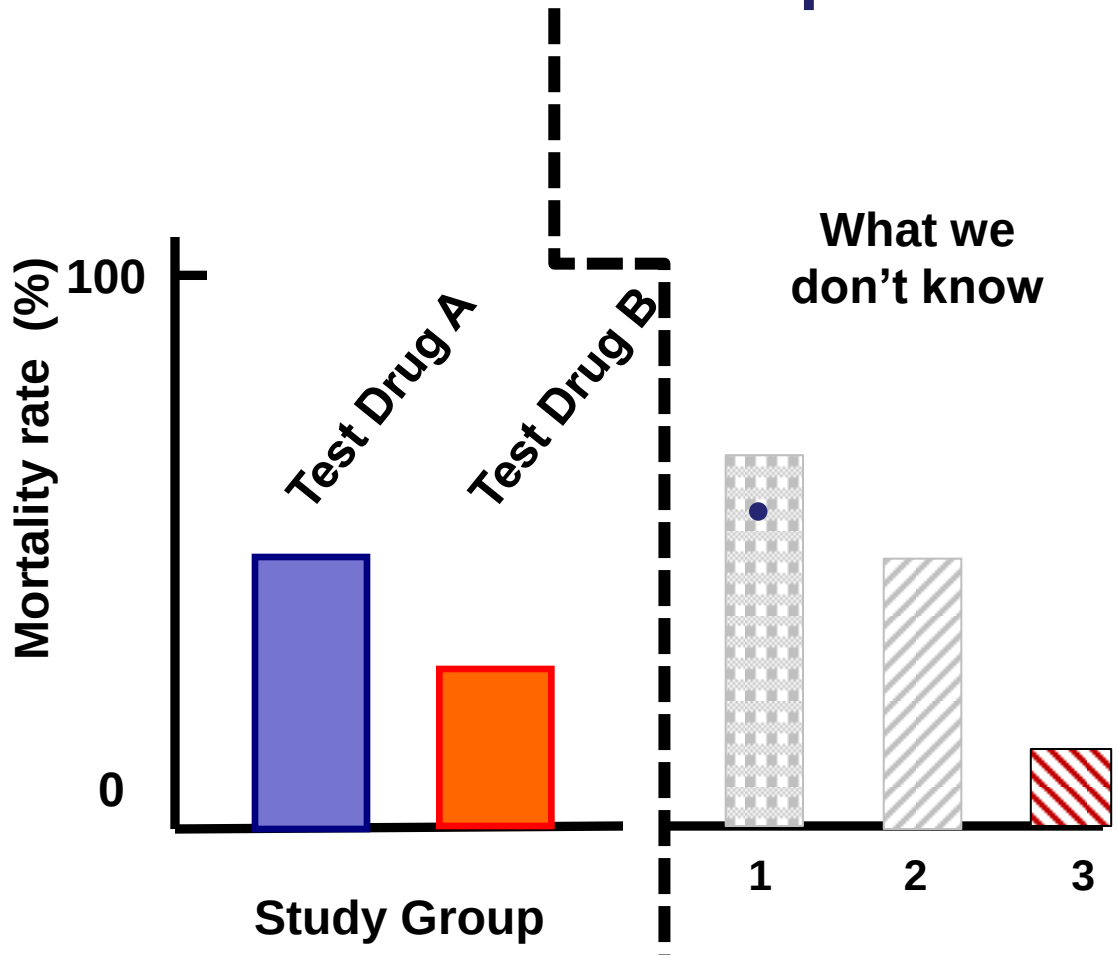
Supportive Care in RCT	
Case 1	70%
Case 2	50%

Historical vs Randomized Concurrent Ctrl (RCC) Possible Implications



Study Group	Mortality Rate % (n/N)
Test Drug A	50 %
Test Drug B	30 %
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"True" Control Rate	
Case 1	70%
Case 2	50%
Case 3	20%

A Few Concluding Points - 1

- The desire to give everyone a putative active investigational drug is understandable
- Critically important to understand what helps and what harms patients based on valid conclusions
- Performing properly designed trials isn't easy, but it is very important to get this right for all the patients that will depend on these therapies
- What may be an appropriate trial design for studying a drug therapy for one disease may not be an appropriate trial design for studying a drug therapy for a different disease because of differing drug or disease characteristics

A Few Concluding Points - 2

- Need to get to valid answers quickly and efficiently in order to help patients and avoid harm
- Erroneous conclusions could lead to patient harm and delay development of truly effective therapies
- Appropriate science and clinical trial designs are the foundation on which sound clinical research ethics are built

- Thank you