**Summary of External Scientific Panel/Steering Committee Meeting: April 2023**

April 6, Zoom

1. **Return of Results progress | Wendy Chung (Columbia), Margaret Harr (CHOP)** 
   1. Seven sites have started returning results with 462 GIRA generated and 329 returned.
   2. Approximately 70% of GIRAs returned are adults and about 70% of GIRAs are not at high risk.
      1. Of the high risk returns, ~60% are due to high PRS, 34% are due to family history, and ~7% are due to high monogenic results.
      2. CHD is the condition with the highest percentage of high risk returns.
   3. Sites perform a GIRA review prior to generating a GIRA report.
   4. High risk results are returned in person or by video/phone call with a genetic counselor or other study staff member.
   5. The GIRA has undergone updates since returns have started.
      1. The description and list of conditions have been moved to the table of contents so the risk assessment is seen on the summary page.
      2. The care recommendations table was reformatted to decrease white space on the page.
      3. Additional text was added to explain risk differences between PRS and BOADICEA results for breast cancer.
   6. A new subgroup was created since sites have started returns.
      1. RoR roundtables are being held every two weeks to share experiences with one another.
   7. Some lessons learned include reallocation of staff due to longer GIRA generation processes than anticipated, confusion with completing MeTree, and difficulty with obesity counseling in adults.
   8. A healthcare provider survey has been developed to analyze provider feedback on returning GIRA and will be submitted for IRB approval in the future.
2. **Outcomes phenotypes & planned data analysis | Dave Veenstra (UW)** 
   1. The interim data freeze is planned for late spring/early summer 2023.
   2. The six-month follow up survey will not be included in the interim analysis. This interim analysis will focus on quality control and processes.
   3. The data pull will include the CPT and ICD codes in full.
   4. More information is needed on which medications and which labs will be included.
   5. Another issue discussed was how far back the data pull should go, the network is proposing 5 years prior to return for medications and lab results.
   6. For primary overall analysis, comparison of what happens to high risk people from RoR going forward. The analysis will be comparing them to the not high risk people going forward.
   7. Some work has been done to develop data dictionaries on specific phenotypes in order to analyze outcome data specifically for conditions.
   8. The data dictionaries include inputs from the EHR and from patient surveys to be as complete as possible.
   9. The data freeze will be important to confirm that variables are consistent across sites.
   10. A plan for an interim analysis of 6-month post-RoR participant surveys needs to be developed.
   11. Regarding site variation, the Network have had discussions on how to pull the most consistent data possible for data analysis.
3. **Questions/discussion | Rex Chisholm (NU)**
   1. A question was asked on how to address collecting data generated outside of the institution.
      1. An example of someone getting a breast MRI at a private institution and not at the site was given.
      2. A specific set of rules on how to handle a situation like this need to be developed.
   2. A follow-up question was asked if the physician orders or referrals are captured in a data pull.
      1. The raw data base may have this information but not currently known for sure at this time.
   3. An update to the overall timeline was provided.
      1. All sites are currently recruiting with about half of the sites now returning results.
      2. There has been a strong emphasis on completing recruitment by June 2024.
      3. Sites should see an improvement in time it takes to return as more are done.
   4. The biggest challenge to meeting targets in the timeline include getting all sites returning results.
      1. Another big challenge identified is ensuring all sites recruit 2500 participants each.
   5. The topic of allowing sites that reach their recruitment goal to continue recruitment to help reach the overall target of 25,000 was discussed.
      1. This has been discussed at Leadership meetings but a solution hasn’t been reached yet.
      2. Moving money from site to site to allow for extra recruitment is a hurdle.
      3. Sequencing costs at Invitae is also an issue.
   6. The ESP is in favor of extending time to collect additional outcome data but not as enthusiastic to extend time for recruitment and return.
4. **Input and feedback from the ESP**
   1. The ESP reiterates how impressed they are with the work that has been done up to this point.
   2. The ESP is also happy to see recruitment and returns rates ticking up.
   3. They would like to see some degree of continuous quality improvement to continue.
      1. Sharing lessons learned and best practices across sites, especially around recruitment, is important.
   4. Time was spent talking about the issue of meeting groups' goals of recruitment within the study timeframe.
   5. The ESP feels like that overall number is pretty important based on power calculations that were done prior to starting.
   6. The ESP encouraged the Network to consider allowing sites to continue recruitment beyond 2500 participants in order to reach the overall goal of 25,000.
      1. This topic does not anticipate the need to over-enroll adults at the expense of pediatrics.
   7. The ESP is very supportive of extending the timeline on the backend to support collection of outcome data.
   8. A question was asked on what steps are being taken to mitigate the issues with completing MeTree and baseline survey completion.
      1. Some sites have been directly helping participants complete these surveys while others are monitoring the data after MeTree is completed for completeness/accuracy and fixing obvious errors.
5. **Official ESP Recommendations**

Meeting Summary

eMERGE Network- External Scientific Panel and Steering Committee

*Executive Session – 09/29/2022*

|  |  |  |  |
| --- | --- | --- | --- |
| **ESP** | **Dan Rader,** University of Pennsylvania**– Chair**  **Kimberly Doheny,**Johns Hopkins University  **Stanley Huff**, Intermountain Healthcare\*  **Janina Jeff**, Illumina†  **Brendan Lee**, Baylor College of Medicine  **Lisa Parker**, University of Pittsburgh  **John Witte**, Stanford University | **NHGRI** | **Teri Manolio**  **Jahnavi Narula**  **Rene Sterling** |

The External Scientific Panel (ESP) met with NHGRI program staff during the executive session of the eMERGE ESP Teleconference held on April 6, 2023. The ESP was very impressed with how much the Network has accomplished, especially given the complexity of the project, and noted that “new ground has been broken.” The ESP provided observations and recommendations about several aspects of the research to help move efforts forward. Initial feedback is elaborated upon in the summary below.

**The Network should track the rate of recruitment and create clear targets for each site.**

The ESP was concerned with potential issues related to recruitment. They recommended that the Network evaluate current recruitment numbers and variations by site to help determine what adjustments might be needed. They noted that the Network might need well-performing sites to over enroll to reach recruitment goals. The ESP encouraged the Network to perform this analysis soon to help manage expectations of all the sites (for example, with staffing and funding). The ESP also recommended doing monthly assessments of recruitment with clear targets for each site to help identify any issues as early as possible so that adjustments can be made. The ESP requested that these site-specific recruitment numbers and goals be shared with them.

**The Network should investigate the advantages and disadvantages of modifying the GIRA.**

The ESP noted that the Network should avoid making any changes to the GIRA after results have been returned. The ESP did not recommend ruling out the possibility of modifying the GIRA due to future major changes in PRS, but also did not recommend building it in the study at this stage. Given that reanalysis of returned GIRAs would likely happen only if there was a significant development in relevant PRS, the Network could consider defining what would constitute a significant change. They noted that a significant change to PRS would be more likely to happen if the study were extended further. The Network should also continue to include family history as part of the GIRA since this is a key component.

**The Network should investigate the reasons why participants may be passively withdrawing.**

The ESP recommended that the Network look into the reason some participants appear to be uninvolved to ensure that the study is not missing certain populations. They also noted that including participants with incomplete data has the potential to compromise the outcomes of the study if there is significant withdrawal. The current retention number is 86%, with 14% of participants missing data. ESP felt that this rate of missing data was slightly high and noted that the Network may need to recruit additional participants to compensate for it.

ESP Recommendations for the Network:

1. The Network should evaluate current recruitment numbers to help set clear targets and avoid surprises. ESP recommends that this analysis be done as soon as possible. Once this is completed, the Network should establish site-specific recruitment goals The ESP would like an update on recruitment in July.
2. If there are changes to be made in the GIRA, they should be made prior to return. Additionally, the Network should consider establishing a threshold for what constitutes a significant development in PRS and whether such development would prompt reanalysis.
3. The Network should investigate the reasons participants may be passively withdrawing from the study and consider additional recruitment to reduce the percentage of participants with missing data.