**Meeting Minutes**

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| Meeting: | SPAN Steering Committee Meeting |
| Date and Time: | 9/24/20 11am-12pm PST |
| Present: | Patrick Lyden, Jessica Lamb, Shuning Huang, Rakesh Patel, Anil Chauhan, Senthil Gounder, Andrew Goh, Siyue Li, MB Khan, Steve Lannon, Enrique Leira, Andreia Morais, Pradip Kamat, Kris Dhandapani, Marcio Diniz, Ligia Boisserand, Tao Qin, Dan Thedens, Jim Koenig, Basav Sanganahalli, Monica Estrada, Ali Herman, David Hess, Ray Koehler, Ryan Cabeen, Francesca Bosetti, Andre Rogatko, Jarek Aronowski, Lauren Sansing, Mariia Kumskova, Suyi Cao, Yanrong Shi, Fahmeed Hyder, Karisma Nagarkatti |

**Agenda Items**

1. **Pilot Study and Final Decisions about Stage 1**
   1. Review Site Enrollment (Jessica)
      1. 71 animals were randomized and completed surgeries. 5 females were included in the Pilot. The subjects average age was 3mths old. All surgeries were completed on right side. 61 surgeries used protocol suggested anesthesia.
      2. Yale suggestion: Minimize redundant data entry in Surgical form in REDCap.
         1. Each site to ask teams and email feedback/suggestions for fields that are not needed. REDCap cannot repopulate the form.
   2. Review Video Upload/Scores submitted
      1. Video Score Updates as of 9/23:
         1. The CC notes there have been a total of 200 uploads.CC is working with IDA to reconcile that videos uploaded into IDA match with videos uploaded into REDCap.
            1. AG= 20 uploads
            2. YL= 36 uploads
            3. UT=30 uploads
            4. MG=26 uploads
            5. IW=48 uploads
            6. JH=40 uploads
         2. 77% of the assigned videos have received scores. The CC is still waiting on 140 scores.
         3. CC states the sooner sites send in scores the quicker the CC can reduce the number of raters.
   3. Review Interim Analysis (Marcio)
      1. Pilot Study Data analyzed based on 9/18/2020 submission deadline. Not all sites will start Stage 1 on time and are asked to finish up the pilot study as quickly as possible. Once all data has been entered into REDCap, the Pilot study will end then CC will thoroughly analyze it and offer more recommendations. The CC will be finished Pilot phase analysis during Stage 1 start.
      2. Anesthesia duration:
         1. IV/IP: Significant statistics are shown for a smaller anesthesia duration for IP and asleep has a longer anesthesia duration. IV/IP results are consistent with the protocol. Data shows randomization worked. However, animals were anesthetized differently at each site. There is obvious site variation.
         2. IP/IV was randomized by the CC. Asleep/Awake decision was made by the site. Within each site the protocol was followed pretty consistently but across sites the protocol differed. JH had a different approach to awake anesthesia, notably a very brief period of awakening near the end of the occlusion period.
         3. Site Feedback: Dr. Koehler provided instructions to wake up, but Liang did not wake up very quickly, since that time JH has been doing a lot practice. Woke up at the end to do the NDS scoring and put back to sleep.
         4. CC recommends keeping the animals that receive IP injection asleep for additional 15 min. after reperfusion to equalize anesthesia duration with IV group. [Note: subsequent to this meeting, on 9/30/2020 the group voted NOT to extend anesthesia time for the IP group.]
      3. Corner Test:
         1. Missing Data: No Baseline data was provided from MGH. There were 4 mice from MGH at D7/D28 but data is matched to baseline so mice were excluded.
         2. Baseline/D7: Corner Test D7 compared to Baseline had a Pearson correlation of 0.58. Baseline/D7 are correlated.
         3. Do groups differ at corner test D7? IV asleep is different from IV awake.
         4. Baseline/D28: Corner Test D28 had no association to baseline. The Pearson correlation was 0.049. This indicates that we cannot predict D28 from Baseline turning preference. Groups differ on Day 28, there do not appear to be many differences, but this might be because the sample collected is smaller. No stroke mice were included in the analysis. In conclusion, there is no evidence yet that proves an effect of baseline turning preference on stroke outcomes.
         5. Site feedback: D28 goes back to 50% turning. Baseline significantly associated with D7 but not associated with D28. Sites would like analysis of D7 vs. D28. MGH suggested D28 correlation (subtracting the baseline change from baseline). If results are the same or identical may not need baseline. Consensus that based on this data Corner Test Baseline is needed.
         6. CC Concern: One issue is that the std. deviation across observers is not acceptable. CC to troubleshoot to run QC reports per site to identify errors.
         7. CC requests PI take ownership of Data Accuracy to try to cross check or use double entry.
         8. Sites requested to send suggestions for other analyses to be run on the pilot data set. It is important that the data analysis plan be finalized prior to running the analyses.
      4. Number of Raters:
         1. Small descriptive analysis was conducted based on 3 raters per video. A few outliers were identified and need to be Quality Controlled by the CC.
         2. Data intraclass correlation showing how much variability is within animal event shows that there is not a lot of correlation between the raters. This may be because of outliers identified in data analysis.
         3. Site feedback: Workshop videos may have impacted variability. Marcio noted that some raters may be inputting scores incorrectly in terms of data entry. For instance, the same video is scored with a rating 2L 18 R, and another rater scores 18L 2 R.
   4. Review MRI results from Interim Analysis (Lyden)
      1. MRI workflow: MRI images are uploaded into IDA, lesion volume is calculated from Ryan’s pipeline, these results are sent to the CC.
      2. Looking at the frequency distribution histogram, we note that 50% of lesions are very small.
      3. Lesion Volume by site: Iowa started early and finished surgeries before workshop. UT has not uploaded many MRI’s yet.
      4. D2 MRI: there are many “no stroke” subjects.
      5. D28 MRI: there is not a lot of data uploaded on the late timepoint
      6. Asleep vs. Awake MRI Analysis: Being asleep may have an effect on lesion volume. CC looked at anesthesia duration as a continuous variable against lesion volume. Anesthesia duration as previously discussed differs across site.
      7. CC Concern: The effect of anesthesia duration on lesion volume. Each site did not contribute the same amount of awake/asleep. 3 sites did only asleep and 3 sites did a mix of asleep/awake.
         1. MGH feedback: CC might consider comparing stroke lesion within groups.
   5. Will Stage 1 use Male, Female, or both? Sample size will not be changed.
      * 1. MG-both
        2. UT- both, maybe cage the females in the same cage. CC has ensured that randomization stratifies male female.
        3. UI- both
        4. JH: randomizing for 50% m/f
        5. **Consensus:** Males and Females will be used in Stage 1.
      1. Behavior:
         1. Will there be a Baseline Corner? Data supports that sites continue to do Baseline until proven unnecessary. Tentatively left in, don’t see it changing by 10/5/2020.
         2. Site Feedback:
            1. IW: not in favor of baseline because clinically not relevant and workload
            2. YL: if we excluded the strongly biased mice, would we lose that correlation later. We used 0.8 as the threshold.
            3. Marcio: to try analysis excluding the extreme 0,1. We only have an upper limit. We do not have a lower limit. If you throw out the .8 need to throw out the .2’s.
            4. UT: exclude animals because of some physical changes either in their brain or they had 100% preference to one direction. We should not make a statement somewhere that if your animal has an over preference, then exclude them from the story. CC to take under advisement. Would need to be a post-hoc analysis.
            5. MGH: would it be possible to do a post-hoc exclusion. If you get a severe score he would be excluded from the trial. Still in the intention to treat but excluded. CC to take under advisement.
         3. **Consensus:** Sites to conduct Baseline Corner Test pre-surgery in Stage 1. Sites will NOT exclude any animals based on turning preferences.
      2. Will there be 10 turns for Corner? Data not available yet for 10 turns. Tried to look at interim analysis to see if 1st 10 turns were sufficient.
         * 1. AG: 10 preferred
           2. JH: reason to go to 20 to improve the precision of the test. With so much variability may not need to go to 20. I was initially a proponent of the 20 turns.
           3. YL: if animal has a good deficit will only turn to the right side. If animal has a preference the animal will turn only to a specific side.
           4. CC: Prior to 10/5 we will not have an answer.
      3. Will sites be required to assess behavior using light/dark Cycle?
         * 1. Eng lo answered that both surgeries and behavior would be done during the animal’s active cycle.
           2. MGH: this would require sites to change the light/dark cycle
           3. IW: not capable of controlling that.
           4. UT: because we are going to have an equal distribution. If we are going to have an even number done for each treatment in a different cycle could be a problem.
           5. MGH: time of day would be a randomization factor.
           6. CC: Sites please ensure that your investigators are accurately recording time of surgery for post-hoc analysis. Won’t be possible to randomize on time of day currently. Time is not a binary variable it is a continuous variable, CC to ask Marcio how to randomize.
           7. Marcio: may need to control for the time in a regression model or separate the time point into dichotomous variable.
           8. YL: This would require a lot of reorganization to do light/dark cycle at yale but let’s analyze the data in stage 1 and make a decision based on data to determine whether we do this in later stages.
         1. Consensus: All sites do not have a facility to use the light/dark cycle for stage 1
         2. Rater assignment to 3 raters? Data does not support elimination to fewer raters
         3. Will 3 behavior assessments be conducted in Stage 1? Data does not support elimination of behavior assessments.
      4. Surgery
         1. Will sites do Asleep or Awake MCAo? Sites to feedback to CC. Data supports Asleep MCAo.
         2. Duration of Surgery? Sites to feedback to CC.
         3. Suture size for stage 1? Sites to feedback to CC.
2. **Stage 1 Workshop to be held 9/30 12pm-2pm PST**
   1. Experimental Stage 1 Protocol to be sent prior to Workshop
   2. Decisions to be made at Workshop
3. **Sites to send CC both TTC images and data** 
   1. Sites regardless of whether TTC or histology was conducted are requested to send pictures of hemorrhages with the data to the CC
   2. The MRI group can use these images/data to get the sequences to work to measure the hemorrhage.
4. **Update on Coordinating Center Logistics**
   1. Group email for [spancc@usc.edu](mailto:spancc@usc.edu)
   2. [plyden@usc.edu](mailto:plyden@usc.edu) -Patrick Lyden (CC PI)
   3. lambj@usc.edu – Jessica Lamb (CC Network Manager)
   4. [karisma.nagarkatti@usc.edu](mailto:karisma.nagarkatti@usc.edu) – Karisma Nagarkatti (CC Coordinator)
5. **Miscellaneous**

**Work Items**

1. Sites to feedback to CC responses to Stage 1 Variable poll
2. Sites to send suggestions for added data analysis to CC
3. PI’s to take ownership of Data Quality Checks at site
4. CC to review rater scores and provide feedback to site PI’s

**Consensus**

1. Males and Females to be used in Stage 1
2. Sites to conduct Baseline Corner Test pre-surgery in Stage 1. Sites will NOT exclude any animals based on turning preferences.
3. All sites do not have a facility to accommodate the light/dark cycle in Stage 1.

**Next Meeting date: 10/29/20 11am PST**