Must a randomized trial focus on hypothesis testing? Assessing risks and benefits of withdrawal from therapy when the acceptable risk margin is unclear

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Systemic Lupus Erythematosus (SLE)

- Chronic systemic autoimmune disease
- Prevalence estimated at 1/2000
- Predominantly women and ethnic minorities
- Heterogeneous in manifestation
  - Chronic active disease (14-35%)
  - Relapsing remitting (25-37%)
- 25-37% have periods of long-term quiescence

Mycophenolate Mofetil (MMF)

- Used to control active disease and reduce steroid dependency
- Potentially toxic immunosuppressive agent
- Not FDA-approved for this indication
- Long-term utility of MMF is unclear
  - Spontaneous disease amelioration?
  - Drug-dependent disease suppression?

Withdrawing from MMF

- Well documented toxicities
  - Common and opportunistic infections
  - Known teratogen
  - Hematological derangements
  - Lymphoproliferative disease
- Risks of withdrawal
  - Recurrence of lupus
  - Side effects of corticosteroids and/or cyclophosphamide
- No standards to support withdrawal decision in patients with quiescent disease

Withdrawing from MMF Patient's Perspective

- Risk tolerance varies substantially
- A given estimated risk difference (and associated confidence interval) lead to different decisions in different patients
  - 27 year old woman who wants to have a baby
  - Patient with lupus nephritis

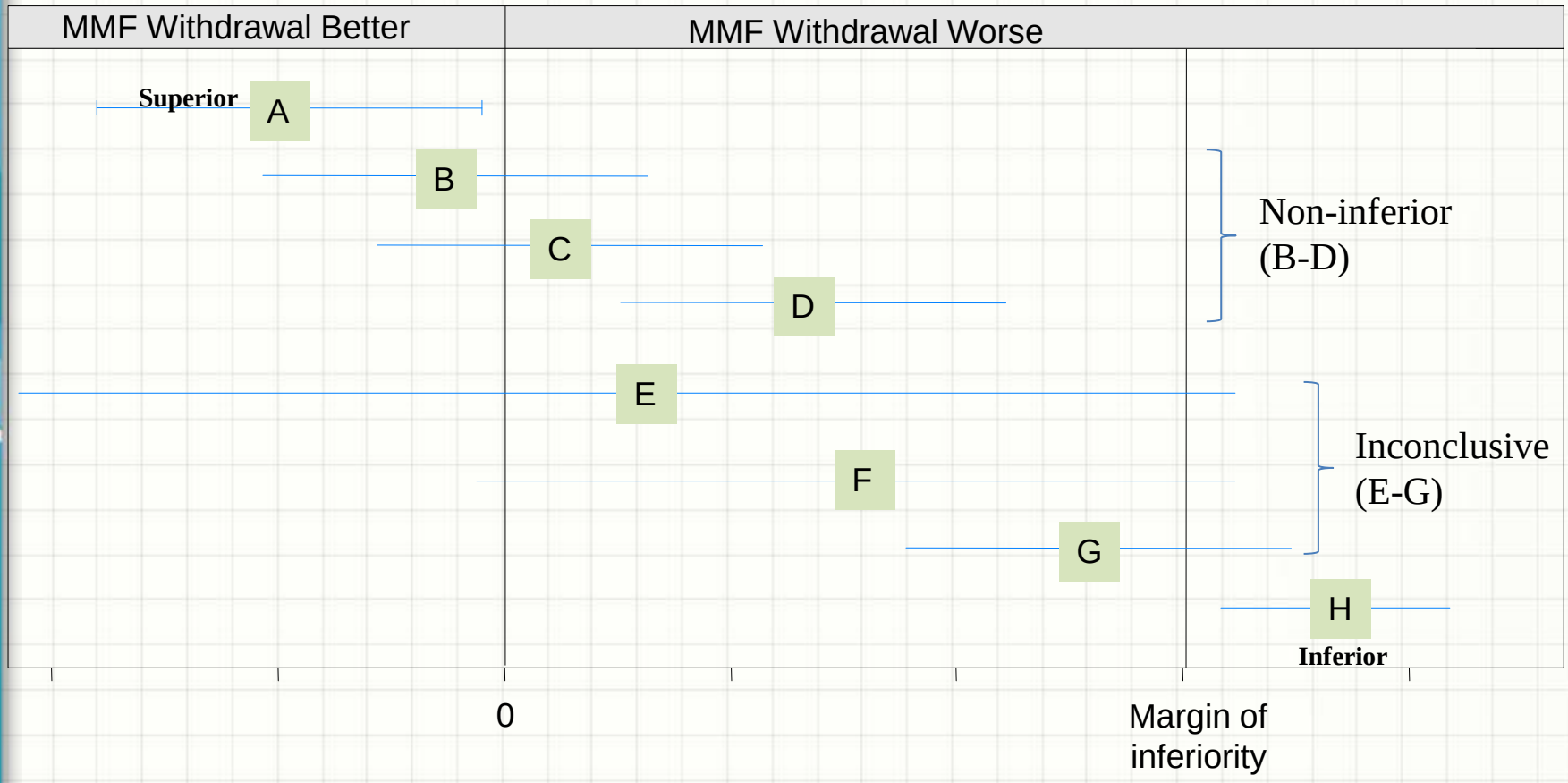
Testing the Withdrawal Strategy

- Double-blind randomized trial
  - NIAID-funded Autoimmunity Centers of Excellence
- SLE, long-term MMF therapy with stable disease
- Maintenance MMF or withdrawal to placebo
- Follow for 15 months
- Efficacy endpoints
  - Clinically significant disease reactivation
  - Disease severity measures
  - Addition of other therapies
  - QoL and fatigue measures
- Safety endpoints: adverse events, infections, malignancies

Selecting the Appropriate Design

- Superiority hypothesis
  - Does not address scientific question of interest
  - Expect higher flare rate in withdrawal arm
  - Ethically problematic
- Want to know if increase is “too much”
- Non-inferiority hypothesis
  - Requires specification of the margin of inferiority

Non-Inferiority: Interpretation



Margin of Inferiority

- Decision to withdraw is multifactorial
  - Increased risk of flare
  - Reason for initial use
  - Decreased risk of toxicities, QoL, plans for pregnancy
- Highly individual and hard to quantify
  - Varies by physician and by patient
  - No supporting data
- Any risk margin selected is artificial

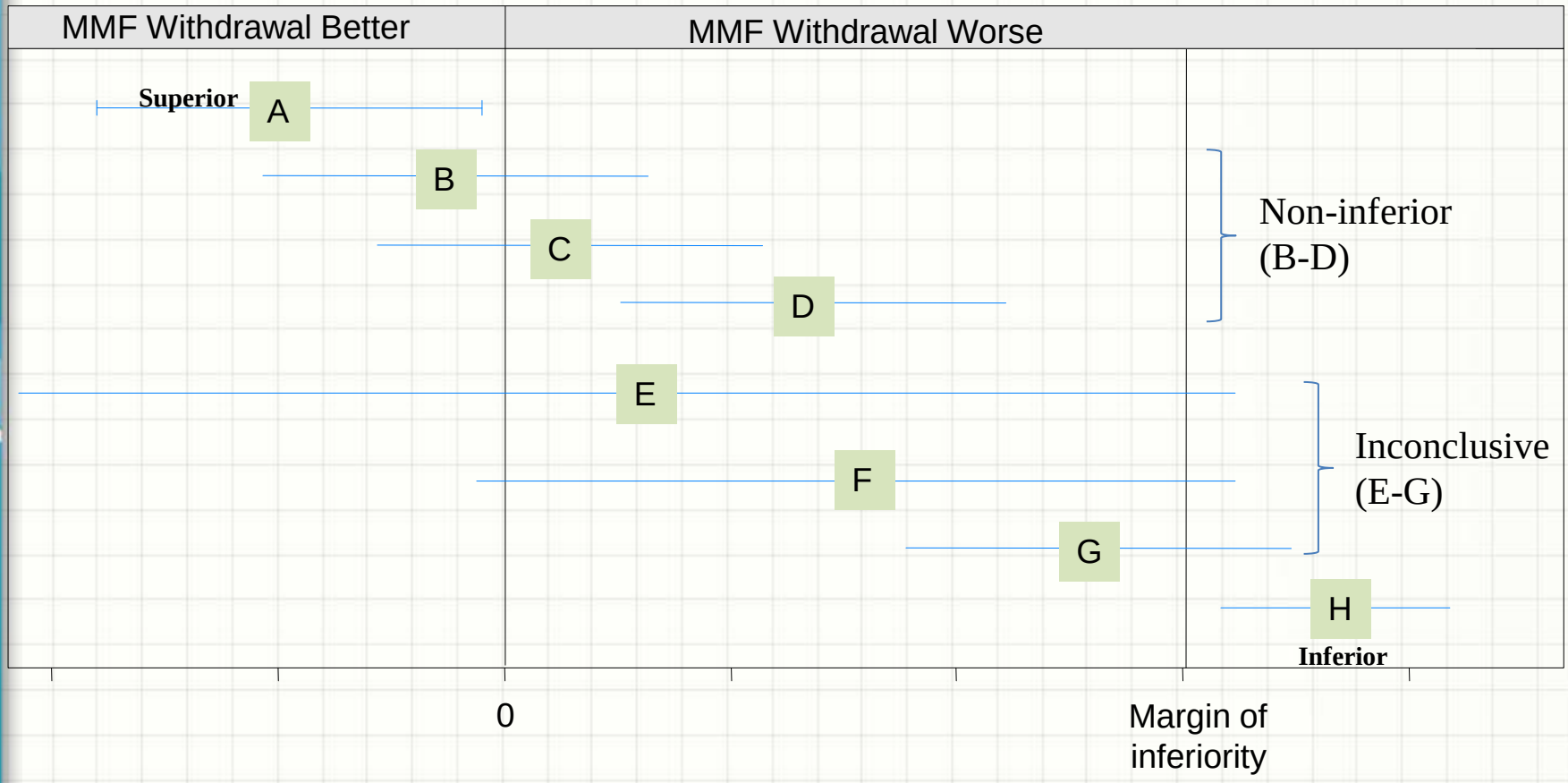
Estimation Trial

- Focus on estimation of risks and benefits, rather than testing an arbitrary hypothesis
- Report effect estimates and confidence intervals
  - Risk of disease reactivation
  - Other disease activity measures
  - QoL and medication use endpoints
  - Safety endpoints
- Estimates guide decisions based on individualized assessments of acceptable risk

Presentation of Results

- Readers of medical literature used to p-values
- Emphasize interpretation of confidence intervals rather than point estimates
- Encourage clinicians to discuss acceptable level of increased risk of flare with patients
- Compare upper confidence limit on risk difference to acceptable level of increased risk
- Similar discussions for secondary endpoints
- Support discussion with figures

Non-Inferiority: Interpretation



Conclusion

- Usual hypothesis tests do not always address scientific question of interest
- Randomized trial based on estimation of effect may be appropriate
- Challenges for dissemination of results
- Requires careful discussion of interpretation of point estimates and confidence intervals
- Careful discussion with patients