When to stop a trial for benefit

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Early stopping of a trial impacts:

- Clinicians deciding best practice
- Patients in trial
- Future patients
- Investigators/regulators
- ?
EMPHASIS-HF trial

- Eplerenone in patients with heart failure symptoms
- Primary endpoint death from cardiac cause, or hospitalization for heart failure
- DMC had 2 pre-specified interims with stop of $p < .001$
- Sample size had to be increased based on blinded overall event rate lower than expected. $N=3100$
Second interim

- DMC reported boundary crossed on time to first of the 2 events (death, HF hosp)
  - 2737 patients
  - Logrank $p<.00001$
  - 249 events in E vs 356 in P
  - 171 died in E vs 213 in P
- Study closed and final results published
Principles used in decision

• Consistent with pre-specified guidelines in DMC charter
• Level of significance minimized concerns that results would reverse
• Findings consistent when components analyzed individually
• Results consistent with previous trials of the drug
• Recommended to Exec Cmtee to close the trial
Concerns

- Would miss chance to show impact on survival
- \( P = .044 \) at interim. May not persist
- Mortality important, but was secondary in the design

Stopped because:
- No longer equipoise—ethics (especially for placebo patients)
- No longer blinded because Exec Committee knew results—could compromise the trial
- ? Other issues
Challenges and implications for early stopping of a trial

• End point considerations— with composite endpoint?
  • Earlier endpoint will drive the composite--survival has less leverage
  • Will the results change practice?
  • How can this be handled?

• Unambiguous endpoint—hospitalization is subjective

• Consider primary as well as trend in all component endpoints

• Consider advantages to waiting for more data

• What is lesson of ASCOT-BPLA trial (page 295)?
Effect of stopping early on knowledge

- Magnitude and precision of effect is impacted by stopping early
  - Examples?
  - The bias of early stopping. What is it?
- What information lost that would come in over time?
- CHARM study (p 296)
  - Only close early if results would change clinical practice
  - Caution about stopping too early (too few events) because there can be “regression to the truth”
- What degree of benefit needed to justify ending early?
- What impact on science when close early?
Totality of Evidence

• Evidence
  • Primary, secondary endpoints and side effects
  • Other trial results

• New class drugs vs existing drug used in other RCTs
  • Example SHIFT trial crossed boundary but another trial of drug class was negative

• What else do we need to consider about side effects?
Responsibility to Subjects: treating participants after stop trial early

- Ethical responsibility for treating others?
  - Include plans in the protocol for this

- Any reason to not switch control patients?
What should be included in the DMC Charter?

• Guidelines for sufficient evidence?
  • Number of events and follow-up
  • Other studies being done or completed?
  • Adjudication of soft endpoints

• How many looks and what boundary?

• How to communicate DMC decision?

• Confidentiality!

• Experienced DMC members—how can we train people?
Conclusion

• Balance integrity of trial and quality of results versus speed of availability of new drug to participants and wider patient community

• Decision is made in the context of a wider clinical, academic and business community. Impact?

• How can statisticians help to ensure that the best decisions are made?