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**Developing Treatment, Treatment Validation, and Treatment Scope in the Setting of an Autism Clinical Trial**

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| <b>13. SUPPLEMENTARY NOTES</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                         |                                 |                                             |                                                     |                                                   |
| <b>14. ABSTRACT</b><br>We submitted and received approval for our latest Continuing Review (CR). In addition a restructuring of this project was done along with related changes to the protocol to help increase the rate of subject recruitment including an amendment to our protocol to allow recruitment from AutismMatch. A second, 6-month no cost extension was applied for and approved to maximize subject recruitment. We attended the annual conference of Autism NJ. This conference is the largest of its kind in the state. We had a booth to distribute our recruitment materials and Dr's. Ming and Wasiulla and Mr. Stenroos attended the conference with the goal of informing autism families, doctors, representatives of autism schools and autism centers/departments of hospitals as well as researchers of our study and making contact with potential recruitment sources. We addressed an unforeseen problem with scheduling sample collections and baseline testing with our internal lab. We continue to treat and evaluate enrolled subjects (tasks 3-7). We convened our DSMB board in November of 2011 and received approval to continue. We are preparing for our next DSMB meeting. We continue to search for additional funding and to continue to refine and increase our recruitment tools and sources to achieve our goal. We continue to look for additional funding to extend this project and to maximize enrollment. Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729. |                         |                                 |                                             |                                                     |                                                   |
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**Introduction:**

This project is to test to see if DHA treatment can beneficially affect excretion of urinary biomarkers of oxidative stress and the autism clinical phenotype. In addition polymorphic variants of genes of certain enzymes that synthesize and metabolize docosahexaenoic acid (DHA) may contribute to the phenotype of some autism cases. We will test to see if any of these genes are risk factors for autism. We will also measure changes in excretion of the polyunsaturated fatty acid (PUFA) derived biomarkers of oxidative stress (isoprostanes and neuroprostanes) together with the changes in production of anti-inflammatory lipid mediators. We will test these biomarkers to see if we can monitor and validate effectiveness of DHA therapy. We will also test the genotypes of key DHA-metabolizing enzymes can predict which patients will respond to therapy.

Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729.

**Body:****Project 1: PI Sherie Novotny, MD, Partnering PI, W81XWH-08-1-0730**

Please see initiating project W81XWH-08-1-0728 and partnering project W81XWH-08-1-0729.

**Task 1 Full board review with pending IRB approval prior to beginning (4-6 months, S. Novotny).**

Our latest Continuing Review was approved on September 27<sup>th</sup> 2012. An amendment was submitted along with this continuing review to remove Rakhee Wasiulla from the study who has left the university. Also in the amendment was an extension of the end date of the study. These changes were also approved by our (Institutional Review Board) IRB on September 27<sup>th</sup> 2012. The approved CR was sent to the HRPO on October 4<sup>th</sup> 2012. Please also see partnering project W81XWH-08-1-0728 Tasks #1 and #2.

Additional amendments in the past year:

We submitted an amendment on January 18<sup>th</sup> 2012 to allow us to recruit from AutismMatch. Included in this amendment were a new consent, a new flier and an updated protocol. This amendment was approval on February 29<sup>th</sup> 2012.

**Task 2 Volunteers recruited from local clinics, support groups and advocacy groups (6-30 months).Forty four child or adolescent outpatients per year with age ranges from 5-17, for three years totaling 132 patients, will be randomized into the 12-week double-blind, placebo-controlled parallel treatment study.**

**Subject Recruitment:**

We applied for and received an additional 6 month no cost extension to maximize our ability to collect subjects.

We attended the annual conference of Autism NJ. This conference is the largest of its kind in the state. It is a large and valuable tool and is attended by families of individuals with autism, doctors, and representatives of autism schools and autism centers/departments of hospitals as well as researchers.

We had a booth to distribute our recruitment materials and Dr's. Ming and Wasiulla and Mr. Stenroos attended the conference with the goal of informing autism families, doctors, representatives of autism schools and autism centers/departments of hospitals as well as researchers of our study and making contact with potential recruitment sources.

An unforeseen problem was scheduling sample collections and baseline testing with our internal lab in Newark. It was decided to help Dr. Ming an account was to be set up with Quest Diagnostics for sample baseline testing. We began the application process with Quest in October. The account was finalized and activated on December 27<sup>th</sup> 2011.

The annual Data and Safety Monitoring Board (DSMB ) comprised of Dr's Wei-Ting Hwang of UPenn, Kapila Seshadri of UMDNJ-RWJ and Bart Kamen of UMDNJ-RWJMS, met in November of 2011. We were notified on November 18<sup>th</sup> 2011 of their approval to continue the study. We began the process of preparing for their next meeting when we learned that unfortunately Dr. Kamen died. We started the process to find an appropriate replacement and we recently found one. We are in the process of submitting a modification to our IRB to make this change. Once this is done we will send out report to the members of our DSMB for review.

We have continually updated and improved our recruitment techniques and tools (please see Task #1 for specific protocol changes).

We sent out 50 letters to subjects of Dr. Lambert's previous studies that expressed interest in future studies.

In our follow ups from the Autism NJ conference we began speaking with autismMatch of the Children's Hospital of Philadelphia. (CHOP). They informed us that they had about 40 families in our region that had already been tested with ADOS and ADI that expressed interest in joining studies like ours. We submitted an amendment to our IRB on January 17<sup>th</sup> 2012. We received approval on February 29<sup>th</sup> 2012. We applied to autismMatch and were approved on March 6<sup>th</sup> 2012. autismMatch began notifying their families on March 7<sup>th</sup> 2012.

The IRB protocol has been amended to allow the use of AutismMatch for recruitment and to remove Dr. Waiulla from the study (see Task #1)...

In addition we audited subjects that contacted us about our study but were not enrolled. We found that 34 families were lost to follow up at some stage for reasons including incorrect contact information, schedule issues travel issues. We began contacting these families and have so far been able to speak with 6 families. Of these 4 are interested in the study and have been scheduled to start with either Dr. Novotny or Ming. Of the other two one is no longer interested and the other is not eligible. We will continue trying to speak with the other 28. Since these families contacted us due to interest in our study we expect to be able to recruit a good number of them.

We were very optimistic about recruiting from Children's Specialized Hospital but so far this has not been fruitful. We have recruited no subjects from them to date. To address this Dr. Johnson met with their Autism Director and autism pediatric neurologists on several occasions to come to an agreement about recruiting their subjects. No progress has been made at this time.

As per our IRB we began sending Genetic Information Nondiscrimination Act (Gina) letters to our subjects that were consented before our last Continuing Review when GINA language was added.

We are continuing to go through our list of subjects that expressed an interest but are not as of yet entered into the study.

We continued to look for new recruitment sources.

### ***Task 3 Informed consent/assent obtained (6-51 months).***

This task has begun and will continue until recruitment is closed. To date we have consented 34 subjects and assented 2.

***Task 4 Full diagnostic assessment with Autism Diagnostic Interview-revised (ADI-R), Autism Diagnostic Observation Scale (ADOS), Vineland Adaptive behavior scale and Leiter Intelligence Scale (E Roberts); DSM IV criteria (S. Novotny) for eligibility & diagnosis. Parents will complete baseline Aberrant Behavior Checklist; study psychiatrist will complete Clinical Global Improvement, baseline Severity Scale (6-30 months, 21-51 months in the current SOW).***

This task has begun and will continue until recruitment is closed. To date 32 subjects have undergone ADOS, ADI, Vineland and Leiter,

***Task 5 Cases undergo full medical evaluation to determine health; at this visit will have phlebotomy including 10 mls for blood chemistry, PT/PTT, hematology, 10 ml for genotyping (Project III), urine for pregnancy test, drug screen as indicated, routine urinalysis; urine collected for Project II.***

This task has begun and will continue until recruitment is closed. To date 27 subjects have undergone full medical evaluation and had phlebotomy.

**Task 6 Cases randomized to receive either DHA, 200mg daily, or placebo. Cases given DHA after physical exam and routine lab-work completed.**

This task has begun and will continue until recruitment is closed. To date 26 subjects have been randomized and received either DHA, 200mg daily, or placebo 4 of which have dropped out.

**Task 7 Cases seen weekly for four weeks and biweekly for the remaining 8 weeks. Aberrant Behavior Checklist done every 4 weeks and at termination and Clinical Global Improvement Scale done every 2 weeks and at termination.**

This task has begun and will continue until recruitment is closed. To date, 18 subjects have completed the study, so ABC's and CGI's were completed by those 18 and the 4 currently undergoing treatment who are being administered these tests bi weekly for a total of 22.

**Task 8 Cases complete the study with repeat ADOS, Vineland Adaptive Behavior Scale (E Roberts) and Aberrant Behavior checklist (parent) and Clinical Global Improvement Scale (S Novotny). Blood work for safety measures; urine will be collected for Project II during last week of DHA or placebo.**

This task has begun and will continue until recruitment is closed. To date, 18 subjects have completed the study and therefore this task.

**Task 9 Data will be collected and analyzed (6-36 months, 04 year as per the current SOW S Buyske).**

This task has not begun yet. This will start once when analysis of samples is completed.

**Task 10 Manuscripts prepared and submitted for publication (03 year, 04 year as per the current SOW all investigators)**

This task is to be done when the analysis of the data is completed.

### **Key Research Accomplishments**

There are no Key Research Accomplishments yet.

### **Reportable Outcomes:**

Dr. Novotny gave a presentation titled "Alternative Treatments in Autism" at the Autism NJ conference. She spoke of the use of Omega-3 fatty acids in autism.

**Conclusion:**

A large amount of time was spent on getting IRB approval for this project. We are now working on making up the lost time. We continue to adjust our recruitment including an amendment to our protocol to allow recruitment from AutismMatch. A second, 6-month no cost extension was applied for and approved to maximize subject recruitment. We continue to treat and evaluate enrolled subjects (tasks 3-7). We convened our DSMB board in November of 2011 and received approval to continue. We are preparing for our next DSMB meeting. We continue to search for additional funding and to continue to refine and increase our recruitment tools and sources to achieve our goal.

**References: None.**

**Appendices: None.**