

reassure the child that he/she is not expected to answer all the questions and it is only expected that he/she try his/her best on the task. All test administrators will have psychological training and experience with interacting and assessing children. If for some reason the child states that he/she does not want to continue, the assessment will cease. We will then consult with the parent and child to ascertain whether the testing will continue.

There are an estimated six partial or whole days that a child could miss school while participating in this trial. We will recommend to the parent (parents, legal guardians) that he/she should discuss school policies for excused absences and make necessary arrangements for make-up work.

## 7.0 Statistics

**Determination of sample size:** No data exist on the effects of Lovastatin in children with NF1. A clinical and meaningful difference for primary efficacy measures is defined as an effect size of one half of a standard deviation, which is classified as a treatment effect of medium magnitude (Cohen, 1988). A sample size of 64 participants per treatment group (128 total) will be sufficient to detect an effect size of half a standard deviation at the two-sided 0.05 significance level with power of 0.80 (Peat, Mellis, Williams & Xuan, 2001). To allow for a 10% dropout rate prior to the 16-week point, a total of 142 participants will be enrolled.

**Interim analyses:** Interim analyses will be done under the purview of the DSMB, which will set the content and frequency of analyses. We will propose a Charter containing a data monitoring plan that will include stopping guidelines. We expect these to be the Lan DeMets modifications of the O'Brien Fleming boundaries (Lan & DeMets, 1983; O'Brien & Fleming, 1979)). It is expected that the DSMB will review this charter during its first meeting.

**Data analysis:** Demographic and baseline characteristics will be summarized for each group using descriptive statistics. Intention-to-treat analyses will be conducted for the primary outcomes measures. An intention-to-treat analysis provides an unbiased, conservative and consistent estimate of a treatment effect (Heritier, Gebiski & Keech, 2003).

Analyzing change scores from baseline to post-treatment does not control for baseline imbalance because of the regression to the mean (Vickers & Altman, 2001). Also, with changes scores, if the treatment is effective, the statistical significance of the treatment effect will depend upon the correlation between baseline and follow-up scores. Therefore, to determine whether there has been a significant change from baseline to post-treatment, primary and secondary outcomes will be analyzed using ANCOVA, which is a better approach than analyzing change scores with independent t-tests (Vickers & Altman, 2001).

In addition, at an individual case level to determine whether test-retest change scores from baseline to post-treatment are reliable and clinically meaningful, standardized regression based

change scores (RBC) will be also be calculated. RBC can account for measurement error, differential practice effects and regression to the mean (Sherman et al., 2003). However, RBC scores do not necessarily indicate whether a significant change from baseline has occurred (Sherman et al., 2003). Similar statistical analysis will be conducted for scores from post-treatment to follow-up. Linear mixed models may also be conducted to examine changes over time. In addition, a number of sub-group analyses are planned to help identify individuals more likely to benefit from, or be harmed by, the treatment. In regard to treatment effects, definition of subgroups will rely on baseline data, not data measured after randomization. Such subgroups might include age (including comparison of 8-9 years to 10 years and older), gender, and presence of ADHD (on or off stimulant medication) (if there are sufficient cases). Exploratory data derived through subgroup analyses will serve primarily to generate new hypothesis for subsequent studies.

## **8.0 Data Management**

Data sets will follow all standards as per Data Coordinating Center's guidelines and recommendations. All paper charts, forms, and information associated with this study will be kept in a locked cabinet at the clinical sites. Access to this cabinet is available only to investigators on the study and research assistants. All participant information from this study will be strictly confidential. On entry to the study, participants will be assigned a unique PIN that will be used throughout the study. All data stored in computer systems will be password protected and stored using participant PINs only (see next section for more information regarding database security). Participant names will not be used in any computer databases associated with this project. A list of participant names and coordinating PINs will be kept separately on the password-protected principal investigator's computer. This information will be kept in accordance with the requirements of the Department of Defense.

### **8.1 Medical Monitor and Data Safety Monitoring Plan**

The Data Safety and Monitoring Plan for this study will follow the NIH guidelines. The External Advisory Board (EAB) will serve as external reviewers and advisors to DoD and the Governing Body. The EAB will review and approve the protocol with respect to ethical and safety standards. Its primary responsibility will be to monitor the emerging results of the trial to assess treatment representatives are *ex officio* members of the EAB. The EAB will determine the content and frequency of safety reports it will review and will periodically review interim analyses of data collected for this study.

In addition, the DSMB will protect the integrity of the study by ensuring that recruitment targets can be met within the study timelines. This will be achieved by comparing actual recruitment against planned and by monitoring participant drop-out rates. In the event that the number of accrued patients is less than 20% of the planned value, the DSMB will advise on appropriate remedial action. Possible remedial actions may include, but are not limited to, the extension of the recruitment period, review and amendment of inclusion criteria.

Dr. Tena Rosser will be the medical monitor for this study. She is a qualified physician and is not associated with this protocol. She will work closely with the Principal Investigator to monitor the participants' treatment while on this study. The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject related deaths associated with the protocol, providing an unbiased written report of the event. At minimum, the medical monitor should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor should also indicate whether she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or the medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the USAMRMC ORP HRPO.

It is expected that summaries of accrual, retention, and adverse events will be disseminated to the clinical centers periodically. To maintain the blind, adverse events will be aggregated across treatment arms.

## 8.2 Confidentiality

Data will be obtained and stored consistent with IRB and HIPAA guidelines. All participant charts, standardized study forms, and information associated with this study will be kept in a locked cabinet in the principal investigator's office. Access to this cabinet is available only to the principal investigator and the research team. All participant information from this study will be strictly confidential. On entry to the study, participants will be assigned a unique participant PIN that will be used throughout the study. All data stored in computer systems will be password protected and stored using PINS only. Participant names will not be used in any computer databases associated with this project. A list of participant names and coordinating PINs will be kept separately on the password protected principal investigator's computer. This information will be kept in accordance with the requirements of the Department of Defense.

## 9.0 Ethical and Regulatory Consideration

### 9.1 Consent/Assent/HIPAA Process and Documentation

The investigational nature and objectives of the study, procedures involved, treatments involved, medication side effects, risks, benefits and alternative therapies will be carefully explained to potential participants and their parents/legal guardians. Potential participants will be allowed to take their time in deciding whether to join the trial and will be given privacy to make their decision. They will also be encouraged to discuss their concerns or questions about joining the trial with their parents/guardian. Consent will be obtained from parents/legal guardians and assent will be obtained from children aged 8 years to less than 16 years, with signatures obtained as appropriate. This trial will be conducted in compliance with the Good Clinical Practice guidelines and the applicable regulatory requirements.