**Meeting Agenda**

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| Meeting: | SPAN Steering Committee Meeting |
| Date/ Time: | 5/26/21 11am-12pm PT |
| Present: | Patrick Lyden, Jessica Lamb, Pradip Kamat, Basav Sanganahalli, Cenk Ayata, David Hess, Enrique Leira, Fahmeed Hyder, Jarek Aronowski, Kris Dhandapani, Kris Wood, Lauren Sansing, Ligia Boisserand, Marcio Diniz, Nirav Dhanesha, Rakesh Patel, Ray Koehler, Takahiko Imai, Taylan Erdogan,Kris Dhandapani, Andrew Goh, MB Khan, Tom Qin, Dan Thedens, Anil Chauhan, Andre Rogatko, Lydia Obertas, Andrew Goh, Mariia Kumskova, Karisma Nagarkatti |

**Agenda Items**

1. **SPAN Analysis- Stage 1** 
   1. Tentative Decision Date June 9th
2. **MRI Pipeline Validation** 
   1. MGH, Augusta and Yale have submitted TTC images as of 5/19; UTH uploaded MRI scans for validation
   2. Email TTC scans to [spancc@usc.edu](mailto:spancc@usc.edu)
   3. Upload D2 MRI scans into ‘MRI Validation D2’ visit code in IDA
      1. Inform the CC when scans have been uploaded into IDA, specify the Animal ID
   4. Histomorphometry
      1. Sites will pay for shipping brains to MGH or USC (Dr. Ayata or Dr. Lyden labs). Instructions will be sent out to sites for shipping.
3. **Automated Corner Test Scoring with DeepLabCut software—**CC working on a solution with LONI.
4. **LONI IDA Video Uploader 2.0**
   1. The new software will impact video and MRI uploads.
   2. Software may require special permission from each institution’s IT department. Information regarding the software details was sent by the CC last month.
   3. The main differences between IDA1 and IDA2 uploaders:
      1. IDA 2.0 upload process is similar to what sites have been using for video in the respect of having 2 steps - upload + finish but all steps are part of a GUI (no command line)
      2. MRI uploaded in IDA 2.0 and then downloaded will have a different directory path and file naming convention. As long as Ryan can parse the subject ID from the file name, he does not foresee any problems
      3. MRI uploaded in IDA 2.0 can only be downloaded in DICOM - no file format translations are supported. Again, Ryan downloads MRI in DICOM so no impact on him. Do other sites rely IDA1 built-in file format translation to NIfTI/Analyze format?
   4. Finish uploading MRIs for the TTC project we can start incorporating the new IDA Video Uploader
   5. No site objection to transitioning to IDA Video Uploader 2.0
5. **Stage 2 Planning**
   1. Start date 7/5/2021 if all issues can be resolved.
   2. IACUC Protocol once approved must be sent to CC
   3. MRI/Video uploads in Run-in
      1. Sites will need to alert CC (spancc@usc.edu) when video or MRI scan is uploaded into ‘Stage 2 Pilot’ visit code. Send CC the Animal ID, date of upload, model type, MCAo duration
   4. Timeline for Run-in phase
      1. AG (aged, SHR) will finish end of May. Aged performed end of April until currently
      2. IW: (OB, SHR) SHR by end of May. OB surgery Jun 24th
      3. JH: (aged, SHR) aged 28d behavior planned 6/8 SHR 28d behavior 6/30
      4. MG: (OB, SHR) planned SHR 6/2-6/14. OB model 6/23-7/12
      5. UT:(OB, aged) will perform surgery on aged mice as they become available. OB mice will be ready the end of June
      6. YL: (OB, aged) OB will be ready end of June
6. **Stage 1 Results Comments**
   1. Maintaining blinding as long as each treatment group is labeled A, B,C and CC does not reveal each sites sample sizes or mortality for each drug. One issue is infarct volumes, and potentially behavioral scores differ by site. Dr. Ayata would like to see a breakdown of treatment outcome at each site. All agreed to wait, however, for regression analysis that Marcio is working on. If the treatment x site interaction is not significant, then this is not an issue.
   2. Dr. Sansing also desires to see treatment effects broken down by site. If not it is not possible to discern anything, looking at the distribution of infarct volume across the sites it does seem that two sites have the biggest, 2 that have medium, and 2 that have smaller. Would it be possible to group sites by two if separating by site is not possible?
      1. The Concern is intersite variation could obscure treatment effect or that the stroke is too small or too large for the treatment to work.
      2. Marcio Diniz response: I did not look at the difference among treatments for each site separately because we are randomizing treatments over the sites equally that means that variability should be balanced over the treatments.
      3. Is your model incorporating site as an independent variable of the outcome? There are a number of protections in the study to avoid site level bias. First of all, randomization is stratified by site. This assures equal randomization across sites in each treatment group (except RIC that is done only at 5 sites). Stratification and randomization are the gold-standard methods to avoid site-level biase in clinical trial outcomes. Secondly, the coefficient of variation (CV) within sites and between sites is 100% which is exactly what was assumed during trial planning. Because the global trial CV is alos 100%, this assures there is no contribution of inter-site variation to trial outcomes. On the other hand, heterogeneity across sites allows SPAN to take advantage of the inter-site variance and in the end enhances generalizability of the final results. Third, Marcio is engaged in a multi-variable regression analysis of the corner test results. Site is one independent variable in that regression. If the site x treatment interaction term is not significant, then it is confirmed that site variance is not contributing to the variation in the results.
   3. If difference between the sites is very great detecting treatment effect will be difficult to detect.
      1. Dr. Rogatko: These concerns will be addressed in the regression model that will be conducted. Randomization and site stratification balances all this variation as well. See above.
   4. Suggestion to compare control and treatment within each site
   5. Dr. Lyden recommends that we look at the regression analysis. If regression shows that site is significantly interacting with treatment, then site concerns are justified.
   6. IP controls should compare to IP treatments and IV controls should be compared to IV treatments. This analysis is on the to-do list for stats.
   7. In the regression approach how are you handling missing data?
      1. Marcio Diniz: We use multiple imputation. The most naïve approach would be to replace the missing mice with the average results from that treatment at that site. We do that several times (100x,1000x) not exactly with the average, but we look at mice similar to the missing one and find a mouse with complete information and estimate the value from there. Per protocol we are only using data that was observed in mITT we are using multiple imputation. It considers volume lesion at D2.
   8. What happens if we do not have D2 MRI?
      1. For the per protocol animals for mITT we have MRI data for all the animals.
7. **Work Items**
   1. Sites to submit TTC/MRI validation Data as soon as possible
   2. CC to send out instructions for the shipping brains for histomorphometry
   3. Decision: IDA Video Uploader 2.0 will be incorporated for Stage 2
   4. Dr. Lyden to send out blinded data to PI for their consideration
   5. Steering meeting to be held the week of June 6th, doodle poll to be sent out