Outline:

* Introduction/Background
  + Include limitations of subgroup analyses; ensure audience is reminded about these (despite newer tools)
  + Cautions exist even when results look good/consistent
  + Cautions about limitations based on sample size
  + Some will be required
* Usefulness/Applications/Objectives by Phase, where are subgroup analyses required
  + Phase 2:
    - Pre-planned subgroup analyses to evaluate consistency of effect and contribute to plans for next phase
    - *Stratified medicine analyses for identification of prognostic factors and/or predictive factors (includes biomarker analyses?) – issues here on sample size limiting ability to detect subgroups of interest*
      * *Pull practical information from Thomas’s document*
    - Ad-hoc analysis requests
  + Phase 3:
    - Pre-planned subgroup analyses (defined in protocol) to evaluate consistency of effect
    - Country/Regional specific analyses
    - Ad-hoc analysis requests
      * From clinical
      * From regulators/reimbursement agencies
    - Pre-planned subgroup analyses for HTA dossier/HE model development – based on William Malbecq’s guidance
* For each application:
* Purpose – how it will be used in practice – what are the questions we can address
  + Example:  do we have consistency?  What do we do about
* Practical Considerations
  + Where to adjust for multiplicity
  + Where to caution – pre-templated statements? Include caveats
  + Methodology: Consistency with primary endpoint methodology
  + How to determine rules around when not to do it – how small is small based on treatment effect/number of events
* Available methods

Phase 2:

* Is there a big enough effect that we would believe it?
* Is there justification for different stratification?
* Are the subgroups actionable?

* Right questions
* What approaches
* Gives guidance
* Could we do a decision tree?  Ensure that there’s a path to stopping.
  + Only do specific investigations in specific situations (limited)

What is Merck’s perspective?

How to think about requested analyses