ADNI Biostatistics conference call minutes
11 November 2008

Present on call: Laurel Beckett, Danielle Harvey, Hao Zhang, Fred Immerman, John Kornak, Jian Han.

Laurel notes that we are trying to update the analytic plan, per suggestions from Mike Weiner and other leaders. One idea that keeps being raised is a change in the comparison rate for clinical trials, for our sample size calculation. For example, people have suggested that instead of calculating the sample size needed to get a 25% or 50% reduction toward no change, we calculate the sample size needed to reduce toward the rate of change in the normal controls. Laurel views this as a mistake for two reasons. First, the normal controls may well be contaminated with people with early AD, so that change may in fact not reflect normal aging. Second, if the rate of change in normal controls differs across potential biomarkers, then we are comparing apples and oranges, as the sample size would depend not just on the precision of the biomarker but on how much it is picking up change in normal controls. If the biomarkers differ systematically in what happens in normals, we should examine that as a separate question. And if they don't differ systematically in the normal controls, then the relative efficiency would be based strictly on precision of estimated rate of change, and it doesn't matter what you take as a baseline for comparison, so for simplicity you might as well use no change. Fred agrees that use of rate in normal controls as a "target" for rate of change is problematic for drug companies, also. We could, however, add this discussion and explanation to the analytic plan, to explain why we chose the approach we are using.

There are two main areas that we will add to the existing plans. The first is to add the kind of work we have done on the normals and early MCI, looking at biomarkers that show change (and hang together in a pattern?). We would like to identify both a set of biomarkers that seem to be detecting early change, and a set of people who might be targeted as possible earliest biological changes leading to AD. This could help us also in designing ADNI II; for example, we might be able to do a larger-scale screening phase, and take a stratified sample based on marker data and APO-e4.

The second area where we need to expand our analytic plan is the possibility of a better composite measure for clinical change. Can we get an improved measure of clinical change, at least for the purposes of comparison as a reference or better "gold standard" for the biomarkers? Fred says that industry is also trying to use ADNI to improve the outcome measures for clinical trials. FDA would like to see evidence from larger studies and use this as evidence before modifying the criteria for approval.

A third area that is mentioned briefly but could use a little more detail is the work that UCSD folks have done on regression modeling using biomarkers; we have also looked at some variations on this idea. This ties in with improvements to the standard measures of clinical change.

We are hoping to get these revisions out by 1 December and discussed on our December call, then out to Executive Committee, and general approval by early January.

We will need to start the analyses for the April meetings fairly early in 2009. Danielle reports that the PET group is well ahead on getting all the scans processed and data

summaries carried out. The MRI group is talking about getting everything processed by end of year. We should have a good chunk of the data completely ready by 1 January so that we can set up analyses and finish them after the final data upload. Mike and Norbert at UCSF are shifting to freesurfer for their work; Anders has done some modifications to freesurfer but he has not submitted any data for some time and we don't know if he will submit more.

Danielle has spent a lot of time tracking all the scans and summaries. There are scans that have not been uploaded to LONI in raw form but should have, and scans that are at LONI but haven't been processed by Mayo. Then there are scans that Mayo has processed that still need to be read and processed by the labs. The Mayo, LONI and clinical folks at ADCS are all working together to track down anything that is missing, and to account for those and fix when possible.

The next call will be on 9 December at 10 AM Pacific time.