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14. ABSTRACT

The Statistical Core works mainly with PIs in the Clinical Working Group and the contracted data management service, Silverwind Research, Inc. to plan and manage data collection for the Integrated Clinical Protocol (Specific Aims 2 and 3.1). We are also available to consult on statistics and design issues for any of the PIs and the Steering Committee. In Year 3, the focus has been on transitioning from paper CRFs to our automated data entry system, with data collected "real-time" on secure study lap-top computers, as well as getting the backlog of paper CRFs entered into the system. In addition, we are also prepared to do data analyses where they might be required for
publications based on initial data collections.

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Introduction

As statistician for Specific Aims 2 and 3.1, the Statistical Core has worked mainly with PIs in the Clinical Working Group and the contracted data management service, Silverwind Research, Inc. to plan and manage data collection for the Integrated Clinical Protocol. We are also available to consult on statistics and design issues for any of the PIs and the Steering Committee. The purpose of the Statistical Core is to assist the Clinical Working Group Investigators in matters of design, data collection, data management, and to provide, as requested, statistical analyses. In addition, we will aid in the dissemination of results, including but not limited to preparation of manuscripts and presentations. During the first year of the project we were involved in advising PIs on issues of design and data collection, assistance in setting up data bases and developing programs to aid in data cleaning. During year 2 we continued advising PIs on these issues and assisted in setting up the electronic data bases where study data will be stored. In this third Year, the focus has been on transitioning from paper CRFs to our automated data entry system, with data collected "real-time" on secure study lap-top computers. In addition, we are also prepared to do data analyses where they might be required for publications based on initial data collections. However, most of the data analyses will take place in the final year when all relevant data has been collected.

Body of the Report

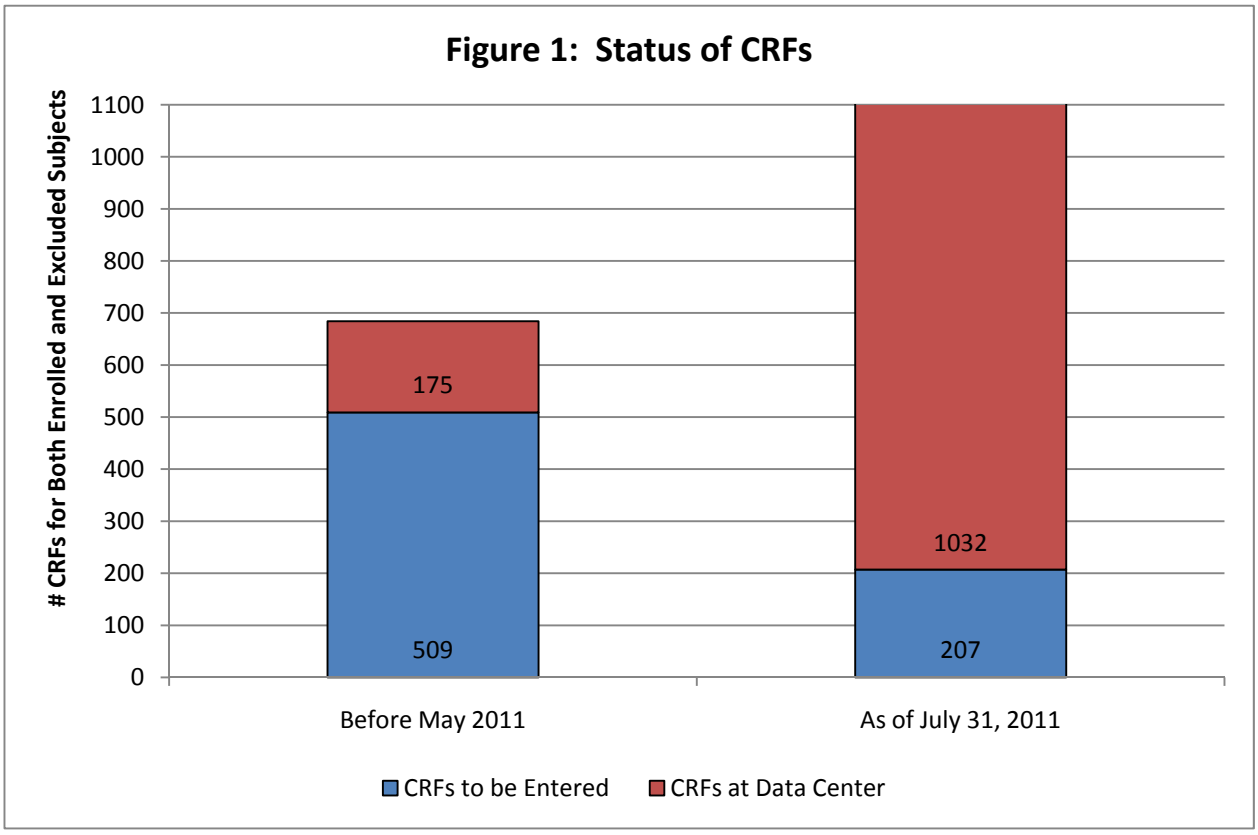
The Consortium has compiled four clinical projects into the Integrated Clinical Protocol. These projects are: Specific Aims 2.1 (PI Levin), 2.2 (PI Papanicalaou), 2.3 (PI Masel), and 3.1 (PI Robertson. The Integrated Clinical Protocol (ICP) consists of three observational studies (Specific Aims 2.1, 2.2, and 2.3) and one Phase II randomized clinical trial (Specific Aim 3.1) that will use a shared group of subjects. A full discussion of the screening and enrollment activity for the Integrated Clinical Protocol (ICP) is presented in Dr. Harvey Levin's report.

In this report, the role and contributions of the Statistical Core to the ICP will be presented. While enrollment has begun and some data has been collected, the electronic data entry system is as yet incomplete so that no data has been entered. We have been working closely with our contracted data management service, Silverwind Research. Progress toward our goal of an electronic data entry system includes:

- Creation of electronic visit documents for the CRFs for:
    - 26 neuropsychological tests (See Dr. Levin's report, Neuropsychological Core section for a complete list)
    - 11 visit-related CRFs – Visit CRFs include all of the subject and operational data required for that visit, as well as all of the neuropsychological tests to be performed. In the electronic CRF, the tests are presented in a predetermined order and alert the Research Coordinators when to administer delayed memory recall measures thereby minimizing data loss. The CRFs have been carefully designed to minimize data entry errors with range checks and other similar features. Please see Dr. Levin's report for a full discussion of the neuropsychological testing procedures and data collection. The visit-related CRFs include:
        - Screening

        - Baseline Visit
        - Baseline Visit studies (EEG, MRI)
        - Day 3-4 Phone Call
        - 1 Week Visit
        - Day 19-20 Phone Call
        - 1 Month Visit
        - 3 Month Visit
        - 3 Month Visit studies (EEG, MRI, MEG)
        - 6 Month Visit
    - 3 study findings CRFs – These CRFs provide a mechanism for investigators to add their specific findings and analyses of procedures to the study database.
        - The MRI Findings electronic CRF document has been reviewed by the Clinical Working Group, led by Dr. Lisa Wilde, for content to ensure that all data points that need to be captured have been included in the CRF.
        - The EEG findings are captured using an existing computer-based quantitative EEG analysis program developed at Baylor College of Medicine (J.D. Frost, Jr, M.D.) which takes raw EEG data obtained from recordings made at the Neurophysiology Laboratories of Memorial Hermann Hospital. The procedures for uploading Dr. Frost's Excel spreadsheet analysis for each subject into the Consortium Research Database have been completed and tested satisfactorily. The upload process for subjects enrolled to date is underway and will be completed in the near future.
        - The MEG CRF has been designed and reviewed by Dr. Papanicolaou, and it will be completed after the MRI Findings CRF is completed.
    - 3 non-visit related CRFs
        - Study Completion
        - AE/SAE Documentation
        - Protocol Deviation/Violation
    - To date, all electronic CRFs have been completed except:
        - The 6 Month Visit electronic document is still in User Acceptance Testing (UAT). We anticipate that it will be ready for use in the near future.
        - The MEG Findings CRF is in the final stages of review and approval by the investigator.
- The Research Team made the transition in May 2011 from paper CRFs to their automated versions, with the exception of the 6 Month Visit CRF, which is currently in final user testing.
    - Since May, 2011, all CRFs, except the 6 Month Visit and the Study Findings CRFs, are now completed by Research Team members "real-time" on secure study lap-top computers.
    - We have been collecting data on paper CRFs since the start of subject enrollment in February, 2010. This resulted in a large backlog of forms that must be entered into the automated system.
        - Since May, 2011, the Research Team has been working to get the backlog of paper CRFs entered into the automated system. In addition, CRFs for all new enrollments and follow-up visits have been done directly into the automated CRFs.

- Before the transition to the automated CRFs in May, 684 CRFs were created. We had entered and submitted 175 (25%) of these to the data center, in the process of testing the system, with 509 still in paper form (74%). As of July 31, 2011, 1032 CRFs (83%) have been entered and submitted to the data center, with 207 (17%) remaining to be done.



- Silverwind is finalizing the design of the Analysis database for SQL Server. The Analysis database will contain only the latest version of any completed electronic form. The table formats in this database have been optimized for Biostatistical analysis.
  - A detailed review of field names, field contents, table structures, and data storage plans has been submitted by Silverwind and reviewed by Dr. Swank, Dr. Miller, and Dr. McCauley.
  - Currently Silverwind is building the database and transfer routines from the Clinical database (where the electronic forms data is originally imported into) into the Analysis database on the Microsoft SQL platform. This work is approximately 40% completed and will be finished and validated by late October.
  - Once approved, Silverwind will begin live use of this database. This is the database that will be the source of datasets provided to Investigators.
- The study's website continues to be used as a source of collaboration and sharing of information.
  - The Research Team is maintaining the screening logs, tracking of subject follow-up visits and regulatory binder on a daily basis. Recently the tracking of the study's

equipment was added to the clinical operations.

- All Investigator Reports and Meeting Minutes are also available on the website. When the presentation materials from the March 4 retreat were posted on the site, there was a significant increase in Investigator use of the site, and this has continued since that time.

For Specific Aim 3.1, the clinical trial of atorvastatin in the MTIB subjects, we prepared a randomization scheme and are working closely with the Memorial Hermann Hospital Research Pharmacy and Silverwind Research. On-going monitoring of this process indicates that the correct procedures are being followed.

In addition, we have continued to work with Dr. Levin's team to establish a mechanism by which reliability of the data collected as part of the clinical protocol and have evaluated several measures for inter-rater reliability. Please see the section on Research Staff Organization and Training in Dr. Levin's report for a description of this process and the on-going monitoring procedures.

Key Research Accomplishments

- We continue to collaborate on revisions of the clinical protocol and to the Human Subjects applications and amendments, through regular participation in the Clinical Working Group meetings and through frequent consultation with various investigators and the Study Coordinator, Dr. Emmy Miller.
- The transition from paper to electronic CRFs is almost complete, with only 17% of paper CRFs remaining to be entered and submitted to the data center.
- Development of the Analysis database is well underway, and the necessary procedures to populate it with data from the electronic CRFs currently stored in the Clinical database are in place to accomplish this once completed.
- Procedures are in place for establishment and maintenance of inter-rater reliability for the measures of the clinical studies, working closely with Dr. Stephen McCauley, the Outcome Monitor of the Neuropsychological Core. The current IRR is 95%.
- The subject randomization procedure for Specific Aim 3.1 is working well operationally and procedures are being followed correctly.

Reportable Outcomes

As subject enrollment is still underway, there have not been any analyses of data for publications or external presentations to date, with the exception of Dr. Levin's presentation of a preliminary review of the ANAM data in August 2011. We anticipate that as the number of enrolled subjects increases, the interest in and need for preliminary analyses of data from the observational studies will occur.

Conclusions

In the absence of sufficient data for analysis being collected as yet, we have been involved primarily in data management procedures, with the focus in Year 3 on the transition from paper to electronic CRFs and entry of the backlog of paper forms. This process has been tedious and time-consuming,

but the data-entry of the backlog of paper forms is almost finished, the preparations for the Analysis database are moving forward smoothly, and we anticipate a robust and comprehensive data set for analysis as we move into that stage of the project.

References

None

Appendices

None