September 13

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Contribution of components for fixed sample trial

- Four-arm confirmatory clinical trial
  - Randomization to comparator arm C, M1, M2 and M12 (combination of M1 and M2)
  - None of M1/M2/M12 currently approved
- Main interest is showing that M12 is superior to C
  - Typically would not suffice for regulatory approval of M12
- Do both components of M12 add efficacy?
  - May need to show that M12 is superior to both M1 and M2
  - Criteria for how M1 and M2 fared in the four-arm trial?
- For which comparisons must familywise error be strongly controlled?
  - M12 vs C, M12 vs M1, M12 vs M2, M1 vs C, M2 vs C are possible candidates
  - Prospective engagement with health authorities critical

Contribution of components for trial with interim analyses

- Consider group sequential design
  - Same comparisons of interest as for fixed sample design
  - Strongly control alpha for all comparisons across interim/final analyses?

- Suppose that M12 vs C efficacy boundary is crossed at interim
  - Which other boundaries must be crossed for formal approval?
  - What if only a subset of boundaries is crossed at the same interim?
  - Is interim submission meaningful unless all boundaries have been crossed?

Other means of establishing CoC

- Suppose superiority of M12 to C has been demonstrated

- Complementary means to assess other hypotheses of interest
  - Within-trial data on other endpoints?
  - Bayesian approaches incorporating historical/external data?
  - Scientific reasoning/modelling based on mechanism of action(s)?

- Additional considerations
  - Establishing CoC in two trials would increase complexity, any suggestions?