Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title: Fluoxetine treatment of depression in adults with Down syndrome

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1. Background and Significance

Down syndrome (DS) or trisomy 21, is a common genetic syndrome, resulting from an extra copy of chromosome 21. According to the Centers for Disease Control and Prevention, about 6,000 babies are born with DS each year [1] and overall, DS occurs in about 1 in 700 live births [2]. Down syndrome commonly includes characteristic physical features, a variable degree of cognitive impairment, and several medical comorbidities. Medical comorbidities commonly associated with DS include congenital heart defects, thyroid disease, gastrointestinal problems, hematological disorders, hearing loss, ocular disorders, and obstructive sleep apnea [3]. In addition to elevated rates of medical comorbidity, individuals with DS have an increased risk of psychiatric disorders compared to the general population [4–6]. Prevalence rates of psychiatric comorbidities have been reported to be as high as 38% and 35% in children and adults with DS, respectively [4,5]. Externalizing symptoms such as oppositionality, impulsivity, and hyperactivity are more common in children with DS, whereas internalizing symptoms such as depression, anxiety, and social avoidance become more prevalent in adolescence and adulthood [7–9].

Depression is a common comorbidity in adults with DS which is likely underestimated in naturalistic prevalence studies; reported prevalence rates range from 6-18% [9–13]. A recent study which included 605 individuals with DS from England and Wales demonstrated that 12.4% of younger adults (16-35 years) and 18.4% of older adults (≥36 years) had a lifetime history of depression based on medical record review [13]. Females and males with DS had a four- and five-fold increased risk of depression respectively, compared to the general United Kingdom adult population [13]. In a separate longitudinal cohort study, 134 adolescents and adults with DS (≥16 years) participated in a detailed psychiatric assessment with psychiatrists who had expertise in DS at baseline and two years later [12]. The two-year incidence of a major depressive episode in this study was 5.2% [12]. Adults with DS have several unique risk factors for developing depression compared to the general population including cognitive impairment [14], reduced serotonin brain tissue concentration in post-mortem studies [15], high prevalence of thyroid disorders [3], and significant emotional stressors related to the transition to adulthood and the accompanying loss of school-based programming and services.

Depression is often underrecognized and undertreated in adults with DS. There are several diagnostic challenges related to the inherent communicative and cognitive limitations. While the clinical characteristics of depression in individuals with DS are often similar to those seen in the general population including sad mood, diminished experience of pleasure, decreased appetite and weight loss, social withdrawal, reduced speech, low energy, and psychomotor slowing [6], individuals with DS may have difficulty expressing depressive thoughts such as of guilt, worthlessness, self-deprecation, or thoughts of suicide [10]. These clinical features may necessitate taking into account behavioral observations and caregiver report rather than strict application of diagnostic criteria. A retrospective study assessing the clinical features of depression in DS reported that when strict Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III-R) criteria were applied, only 50% of depressive episodes diagnosed by expert clinicians met full criteria [10]. This study also demonstrated that depression was frequently misdiagnosed as dementia in individuals with DS and therefore left untreated

[10]. In a retrospective study of 42 adults with DS, not all patients with depression received pharmacotherapy and no patients received a second medication trial if the first was ineffective [10], suggesting under treatment of a generally treatable psychiatric comorbidity.

Under treatment of depression in DS is, in part, related to the lack of data on effective treatment approaches. A review article on depression in DS published in 2011 highlighted that systematic studies on the treatment of depression were critically needed [16]. Even so, now 10 years later, no additional studies have been published and the literature on pharmacotherapy for depression in DS is limited to small case reports and case series [6]. No systematic, prospective studies on the effectiveness, tolerability, and safety of antidepressants in DS have been conducted. Three case series on pharmacotherapy for depression in DS were published more than 20 years ago, prior to the widespread use of modern antidepressants. These three case series reported on the clinical response to tricyclic antidepressants (TCAs) [17–19] and one of these case series also reported on three patients' response to fluoxetine, a selective serotonin reuptake inhibitor (SSRI) [18]. All three patients who received treatment with fluoxetine had a positive response, two of whom had previously failed to respond to TCAs. Of the remaining six patients described in this case series, three other patients responded to TCAs, one responded to a first generation antipsychotic, and two did not receive pharmacologic treatments. Medication side effects are not reported in any of these case series. The significant medical comorbidities and neurocognitive atypicalities associated with DS limit the extent to which our knowledge of the safety and efficacy of antidepressants in the general population can be extrapolated. Our team has collected preliminary data from 11 patients with DS treated with SSRIs for depression which indicate that patients with DS respond to much lower dosages of SSRIs than the general population and may be more sensitive to behavioral side effects at higher dosages [20]. Because of these issues, DS-specific prospective antidepressant trials are needed to inform clinical best practices.

Selective serotonin reuptake inhibitors are a class of medications which include fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and escitalopram. They selectively block the uptake of serotonin and have several Food and Drug Administration (FDA) indications including for the treatment of depression, anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder. Selective serotonin reuptake inhibitors have largely replaced the TCAs as first-line treatment for depressive disorders due to similar efficacy, improved tolerability, and a much safer side effect profile [21]. Unlike TCAs, SSRIs are generally nonlethal in overdose, are not associated with cardiac toxicity, and do not lower the seizure threshold. Modern clinical practice guidelines include SSRIs among the first-line medications for the treatment of depression [22]. Tricyclic antidepressants are considered second-line medications, only to be used after the failure of one or more first-line medications [22]. In clinical practice, SSRIs are typically the first class of medications used to treat depression. A recent study demonstrated that SSRIs comprised 93% of first-line medications for depression in primary care [23]. Selective serotonin reuptake inhibitors have a relatively benign side effect profile and are generally well tolerated. The most common side effects include impaired sexual functioning, sleepiness, and weight gain; 25% of patients consider side effects to be either "very bothersome" or "extremely bothersome" [24]. Despite the widespread use of SSRIs in the general population, their use in patients with DS has only been reported in three patients in a single case series which did not include data on adverse effects or safety [18].

Depression is a common psychiatric comorbidity with a lifetime prevalence of 16.6% in the United States [25]. Adults with DS have a four- to five-times increased risk of developing depression compared to the general population [13], suggesting that up to 70% of individuals with DS may experience depression in their lifetime. Compared to other known comorbidities associated with DS such as obstructive sleep apnea, congenital heart defects, blood cancers, and cataracts, depression is both relatively more highly prevalent and understudied. No reports on the use of modern antidepressants in DS have been published in the past more than 25 years. Our knowledge of the safety and efficacy of antidepressants in the general population may not be applicable to patients with DS because of the associated medical comorbidities and neurocognitive differences.

The central hypothesis of this project is that adults with major depression and DS will experience an improvement in depressive symptoms after a course of fluoxetine treatment. We also expect that fluoxetine will be safe and well tolerated. This study will provide much needed preliminary prospective

data regarding the effectiveness and tolerability of fluoxetine for these symptoms in DS and is a necessary first step prior to conducting a larger, more definitive placebo-controlled trial.

2. Specific Aims and Objectives

Specific Aim 1: Determine whether a 16-week prospective, open-label trial of fluoxetine shows preliminary evidence of effectiveness, safety, and tolerability in adults with DS and major depressive disorder (MDD).
This aim addresses our central hypothesis that fluoxetine will be effective and safe in the treatment of depression in adults with DS.

A) For preliminary evidence of effectiveness, we will require an observed response rate (where response is defined as a 16-week CGI-I rating of "much improved" or "very much improved") of 35% or greater. We will use the CGI-I rather than a depression scale for our effectiveness criterion because of the absence of existing data supporting the usefulness of common scales for quantifying depression severity in adults with DS.

B) For preliminary evidence of safety, we will require no observation of serious or severe adverse effects possibly, probably, or definitely associated with fluoxetine.

C) For preliminary evidence of tolerability, we will require an observed drop-out rate due to adverse effects less than 36%.

Specific Aim 2: Collect preliminary data comparing the usefulness of existing depression rating scales in characterizing participants and assessing depression treatment effects.
A variety of outcome measures of depression will be used to better assess their applicability and feasibility in the DS population. The relative performance of the scales will be evaluated based on their sensitivity to change and their association with clinical improvement ratings. Percent of item-level missing data, and any feedback on the appropriateness or ease of use of the scales from participants, including their legal guardians, or study personnel, will also be taken into account.

Specific Aim 3: Estimate the mean therapeutic dose of fluoxetine for adults with DS for treating major depressive disorder (MDD).
We will report the average dose of fluoxetine at the end of 16 weeks of treatment.

We expect our results to: 1) provide preliminary evidence on the safety, effectiveness, and tolerability of fluoxetine for the treatment of MDD in DS; 2) assess the relative performance of existing depression rating scales in DS; and 3) provide information on fluoxetine dosing. Currently there is no prospective evidence on the safety, efficacy, and tolerability of any medication for the treatment of depression in DS. The lack of evidence-based guidelines for the treatment of depression in DS likely contributes to the decreased awareness of and under/misdiagnosis of this largely treatable condition. Adults with DS and comorbid depression may be mistakenly diagnosed with dementia, another neuropsychiatric condition for which there is much greater awareness in DS, but few effective treatments.

Data from this study will lay the foundation for the development of evidence-based guidelines for the treatment of depression in DS which will help increase awareness of this comorbidity and promote systematic screening and treatment. Medication treatment strategies for depression used in the general population likely need to be adapted to be safe, tolerable, and effective for adults with DS. Our clinical experience and pilot data suggest that adults with DS may respond to much lower dosages of fluoxetine than are used in the general population and that higher dosages may be associated with intolerable behavioral side effects such as anxiety or behavioral activation [20]. Data from this proposed study will inform best practices for dosing antidepressants in adults with DS. Finally, no specific depression rating

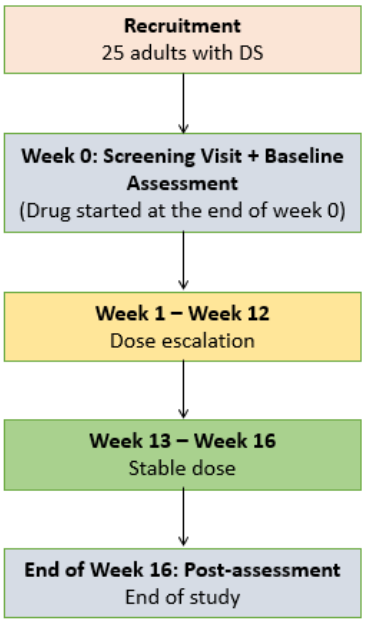
scales have been developed for or validated in DS. Data from this proposed study will inform which existing rating scales can detect depression in DS and which are sensitive to change with treatment. All the rating scales used in this study are in the public domain and therefore can easily be used in clinical practice. The identification of an appropriate rating scale will allow non-psychiatric specialists such as primary care providers as well as psychiatrists with less experience treating adults with developmental disabilities to screen for depression and monitor treatment effects. Overall, the data from this study is expected to improve the accessibility and quality of treatment for depression in DS, a common comorbidity which affects up to 70% of adults with this syndrome

3. General Description of Study Design

We are proposing a 16-week, prospective flexibly-dosed, open-label trial of fluoxetine for the treatment of major depressive disorder (MDD) in adults with DS. Participants will be seen at screen, baseline, and following 4, 8, 12, and 16 weeks of treatment. The duration of the trial will allow us to adjust the dose of fluoxetine over the first 12 weeks and allow for stable dosing during the final 4 weeks of the trial. We may complete visits remotely utilizing secure videoconferencing platforms such as Zoom or by phone, as necessary.

*Accommodations for Out of state patients and virtual visits**
The same IRB-approved accommodations for out of state patients our group is using in a similar open-label drug trial of buspirone for anxiety in Williams syndrome (Protocol #2021P000376) will be utilized for this study. All participants will be seen for either an in-person or virtual visit for the screen and baseline visits, the primary purpose of which are to establish care and determine the diagnosis and treatment plan. The prescription of fluoxetine will occur at the time of the baseline visit. In accordance with the Mass General Brigham Virtual Visit Procedures (applicable as of April 1, 2021), virtual visits will only be conducted with patients who are located in New England and Florida at the time of the visit and only by attending physicians who are licensed in those states. In accordance with the "FAQs for Mass General Brigham Clinicians: Changes to Procedures for Out of State Virtual Visits" (July 15, 2021) guidelines, the weeks 2, 4, 6, 8, 10, 12, and 16 visits will be conducted as "Customary telephone calls." These visits will consist of brief, logistical conversations with the purpose of communicating with subjects, adjusting prescriptions, and ensuring continuity of care by reviewing adverse effects and concomitant treatments/medications. If at any time during a "Customary telephone call" the study team learns of information concerning for new symptoms that are inconsistent with the diagnosis established during the baseline visit, symptoms that warrant a different treatment plan, or any other reason that in the attending physician's judgment that warrants a medical visit, the subject will be referred for either local clinical care within their state or offered an in-person visit in Massachusetts.
**In person regular and endpoint visits will be offered for all participants who are able to attend and participate in study procedures.*

Study staff will provide participants with information on how to access the video conferencing platform. Study staff will launch the video conferencing in a private and secure area and ask participants to refrain from taking screenshots, photographs, or recordings of any kind with any electronic equipment. Study staff will remind participants that video/phone meetings are similar to a home visit and that we may learn more about their home and/or the people living with them than during a visit at the hospital. For example, study staff may learn information that must be reported to public health or public safety authorities. The Informed consent describes the legal obligation to report known or suspected child or elder abuse. If study staff make such a report, the public health and safety authorities can use the information as they see fit and may end up sharing it with other government agencies.



4. Subject Selection

Twenty-five adults (18-45 years of age), with a diagnosis of DS exhibiting clinically significant symptoms of MDD on standardized rating scales will be included in this trial. Subjects will be selected to participate in the study based on the following Eligibility Criteria:

Inclusion Criteria

1. **Age 18-45 years.**
2. **Diagnosis of DS** confirmed via genetic testing or a clinical diagnosis made by a clinician with significant experience treating patients with DS.
3. **Diagnosis of major depressive disorder** based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, confirmed through the Structured Clinical Interview for DSM-5 (SCID-5).
4. **Moderately severe depression as evidenced by a Montgomery-Asberg Depression Rating Scale (MADRS) score of 20 or greater** at Screen and Baseline**.** A severity score on the MADRS was chosen as an inclusion criterion since it has been demonstrated to be sensitive to change in adults with MDD [27].
5. **A Clinical Global Impression Severity Item score ≥ 4 (moderate)** for depression symptoms at Screen and Baseline.

Exclusion Criteria

1. **Active primary diagnosis of obsessive-compulsive disorder, posttraumatic stress disorder, bipolar disorder, psychosis, or substance use disorder.** These disorders are exclusionary since the primary treatment of these disorders may require acute psychosocial or medication treatments that would confound the assessments used in this study. We will evaluate for these disorders using the corresponding SCID-5 modules.
2. **Current or previous diagnosis of dementia, or use of medication to treat dementia.** Given the potential overlap between depression and dementia symptoms, we want to ensure we are administering fluoxetine to patients with a diagnosis of depression.

3. **Presence of any past or present conditions that would make treatment with fluoxetine unsafe.** This includes allergy to fluoxetine, liver or kidney disease, unstable heart disease, and/or pregnancy (or being sexually active without using acceptable methods to prevent pregnancy).
4. **Use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), bupropion, mirtazapine, antipsychotics, lithium, valproic acid, or carbamazepine.** Subjects will need to be off these classes of medications for at least 5 elimination half-lives prior to beginning the trial.
5. **Use of other psychotropic medications which are ineffective, poorly tolerated, or sub-optimal in terms of dose.** A board-certified psychiatrist will assess any other psychotropic medications being used and determine whether they are effective, tolerated, and optimal in terms of dose. If medications are ineffective, poorly tolerated, or sub-optimal in terms of dose, the study psychiatrist will work with the subject and his/her treatment team to either taper or optimize the dose of psychotropic medications prior to study enrollment. Concurrent use of a psychotropic medication (other than SSRIs, SNRIs, TCAs, MAOIs, bupropion, mirtazapine, antipsychotics, lithium, valproic acid, or carbamazepine) will be allowed if the dose has been stable for 30 days and if they meet the criteria of effectiveness, tolerability, and dose.
6. **Previous adequate trial of fluoxetine.** An adequate trial will be defined as a total daily dose of ≥30 mg for at least 4 weeks. In addition, subjects who developed significant adverse effects during a trial of fluoxetine at any dose or duration will be excluded.
7. **Severe or profound intellectual disability based on clinical assessment and review of standardized assessment of cognitive skills.** Participants determined to have severe or profound intellectual disability will be excluded.
8. **Use of medications that pose a clinically significant risk of a drug-drug interaction with fluoxetine.**

Participants will be recruited from several different sources. We will advertise this study in the community (primary and subspecialty pediatric and adult clinics such as the Lurie Center) and via the National Down Syndrome Society. In addition, Dr. Palumbo (Co-Investigator) is the Chief of the MGH Down Syndrome Psychiatry Clinic and is the primary psychiatrist for the MGH Down Syndrome Program. She receives more than 30 referrals for new DS psychiatric consultations each year. Given the size of the Massachusetts General Hospital Down Syndrome Program, we anticipate local advertisements, flyers, recruitment letters and social media posts will supplement our recruitment efforts. Subjects will be recruited using an advertisement in MGB's Rally platform. Subjects will also be recruited from the clinic's recruitment database (Lurie Center Research Recruitment) that has been approved by the IRB (2023P000099). The approved study research invitation letter will also be sent via patient gateway to Mass General Brigham patients diagnosed with Down syndrome and meeting age criteria utilizing a queried list from the Mass General Brigham Research Patient Data Registry (RPDR) (2013P000347). All advertisements will be pre-approved by the Institutional Review Board.

All genders and racial groups will be recruited as they are represented in the population of study. Minority group members will be recruited in approximate proportion to their representation in the regions represented. We are committed to ensuring that the minority representation of this study population is characteristic of the regions involved and that the findings are thus generalizable.

5. Subject Enrollment

Informed Consent and Assent Procedures

Subjects and their legal guardians who are interested in participating in the study will have a face-to-face interview with the PI, co-I, and/or the research coordinator/assistant where the nature of the project, the risks, the benefits, and the alternatives to participation in the project are discussed. Prior to engaging in research, formal written consent will be obtained from the parent(s)/legal guardian(s) on an IRB-approved consent form. The signed consent form will be scanned into EPIC. Based upon parent report and/or clinical observation, if the subject is able to comprehend the consent document and understands the risks

and benefits involved in the study, verbal or written assent will be obtained, and an IRB-approved form will be used for this purpose. The only exception will be for subjects with lower developmental levels who are assessed as incapable of participating in even a simplified discussion of benefits, risks, and alternatives. The PI or other physician co-investigator will sign a consent/assent checklist. The signature indicates the physician's assessment of the subject's capacity to provide assent, and if so, the type of assent (verbal or written). How capacity to assent was determined will also be documented. The determination of capacity to assent includes a clinical assent evaluation performed by a physician. The evaluation includes assessing the subject's ability to remain present and attentive to the discussion of study procedures, ability to understand study procedures, ability to communicate a choice clearly and consistently as to whether to participate, the subject's understanding of the risks/benefits/alternatives to study participation, and feedback from the subject's LAR. If the physician determines the subject does have the capacity to assent, then the type of assent is determined based on verbal and written abilities observed in the consent/assent discussion and information on the subject's abilities gathered from the LAR. All attempts to obtain assent and/or observation regarding the subject's ability to provide assent will be thoroughly documented. To minimize coercion, an investigator who is also the treating physician of a potential subject will **not** be present during the consent process.

We anticipate that some adults with DS may not be able to fully participate in all study visits for a variety of reasons, including cognitive/communicative limitations and lack of cooperation resulting in inability to fully complete all depression assessments and questionnaires. Lack of cooperation during study visits due to emotional dysregulation such as repeated requests for a break, and verbalizations of distress will not be considered withdrawal of assent. However, the study physician would evaluate the subject on a case-by-case basis to determine if more sustained and significant behaviors, such as refusal to take the study medication and/or refusal to participate in even brief evaluations with the study physician during visits, would constitute withdrawal of assent.

Non-English speaking individuals will not be enrolled in this study as most of the outcome measures are validated and normed for the English language only.

6. STUDY PROCEDURES

Screen Visit:

The purpose of the *screen visit* is to ensure participants meet the eligibility criteria as defined above in Subject Selection.

In order to distinguish subjects who should be excluded due to profound intellectual disability from subjects who are not able to provide assent, the presence of severe or profound intellectual disability will be determined based on a clinical evaluation by a board-certified psychiatrist and psychologist (both experienced in the care of and conducting research involving adults with developmental disabilities) which takes into account a clinical assessment, review of cognitive testing (if available), and the clinically appropriate use of standardized scales (Stanford-Binet Intelligence Scales Weschler Abbreviated Scale of Intelligence, Second Edition; or Developmental Profile, Fourth Edition).

If it is clear that participants meet all eligibility criteria, the *Screen* and *Baseline* visits may be combined into a single visit during which the Montgomery-Asberg Depression Rating Scale (MADRS) would only be conducted once.

Baseline Characterization:

All subjects will have a baseline psychiatric diagnostic evaluation done to gather a thorough developmental, medical, and psychiatric history, as well as a mental status examination, and vital signs will be obtained for subjects evaluated in the clinic if subject cooperation allows. This will be determined by a board-certified psychiatrist experienced in the care of adults with developmental disabilities. Examples of lack of cooperation due to emotional dysregulation include refusal to participate, repeated requests for a break, and verbalizations of distress. Lack of cooperation may occur and is expected occasionally in this population. In visits where subject measures cannot be completed, measures from the caregiver will be collected only. In clinical care it is standard for caregivers to be the primary reporters of response to medication, therefore it is still valuable to collect non-primary outcome measures from the caregiver. Lack of cooperation would only become withdrawal of assent if behaviors stated in the assent section occur, for example regularly refusing to take the medication. If the visits are conducted remotely, not all vital signs will be obtained. The medical history will be aimed at ruling out other medical conditions that could exacerbate depression or behavioral symptoms (e.g., chronic gastrointestinal disease, obstructive sleep apnea, thyroid disease). The following standardized scales and testing may also be conducted. If cognitive testing has been completed within the past five years, these medical records may be requested and reviewed to inform study eligibility criteria.

1. **Stanford-Binet Intelligence Scales, Fifth Edition (SB-5)** [33]. The SB-5 may be used to calculate an abbreviated battery IQ. The abbreviated IQ was chosen to limit subject burden given that a number of other measures will be conducted at screening.
2. **The Weschler Abbreviated Scale of Intelligence, Second Edition (WASI-II)** [34]**.** The WASI-II can also be administered remotely and will be used for subjects depending on age and ability**.**
3. **Developmental Profile, Fourth Edition (DP-4)** [35]**.** If patients are unable to obtain a valid score on the SB-5 ABIQ or WASI-II due to constraints of a virtual visit or significantly delayed cognitive skills, the Cognitive and Adaptive Behavior subscales of the Developmental Profile (DP-4) Parent/Caregiver Interview Form may be administered. DP-4 scores will require a minimum age-equivalency cutoff of 24 months.

Fluoxetine Treatment:

Subjects will receive fluoxetine 5 mg each morning at the start of the trial. The dose will be flexibly increased by 5 mg every two weeks depending on effectiveness and tolerability. During the first 12 weeks, patients will be seen monthly with additional telephone visits conducted in between clinical visits for additional monitoring of adverse effects and for dosing adjustment as necessary. The optimal dose (between 5-30 mg per day), based on effectiveness and tolerability, will be reached by week 12 of treatment. A final visit will be conducted at week 16. At the end of the 16-week trial, participants will be referred for ongoing care either at the Lurie Center or locally, per their preference. The decision to continue or discontinue fluoxetine at the end of the trial will be made collectively by the research psychiatrist, the patient, and their family.

The minimum starting dose will be 5 mg and the maximum total daily dose will be 30 mg. If up titration is not tolerated, no more than one repeat attempt at up titration will be made. The decision to attempt a repeat up titration will be made by the research psychiatrist taking into account the full clinical picture of probable risks and benefits as well as the patient/family's preference. Fluoxetine is prepared in 10 mg tablets as well as a liquid formulation and will be dosed daily (see example of dosing schedule below).

Example Dosing Schedule	
	Dose (mg)
Weeks 1 & 2	5
Weeks 3 & 4	10
Weeks 5 & 6	15
Weeks 7 & 8	20
Weeks 9 & 10	25
Weeks 11 & 12	30

Weeks 13-16	Stable dose for last 4 weeks of study
** The schedule is a guide and may be adjusted depending on tolerability and effectiveness.*	

The rationale for this dosing schedule is based upon pilot data our group obtained. A retrospective chart review study from our clinic included 11 adults with DS and depression who were treated with a selective serotonin reuptake inhibitor (most commonly fluoxetine). The overall response rate was 82%. The mean starting dose for fluoxetine was 4.9 mg per day and the mean maximal dose was 25.5 mg per day. [20]

Study medication will be prescribed to participants by the study's psychiatrist and the cost will be billed to their insurance following the same procedures as routine clinical care. The Lurie Center has clinical infrastructure including Medical Assistants and Nursing Staff to assist with Prior Authorizations as needed. We plan to prescribe a one-month supply of medication to mimic real-world clinical practice but can prescribe up to a three-month supply if required by insurance.

Outcome Measures:

1. **Montgomery-Asberg Depression Rating Scale (MADRS)**. Change in MADRS total score between baseline and 16 weeks will be a secondary outcome measure. The MADRS is one of the most frequently used outcome measures in antidepressant efficacy trials and was developed to assess change in depressive symptoms after treatment with antidepressants [27]. The scale is clinician-rated and consists of 10 items, each rated on a 0-6 scale and summed to determine the total score. A total score of 7-19 is indicative of mild depression, 20-34 of moderate depression, 35-59 of severe depression, and 60 or greater of very severe depression. The MADRS will be conducted at screening, baseline, and each follow-up visit.
2. **Hamilton Depression Rating Scale (HAM-D)**. Change in HAM-D total score between baseline and 16 weeks will be a secondary outcome measure. The 17-item HAM-D is one of the most frequently utilized outcomes measures in clinical trials for depression and is a clinician-rated scale with scores based on clinical interview and family report [28]. It addresses both somatic and psychological symptoms of depression. Items are rated on either a 5-point scale (0 to 4) or 3-point scale (0 to 2), where higher scores represent increasing severity of depression. The scores of the 17 items are summed to obtain a total score. The HAM-D will be optional and possibly conducted at baseline and each follow-up visit if time allows.
3. **Glasgow Depression Scale for people with a Learning Disability (GDS-LD) and Carer Supplement (GDS-CS)**. Change in GDS-LD total score and change in GDS-CS total score between baseline and 16 weeks will each be secondary outcome measures. The GDS-LD and GDS-CS were developed to describe and quantify depressive symptoms in adults with mild-to-moderate learning disabilities [29]. The GDS-LD consists of 20 items scored from 0 to 2. The GDS-CS consists of 16 items scored from 0 to 2. The 20 and 16 item scores are summed to obtain GDS-LD and GDS-CS total scores respectively. Higher scores are indicative of more severe depression. The GDS-LD and GDS-CS will be conducted at baseline and each follow-up visit. The GDS-LD and GDS-CS will be secondary outcome measures.
4. **Pittsburgh Sleep Quality Index (PSQI).** Change in PSQI total score between baseline and 16 weeks will be an exploratory outcome measure. The PSQI is a self-rated 19-item questionnaire which assesses sleep quality and disturbances over a one-month time interval [30]. It will be used to assess the sleep quality of study participants by parent/caregiver report.
5. **Clinical Global Impressions (CGI)**. The percentage of subjects who respond to treatment, with response defined as a 16-week CGI-I rating of 1 or 2, will be the primary outcome measure. A trained clinician will perform the CGI. The CGI is designed to take into account all factors to arrive at an assessment of symptom severity and response to treatment, including parent report, parent-rated measures, and clinician-rated measures (as described below) [31]. The CGI Severity (CGI-S) item is rated on a scale from 1 to 7 (1 = normal, not at all ill; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients). The CGI Global Improvement (CGI-I) item is also rated from 1 to 7 (1 = very much improved; 2 = much improved; 3 =

minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse). Clinically meaningful improvement will be defined as a CGI-I rating of 1 or 2. The CGI-S will be conducted at screen, baseline and the last follow-up visit. The CGI-I will be conducted at each follow-up visit.

Safety Monitoring:

Participants will be monitored for possible pregnancy throughout the study. If a participant is of childbearing potential, a urine pregnancy test will be obtained at Screen. A positive result on a urine pregnancy test will then be confirmed via a blood pregnancy test, and a positive result on a blood pregnancy test will exclude them from study participation. We will continue to assess for pregnancy at all monthly clinic visits by asking participants if they are sexually active and if they are using contraception. Participants of childbearing potential who are sexually active and are not using an approved contraception method will be asked to complete a urine pregnancy test. A positive result on a urine pregnancy test will then be confirmed via a blood pregnancy test, and a positive result on a blood pregnancy test will exclude them from study participation.

Adverse events will be collected via a structured side effect rating scale completed with the participant and their primary caregiver. This will include a list of side-effects that have been reported with fluoxetine at a rate greater than 10% including sexual dysfunction, anorexia, diarrhea, nausea, dry mouth, anxiety, drowsiness, headache, insomnia, yawning, asthenia, tremor, and pharyngitis. Each of these side effects plus any additional complaints will be rated at baseline on a 4-point scale by the caregiver as follows: 0 = none; 1 = mild; 2 = moderate; 3 = severe. This scale is similar to that used by the RUPP Autism Network. Suicidality will be assessed at each visit by directly asking the subject (when verbal skills are sufficient) and the caregiver about any thoughts or behaviors that directly or indirectly might indicate suicidality (e.g., morbid thoughts, self-injury, statements about life being not worth living), when indicated by positive responses. At baseline, if suicidality is endorsed, the Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered per the instructions at www.cssrs.columbia/ed/clinical_trials.html. The C-SSRS will also be administered at each subsequent visit following the first report of suicidality. Subjects and caregivers will also have information on how to contact the on-call physician from our practice group who provides coverage 24 hours/day and 365 days/year. Physicians taking call are familiar with research protocols and can contact the principal investigator at any time.

All adverse events picked up on the rating scale as new will be recorded by the physician. The physician will also ask about any visits to the doctor, new medication use (e.g. OTC cold medicine), or any other complaints, in order to be confident that most adverse events are uncovered. The physician will keep a running log of adverse events that will record the date of onset, date of resolution, seriousness, severity, and relationship to study intervention (e.g., definite, probable, possible, remote, or none) as well as whether the adverse event led to a change in study intervention or other treatment.

A physician will review vital signs as they become available. All significant adverse events as well as the progress of the study will be reviewed and discussed in detail at the biannual meetings of the Lurie Center Data and Safety Monitoring Board (DSMB). The DSMB includes rotating members of the Lurie Center including pediatricians, pediatric and adult neurologists, pediatric and adult psychiatrists, and independent members outside the Lurie Center.

If at any time during the course of the study, the DSMB judges that the risk to subjects outweighs the potential benefits, the DSMB shall have the discretion and responsibility to recommend that the study be terminated.

Schedule of Measures:

Table 1. Schedule of Measures		Treatment Phase

Measure	#Screen ^^	#Baseline ^^^	Week 2^	Week 4^^^	Week 6^	Week 8^^^	Week 10^	Week 12^^^	Week 16^^^
Parent Ratings [1]									
Demographics	X								
SCID-5 [2]	X								
MADRS [3]	X	X		X		X		X	X
HAM-D [4] (optional)		X		X		X		X	X
GDS-CS [5]		X		X		X		X	X
PSQI [6]		X							X
Subject Assessments									
Vital Signs, Height, Weight (optional for remote visits)	X								X
Urine Pregnancy Test [7]	X								
Pregnancy Assessment				X		X		X	X
MADRS**	X	X		X		X		X	X
HAM-D**(optional)		X		X		X		X	X
GDS-LD**		X		X		X		X	X
Stanford-Binet-5 (SB-5) or other cognitive assessment	X								
Treating Clinician									
DS Diagnosis [8]	X								
Diagnostic Exam including medical/psychiatric history	X								
Health/Behavior Review	X								
Adverse Effects Review		X	X	X	X	X	X	X	X
CGI-Severity [9]	X	X							X
CGI-Improvement [10]				X		X		X	X
Suicide Assessment [11] / C-SSRS [12]	X	X	X	X	X	X	X	X	X
Concomitant Treatments	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

#Screen and Baseline Visits may be combined into a single visit if subject clearly meets eligibility criteria. ^Telephone Visit; ^^In clinic; ^^^In clinic, Zoom, or telephone;**Administered when emotional regulation, cognitive, and communicative abilities allow; [1] Parent or primary caretaker ratings; [2] SCID-5 = Structured Clinical Interview for DSM-5; [3] MADRS = Montgomery-Asberg Depression Rating Scale; [4] HAM-D = Hamilton Depression Rating Scale; [5] GDS-CS = Glasgow Depression Scale for people with a Learning Disability Carer Supplement; [6] PSQI = Pittsburgh Sleep Quality Index; [7] Females of child-bearing potential only; [8] genetic testing or clinical diagnosis; [9] CGI-S = Clinical Global Impression for Severity; [10] CGI-I = Clinical Global Impression for Improvement; [11] Suicide Assessment included in Adverse Effect Review; [12] Columbia-Suicide Severity Rating Scale (C-SSRS) will only be administered to participant and/or parent if any positive suicidal ideation is reported on Health/Behavior Review (screen) or Adverse Effects Review (baseline and all subsequent visits). Each visit following the first report of suicidal ideation will include the administration of the C-SSRS.

Drug Compliance

Families will be asked to return drug diaries within 5 business days of the scheduled Week 2, 4, 6, 8, 10, 12, and 16 visits. The study coordinator and/or PI will calculate drug compliance based on the number of missed doses between visits. Adequate compliance will be defined as ≥70% of doses. If compliance falls

below this threshold and/or drug diaries are not returned, the subject may be discontinued from the study, per PI discretion.

7. Risks and Discomforts

Overall, the risk to the subjects in this research are essentially no different from those that would exist in standard clinical practice, but the research proposed offers considerable promise in improving our understanding of the treatment of depression in individuals with Down syndrome. Foreseeable risks and discomforts include:

Drug-free washout interval

Withdrawal of a medication prior to the study will only be pursued in cases for which the current medication is not effective or is causing intolerable side effects. In collaboration with the prescribing clinician, the medication will be gradually tapered according to best clinical practices with close monitoring for symptom worsening.

Fluoxetine Treatment

Fluoxetine, an SSRI, has been well tolerated in children, adolescents, and adults. Common adverse reactions (>10%) include, asthenia, nausea, diarrhea, insomnia, nervousness, anxiety, and somnolence. Less common adverse reactions (<10%) include flu symptoms, decreased appetite, dry mouth, dyspepsia, constipation, dizziness, tremor, sweating, fever, vasodilation, flatulence, vomiting, weight loss, decreased libido, abnormal thinking, yawning, rash, pruritis, and abnormal vision. Very rarely, SSRIs may increase the risk of bleeding, a mixed/manic mood episode, suicidal thoughts, and/or QT prolongation. There is also the rare but potential risk of serotonin syndrome. If discontinued abruptly, fluoxetine discontinuation syndrome including flu-like symptoms, insomnia, nausea, balance problems, sensory disturbances, and hyperarousal may occur.

We will assess for these symptoms at all phone, video, and in-person visits. Any side effects will be closely monitored and recorded. In order to manage a side effect or suspected adverse event, the treating clinician is free to delay a scheduled increase or reduce the dose of the study medication. The dose schedules described above are guides only.

Fluoxetine has a half-life of 4 to 6 days. No specific laboratory monitoring is recommended with fluoxetine treatment.

<u>Allergic Reactions</u>
An allergic reaction can occur. Allergic reactions can be mild or serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. Participants will be instructed to call the study doctor immediately if they suspect they are having an allergic reaction. Participants will also be instructed to call 911 immediately and get medical assistance if they are having trouble breathing.

<u>Risks to an Embryo or Fetus, or to a Breastfeeding Infant</u>
Fluoxetine and its metabolite cross the placenta and are also present in breast milk. The effect of fluoxetine on an embryo or fetus, or on a breastfeeding infant, can be harmful. Due to these risks, individuals cannot take part in this study if they are pregnant, trying to become pregnant or breastfeeding. If a potential female participant is of childbearing age, a urine pregnancy test will be obtained at Screen, and a positive result will exclude them from study participation. Potential participants who are sexually active or able to become pregnant will be required to agree to use an approved birth control method for the entire study and for at least two weeks after the last dose of study drug. Acceptable birth control methods for use in this study are abstinence, condoms, or birth control pills.

Suicide Risk
Suicidality will be assessed at each visit by directly asking the subject (when verbal skills are sufficient) and caregiver about any thoughts or behaviors that directly or indirectly might indicate suicidality (e.g., morbid thoughts, self-injury, statements about life not being worth living). The baseline C-SSRS for any subject who endorses suicidality will be done per the instructions at ww.cssrs.columbia.edu/clinical_trials.html. The C-SSRS will also be administered at each subsequent visit following the first report of suicidality. If the subject answers "Yes" to Question 4 or 5 on the C-SSRS, the study physician will be notified immediately, and the subject will be emergently evaluated by a licensed study clinician for appropriate assessment and triage. Subjects who develop significant suicidal ideation (plan, gesture, attempt) will be treated and removed from the study if indicated.

Health Assessments, Behavioral Assessments and Checklists

The data in the study are collected for research purposes, but steps will be taken to minimize any risks and discomforts for participants and families. The content of the clinical measures are not deeply personal in nature and are clearly most relevant to the participant's diagnosis, overall functioning and behavior. To minimize the risk of psychological stress that could result from administration of questionnaires and to allow for more flexibility in time, families will be allowed to complete measures at more than one visit or remotely by phone/videoconference if necessary. Stress during administration of assessments to participants will be minimized by promoting awareness among investigators and coordinators of the signs that a participant may need a break and allowing them to take one.

Loss of Confidentiality

Efforts will be made to avoid loss of confidentiality such that the subject's protected health information will not be shared with other people outside of the research study. All records with identifying information will be kept in a secure (locked, non-public) area located at the Lurie Center.

To minimize the risk of loss of confidentiality, participant protected health information will not be shared with anyone not involved in the research study. Subjects' names and specific individual identifying information will not be disclosed in published reports, although this information may be reviewed by the sponsor and/or its representatives and regulatory agencies for the purposes of verifying clinical trial procedures and or data. Records containing identifying information will be stored in a locked area at the Lurie Center or MGB approved online drive, such as REDCap, to which only approved study staff will have access.

8. Benefits

The subject will benefit from a comprehensive medical and psychiatric evaluation. In addition, the subject will receive close monitoring through clinic visits for the duration of the study. Subjects will have the opportunity to receive drug treatment with the potential to be effective for their disorder.

Down syndrome is a chronic severe illness and depression is a common co-morbidity that affects the well-being of the patient and his/her family. Research is necessary to further understand how best to treat depression in DS including the development of tolerated and effective pharmacologic interventions.

9. Statistical Analysis

Sample Size Considerations:

A meta-analysis investigating the effectiveness of fluoxetine treatment estimated the intent-to-treat probability of response to treatment as measured using the CGI-I to be 44% [32]. In addition, the lower bound of the 95% confidence interval for response to treatment from our retrospective study excluded values less than or equal to 50%. A sample size of 20 provides a greater than 90% chance of observing a response rate of 35% or greater if the population probability of response is 44% or greater and a greater than 90% chance of observing a response rate less than 35% if the true probability of response is 20% or less. For safety outcomes, if there is a serious or severe adverse event associated with fluoxetine treatment in the population of adults with DS that occurs with a frequency of 10% or greater, we will have an 85% or greater chance of observing it in the study and concluding there are safety concerns with fluoxetine use for depression in adults with DS, assuming at least 90% (n=18) of participants remain in the study long enough to experience the event. For tolerability, assuming at least 85% of patients complete treatment or withdraw due to adverse effects, a sample size of 20 provides greater than 90% chance of observing a dropout rate due to side effects less than 36%, assuming at least 80% of adults with DS and depression in the population can tolerate a 16 week treatment course, and at least an 80% chance of observing a dropout rate due to side effects of 36% of greater assuming no more than 50% of adults with DS can tolerate a 16 week treatment course. Assuming an overall completion rate of 70%, a sample size of 20 also allows estimation of mean changes in depression scale score and mean dosage at study completion with a 95% confidence interval half width of 0.6 standard deviations, assuming a correlation of 0.5 between baseline and week 16 measurements.

Statistical Analysis Plan:

We will estimate percentage response to fluoxetine treatment, and corresponding 95% confidence interval, for adults with DS using the proportion of participants with CGI-I scores ≤2 at 16 weeks. Participants with missing 16-week CGI-I scores will be treated as non-responders. Frequency of all side effects and adverse events and corresponding 95% confidence intervals will be tabulated. Percent tolerating treatment and corresponding 95% confidence intervals will be estimated using the proportion of participants who did not withdraw from the study before 16 weeks due to reasons other than side effects or an adverse event who discontinue treatment due to side effects or an adverse event. We will also use the 16-week study retention rate and corresponding 95% confidence interval, calculated as the proportion of the participants enrolling in the study who remain in the study for 16 weeks, as a measure of feasibility.

To estimate changes in depression scale scores, including the MADRS, HAM-D, GDS-LD, and GDS-CS, we will use repeated measures linear regression models, as implemented in PROC MIXED in SAS and fit using REML estimation, with repeated measurements of clinical scores as outcomes and time, in categories, as the predictor. We will allow unstructured covariance between repeated measurements from the same participant. Our primary interest will be only in the difference between baseline and week 16 scores, but all observed scores will be included as outcomes, given that partially observed scores may be informative for estimation. We will obtain an estimate of 16-week change and corresponding 95% confidence interval using a contrast of the week 16 and baseline model parameters. Sensitivity to change will be compared between scales using standardized effect sizes, calculated using the model-estimated 16-week change in each outcome divided by 1) the model-estimated standard deviation of the outcome at baseline and 2) the model-estimated standard deviation of the change score. Spearman correlations will quantify the strength of association between change in depression scale score and CGI-I ratings among those with observed 16-week data. We will also tabulate and compare the percent of item-level missing data for each scale.

Mean dosage and 95% confidence interval will be calculated among those who complete 16 weeks of treatment. Minimum, median, and maximum dosage will also be reported. Confidence intervals for binomial proportions will be calculated using Wilson's method. All confidence intervals will be two-sided.

10. Monitoring and Quality Assurance

Data Monitoring

The substantial effort and resources that will be devoted to collecting data in this project will be matched by an equally substantial commitment of effort and resources to edit, verify, correct, update, and assemble the resulting data files. Our data management system incorporates quality control at every juncture from data collection through analysis. We have found that this bottom-up approach to data quality is essential, since there is no single procedure that will verify and correct erroneous data. The PI and research assistant are responsible for data collection and accuracy of record keeping and the researchers will convey an attitude that the data management procedures be treated with unwavering gravity, therefore maintaining a high level of quality for this project.

When a participant is enrolled in the study, they will be assigned a unique identification number that is used to identify all data associated with that person, including hard copy, biological specimens, and computerized data. Unique identifiers will be linked to personal data such as names and addresses only by use of a restricted password, thus assuring confidentiality. Data will be collected on hard-copy forms and then verified by data entry personnel. All of the hard copy research data is kept in locked file cabinets at the Lurie Center. Only the PI and primary research assistants will have access to these files, ensuring security of the hard copy records.

We have taken several steps to ensure the quality of data entry. Once data is obtained, the clinician will review the form to make sure that all required items are completed before giving it to the research coordinator responsible for data entry. Several quality control measures are built into our computerized data management.

The electronic database used to house these data until analyses are needed will be a web-based electronic data capture program created uniquely for this project. The database will be password protected and only certain users will be given access to the web-based program. This will protect the electronic data against any unauthorized persons from entering the dataset and jeopardizing the integrity of the data or engaging in some sort of malicious piracy.

As this project matures into the data analysis stage, data will be queried and exported to statistical software for data analysis.

Safety Monitoring

A physician will monitor adverse effects at each visit. In addition, he or she will review vital signs and laboratory data, as they become available. All of these values are recorded and then reviewed continuously by the PI. All AEs that arise are recorded by a physician. This includes documenting the date of onset, duration, severity, seriousness, and relationship to study medication. Any severe or serious AEs will be reported as soon as possible to the PI. All significant AEs as well as the progress of the study will be reviewed and discussed in detail at the biannual meetings of the Lurie Center Data and Safety Monitoring Board (DSMB). The Lurie Center DSMB includes rotating members of the Lurie Center including pediatricians, pediatric neurologists, child and adolescent psychiatrists specializing in developmental disabilities. All serious or unexpected AEs that are possibly related to drug treatment will be reported to the Partner's IRB within 3 working days from notification of the event. Examples of serious AEs include: death, life-threatening event, inpatient hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, and events that require medical or surgical intervention to prevent death, disability, or hospitalization. An unexpected AE is one that is not described in the protocol. Any serious or unexpected AE that is possibly related to fluoxetine will be reported to the IRB according to the reporting guidelines. Any action resulting in temporary or permanent suspension of the study will also be reported to our IRB.

Adverse events will be documented on the Adverse Effects Review form and Adverse Events Log as described above. All AE data will be captured in the electronic database and reviewed at the biannual DSMB meetings. The DSMB will report to the investigator any AEs occurring at a greater than expected frequency. The Investigator will provide this information to the local IRB and sponsor at the time of annual renewal.

Quality Assurance

The Principal Investigator will obtain IRB approval of the protocol and informed consent. All research personnel assigned to the protocol, including the Principal Investigator(s), Clinical Coordinator(s), and study staff, will be required to complete a computer-based training course on the Protection of Human Research Subjects as required by Partners Institutional Review Board. The Study Coordinator will maintain annual documentation of continuing IRB approval. The Principal Investigator will ensure compliance with regulations related to protection of human subjects, specifically including Title 21 CFR 50, 56, and 312 and Title 45 CFR 46, and ICH Good Clinical Practice.

Protocol adherence will be monitored by the principal investigator. If any protocol changes are needed, the PI with the help of coordinators will submit a modification request to the IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change as outlined in the Partners Human Research Committee.

11. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐Additional privacy and/or confidentiality protections

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APPENDIX A

Data Monitoring Committee / Data and Safety Monitoring Board Appendix

- *To be completed for studies monitored by Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) if a full DMC/DSMB charter is not available at the time of initial IRB review.*
- *DMC/DSMB Charter and/or Roster can be submitted to the IRB later via Amendment, though these are not required.*

A Data Monitoring Committee (DMC) or Data and Safety Monitoring Board (DSMB) will be convened for safety monitoring of this research study. The following characteristics describe the DMC/DSMB convened for this study (Check all that apply):

☒ The DMC/DSMB is independent from the study team and study sponsor.

☒ A process has been implemented to ensure absence of conflicts of interest by DMC/DSMB members.

☒ The DMC/DSMB has the authority to intervene on study progress in the event of safety concerns, e.g., to suspend or terminate a study if new safety concerns have been identified or need to be investigated.

☐ Describe number and types of (i.e., qualifications of) members:
Click or tap here to enter text.

☒ Describe planned frequency of meetings:
biannual

☒ DMC/DSMB reports with no findings (i.e., "continue without modifications") will be submitted to the IRB at the time of Continuing Review.

☒ DMC/DSMB reports with findings/modifications required will be submitted promptly (within 5 business days/7 calendar days of becoming aware) to the IRB as an Other Event.