FDA resubmission meeting

Addressing reviewer feedback:

1. Emphasize the novelty of adaptive incorporation of external data
   * Provide background on what is currently used in pediatric trials and state that the prospective incorporation of external data is not routinely used at CDER
   * Emphasize that the *prospective* use of external data in a *pre-specified* design provides novelty different than routine sensitivity analyses with different priors, and our structured framework makes these ideas more palatable
2. Add an example with continuous data
   * Find if there is a normally distributed endpoint from the PLUTO study that could be used
   * The computation would involve specifying priors for the mean and variance parameters, and wouldn’t be closed-form when using the generalized normal distribution therefore requiring new code for the numerical integration

Other improvements:

1. Access the actual trial data from PLUTO to demonstrate impact to better demonstrate impact of interim monitoring
   * Matt would access data; Evan would provide the code
2. Adaptive prior was very conservative
   * Consider revising the conservative choice of mixing weight (equation (6)) that inherently gives preference to the skeptical prior to adapt equally to compatibility with skeptical prior
   * This would make our analysis more interesting and relevant to underpowered settings
3. Add a section on how to avoid undesirable evidence deterioration between interim and final results
   * The threshold for interim stoppage would be dependent on the number of subjects in follow-up (i.e. evidence threshold greater when more subjects in follow-up)
   * Computing the necessary posterior probabilities would require MCMC sampling

Additional considerations:

1. Statistics in Medicine has no length requirements
   * Consider moving Web Appendix material from Biometrics submission into the main text as appropriate to demonstrate main concepts
   * Material currently in *Web Appendix A: Bayesian Hypothesis Testing* and *Web Appendix B: Parameterizing Flattened and Concentrated Monitoring Priors* would remain in the supporting information for the Statistics in Medicine submission

* Maybe get actual FDA data for example 2.
  1. PLUTO study.
  2. Matt can access data – I would just give him code.
* Example with normal data – closed form examples (integrate out variance, multivariate T (see 779))
  1. Normal distributed endpoint for PLUTO study.
  2. Might take a while …
* Play up adaptive incorporation more.
  1. The reviewer said it isn’t novel – they are wrong.
  2. Not used at CDER.
  3. Background on what is used in pediatric trials.
  4. They mentioned sensitivity analysis with different priors … but this is prospective use not just a sensitivity analysis.
  5. Prospective and pre-specified.
  6. These ideas haven’t gained traction … our framework makes those ideas more palatable.
* Adaptive prior was very conservative
  1. Perhaps make symmetric response to data consistent with skeptical or enthusiastic prior
  2. Our case becomes a limiting case of conservative
* Stat med has no length requirements
  1. Keep technical piece in appendix
  2. Move in enrollment patterns
* How to prevent unwanted evidence deterioration
  1. Compute posterior probabilities, would have to use MCMC
     1. Would have to sample missing values given observed (e.g. 2^5 options for binary data and 5 patients in follow-up)
  2. Evidence threshold greater when more data in follow-up
  3. Stopping at data 0.975 given XXXX patients in follow-up (not maximum sample size)
     1. E.g. 25 patients with data, 5 patients with follow-up