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Protocol Title: Clinical trial to reduce cardiovascular health risks in patients with serious mental illness

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I. Background and Significance

Individuals with serious mental illness (SMI) experience pre-mature mortality compared with the general population, with cardiovascular disease being a major cause.[1-6] Patients with SMI have elevated risk for both metabolic and cardiovascular complications,[7-10] and treatment with second-generation antipsychotics (2GAs) contributes to these risks. National guidelines recommend regular monitoring for patients receiving 2GAs, however, evidence suggests that screening and treatment for cardiovascular risks by psychiatrists and primary care physicians (PCPs) remains infrequent.[11-13] Focus on primary prevention is also warranted and holds promise given the population's elevated risk levels.[14, 15]

Several safe and efficacious prescription drugs exist to prevent cardiovascular complications.[16-21] In particular, there is substantial evidence supporting primary prevention efficacy (e.g., in improving survival) and safety of statins and angiotensin receptor blockers (ARBs), including in patients with moderate lipid and blood pressure levels.[22-25] Moreover, many of these drugs now are available as low cost generics, which improves their cost-effectiveness.[26, 27] These treatments, however, are largely untested among SMI patients.[28]

Much of the care delivery in the U.S. is fragmented, which has hindered the ability to provide optimal care for many patients. The fragmentation has been associated with poor quality and poor coordination across conditions or sites.[29] Fragmentation is particularly problematic for mental health care due to common health care financing and delivery system characteristics, such as mental health carve-outs, as well as the stigma associated with mental illness. These issues likely contribute to failures in monitoring, treatment and adherence.[30-32] National estimates suggest that as few as 10% of SMI patients receive appropriate care for cardiovascular prevention.[11]Care coordination is a persistent challenge, especially with the SMI patient population. Numerous experiments such as the primary care medical home (PCMH) and accountable care organizations

(ACO) are ongoing, but to date have largely focused on primary care.[33-36] SMI patients, however, may view the psychiatrist's office (or mental health clinic) as their clinical home.[37, 38] They may be poorly adherent with recommendations to seek primary care.[39, 40] There also is evidence to suggest PCPs are less ready to care for SMI patients.[41, 42] Thus, a more patient centered approach for those with SMI would be to build the home in the mental health clinic.

Patient adherence to chronic drug therapy often is poor.[43-46] Non-adherence is exacerbated by complex regimens and polypharmacy, both of which are common for SMI patients.[47-51] Poor adherence affects not only the effectiveness of treatment but also presents challenges in analyzing intervention effects in RCTs, e.g., ITT estimates could be biased estimates of the per-protocol effect.[52-56] For example, post-randomization confounding will arise if sicker patients are less able to tolerate treatment or more likely to be non-adherent. Examples of potential confounders include the insight and cognitive ability.

A fixed-dose combination of pills could serve as a useful tool for minimizing non-adherence to treatment.[57-61] Use of moderate doses also yields clinical benefits with fewer side effects and complications.[62-64] Multiple trials have demonstrated that simplifying the regimen could facilitate effectiveness by improving treatment adherence.[65-70] A simplified, initial treatment strategy also could be more feasible for busy mental health clinics to implement. We propose that augmenting cardiovascular care within the mental health clinic could be a better structural integration strategy versus locating these efforts in primary care.[38, 71-73] This behavioral health home model arguably is the most patient centered design for the subset of patients with these established relationships and illnesses that require specialized care.[74-77] The intervention also could serve as a prevention strategy for behavioral health homes, i.e., "software" that supports the "hardware" of structural reforms.[78-81]

II. Specific Aims:

Our model posits that two major barriers to recommended cardiovascular treatment of patients with SMI are the fragmentation of medical care and poor treatment adherence. SMI patients typically receive care from psychiatrists located in mental health clinics; psychiatrists not surprisingly tend to focus on psychiatric illness, and are less comfortable prescribing non-psychiatric treatments given the range of initiation points, drug choices, starting doses, and treatment targets.[28, 83, 84] Moreover, mental health care in the US has significant resource constraints including on the number of clinicians, who in turn have limited time to address all patient needs.[85, 86] Thus, physical health concerns often are left to the primary care physician (PCP), who monitors potential metabolic or cardiovascular complications and initiates medical treatments; however, PCPs practice in different locations. Communication between psychiatrists and PCPs about individual patients can be difficult, especially in the absence of electronic health records and information exchanges, and a priori agreements about treatment goals and individual clinician roles and responsibilities.[87-92] Moreover, patients need to visit the PCP, with whom they may not have the same levels of access, relationship, or contact,

as they do with their psychiatrist;[93, 94] in addition to this PCP-visit adherence, patients also would need to adhere to the monitoring/treatment recommendations, which given the multiple drugs with potentially different administration schedules and symptoms of their mental illness could be challenging. Our intervention addresses both fragmentation and adherence by embedding treatment within the mental health clinic and simplifying the prescribing process by reducing the treatment options to a single one.

Our specific aims are as follows:
1) To compare the proportions of subjects in each arm who are on a cardiovascular treatment regimen and adherent to therapy during follow-up
2) To compare changes in composite and individual risk factor levels by arm
3) To compare composite and individual risk factor levels by arm, accounting for adherence variation over time via causal inference techniques.

Our hypotheses are that subjects in the intervention arm will have higher adherence and greater cardiovascular risk reduction compared with subjects in the control arm. We also hypothesize that the improvement in cardiovascular risk reduction will be mitigated after we account for adherence variation over time.

Trial Study Design Overview: This is an open-label, multi-site, randomized controlled trial aimed at assessing a simplified initial treatment approach (fixed-, moderate-dose combination) of statin and/or ARB, in this case simvastatin 20 mg once per day, and/or losartan 25mg once per day; for reducing cardiovascular risks among SMI patients who have received standing 2GA therapy anytime within 6 months prior to study enrollment. These patients are at elevated cardiovascular risk but frequently do not receive recommended monitoring or treatment. We hypothesize that this monitoring/treatment failure reflects both the fragmentation of care delivery for these patients and low patient adherence; accordingly, our trial assesses a simplified treatment initiation strategy that uses a moderate-dose, fixed drug regimen, which has been tested successfully in other patient populations and in other parts of the world. We have two study arms: 1) Intervention consisting of treatment initiation with a fixed-dose regimen of a statin and/or an ARB; and 2) Usual treatment; We will also follow non-Randomized subjects who signed consent, but were not eligible to continue on to randomization into the Intervention or Usual Treatment arms. Table 1 displays the six assessment steps. Assessment steps will be the same for each study site.

The efficacy of statins to reduce cholesterol levels and for ARBs to reduce blood pressure is not in doubt. In this study, we are assessing whether our study design enables a high degree of adherence with these medications. As described below, we will prescribe a statin and/or an ARB to eligible patients, including subjects in the study who are already on one of the two study medications and prescribe the one they are not on. In the latter case, we will use adherence with the new medication as the outcome.

Although we have designed this study to ensure the lowest possible adverse event profile by providing a fixed low dose of each medication, some patients nonetheless complain of side effects and some randomized to the intervention arm have decided to

discontinue the study medications as a result. Our goal in this study is to implement a strategy of cardiovascular risk reduction with maximal adherence; therefore we are not testing solely the effects of the specific study medications simvastatin and losartan. Given this logic, we would like to add a set of "second-line" medications to offer patients who would like to stop the simvastatin and/or losartan. Based on considerations of tolerability and cost, we have selected atorvastatin 10mg/d and valsartan 40mg/d as the second line medications. Valsartan and atorvastatin will be referred to as the "second line study drugs" in the remainder of this consent form. At the low dose of 10 mg/day for atorvastatin, adverse effects are less likely. The ASCOT trial found tolerability and safety of 10 mg atorvastatin daily to be comparable to that of placebo during a median of 3.3 years of follow-up; the CARDS trial found no significant difference in overall frequency of adverse or serious reactions between subjects treated with atorvastatin 10 mg daily or placebo during a median follow-up of 3.9 years. Likewise, valsartan at 40 mg/daily is well-tolerated and has evidence of clinical benefit in cardiovascular disease.

When a patient complains of subjective side effects (i.e. side effects that are not attributable to medical complications or reactions, such as elevated CK or rhabodomylosis), we will make the best estimate of which of the two study medications (statin or ARB) may be causing the side effect. This is aided by the fact the two medications often have divergent side effects (in particular myopathy vs. cough respectively). We will offer the patient the second-line medication to replace only the first-line medication that we believe is the culprit. If we cannot distinguish which medication may be causing the side effect, we will offer the option of switching both medications. If the patient tries the switch and ultimately would like to go back on the first-line medication, we will allow that. The rationale is that our goal is to keep patients on fixed low-dose cardioprotective medications, regardless of the specific medication.

Because each subject's medication regimen will be different and the reported side effects can vary greatly, we cannot provide an algorithm about which medication will be switched for which second-line medication. However, our procedure will be as follows: when a participant reports any side effect or adverse event (SE or AE) to study staff, the staff will notify the PI of the report in the same day. The PI will consult with study staff to determine whether it is possible the SE/AE is related to study medications (e.g. whether the subject is in the intervention or control arm, whether they have another condition that accounts for the report, whether they have been in an accident etc). And if so, the team will also assess whether the SE/AE can be attributed to one of the two study medications (e.g. myalgias for statin, or cough for ARB) for patients who are taking both study medications. Note that some patients in the intervention arm are taking only one of the two study medications and in these cases the attribution is more straightforward. If this attribution cannot be made with confidence, the team will consult with other study staff (Dr. John Hsu – coPI for the study from MGH Internal Medicine, Dr. Daniel Singer from MGH Cardiology, Dr. Eldrin Forster from BWH Cardiology) for further discussion of the case and additional recommended laboratory or other assessments.

If the AE/SE is possibly related to study medications:

1) the PI and study staff will consider whether there are potential means for mitigating the complaint (e.g. take with food, change the time of day of medication administration etc) and offer these to the participant.
2) If these are unacceptable to the participant or they are tried and found to be not effective, the participant will be offered the option of stopping the study medication they are on and starting the second-line study medication as outlined in this amendment. The risks and benefits of the second-line medication will be discussed with the participant as was done for first-line medication. For participants who agree to try the second-line medication the team will order and provide the medication as outlined.
3) The staff will remind the participant both at Step (1) and Step (2) that they are free to stop the study medication at any point if they so choose.

Note that when a participant stops a first-line medication and starts a second-line medication, this will likely be out of cycle for our 90-day medication dispensation schedule. To maintain maximum flexibility of scheduling in those cases and to avoid waste, we will have the ability to dispense 45 tablets of the second-line medication instead of 90 so the participant can return for their next scheduled visit and subsequently go on the 90-day schedule.

As always, if a patient chooses to stop the study medication or becomes non-adherent with it despite our offer of second-line medications, we will note this information. Patients will not be offered second line medications in the event of a medically significant adverse reaction such as elevated CK or rhabdomylosis. Participants will only be offered second line medications when complaining of subjective side effects with no medical complications (e.g. headache or abdominal pain with no relevant changes in blood samples). Participants who start second line medications will be asked to return in 2-4 weeks for a safety check similar to when participants started the first line treatments.

Table 1: Assessments

Step 1: Recruitment
Clinicians review their list of scheduled patients to identify potential subjects and ask these patients if they are interested in a research study. If patients agree, the research team approaches them to describe the study, obtain consent, sign DMH authorization form (if applicable), sign the APCD access release (optional), and schedule initial visit.

Step 2: Eligibility Screening
RAs conduct initial interview
Study nurses collect (screening) blood samples and vital signs, e.g., weight and height, and blood pressure
RAs collect urine pregnancy tests for all women of childbearing potential.
After the screening laboratory tests are available, study nurses will assess the eligibility for each potential subject and conduct the initial safety check. For example, if there are any subjects who appear to have signs of active cardiovascular disease or diabetes, we will intervene immediately via referral to PCP office or ED visit as appropriate.

Step 3: Baseline and Medication Visit (eligible subjects asked back for a medication visit)
Random assignment of eligible subjects into one of two study arms: Intervention vs. Usual Treatment
Subjects who are ineligible will have the option of participating as a Non-Randomized subject where study data will be collected.
Study nurse prescribes fixed dose statin and/or ARB drugs (Intervention arm only).
If subjects are randomized into the treatment arm and are already taking either a statin or any anti-hypertensive medication, they will be prescribed only the drug they are not already taking (e.g. participants on a statin will be prescribed only losartan).
If subjects are already taking either a statin or anti-hypertensive medication, we will not alter the dosage of the previously prescribed medication.
We will send letters about the trial to the subject's PCP, regardless of subject's randomization.
Intervention arm subjects will get an additional blood draw in-between the medication visit and first follow-up visit to ensure it is safe for them to continue taking the study medications.

Step 4: Follow-up Visits (every 3 months for 12 months)
RAs conduct follow-up interviews, perform pill counts, and collect urine pregnancy tests (all arms)
Study nurses collect blood samples and vital signs; conduct safety checks; track visits (dates, clinician type), diagnoses, prescription drugs (names, doses, pill counts of cardiovascular drugs), and medical events (all arms)
Study nurses will record and reconcile medication lists at every visit, and note changes in medications.
Study nurse prescribes additional fixed dose statin and/or ARB drugs (Intervention arm only).
Participants who have baseline CK values within 2*ULN will be enrolled in the study. If these participants are randomized into the treatment arm, and will be receiving treatment with a statin, they will be asked to come for additional safety blood draws once per month in addition to one draw one week following the first dose of study drugs. This draws will be done to ensure participant safety while taking the study medications. If a trend of increasing CK is observed, the study medications will be discontinued (Intervention arm only).

Participants prescribed the ARB who exhibit symptoms of hypotension (e.g., syncope, dizziness) and/or have an SBP measurement of <100 mmHg at the follow-up visit will additionally be evaluated for orthostatic hypotension and tachycardia. Study PIs will be notified, and will make a decision based on these criteria to either continue or discontinue the ARB at this time. These participants will be asked to come back within one week of their follow-up visit for an additional blood pressure check. (Intervention arm only).
Step 5: Final Assessment All items from step 2 (Eligibility Screening), plus below items: RAs conduct final exit interview Study nurses conduct study exit plans / transfer of care
Step 6: Post-Study Follow-up Visits (every 6 months for 12 months after Final Assessment - Participants in all study arms) RAs conduct follow-up interviews and perform pill counts. Study nurses collect blood samples and vital signs; track visits (dates, clinician type), diagnoses, prescription drugs (names, doses, pill counts of cardiovascular drugs), and medical events Study nurses record and reconcile medication lists at every visit, and note changes in medications. The 12-month post follow-up visit will follow the same protocol as Step 5.

III. Subject Selection

Eligibility: Eligible subjects will have incident or prevalent (i.e., first episode or chronic) cases of SMI. In this study we have defined SMI as schizophrenia, schizoaffective disorder, or bipolar disorder. The study's definition of SMI also includes subjects with major depressive disorder, or psychosis NOS with some evidence of functional impairment (an inability to work or live independently and/or being on disability income). Note that the bipolar patients, and some unipolar depression patients, at our study site generally have severe disease and many are on chronic 2GA regimens. Also, many subjects with MDD at our study sites have psychotic features and require chronic 2GA treatment as well. Subjects must have received standing treatment with a 2GA anytime in the past 6 months, and receive their mental health care at one of 4 study sites: McLean Hospital, BayCove Gill Clinic, Mass Mental Health Center, Edinburg Center or Massachusetts General Hospital Outpatient Bipolar Clinic. We will not carry out diagnostic interviews and instead will include all patients with an eligible chart diagnosis, as indicated by subject's psychiatrist, in order to maximize the representative nature of the sample and to more closely approximate how this intervention could be operationalized in real-world practices.

Eligible subjects also must be stable with respect to their psychiatric conditions, e.g., prevalent cases have no psychiatric hospitalizations in the past 4 weeks. Because we are interested in a viable, real-world intervention, we will include subjects with existing relationships with other non-psychiatric clinicians and collect information on physicians seen before and after randomization; we will also include subjects who are already

receiving treatment for increased cardiovascular risk (i.e. subjects who are already prescribed either a statin or ARB drug). In this case, subjects will be given the remaining non-prescribed medication (e.g. subjects already receiving treatment with a statin will be prescribed losartan, and subjects receiving any anti-hypertensive treatment will be prescribed simvastatin). We will not alter the dosing of any previously prescribed medication, including any statin or anti-hypertensive medications. Subjects who are already receiving both medications, will be included in the non-randomized group. We will include patients with state appointed legal guardians or health proxies with durable power of attorney who have the specific authority to make mental health care decisions or to consent to participate in research. Guardians or proxies will use substituted judgment when deciding to enroll the patient in this research study. State sponsored legal guardians are the preferred surrogate, however, we will accept health care proxies with durable power of attorney; no other form of surrogate will be accepted, participants with other forms of surrogates that are unable to provide consent on their own will be excluded. The relationship between the participant and surrogate will be recorded on the informed consent form that all parties have signed. We will include patients who cannot speak English. We will follow the PHRC policy on Obtaining and Documenting Informed Consent of Subjects who do not Speak English as found on the PHRC website at http://navigator.partners.org/ClinicalResearch/Non-English_Speaking_Subjects.pdf. An attempt to administer all aspects of the proposed research will be made through the use of an official translating service (i.e. electronic, phone, or in person translator). The consenting process for non-English speakers will always be done in the presence of an official hospital translator when using the short from consent procedure. Any measures that are invalidated by translation will be discarded during analysis. Since our primary measures are adherence, evidence through pill counts and improvement in metabolic risk factors, there is still value to the study and the subject to participation of non-English speakers.

Other inclusion criteria include the following:

- Incident or prevalent cases of SMI: including schizophrenia, schizoaffective disorder, bipolar disorder, major depressive disorder, and psychosis NOS with some evidence of functional impairment.
- Age 18 years and older.
- Recent treatment with a 2GA, e.g., having received treatment with a standing 2GA anytime in the past 6 months. Concomitant psychotropic medications will be allowed as there are no contraindications with this regimen. Ongoing treatment of their mental illnesses at one of three mental health clinics: McLean Hospital (McLean outpatient clinicians), BayCove, Edinburg Center, and Mass Mental Health Center, defined as entering one of the treatment programs as a de novo patient (new disease) or having been diagnosed >2 years ago and had at least six visits in the past 12 months (prevalent disease).

The exclusion criteria are as follows:

- Unstable/active disease or potential contraindications, e.g., diabetes, unstable angina or recent acute coronary syndrome, pregnancy, very high risk factors on the screening labs (e.g., CPK>2*ULN, liver disease (AST> 2*ULN ALT> 2*ULN)

; A1c>7%;), renal failure (creatinine ≥1.3mg/dL or GFR<60 mL/min/1.73m^2), liver failure, or both statin and angiotension drug contraindications (when possible we will provide the study medication that does not interact with previously prescribed medications, i.e. subjects taking lithium will only be prescribed simvastatin since anti-hypertensives are contraindicated with lithium). Participants whose screening labs indicate high cholesterol (LDL > 200 mg/dL), hypertension (SPB > 160 mmHg), or hypotension (SBP< 120 mmHg) will be included; however we will not prescribe both study medications; we will only provide the study medication that can be taken safely. For example, a participant with high cholesterol will be referred to their PCP for care and administration of a statin, but could still receive losartan in the treatment arm.

- Unable to provide informed consent, e.g., has dementia, developmental disability, other cognitive disorder, or fails screening mini-mental status exam.
- Women who are pregnant or breastfeeding

Subjects that sign consent and but are excluded during the eligibility screening may continue in the study in the Non-Randomized Arm if they choose. The above criteria indicate exclusion from the randomized arms of the study. Participants who meet exclusionary criteria (i.e. receiving medications from both of the study medications classes, incidence cases of diabetes, or elevated lab values) will be included in the non-randomized arm and followed in a similar fashion to the Usual Treatment Group. Participants who would like to participate in this group and have already signed consent will be asked to sign the new consent form that reflects these procedures.

IV. Subject Enrollment

Recruitment: On recruitment days, the study nurse and research assistants (RA) will work with clinicians to identify potential study subjects among the patients scheduled for the day. Clinicians will identify people potentially eligible for participation. Once someone has consented to participate in the study and signed a DMH authorization form, if applicable, and potentially signed the APCD authorization, the study RA and NP may access medical records to verify study eligibility. Study staff will regularly check medical records for the duration of the study period (approximately once every 3-months). Consent will always be obtained, and the consent form signed, by a licensed physician investigator or by an APRN/NP listed on the protocol. In the event that the APRN/NP is not present when a potential participant wants to sign the consent form, the NP will be telephoned so that any questions can be answered prior to the subject signing the consent. The participant will sign the consent form, the RA will initial next to the signature, and then the APRN/NP will then sign the consent form at the first study visit in the presence of the subject. This will provide an additional opportunity for the subject to speak with one of the prescribing clinicians before both parties have signed the form ad study procedures begin. We will also recruit patients through the Partners Online Research Portal (clinicaltrials.partners.org). These advertisements will be approved by the Partners IRB. In addition, we will use the Research Patient Data Registry (RPDR) to screen and recruit potential study participants receiving care at our Partners study sites, McLean Hospital and the Massachusetts General Hospital

Outpatient Bipolar Clinic. After running data queries using the study's inclusion and exclusion criteria, we will request detailed data through RPDR in order to directly contact those patients who are eligible for the study and who have consented to be contacted in future for research purposes. Detailed data requests, including identifying information such as medical information and contact information, will be approved by the Partners IRB.

Random (1:1) allocation: We will assess eligibility, NP's will conduct the informed consent process, then randomize eligible subjects to one of two arms: 1) fixed-dose statin and/or ARB; or 2) usual treatment with greater monitoring. In both arms, the patient's clinical care remains within the original mental health clinics. We will use a computerized random number generator. Participants unable to be randomized due to eligibility issues discovered at the first study visit will still be followed as not-randomized subjects.

Randomization scheme: We will start with a concealed, simple subject-level randomization scheme, e.g., web or telephone delivered random sequence.[104-106] We also will consider concealed, block randomization schemes, e.g., accounting for clinic and time with randomly varied block sizes. An investigator not involved in the arm assignment or clinical care of subjects will perform the generation and allocation concealment.

Intervention: The multi-component intervention exploits a number of strategies from incentive theory and behavioral economics, including: a) a simplified drug regimen; b) free treatments; c); framing of goals and goal setting; and d) focus on immediate cardiovascular risks within a larger plan for risk reduction.[107-114]

Control: We will compare the initial treatment intervention with usual treatment (control arm), with both arms superimposed on a system of regular monitoring base. The RA/APRN pair will make no effort to alter or influence treatment or use of that treatment for subjects in the control arm. Note that our goal in the Control arm is to characterize "usual treatment". We will not intervene in this care except in emergencies requiring us to notify the patient's treatment team. Some patients who need care for metabolic syndrome may not be receiving it – just as they would if not in our trial.

Follow-up: Up to 24 months. We will censor subjects (from the intervention) who receive a diagnosis of diabetes, when they develop a cardiovascular or cerebrovascular event, who die, or who leave the study health care systems. During each follow-up visit, the study nurse will review all prescription drugs and the RA will perform pill counts of cardiovascular drugs (we will ask subjects to bring all of their drugs in to each study visit). The study nurse will perform safety checks comparable to that during baseline evaluation. For subjects in either arm identified during our safety checks or who have events, we will recommend that they receive more intensive care from primary care physicians, cardiologists, or endocrinologists, and will message their clinicians. We will continue to monitor these subjects throughout the follow-up period albeit now on a more intensive treatment regimen.

At the end of the study, we will characterize the clinical care for subjects in both study arms, thus providing a detailed description of "usual treatment," and information about care received from other clinicians for subjects in the intervention arm. We will report on all clinicians seen (specialty, location, visit frequency and timing), conditions diagnosed and treated (psychiatric and medical), and cardiovascular conditions diagnosed and treated (major events such as ED visits or hospitalizations, diagnoses, drugs, doses). We will compile adverse events using the CATIE adverse event reporting tool as a base.[115]

Subjects will have the option to continue coming to follow-up visits after the 12-month endpoint every 6 months for another 12 months. We will not continue to prescribe medicine to subjects in the intervention arm, rather we would continue to collect data so we can get a longer-term picture of "usual treatment" for those in each study arm (including non-randomized). RAs will perform pill counts at these additional follow-up visits, to get information about medication adherence for an additional year. NPs will continue to draw blood and ask subjects about their medications and medical history. Participants who have already signed consent and would like to participate in the post-study year of follow-up visits, will be asked to the new consent form prior to starting study procedures.

Endpoints: The two main study endpoints at 12 months correspond to the study aims: A) cardiovascular prevention treatment including patient adherence to treatment; and B) individual and composite cardiovascular risk factors, e.g., modified Framingham risk scores that includes lipid profiles and blood pressures.
If subjects continue to be followed for an additional year, we will address the same study aims after the randomization portion of the study is over. This will be useful to understand what happens to participants after being a part of the study in terms of their treatment and medication adherence.

Compensation: Subjects will be compensated by check in 2-3 weeks from their study visit. They will receive $20 per study visit for Visits 3-5, and $50 each for the first, second, and both post-study follow-up visits. Participants will receive $100 for the final study visit at 12-months from study enrolment. Subjects randomized into the intervention arm will receive an additional $10 for the safety check blood draw. All additional safety check blood draws will also be compensated at $10 per additional draw. The total expected compensation amount for the first 12-months is $270 (intervention group). Subjects that participate in the post-study follow-up visits will receive $50 for each 6-month follow-up visit for an addition $100. The total expected compensation for a subject who completes the study and post-study follow-ups is $370. Compensation will come in the form of a check, which takes two weeks to process and will then be mailed to participants, or brought to the next study visit.

Visit	**Payment**
Baseline Visit	$50.00
Medication Visit	$50.00
Safety Check (Intervention Group)	$10.00

Follow-Up #1	$20.00
Follow-Up #2	$20.00
Follow-Up #3	$20.00
Final Visit	$100.00
Post-Study Follow-Up	$50.00
Post-Study Final Visit	$50.00
Any additional visit safety-check	$10.00

There is also a **bonus system** for follow-up visits that may earn participants up to $420 (Usual Treatment Group) or $430 (Intervention Group).

In order to receive a bonus, Follow-Up #2 and Follow-Up #3 need to be scheduled and attended within one month after the end of the scheduling window in order to receive the bonus**.** If the participant completes the visit outside of the scheduling window, they will still get paid the baseline payment of $20.00. The scheduling window refers to the two-week window within which a visit is due, which is 83 days from the prior visit. A member of the study team will contact participants to let them know when visits are due.

- If a participant completes Follow-Up #1, then staff will compensate $40.00 for Follow-Up #2.
- If a participant completes Follow-Up #1 and Follow-Up #2, then staff will compensate $60.00 for Follow-Up #3.
- If a participant completes Follow-Up #1 or Follow-Up #2 (but not both visits), then compensation for Follow-Up #3 will be $40.00

V. Study Procedures

Study Site: The study will take place at four sites: McLean Hospital, BayCove Gill Clinic, Mass Mental Health Center, Edinburg Center, and Massachusetts General Hospital Outpatient Bipolar Clinic. Study procedures will be the same at each site. Study staff will bring all study equipment, including study drugs, with them to the separate sites and carry out all study procedures, leaving no burden on staff from these sites.

Contacting patient's current treater: The only information to be shared with the PCP is the "PCP letter" (included in the IRB application). This letter will be sent out between the inclusion/exclusion visit, only for patients eligible to be randomized, and the randomization visit, when we find out what arm of the study the patient is going into. Since this letter is sent prior to randomization, the letter does not include information on what study arm the patient is assigned to. The letter states that the participant will be explicitly removed from the study if requested by the PCP for medical purposes. The logic of this design is as follows: ours is a randomized open-label study. The treatment as usual arm is intended to capture naturalistic primary care of our patients while the intervention arm tests the impact of a cardiovascular preventive regimen. In these trials, "contamination" across study arms is a major concern. This refers to a process

whereby the usual clinical care is enhanced due to awareness of the study aims. Clinicians who are aware that their patients' care is being evaluated on certain criteria may consciously or unconsciously pay more attention to these criteria. This effect typically makes the treatment as usual arm appear more robust and reduces the odds of detecting an intervention effect. Our goal is to avoid this contamination effect while also ensuring that PCPs are adequately informed and have an opportunity to intervene if they deem it necessary. As per our study design, there is no ongoing communication with the PCP. By sending them a letter before study arm assignment, we ensure that the PCP can request the patient be excluded. As the individual responsible for the overall medical care of the participant, the PCP has the power to veto patient participation in this study. The PI's name and contact information on this study will be included in the PCP letter so that the PCP may contact the PI with study design questions. If the PCP desires to know whether the patient is going on the medication arm they then have to go through routine channels (e.g. ask the patient) to obtain this information. If the PCP contacts the research team asking for this information, we will provide it. But this approach minimizes "contamination" from the study team, and approximates routine clinical care if the patient were placed on a medication by another clinician. To further minimize contamination we will not communicate routine lab results to the PCP. However if in the course of the study, should lab results require immediate attention, study nurses will triage and contact subject PCP accordingly.

We will send another letter at study completion informing the participant's PCP of the treatment the participant received as a part of their study.

Anytime staff attempts to contact a participant's PCP or any other provider, staff will confirm the contact information with the participant prior to attempting communication. This will be done to ensure that the participant still receives care from the indicated provider, as participants occasionally change clinics over the course of the study period.

Data Collection: During Recruitment (Step 1 in T1), all participants, or their legal surrogates, will complete a Consent Survey that asks 11 simple questions about the study such as "What is being studied in this study?" and "Will you lose any of your services or benefits if you refuse to participate?" For participants, or guardians/healthcare proxies who do not answer correctly, the study nurse or RA will repeat the information and re-administer the survey. Participants who still cannot complete the survey correctly will be excluded. Participants, or their guardians/proxies, do not need to answer each question exactly as indicated, but rather demonstrate understanding of the correct answer (e.g. participant does not need to provide the names of every illness studied in the research project, but can simply name one or say "psychotic disorders"). The participant's legal surrogate or proxy will make decisions using "substituted judgment," meaning that the surrogate must consider the subject's own views when consenting to this study. The relationship between the guardian or proxy and participant will be recorded on the informed consent form. Participants with legal guardians must still assent to the study verbally and through signing the consent form. Participant assent will be gauged at every study visit, informed consent being

acquired if and when a participant regains legal power of consent. The study visits will consist of 30-minute interviews with the study nurse, followed by 30-60 minute interviews with the RA. The study nurse will collect vital signs, blood samples, and prescribe the fixed-dose study medications for the intervention group. The nurse will also collect information on side effects/adverse events on medication, medication changes, information on ED visits/hospitalizations/PCP or other clinician visits/any other service utilization for medical/psychiatric purposes. The medication adherence assessment will include: self-report, RA pill counts, review of medical records, and independently collected pharmacy data (e.g., APCD) to examine drug dispensing. We will calculate chlorpromazine (CPZ) equivalents for standardized 2GA dose estimates.
In the RA portion of the visit, we will collect ancillary clinical data using standardized forms. Examples of potential items include age, gender, living condition, employment status, internet access, cancer screening history, socioeconomic status (using the Hollingshead scale), social support (using the Duke social support and stress scale), food and diet questionnaires, non-cardiovascular medical conditions, cardiovascular disease risk (using the Global CVD risk assessment), estimated IQ (using the North American Adult Reading Test), smoking status (using the Elyse Tobacco Questionnaire and the Fagerstrom Test for Nicotine Dependence), and clinical insight (using the Scale for Unawareness of Mental Disorder, SUMD). RAs will assess cognition using the BACS (Brief assessment of cognition in schizophrenia). In addition, the RA will complete the WHODAS 2.0 (WHO Disability Assessment Schedule) which assesses cognition, mobility, self-care, social interactions, and life activities (work, school etc.).[116-119]
Subjects will also be assessed on their medication attitude and adherence (using the Drug Attitude Inventory, the Voils medication adherence scale, and the Physician Trust Scale). We will refine the standardized data collection; assess feasibility, interpretability, and respondent burden; insure that the final instruments are feasible within the 30-minute interview; and insure that our instruments are consistent with current literature and latest expert opinion.
At baseline and all subsequent visits, the RAs will quantify psychiatric symptoms; we will train and periodically test RAs ability to do this. Since the SMI participants will be mixed diagnostically, the RA will complete symptom assessments; examples include the Positive and Negative Syndrome Scale (PANSS), Scale for Assessment of Positive Symptoms (SAPS), and Scale for Assessment of Negative Symptoms (SANS) for psychosis but also the Montgomery-Asberg Depression Rating Scale (MADRS)[120] Young Mania Rating Scale (YMRS),[121] Multnomah Community Assessment Scale (MCAS), Fagerstrom Test for Nicotine Dependence, International Physical Activity Questionnaire (IPAQ), and finally a Clinical Global Impression (CGI) scale.[122, 123] All instruments and questionnaires will be administered via Partners RedCap.
After each visit, the RA will also extract data from the patient's mental health clinic chart for information related to diagnostic changes, clinical developments, medication prescription, and any healthcare utilization.

The study nurse also will collect basic vital signs, e.g., EKG, weights, height (BMI, waist circumference), blood pressures and heart rate, and collect blood samples for laboratory tests, e.g., lipid panels, HbA1cs. As part of the baseline safety evaluation, we will collect additional laboratory test values, e.g., liver function tests. The study nurse

will receive laboratory values and provide appropriate follow up, which includes reporting any critical values to patient and care providers, referring for further treatment as indicated and documenting exclusion based on criteria listed in the protocol. The supervising physician of record for APRNs will be Dr. Dost Ongur.

Obtaining Study Drugs: Study nurse practitioners will prescribe study medication for subjects as follows: simvastatin 20 mg once per day, and/or losartan 25mg once per day or atorvastatin 10mg once per day and/or valsartan 40 mg once per day. The grant will pay for study medications at no cost to participants. The McLean Hospital Research pharmacy will procure the study medication for all study sites and dispense prescriptions in 3 month supplies. The study staff will pick up prescriptions from the pharmacy and provide to the subject during the study visit. Since the medications will be provided the same day, investigators will not store medications in any way, other than to transport the mediations to the various study sites. Study staff will follow the same procedures for procuring and dispensing medications at all external sites. That is, study staff will procure medications from The McLean Hospital Research pharmacy the morning of external site visits and transport the medications to dispense at each site.

Additional Data Sources: There are other noteworthy data sources for this trial: 1) clinic records; 2) electronic health records for two clinics; 3) APCD. RAs will systematically review the visit schedules and local medical records from each clinic for each subject. Additionally, McLean is scheduled to roll out its electronic health record (Epic Systems) during the course of this study, which we have extensive experience using in other settings.[131-134] These data sources will provide complementary data sources for cross-validation (e.g., pharmacy fills, see quality checks below) as well as longitudinal information on psychiatric visit adherence, primary care visit frequency, and major unfavorable clinical events, e.g., ED visits and hospitalizations for psychiatric or cardiovascular events.

The study staff will request that participants agree to have All Payers Claim Database (APCD) queried by study staff such that they may access all insurance claims made on behalf of the participant. The APCD is an excellent source of ancillary information to reconcile all patient report and medical record information. Participants will not be required to agree to have the APCD accessed in order to participate. There is a detailed data management plan that details how all data will be kept and how participant information with remain private. For secure data transmissions, we use a secure FTP, which is available through Partners Research Computing (RC). We then keep the data on our dedicated servers managed by RC, which are behind the Partners firewall. We limit data access such that only the programmer/analysts working on the project can access the data; the data remain on the servers at all time; and at no time, do any of the data leave the servers (e.g., no data on laptops, desktops, or other devices).

Blood Pressure Checks: Participants prescribed the ARB who exhibit symptoms of hypotension (e.g., syncope, dizziness) and/or have an SBP measurement of <100 mmHg at the follow-up visit will additionally be evaluated for orthostatic hypotension and

tachycardia. These participants will be asked to come back within one week for an additional blood pressure check and study PIs will be notified.

Subjects who exhibit a combination of any 2 of the 3 criteria (self-reported/observed symptoms, SBP <100 mmHg, or abnormal orthostatic measures) or all 3 criteria will be discontinued from the ARB for at least one week before coming back in for the additional safety follow-up. Study nurses will assess whether the signs/symptoms are still present, or have been alleviated after discontinuing the study drug. Study PIs will be contacted to make the decision to continue/discontinue the study drug.

If a participant exhibits only one of the three criteria at a routine follow-up visit (i.e. just self-report symptoms), we will not discontinue the ARB before the safety follow-up. If the subject continues to meet one of the three criteria at the safety follow-up, subjects will be asked to stop the ARB for at least one week, then come back in for reassessment. Depending on the nature of the symptoms, vitals, and blood pressure levels at this safety follow-up, study nurses will decide whether these symptoms are related to the ARB versus dehydration, other drug use, or other unrelated factors. Study PIs will be contacted and ultimately make the decision to either continue or discontinue the ARB. If the subject self-reports the above symptoms at the visit and they appear to be unrelated to any other physical signs at the safety visit, then study PIs/physicians will consider continuing the study drug and reassessing in a week versus stopping for one week and reassessing.

Once study PIs have come to a decision about continuing/discontinuing the ARB, all subjects will be asked to come back for an additional safety assessment one week after the decision to confirm that they are safe to continue the course of action recommended by our team.

Training/Skills Assessments: We have systematic RA and APRN research training programs in place:
Training: Dr. Öngür's division has an extensive RA training program directed by Ann Shinn, MD, which has sessions on participant recruitment, informed consent, chart review and discussion of symptom scales. Dr. Shinn first conducts live patient interviews watched by RAs, and then the RAs conduct interviews observed by Dr. Shinn. In all cases, trainees complete symptom scale forms; we have excellent inter-rater reliability for symptom scales (0.8-0.9). At the end of training Dr. Shinn certifies RAs as competent to carry out these assessments. RAs also will receive similar training to perform their chart reviews. The APRNs will be certified by the Hospital as able to carry out safety checks, vital signs, and blood draws, as well as prescribe medications in the state of Massachusetts as part their job duties. The APRNs will join the RA training described above for the participant recruitment and informed consent portion. Whenever possible we will use standardized processes and forms, e.g., standardized study laboratory order forms.

Data Entry: We will use several strategies to augment and evaluate the quality of data entry: 1) standardized forms, e.g., for laboratory test orders, subject interviews, and

medical record data abstraction; 2) structured data entry through a secure, server-based database system, e.g., MS Access; 3) double entry of standardized forms with routine error checks, e.g., every third subject; and 4) automated checks for value changes across observation points, e.g., sudden increase or decrease in symptom levels – flag values for additional review.

Additional Quality Checks: We also will perform complementary quality checks: 1) routine checks for missing values; 2) cross-validation of data (e.g., psychiatric symptom levels) by comparing study data vs. medical record information for a random sample of subjects; 3) cross-validation of adherence data: (a) self-report vs. (b) RA pill counts vs. (c) medical record (plus EHR/LMR for the two Partners clinics) vs. (d) APCD pharmacy records (both study arms – includes capture of any drugs prescribed by non-psychiatrists and/or dispensed by pharmacies);[135-137] and 4) periodic trend checks to identify and confirm large changes in any outcome or covariate values. During follow-up, we will ask any subjects who forget to bring their drugs to a visit for the pill count to bring their drugs in to their next clinical appointment for a "catch up" pill count. We will use a standardized process for addressing imputation of missing values or reconciliation of different values.

VI. Biostatistical Analysis

Analysis of Aim 1: Treatment: By design, all subjects in the Intervention arm will start by being under treatment. During the course of follow-up (FU), we expect that some will stay consistently on treatment, some will discontinue treatment (become non-adherent), while others will make transitions on and off treatment in various patterns (e.g., subsequent modifications made by any PCP and/or changes in adherence over time). In contrast, by design, subjects in the Usual Treatment (control) arm do not start on treatment; however, some will initiate treatment as a result of usual clinical care, e.g., PCP initiation. For this aim, in which we study treatment use at various time points, only an intent-to-treat (ITT) approach is relevant since whether or not subjects are on treatment is the outcome itself.

Characterization of Usual Treatment: We also will carefully describe care under Usual Treatment, including the timing of initiation, treatment choice, adherence, prescribing clinicians, and visit patterns for subjects in the control arm. We will characterize the involvement of other clinicians for subjects in both arms, and clinic traits.

Treatment Operational Definition: To start, we will use the same treatment definition for both study arms, i.e., current use of a statin and angiotensin drug. Because there are multiple potential drugs for cardiovascular prevention, we will alter this definition in a series of sensitivity analyses. For example, we will examine a minimal cardiovascular treatment variable in which we define treatment as current use of any cardiovascular drug, independent of the therapeutic class or mechanism of action. We also will examine a partial treatment variable in which we count the number of distinct cardiovascular prevention drugs.

Analysis approach 1: We will plot the percent on "adequate" CVD prevention care, at baseline and the four quarterly follow up times to monitor how treatment activity unfolds over time in the two arms of the trial. At any given follow-up point we will be comparing

two binary outcomes (on or off treatment) and will use standard methods for comparing two proportions to test statistical significance and get confidence intervals for the difference in the percent on treatment in the two arms. We will use a Bonferroni correction so the four separate tests or CIs will have an overall level of 0.05 or 95% CI, respectively.

Analysis approach 2: We will use all available follow-up data to construct a summary measure of the mean percentage of follow-up time during which each group was on treatment. Since we expect the distribution of outcomes to be non-normally distributed, we will get a test of significance for no difference between the mean outcomes in the two arms using a randomization test. A 95% confidence interval for the difference of percentage of time on Tx will be obtained using bootstrap methods. We will use STATA 13.0 for all analyses.

Analysis of Aim 2: ITT Effect on Cardiovascular Risk Factors: For aim 2, our primary outcome is the difference in summary risk level changes (e.g., modified Framingham score) between our two study groups, i.e., do intervention subjects experience differential changes in cardiovascular risk levels compared to control subjects. This outcome will be continuously measured (but not necessarily normally distributed).[138-140] We will also examine individual risk factor levels, including LDL, SBP, and HbA1c. By virtue of randomization and given the size of our study, the mean baseline values will be very close to equal, with the profile of the mean levels of the outcomes diverging over time. Our main analytic strategy is to use an ITT analysis, such that subjects provide data for the group to which they were randomized regardless of protocol adherence. Initially, we will get descriptive plots showing the profile of mean outcome over time in each group. This plot will be suspect if missing data (e.g., loss to follow-up) do not occur completely at random (MCAR). For more definitive analysis, we will use methods for analysis of repeated measures data that provide valid estimates of the profiles of mean outcomes over time under the weaker, missing at random (MAR) assumption that allows the probability of missing data to depend on measured characteristics. We also expect that the outcomes will be non-normally distributed based on our past experience in studying adherence. This likely bimodal adherence distribution could induce a corresponding bimodal distribution in the changes in outcome levels. All of the outcomes are likely to show this sort of non-normality. The HbA1c data also could be skewed. In general, we will therefore use analysis methods that are robust to non-normality.

For analysis of the repeated outcomes data, we will use econometric-style OLS linear model analysis of the repeated mean levels of the outcome over the five observation times (baseline + four follow-up times). This approach is robust to non-normal distributions. For constructing standard errors we will use cluster and heterogeneity robust estimation methods. Among estimation methods for this model, we will emphasize the use of the “fixed effects” (FE) option, which can be implemented in STATA using the xtreg command with the FE option. This essentially amounts to change score analysis that is generalized for use in situations with more than two repeated measures. This will provide estimates of the profiles of mean change from baseline in each of the treatment arms along with significance tests for contrasts between the two profiles. For plotting, the profiles of change will be anchored at the observed mean values in each arm at baseline. Inverse Probability (IP) weighting

methods will be used to account for possible endogenous loss to follow up in connection with the proposed analysis. Weighting will be based on baseline characteristics and for any given subject; the same weights will be applied to each repeated measure. We will finalize our analytic protocol before examining the outcome data, i.e., a priori delineation of the analytic protocol as is becoming the standard of analysis. We will use only marginal distributions to guide the appropriateness of the final choice of methods. Thus, we mitigate the potential for bias resulting from post-hoc choice of analysis or significance testing.

Analysis of Aim 3: Per-Protocol Effect on Cardiovascular Risk Factors: For Aim 3, we will study the same composite and individual risk factor outcomes as for Aim 2, but will estimate the per-protocol effect rather than the ITT effect. ITT is the effect of assignment to the strategies of interest; the per-protocol effect is the effect of following the strategies as indicated in the protocol and is the implicit target of inference. To estimate the per-protocol effect, however, one needs to make assumptions similar to those commonly made in the analysis of observational studies. Specifically, when adjusting for measured covariates, the valid estimation of the per-protocol effect requires that all fixed and time-varying factors that jointly predict the outcome and adherence to the assigned intervention are measured without error. We will adopt two analytic approaches, both involving adjustment via inverse probability (IP) weighting.
Analysis approach 1: We will artificially censor participants when they stop adhering to the assigned strategy. We will censor subjects in the active treatment arm if/when their adherence drops below 80% of the intended dose, based on estimates of the proportion of days covered (PDC).[141-144] In sensitivity analyses, other adherence cutoff points will be used, as in our other past studies.[145] For subjects in the control arm, we will follow two censoring strategies: (i) subjects will be censored if/when they start taking one of the drugs assigned to the active treatment arm, (ii) subjects will never be censored, which is equivalent to interpreting any treatment they receive as standard of care. We will conduct separate analyses under each of these two censoring strategies. We will compare the average outcome between arms at pre-specified time points during the follow-up. The outcome models will be similar to those described for Aim 2, but they will be fit to those remaining uncensored at the corresponding time. This approach requires no assumptions about the dose-response curve for adherence because only adherent subjects contribute to the fit of the outcome model.
Analysis approach 2: We will estimate the parameters of structural models that specify the dose-response curve for adherence in the treatment arm. We will use a flexible dose-response function that incorporates information on both cumulative dose and recency, and builds on previous trial data. This analytic approach is more statistically efficient because it does not involve artificial censoring, but will require extensive sensitivity analyses to ensure that the estimates are not sensitive to the choice of dose-response function.

Power Calculations: We anticipate having adequate power for this trial. To illustrate, we will focus on comparison of treatment use at one time point. By design, all subjects in the intervention arm will receive cardiovascular prevention treatment, while none in the control arm (usual treatment) will have started treatment. At each follow-up time point,

some intervention subjects could be non-adherent (no use), and some control subjects could have started treatment (use). We will test the significance of (with confidence intervals) the difference in the percent on treatment between the two study arms at each time point separately, using Bonferroni multiple comparison methods (exam-specific alpha=0.05/4 to get an overall test with alpha=0.05). Based on the literature, <15% of control subjects might initiate treatment. With one-sided alpha =0.0125 and 150 subjects in each comparison group (classifying subjects lost to follow-up as not on care so that sample size is constant), we estimate having 80% power to detect a 26% difference in use, and 90% power to detect a 20% in cardiovascular treatment use. We also have adequate power (90%) to detect clinically sensible cardiovascular risk changes (e.g., one standard deviation change in LDL levels in the absence of treatment), using modified two-sample normal theory and comparable assumptions (details available on request).

VII. Risks and Discomforts

The core of the intervention involves the administration of new medications, albeit medications that are already recommended by the guidelines, i.e. the trial will assess a population-based approach to provide patients with recommended guidelines, compared with usual practice. We have selected the population-based approach of using the same fixed moderate dose intervention for all eligible subjects randomized to the intervention arm. This ensures that any complications and adverse events are minimized. Nonetheless, any treatment intervention is associated with certain potential adverse events. In this study, we consider 2 categories of concerns: inadvertent disclosure of confidential information, and medication associated side effects.

Disclosure of confidential information:
One potential risk is a breach of the subjects' confidentiality. This could lead to their employer, insurance company, or others finding out that the subject participated in a research study. We minimize this risk by assigning each participant with a subject code to ensure that any protected health information is stored separately from clinical and diagnostic information. Study data to be analyzed will be stored on password-protected computers or else in locked filing cabinets in locked offices. Participants are informed of these potential risks in the consent form. Names of subjects will not be used in any publication of research results. Thus the identities of individual participants will be known only to the research team.

Medication associated side effects:

Common side effects for simvastatin include headache, abdominal pain, constipation, nausea, and upper respiratory infection. There is an increased risk of skeletal muscle effects (e.g. myopathy and rhabdomyolysis) with doses 80mg or higher.

Common side effects for losartan are diarrhea, muscle cramps, insomnia, nasal congestion, dizziness, low blood pressure, and syncope (fainting).

Common side effects for atorvastatin include diarrhea, insomnia, nausea, and upper respiratory infection (common cold). There is an increased risk of skeletal muscle effects (myopathy and rhabdomyolysis) with higher doses. Patients might experience pains or stiffness in the arms and legs if that happens. In addition, there is also an increased risk of stroke or transient ischemic attack at doses of 80mg.

Common side effects for valsartan are diarrhea, joint or back pain, insomnia, fatigue, dizziness, low blood pressure, and syncope (fainting).

Since we are using low to moderate doses of these generic medications and they have had few complications with large amounts of trial and post-marketing data, we expect any adverse effect to be rare and low intensity. Nonetheless, we will handle adverse events as follows:
Any adverse events due to any cause that occurs during the course of this trial, whether or not related to the study medication, will be reported to the Partners IRB, the NIMH, and the FDA in a written report including demographic information and a narrative explanation of the event. The study nurses will inform the study PIs, who will then determine whether to discontinue the medications; this determination could involve members of the DSMB. For example, if a subject reports mild self-resolving fatigue that does not appear to be temporally associated with the study medications, we would record the event for the appropriate reports but could determine that the event was unlikely to a) be related to the medication; b) pose a clinically meaningful risk to the subject. In contract, should a subject report difficulty breathing and the nurse reports signs of edema, we would immediately stop the medication and make sure the subject receives immediate, appropriate treatment.

Several alternative medication treatments exist for reducing cardiovascular risks. Participants will be made aware of these alternative treatment options as well as the potential side effects of the study medications in the informed consent document to allow them to make an informed decision about whether to enroll in this study.

Psychiatric Evaluation:
Some participants might feel uncomfortable answering questions during the psychiatric evaluation. They will not be forced to answer if they do not wish to answer any particular question.

Blood Draws:
Blood draw may lead to a small arm bruise and, in rare cases, clot or infection at the site the blood was drawn. Some people become light-headed during or immediately after a blood draw. These are rare occurrences and in our experience the vast majority of participants tolerate blood draws well. Participants will be monitored for 15 minutes following the blood draws to ensure they are doing well.

VIII. Potential Benefits

It is hoped that results from this study can be used to implement cardiovascular care within mental health clinics. Since cardiovascular disorders are a main source of morbidity and mortality for SMI patients, such an intervention may constitute a major improvement in the health of this population. A fixed-dose combination of pills could serve as a useful tool for minimizing non-adherence to treatment.[57-61] Use of moderate doses also yields clinical benefits with fewer side effects and complications.[62-64] The intervention also could serve as a prevention strategy in behavioral health homes, an emerging new approach to unified care for patients with SMI.

IX. Monitoring and QA

We will capture all psychiatric and medical diagnoses and prescription drugs. We will identify and intervene on any subject who demonstrates unstable psychiatric or medical disease. Potential intervention triggers include finger stick glucose (FSG) levels > 200, QTc>500ms on ECG, or signs of diabetes, renal, or liver failure based on laboratory results. Note that the intervention focuses on cardiovascular prevention, and does not attempt to treat diabetes (though cardiovascular complications are a paramount clinical concern for diabetics); we do not believe that a fixed-dose approach is clinically appropriate for diabetes treatment. Other triggers include symptoms consistent with unstable angina, suicidal/homicidal ideation, or other unstable clinical situation in the judgment of the study staff. In these cases the PI will be notified by pager, and will authorize contact with the patient's psychiatrist and PCP; and in extreme cases, the PI may refer the patient to the emergency department (ED) for immediate evaluation. For subjects without a PCP, but not requiring emergency attention, we will refer the subject to a medical clinic suggested by the mental health staff at the study site. For these events occurring during screening, we will exclude subjects from the trial; for events occurring during the trial, we will report the event to the DSMB.

We will constitute an independent DSMB with a statistician, psychiatrist, cardiologist, and endocrinologist. The board will meet every six months and/or after enrollment of every 50 subjects, will be available for more frequent consultation as needed, and will review the preliminary data on efficacy and safety issues such as major clinical events, unstable disease, and drop-outs, as well as assess trial data quality. Prior to trial start, the DSMB will develop a review protocol and outcomes/thresholds for stopping the trial. We also will register the trial on clinicaltrials.gov and apply for the Investigational New Drug (IND) application

X. References

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