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PROTOCOL TITLE: NAtalizumab for Prevention of Post-partum Relapses in patients with Multiple Sclerosis (NAPPREMS)

INSTRUCTIONS: Complete Research Protocol (HRP-503)

- *Depending on the nature of what you are doing, some sections may not be applicable to your research. If so, you must provide the reason why the section is not applicable for the response. For example, most behavioral studies would answer all questions in section 30 with words to the effect of "drugs and medical devices are not used in this study."*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
- *Do not remove the italics instructions or headings.*
- *If you are pasting information from other documents be sure to use the "Merge Formatting" paste option so that the formatting of the response boxes is not lost. If information is presented outside of the response boxes, it will not be accepted.*
- *If this study involves multiple participant groups who participate in different research procedures, consent processes, etc., be certain to provide information in each applicable section for each participant group and clearly label each participant group within a section or subsection.*

PROTOCOL TITLE:

Include the full protocol title.

Response:

NAtalizumab for Prevention of Post-partum Relapses in patients with Multiple Sclerosis (NAPPREMS)

PRINCIPAL INVESTIGATOR:

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Response:

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VERSION NUMBER:

Include the version number of this protocol.

Response:

Version 5

DATE:

Include the date of submission or revision.

Response:

05/15/2019

Grant Applicability:

Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.

Response:

Study specific procedures (Physical and neurological examinations, completion of QOL questionnaires) are covered by the grant. Subjects may receive medication that is standard of care. Treatment related testing (that related to medication) required during the study is standard of care.

Table of Contents

1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

Response:

The primary objective of the trial is to assess the efficacy of IV administered natalizumab, monthly for 1 year, in preventing relapses during the postpartum period.

The secondary objectives of the trial are to assess the efficacy of natalizumab in decreasing the risk for disability progression during the postpartum period and to prevent the appearance of new and/or enlarging brain MRI lesions as measured by qualitative MRI analysis.

The tertiary objective is to assess the association of the clinical outcomes with subject evaluations including patient reported outcomes (QOL, satisfaction).

1.2 State the hypotheses to be tested.

Response:

Natalizumab therapy instituted shortly after delivery will decrease the risk of relapses and /or MRI activity in the immediate postpartum period.

2.0 Background

2.1 Describe the relevant prior experience and gaps in current knowledge.

Response:

Multiple sclerosis (MS) has a higher prevalence in women than men and recent literature suggests that the gender gap is widening .[1] As the disease onset of MS is most likely to occur during child-bearing years, concerns about pregnancy and child rearing are frequently observed among MS patients. Even though there are no negative short-term effects of pregnancy on MS disease outcomes, and studies indicate there might even be beneficial long-term effects,[2,3] a short rebound of disease activity is frequently observed after pregnancy. Recent studies have shown that relapse frequency during pregnancy decreased during the first three trimesters, after which a sharp increase can be observed three months postpartum.[4] While not all women experience a rebound in relapse rates, there are indications that an increased relapse rate in the year prior to pregnancy, an increased relapse rate during pregnancy, and a higher Kurtzke's Disability Status Scale at pregnancy onset are important indicators of an increased likelihood of postpartum exacerbations.[5] Other results indicate that there are no effects

of epidural analgesia or breastfeeding on the risk of having postpartum relapses.[6]

Several methods have been tried in order to prevent a rebound of relapses, which included treatment with IV steroids intravenous immunoglobulin (IVIg),[7-9] sex hormones,[10] and breast feeding.[11] While some have been found to be beneficial in reducing the frequencies of relapses, none have been able to work consistently in preventing it. Studies investigating the therapeutic effect of IVIg on postpartum relapses have looked at both (re)starting treatment during the postpartum period, as well as continuing medication use throughout the pregnancy and postpartum period. Women who were treated throughout their pregnancy, and those who were treated postpartum showed significantly fewer relapses compared to women who did not receive treatment.[12] While the effects of breastfeeding seemed notable when studies were first published, more recent literature suggests little to no benefit.[13,14] Most recent data available from a retrospective assessment querying MSBase registry, a recent database including 24 months pre-conception and 2 years post- delivery information obtained from 674 females with 893 pregnancies identified a raise in in ARR from 0.32 pre-pregnancy level to 0.13 during the third trimester and 0.61 in the first 3 months-postpartum.[15] Pre-conception ARR and disease modifying therapy predicted early post-partum relapses. Interestingly pre-conception DMT use and low ARR were shown to be independently protective against postpartum relapses.

Natalizumab has been found to be very successful in minimizing MS disease activity. No increase in negative birth outcomes after natalizumab exposure was found during pregnancy, and a trend towards a reduced number of relapses in women treated with natalizumab compared to women who were DMT naive was reported.[16] While none of the above mentioned studies had patients that were treated with natalizumab during the whole gestational period, a recent case report showed no negative birth outcomes in a patient that was treated throughout her pregnancy with no signs of disease activity postpartum. [17]

It is generally advised to avoid exposure if possible to DMTs during pregnancy. There are currently no studies investigating the effects of natalizumab in preventing the anticipated postpartum increase in disease activity. Use of natalizumab, a high efficacy therapy for the 1 year post-partum, emerges as an appropriate intervention to control the high inflammatory milieu that characterize the post-partum period. The primary concern

related to the use of natalizumab is the risk to develop progressive multifocal encephalopathy (PML). The risk for development PML in patients treated with natalizumab is primarily linked to prolonged therapy (over 2 years), previous exposure to chemotherapy and being anti JCV antibody positive (STRATIFY JCV). As the risk for relapses in post-partum period is in general limited to 1 year we propose to evaluate the efficacy of natalizumab therapy for this period. Continuing natalizumab vs. switching to another disease modifying therapy after 1 year should be re-assessed in case to case bases.

2.2 Describe any relevant preliminary data.

Response:

A recent retrospective small French study[18] reports the benefit of natalizumab use in postpartum period in 6 previously very active MS patients. The annualized relapse rate (ARR) between natalizumab withdrawal and onset of pregnancy was 1.8 ±0.7. Six relapses occurred before onset of pregnancy and seven during pregnancy. Natalizumab was restarted 7.8 days after delivery (between day 2 and 8 for five patients and on day 23 for one). Only one patient, who had restarted natalizumab 2 days after delivery, had a relapse 2 weeks later. The others five patients were relapse free after a mean of 14.2 ±9.1 months of follow-up. The conclusion of the study: "Despite a known high risk of post-partum relapses, early redosing of natalizumab led to a complete disappearance of disease activity in all but one patient. These data suggest that natalizumab could be a good candidate for preventing early post-partum relapses".

2.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Response:

As presented in the background section the post-partum period (especially the first 3 months) is characterized by an increased risk for relapses in MS patients. Although many disease-modifying drugs (DMTs) have come to market in the past two decades, when used during pregnancy and lactation, their beneficial effects on the course of MS have to be balanced with fears concerning potential risks to the fetus or child. Therefore the general recommendation is to discontinue therapy during pregnancy and often even at the time of considering conception. As for the post-delivery period, breastfeeding and treatment options after delivery should be discussed to outline

the options for prevention of postpartum relapses, and the possible resumption of disease-modifying drugs Multiple interventions were considered in the postpartum period including: Immunoglobulins (IVIG), steroids[9], estrogens[10], none of which were able to show a significant positive effect in preventing the postpartum relapses as compared to no intervention.

Based on the well-established natalizumab efficacy, especially seen in high risk patients, we expect that initiation of this therapy shortly after delivery can prevent relapses in a more effective manner than any other interventions.

2.4 Include complete specific citations/references.

Response:

1. *Orton S-M, Herrera BM, Yee IM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet neurology. 2006;5:932-936.*

2. *D'hooghe M. Long-term effects of childbirth in MS. Journal of Neurology, Neurosurgery& Psychiatry. 2010;81(1):38-41.*

3. *Teter B, Kavak K, Kolb-Sobieraj C, Coyle P, Weinstock-Guttman B. Parity Associated with Long-Term Disease Progression in Women with Multiple Sclerosis. Journal of Multiple Sclerosis. 2014;1(101):doi: 10.4172/jmso.1000101.*

4. *Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group. N Engl J Med. 1998;339:285-291.*

5. *Vukusic S, Hutchinson M, Hours M, et al. Pregnancy and multiple sclerosis (the PRIMS study): clinical predictors of post-partum relapse. Brain. 2004;127:1353-1360.*

6. *Vukusic S, Confavreux C. Pregnancy and multiple sclerosis: the children of PRIMS. Clin Neurol Neurosurg. 2006;108:266-270.*

7. *Haas J, Hommes OR. A dose comparison study of IVIG in postpartum relapsing-remitting multiple sclerosis. Mult Scler. Aug 2007;13(7):900-908.*

8. *Hellwig K, Beste C, Schimrigk S, Chan A. Immunomodulation and postpartum relapses in patients with multiple sclerosis. Ther Adv Neurol Disord. Jan 2009;2(1):7-11.*

9. *de Seze J, Chapelotte M, Delalande S, Ferriby D, Stojkovic T, Vermersch P. Intravenous corticosteroids in the postpartum*

period for reduction of acute exacerbations in multiple sclerosis. Mult Scler. Oct 2004;10(5):596-597.

10. *Vukusic S, Ionescu I, El-Etr M, et al. The Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis (POPART'MUS) trial: rationale, objectives and state of advancement. J Neurol Sci. Nov 15 2009;286(1-2):114-118.*

11. *Langer-Gould A, Huang SM, Gupta R, et al. Exclusive breastfeeding and the risk of postpartum relapses in women with multiple sclerosis. Arch Neurol. Aug 2009;66(8):958-963.*

12. *Achiron A, Kishner I, Dolev M, et al. Effect of intravenous immunoglobulin treatment on pregnancy and postpartum-related relapses in multiple sclerosis. J Neurol. 2004;251:1133-1137.*

13. *Airas L, Jalkanen A, Alanen A, Pirttila T, Marttila RJ. Breast-feeding, postpartum and prepregnancy disease activity in multiple sclerosis. Neurology. Aug 3 2010;75(5):474-476.*

14. *Portaccio E, Ghezzi A, Hakiki B, et al. Breastfeeding is not related to postpartum relapses in multiple sclerosis. Neurology. Jul 12 2011;77(2):145-150.*

15. *Hughes SE, Spelman T, Gray OM, et al. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. Mult Scler. May 2014;20(6):739-746.*

16. *Hellwig, K., Haghikia, A. & Gold, R. Pregnancy and natalizumab: results of an observational study in 35 accidental pregnancies during natalizumab treatment. Mult Scler **17**, 958-963 (2011).*

17. *Fagius, J. & Burman, J. Normal outcome of pregnancy with ongoing treatment with natalizumab. Acta Neurol Scand **129**, e27-29 (2014).*

18. *Vukusic, S., et al. Natalizumab for the prevention of post-partum relapses in women with multiple sclerosis. Mult Scler **21**, 953-955 (2015).*

19. *Horakova, D., et al. Environmental factors associated with disease progression after the first demyelinating event: results from the multi-center SET study. PLoS One **8**, e53996 (2013).*

20. *Weinstock-Guttman, B., et al. Lipid profiles are associated with lesion formation over 24 months in interferon-beta treated patients following the first demyelinating event. J Neurol Neurosurg Psychiatry **84**, 1186-1191 (2013).*

21. *Browne, R.W., et al. Apolipoproteins are associated with new MRI lesions and deep grey matter atrophy in clinically isolated syndromes. J Neurol Neurosurg Psychiatry **85**, 859-864 (2014).*

22. *Messina, S., et al. Increased leptin and A-FABP levels in relapsing and progressive forms of MS. BMC Neurol **13**, 172 (2013).*

3.0 Inclusion and Exclusion Criteria

3.1 Describe the criteria that define who will be included or excluded in your final study sample.

Response:

Subjects meeting all of the inclusion and none of the exclusion criteria provided below are eligible for enrollment in the natalizumab group.

Inclusion Criteria:

1. Female subjects postpartum, 0-30 days postpartum at the time of informed consent.

2. Diagnosis of relapsing form of MS.

3. Willing to initiating natalizumab and enroll in the TOUCH system.

4. Willing and able to comply with the study procedures for the duration of the trial.

5. Signed informed consent and HIPAA authorization.

Exclusion Criteria:

1. Diagnosis of primary progressive MS.

2. Breastfeeding

3. Use of IVIG in Tysabri treated subjects.

4. Significant renal or hepatic impairment (in the opinion of the investigator) or other significant disease (e.g., cognitive impairment) that would compromise adherence and completion of the trial.

5. History of hypersensitivity to previous exposure or presence of antibodies to natalizumab.

6. Any other factor that, in the opinion of the investigator, would make the subject unsuitable for participation in this study.

7. Patients that experience relapses and/or initiated DMT's during pregnancy

<u>The Control group</u> will consist of relapsing MS patients post-delivery who decline natalizumab therapy but open to enroll in the study.

Similar Inclusion and Exclusion criteria as the Natalizumab group with the exception of requiring TOUCH enrollment program. The Control group will be allowed to initiate any FDA approved DMT at any time post delivery or remain on no therapy while breastfeeding.

3.2 Describe how individuals will be screened for eligibility.

Response:

During routine clinical visits patients who fulfill the inclusion criteria may be identified as potential candidates.

Women are routinely seen in clinic for evaluation postpartum to discuss treatment options. Clinic staff may identify potential candidates during routine clinic visits and offer the opportunity to enroll in this study.

3.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Response:

Vulnerable populations (adults unable to consent, individuals who are not yet adults, pregnant women, and prisoners) will not participate in this research.

3.4 Indicate whether you will include non-English speaking individuals. Provide justification if you will exclude non-English speaking individuals.
(In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may not be routinely excluded from research. In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English: e.g., pilot studies, small unfunded studies with validated instruments

not available in other languages, numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.)

Response:

As this study will require patient reported outcomes in the form of Quality of Life questionnaires that are in the English language, we will enroll only patients who are fluent in English. It is not feasible to have the patient reported outcomes tools translated for this small study.

4.0 Study-Wide Number of Subjects (Multisite/Multicenter Only)

4.1 If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

Response:

30 subjects will be enrolled study wide.

5.0 Study-Wide Recruitment Methods (Multisite/Multicenter Only)

If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.

5.1 Describe when, where, and how potential subjects will be recruited.

Response:

Patients will be identified during routine clinical visits.

5.2 Describe the methods that will be used to identify potential subjects.

Response:

MS patients enrolled at one of the 2 participating centers. Women are routinely seen in clinic for evaluation postpartum to discuss treatment options. Clinic staff will identify potential candidates during routine clinic visits and offer the opportunity to enroll in this study.

5.3 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response:

No advertisement will be used for this study.

6.0 Multi-Site Research (Multisite/Multicenter Only)

6.1 If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

Response:

The coordinating center will provide the protocol (including source and questionnaires) to the participating sites. Any amendments to the protocol will be communicated to the sites to be implemented appropriately. The sites will provide proof of their local IRB approval prior to beginning research activity with subjects and any amendments will require approval prior to implementation. IRB approvals for participating sites will be provided to the UBIRB as they are submitted to the coordinating center at UBMD Neurology.

Each site will follow its own local regulatory requirements.

6.2 Describe the method for communicating to engaged participating sites:

- *Problems.*
- *Interim results.*
- *The closure of a study*

Response:

Site will receive status reports. We do not anticipate problems with the conduct of the study, if any arise, communication with sites will be made as needed via email or telephone.

If difficulty with enrollment within year 1 (less than 50% of expected enrollment) is encountered, consideration will be given to adding additional sites.

7.0 Study Timelines

7.1 Describe the duration of an individual subject's participation in the study.

Response:

Subjects will be followed for 1 year after enrollment.

7.2 Describe the duration anticipated to enroll all study subjects.

Response:

Approximately 18 months after all sites are approved to begin enrollment.

7.3 Describe the estimated date for the investigators to complete this study (complete primary analyses)

Response:

Approximately 18 months year for study completion after the last subject completes the study.

8.0 Study Endpoints

8.1 Describe the primary and secondary study endpoints.

Response:

The primary endpoint is the proportion of patients who experience a relapse postpartum (proportion of patients relapsed, PPR) during 1 year post-delivery in patients treated with natalizumab. This will be compared to the PPR in the parallel control group.

The secondary endpoints are:

1. If appropriate, annualized relapse rate (ARR) between the natalizumab-treated group and the control group (who may remain off treatment or be on other DMTs).

2. Confirmed (12 week) EDSS change of 1 point or more for a baseline EDSS > 1, or a confirmed increase of 1.5 points for an EDSS of 0-1, at Week 48 as compared to baseline between the 2 groups.

3. Change in MRI: MRI at Week 48 for: new or enlarging T2, and T1 gadolinium-enhancing (GdE) lesions counts compared to the change in MRI control group.

4. Percent of patients that discontinued the primary therapy initiated post-partum (efficacy/tolerability)

Tertiary endpoints:

Change in QOL measures that will include: SF12v2, FSMC, and MSIS-29 v2 from baseline to week 24 and 48 as compared to the control group.

8.2 Describe any primary or secondary safety endpoints

Response: **All serious adverse events (SAEs), will be collected and summarized descriptively in the clinical study report and appropriate aggregate safety report.**

9.0 Procedures Involved

9.1 Describe and explain the study design.

Response:

This is a Phase IV, prospective, open-label, multicenter trial. Postpartum patients with a diagnosis of MS will be invited to enroll in this study that will evaluate the efficacy of IV natalizumab 300 mg to prevent postpartum relapses. Natalizumab, administered q 4 weeks, will be initiated postpartum (0-30) days post-delivery. Breastfeeding will be permitted up to 30 days postpartum in subjects opting to initiate Natalizumab (breastfeeding must be discontinued at natalizumab initiation). Patients who decline natalizumab treatment postpartum will be invited to enroll in the study in the control group. The control group will have similar inclusion, exclusion criteria, scheduled visit and study procedures as the active natalizumab treatment group. This group will be permitted to continue breastfeeding if they will remain off DMT. Approximately 30 subjects will be enrolled study wide.

9.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Response:

At Visit 1 (Screening/Baseline: 0-30 days post-delivery), patients provide informed consent/Health Insurance Portability and Accountability Act (HIPAA) then undergo evaluation of inclusion/exclusion eligibility criteria, provide a complete medical history including relapse history (1 year before pregnancy and during pregnancy), undergo full physical and neurological examinations (including EDSS). Recording of concomitant medications/procedures and laboratory testing will also be performed at screening/baseline (lab testing if applicable as part of standard of care). An MRI evaluation after delivery represents a routine clinical accepted requirement. Laboratory testing includes: CBC/diff, CMP, JCV antibody status (STRATIFY JCV), urinalysis with culture at screening and q 3 months as part of standard of care for those on natalizumab treatment.

The investigator will review the baseline lab results to confirm there are no abnormalities that prevent inclusion in the study, for those entering natalizumab treatment group. The first dose of natalizumab will be administered after the MRI and baseline lab testing are obtained. Breastfeeding, if initiated, should be discontinued if patient is assigned to start natalizumab therapy. Subjects will visit the clinic for assessments on Visit 2 (Week 12), Visit 3 (Week 24), Visit 4 (Week 36) and Visit 5 (week 48) for monitoring of their status, well-being, EDSS, and completion of PROs. SAEs will be monitored on an on-going basis throughout the study. An additional standard of care MRI will be performed at week 48, final visit of the study. Additional non-scheduled visits during possible relapses will be scheduled within 72 hours from development of new symptoms suggesting of a relapse.

The control group will be evaluated at same time points and can consider different intervention (including any FDA approved DMTs or breastfeeding only).

Patients who experience relapses will be treated with 3-5 days IV Methylprednisolone. They will continue to be followed as per study visits schedule. Steroid therapy will be allowed if new symptoms or activity on baseline MRI will be identified before enrolling in the study. The control group patients will be maintained in the study while continuing on their same DMT initiated postpartum. As the treating physician and/or patient will consider a switch to any other DMT (including natalizumab). Patients who switched to rescue therapy will be discontinued from the study. The percent of patient that require discontinuation (i.e. related to efficacy vs. tolerability) will be also assessed and compared between the groups.

9.3 Describe procedures performed to lessen the probability or magnitude of risks.

Response:

This is not an interventional study. The risks associated with participation are limited to potential loss of confidentiality. The management of this risk is described in Section 11.

9.4 Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Response:

There are no drugs or devices used for research purposes in this study.

All treatments mentioned are FDA approved therapies that have been prescribed to the subjects as part of standard of care.

9.5 Describe the source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)

Response:

Data will be collected on paper source documents. Subjects will complete hardcopy questionnaires. Source forms and Quality of Life questionnaires are provided as part of submission.

9.6 What data will be collected including long-term follow-up?

Response:

An overview of the data that will be collected includes demographics, medical history, MS history, MS treatment history, physical exam, neurological exam, and vitals. Subjects also complete questionnaires. The source documents with the exact data to be collected at study visits and the questionnaires are provided as part of submission.

In addition, MRI data will be obtained for subjects and a counting of new and/or enlarging T2 lesions as well the number of T1 Gd enhancing lesions present at baseline and at the 1-year repeat brain MRI. MRI data will be obtained electronically. Hardcopy MRI reports will be provided by the Investigator for data entry.

9.7 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response:

No device will be evaluated and/or included in the study

10.0 Data and Specimen Banking

10.1 If data or specimens will be banked for future use, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.

Response:

No data or specimen will be banked for future use.

10.2 List the data to be stored or associated with each specimen.

Response:

Not applicable

10.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who

can obtain data or specimens, and the data to be provided with specimens.

Response:

Not applicable

11.0 Data Management

11.1 Describe the data analysis plan, including any statistical procedures.

Response:

General Methods

All collected data will be displayed in patient data listings. Statistical analyses will be performed using SPSS for Windows. All analyses will be performed on the Full Analysis Set (FAS) defined as the set of all enrolled patients who received at least one dose of study drug.

Descriptive statistics (n, mean, standard deviation [SD], median, Q1, Q3, minimum, maximum) will be calculated for all patients in the FAS. Frequencies and percentages will be presented for categorical and ordinal variables. Where appropriate, 95% confidence intervals (CIs) will be presented.

As no randomization will be considered in this study the statistical analysis will control for demographic and clinical identified significant differences (see above the subanalysis metrics). Additional analysis will be considered using the propensity scores method.

A block enrollment of 20 per group (natalizumab vs controls) will be required to provide an even enrollment between the 2 groups and prevent a possible overenrollment in the control group before the natalizumab will be completed.

Baseline Analyses

Demographics and baseline characteristics will be analyzed descriptively.

Baseline analyses will also include descriptive analyses of medical history, physical exam, neurological exam, baseline QoL assessment, and concomitant medications.

11.2 Provide a power analysis.

Response:

A sample size of thirty (30) patients will be sufficient to provide evidence of a statistical trend in the difference in PPR between

participants who utilize natalizumab postpartum and the control group.

11.3 Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Response:

All research staff is trained in proper data handle procedures. Files are maintained in locked cabinets in locked rooms in the offices of the department of Neurology (UBMB Neurology) located at 1010 Main Street, 2nd Floor, Buffalo, NY 14202. Data is maintained in a password protected encrypted database. Access is limited to only those directly involved in the conduct of the research, including data entry and analysis.

11.4 Describe any procedures that will be used for quality control of collected data.

Response:

Data is subjected to quality review by research staff at time of data entry. The data is cleaned using a logic check system to ensure accuracy. Data that does not pass logic check criteria is queried for clarification.

11.5 Describe how data and specimens will be handled study-wide:

Response:

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. The subject's data collected in the trial will be stored under this number. Only the Site Investigator will be able to link the subject's trial data to the subject via an identification list kept at the site.

CRFs will be provided by the Coordinating Center (CC) that will be located in Buffalo at UBMD Neurology. The completed forms required for a visit will be sent to the CC via fax or email within 7 days of each visit. The CC data coordinator assigned to this study will record receipt of the data transmittal on a log all the CRFs contained in that transmittal. CRFs will be reviewed for clarity and completeness. Incomplete or incorrectly completed forms will generate queries which will be faxed or e-mailed to the originating site on a Data Clarification Form (DCF). The DCF will identify the subject, visit number, and CRF in question, and the data elements that have been flagged for review. The originating site investigate the discrepancy. The DCF must be

completed showing what corrections need to be made (or indicating why no changes are necessary) and returned to the CC within 7 days of receipt. Data entry staff at the CC will make the appropriate changes to the database. The original DCF will be filed by the site coordinator with the CRF source documents for that visit. The CC will keep a copy of the corrected DCF as well, attached to the corresponding CRF.

The data will be entered into a validated database. The CC will be responsible for data processing. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed.

Files are maintained in locked cabinets in locked rooms in the offices of the department of Neurology (UBMB Neurology) located at 1010 Main Street, 2nd Floor, Buffalo, NY 14202. Data is maintained in a password protected encrypted database. Access is limited to only those directly involved in the conduct of the research, including data entry and analysis.

11.6 What information will be included in that data or associated with the specimens?

Response:

The data described in Sections 9.5 and 9.6 will be included in database.

No specimens are being collected.

11.7 Where and how data or specimens will be stored?

Response:

Files are maintained in locked cabinets in locked rooms in the offices of the department of Neurology (UBMB Neurology) located at 1010 Main Street, 2nd Floor, Buffalo, NY 14202. Data is maintained in a password protected encrypted database. Access is limited to only those directly involved in the conduct of the research, including data entry and analysis.

No specimens are being collected.

11.8 How long the data or specimens will be stored?

Response:

Data may be stored for up to 10 years.

No specimens are being collected.

11.9 Who will have access to the data or specimens?

Response:

The Principal Investigator and delegated research staff will have access to data as necessary for data entry, data clarification and analysis.

No specimens are being collected.

11.10Who is responsible for receipt or transmission of the data or specimens?

Response:

The Principal Investigator and delegated research staff at sites will be responsible for the transmission of the data for entry into the database.

11.11How data and specimens will be transported?

Response:

Data will be transmitted from external sites via fax or email.

No specimens are being collected.

12.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

12.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response:

This is not an interventional study. It is an observational study. Subject safety is not the primary outcome being evaluated. The data being obtained is subjected to database logic check system to ensure accuracy.

12.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response:

This is not an interventional trial. The data will include patient reported quality of life as related to the ongoing use of therapy or no therapy. In addition clinical data including vitals, relapses, and disability score will be obtained.

12.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response:

Subject data will be collected at study visits. Data will be recorded on case report forms by research staff. Quality of Life questionnaires are completed by subjects. If a subject experiences a relapse between regularly scheduled study visits she may contact the office by telephone to report

symptoms and the investigator will collect initial data and schedule and "unscheduled study visit" as necessary.

12.4 Describe the frequency of data collection, including when safety data collection starts.

Response:

Subjects are evaluation at 5 visits. After enrollment (baseline visit), all visits occur at 12 week intervals. Relapse assessment is on-going throughout the study. SAEs will be reported after informed consent is obtained.

Subjects enrolled in the Tysabri treated group are treated per standard of care every 4 weeks.

12.5 Describe who will review the data.

Response:

Research staff will review data at the time of collection. Data is subjected to quality review by research staff at time of data entry. The investigator may review the subject data at any time throughout the subject's participation as necessary.

12.6 Describe the frequency or periodicity of review of cumulative data.

Response:

Data will be reviewed and analyzed at the end of the study. No interim analysis is planned.

12.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response:

This study is not using new therapeutic intervention or non FDA approved drugs. The study will evaluate demographics, patient-reported outcome and usual routine clinical measurements.

12.8 Describe any conditions that trigger an immediate suspension of the research.

Response:

This is not an interventional study. As such there are no anticipated safety concerns that would warrant an immediate suspension of the research.

13.0 Withdrawal of Subjects

13.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Response:

A subject must be withdrawn in the event of any of the following:

- **Participation in any other interventional trial during the duration of this trial**
- **Occurrence of an exclusion criterion which is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator**
- **Occurrence of pregnancy**
- **Non-compliance with study procedures (in the opinion of the investigator)**
- **Discontinuation of the study drug for any reason (including but not limited: therapeutic failure requiring urgent additional drug, occurrence of adverse events (AEs), if discontinuation of trial drug is desired or considered necessary by the Investigator and/or the subject)***

***Patients may opt to continue to be followed for the remainder of the 48 week study.**

Patients enrolled in the control group will be permitted to initiate any FDA approved DMT excluding natalizumab therapy. However the patients failing a first DMT will be considered treatment failure and will be discontinued from the study. A subanalysis will be performed based on the reason for DMT change related to efficacy vs. tolerability.

13.2 Describe any procedures for orderly termination.

Response:

If a subject is to be withdrawn, either self-withdrawn or by an investigator, the subject may be immediately withdrawn, no procedures need to be performed other than to document the reason for withdrawal, if provided by the subject.

13.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Response:

In case of premature withdrawal from the trial, the investigations scheduled for the last visit should be performed, if possible. In any case, the appropriate Case Report Form (CRF) section must be completed capturing the reason for discontinuation.

If for any reason patient is withdrawn from the study her data will not be removed from the dataset.

14.0 Risks to Subjects

14.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Response:

No discomfort is expected as patients will have to complete only questionnaires and undergo examinations which are routine and noninvasive in nature.

14.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Response:

No procedures should be unforeseeable.

14.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response:

Not applicable

14.4 If applicable, describe risks to others who are not subjects.

Response:

Not applicable

15.0 Potential Benefits to Subjects

15.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

Response:

There is no clear immediate benefit to the individual patient. However, if the results of the study are positive, it will clearly provide significant general therapeutic information: To consider initiating natalizumab therapy immediately post-partum.

15.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

Response:

There is no clear immediate benefit to the individual patient.

16.0 Vulnerable Populations

16.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.*

Response:

Not applicable. The study will not include vulnerable populations.

17.0 Community-Based Participatory Research

17.1 Describe involvement of the community in the design and conduct of the research.

Response:

This study will not involve community based participants in its design and conduct of the research

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each

brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

18.0 Sharing of Results with Subjects

18.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Response:

No genetic testing is performed.

If abnormal findings are identified during testing (i.e. MRI) these will be communicated to the patient and PMD as applicable.

19.0 Setting

19.1 Describe the sites or locations where your research team will conduct the research.

Response:

The research will be conducted in the Conventus building (1001 Main Street, Buffalo, NY 14203) at the Buffalo Niagara Medical Campus in the department of neurology outpatient offices (UBMD Neurology). Study visits will occur in private exam rooms.

19.2 Identify where your research team will identify and recruit potential subjects.

Response:

Recruitment will be performed during the routine clinical visits as described in Section 22.

19.3 Identify where research procedures will be performed.

Response:

The research will be conducted in the Conventus building (1001 Main Street, Buffalo, NY 14203) at the Buffalo Niagara Medical Campus in the department of neurology outpatient offices (UBMD Neurology). Study visits will occur in private exam rooms.

19.4 Describe the composition and involvement of any community advisory board.

Response:

No community advisory board will be involved.

19.5 For research conducted outside of the organization and its affiliates describe:

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Response:

All centers will develop an updated protocol and consent form as per their local IRB requirements.

20.0 Resources Available

20.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. Note- If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.

Response:

All local research staff has completed CITI training and the PI and research coordinators have completed CITI GCP training. All research staff has extensive experience conducting clinical trials. The physicians conducting the research specialize in treating the disease under study.

Describe other resources available to conduct the research: For example, as appropriate:

20.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response:

It is estimated that the site may have approximately 40 patients who meet the eligibility criteria during the enrollment period. Of those it is anticipated that 25-28 will be interested in participating.

20.3 Describe the time that you will devote to conducting and completing the research.

Response:

10% of PI effort

20.4 Describe your facilities.

Response:

The department of neurology outpatient offices (UBMD Neurology) in the Conventus building (1001 Main Street, Buffalo, NY 14203) at the Buffalo Niagara Medical Campus consist of private exam rooms in which patients are seen for all procedures. Study procedures are performed in private areas after subjects check in with at the reception area. Study documents are maintained in a locked staff office that is only accessed by designated personnel.

20.5 Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

Response:

No unexpected or anticipated consequences are foreseen during this study that require only questionnaire completion.

In the event it becomes necessary, referrals to appropriate medical facilities and/or specialists will be provided in the event a subjects experiences an adverse event during participation the research.

20.6 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response:

All study staff is trained on the study protocol by first reviewing the protocol itself in detail. The PI conducts a training session to ensure research team understand the protocol and each individuals' responsibility. A major focus of training for an observational study for is to ensure the confidentiality measures are in place and will be followed.

21.0 Prior Approvals

21.1 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

Response:

IRB approval and executed contract with funding agency. Prior to other sites initiating research activity, proof of IRB approval must be provided.

22.0 Recruitment Methods

22.1 Describe when, where, and how potential subjects will be recruited.

Response:

Subjects will be identified during routine clinic evaluation (the neurologists who see MS patients in the UBMD Neurology private practice are all investigators on the study therefore familiar with the requirements of the protocol) and approached for interest in participation in the study. A neurologist will identify that a subject meets basic eligibility criteria (diagnosis, age, postpartum status) during routine clinical evaluation and inquire if the subject has interest in participating in research in general (if no interest, then no further action is taken). If the subject has interest, then the research coordinator is called and the potential subject is provided with an informed consent form as a means to provide her with additional information about the study. If the subject is interested, a study visit is scheduled.

The site is not utilized posters, flyers or any other site specific advertisement.

22.2 Describe the source of subjects.

Response:

Subjects may be identified from the UBMD Neurology practice as described in 22.1.

22.3 Describe the methods that will be used to identify potential subjects.

Response:

Subjects may be identified from the UBMD Neurology practice as described in 22.1.

22.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response:

No advertisement will be necessary

22.5 Describe the amount and timing of any payments to subjects.

Response:

Subjects will not be compensated for participation.

23.0 Local Number of Subjects

23.1 Indicate the total number of subjects to be accrued locally.

Response:

Approximately 25-28

23.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Response:

There are no screening procedures for the study. It is expected that subjects who agree to participate will enroll in the study.

24.0 Confidentiality

Describe the local procedures for maintenance of confidentiality.

24.1 Where and how data or specimens will be stored locally?

Response:

Files are maintained in locked cabinets in locked rooms in the offices of the department of Neurology (UBMB Neurology) located at 1010 Main Street, 2nd Floor, Buffalo, NY 14202. Data is maintained in an encrypted database. Access is limited to only those directly involved in the conduct of the research, including data entry and analysis.

No specimens are being collected.

24.2 How long the data or specimens will be stored locally?

Response:

Data may be stored for up to 10 years.

No specimens are being collected.

24.3 Who will have access to the data or specimens locally?

Response:

The investigators and designated staff will have access to the data.

No specimens are being collected.

24.4 Who is responsible for receipt or transmission of the data or specimens locally?

Response:

The Principal Investigator and delegated research staff.

24.5 How data and specimens will be transported locally?

Response:

Completed forms are maintained internally, no transportation is required.

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Response:

Study procedures are performed in private exam areas. Study procedures are performed only by study staff. Study documents are maintained in a locked staff office that is only accessed by designated personnel.

25.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Response:

Subjects are made to feel at ease by ensuring that they understand every aspect of the research process. Study visits occur in a comfortable environment, with which subjects are familiar. They are familiar with the research staff and are made to feel comfortable and confident in their situation.

25.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Response:

Study procedures are performed in private exam areas. Study procedures are performed only by study staff. Study documents are maintained in a locked staff office that is only accessed by designated personnel.

26.0 Compensation for Research-Related Injury

26.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

Response:

The research does not involve any more than minimal risk procedure.

26.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Response:

No injury is foreseen during questionnaire completion or during the conduct of physical or neurological examinations.

27.0 Economic Burden to Subjects

27.1 Describe any costs that subjects may be responsible for because of participation in the research.

Response:

No additional cost for subjects is foreseen. The study is observational in nature, all procedures that are strictly study related are paid for by the study. Other costs are standard of care that the subject would incur regardless of participation.

28.0 Consent Process

28.1 Indicate whether you will be obtaining consent

Response:

Informed consent will be obtained from subjects.

28.2 Describe where the consent process take place

Response:

Informed consent will be obtained in the Conventus building (1001 Main Street, Buffalo, NY 14203) at the Buffalo Niagara Medical Campus in the department of neurology outpatient offices (UBMD Neurology). The process itself will occur in a private exam room.

28.3 Describe any waiting period available between informing the prospective subject and obtaining the consent.

Response:

Subjects may take as much time as they wish to consider participation.

28.4 Describe any process to ensure ongoing consent.

Response:

It is regularly reinforced with subjects that they are participating in a research study and that participation is voluntary and that they may ask questions at any time. In addition, at any time new or updated information is available the informed consent form will be updated and subjects will be reconsented.

28.5 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

Response:

Informed consent will be obtained following SOP HRP-090.

Non-English Speaking Subjects

28.6 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response:

Only subjects who speak English will be enrolled in the study. The purpose of the study is patient reported outcomes which are in English and it is not feasible to have the study documents translated into other languages for this small study. Therefore we will not obtain consent from subject who do not speak English.

28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Response:

Not applicable

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

28.8 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

Not applicable

28.9 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response:

Not applicable

Subjects who are not yet adults (infants, children, teenagers)

28.10Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

Response:

Not applicable

28.11For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response:

Not applicable

28.12Describe whether parental permission will be obtained from:

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

Response:

Not applicable

28.13Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.

Response:

Not applicable

28.14Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

Response:

Not applicable

28.15When assent of children is obtained describe whether and how it will be documented.

Response:

Not applicable

Cognitively Impaired Adults

28.16Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.

Response:

Not applicable

Adults Unable to Consent

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent and, where possible, assent of the individual should also be solicited.

28.17List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for NYS.

Response:

Not applicable

28.18For research conducted outside of NY state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response:

Not applicable

28.19Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

Response:

Not applicable

28.20For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response:

Not applicable

29.0 Process to Document Consent in Writing

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)

29.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

Response:

Documentation of consent in writing will be performed following SOP HRP-091.

30.0 Drugs or Devices

30.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response:

The study will not involve drugs or devices. Subjects will be utilizing medications as part of standard of care.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

30.2 Identify the holder of the IND/IDE/Abbreviated IDE.

Response:

The study will not use investigational drugs or devices

30.3 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response:

Not applicable