Protocol for Safety Use of Antipsychotics in Youth (SUAY)

Title: Safer Use of Antipsychotics in Youth (SUAY)

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SUAY
Safer Use of Antipsychotics in Youth

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PHASE 3 – PRAGMATIC TRIAL

Contract Number: HHSN 2712016000002 C

Principal Investigator: Robert Penfold, PhD

Contracting Officer's Representative: Adam Haim, PhD

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SIGNATURE PAGE

Signatures constituting approval of this protocol and the attachments, and providing necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and guidelines are maintained electronically due to the multiple health systems and IRBs involved in this study Signatures can be found on the study's private web portal.

Signatories for this protocol are:

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LIST OF ABBREVIATIONS

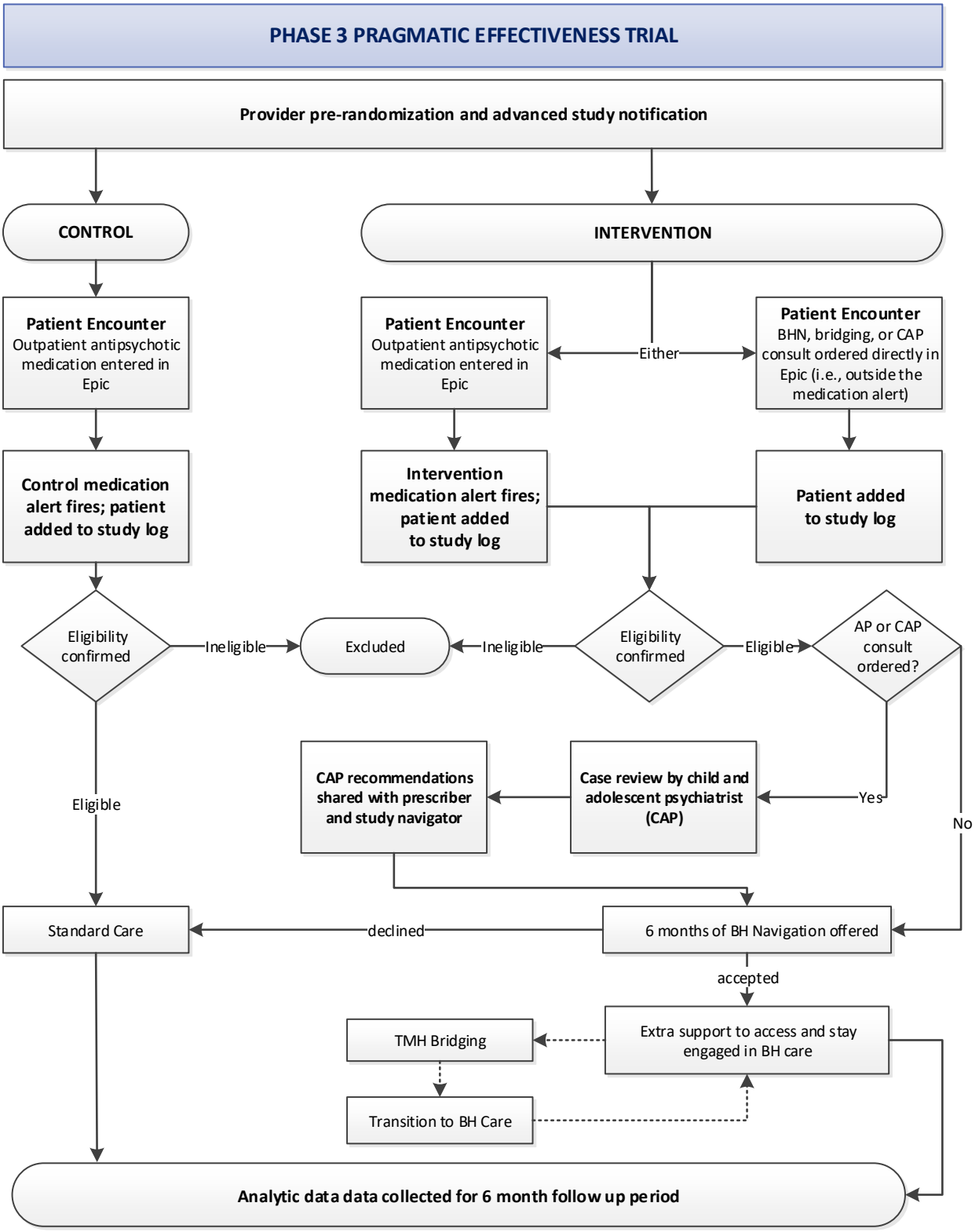
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event/Adverse Experience
APA	American Psychiatric Association
BH	Behavioral Health
CAP	Child and Adolescent Psychiatrist
CD	Conduct Disorder
CFR	Code of Federal Regulations
DSMB	Data and Safety Monitoring Board
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FTE	Full Time Equivalent
FTP	Secure File Transfer Protocol
HCSRN	Health Care Systems Research Network
HIPAA	Health Information Portability and Accountability Act
IRB	Institutional Review Board
KP	Kaiser Permanente
KPWA	KP Washington
KPWHRI	KP Washington Health Research Institute
MHRN	Mental Health Research Network, HCSRN
NIMH	National Institute of Mental Health, NIH
ODD	Oppositional Defiant Disorder
OHRP	Office of Human Research Protections
PAL	Partnership Access Line
QMP	Quality Management Plan
SAE	Serious Adverse Event/Serious Adverse Experience
SUAY	Safer Use of Antipsychotics in Youth
TMH	Telemental Health

PROTOCOL SUMMARY – SUAY PRAGMATIC EFFECTIVENESS TRIAL

Title:	*A Pragmatic Effectiveness Trial: Safer Use of Antipsychotics in Youth (SUAY)*
Précis:	A pragmatic encouragement trial will test the effectiveness of an intervention aiming to improve the targeted and safer use of antipsychotic medications by guiding clinician-prescribing behavior of antipsychotics for children aged ≥ 3 and < 18 years and encouraging psychosocial therapy for eligible youth. The intervention includes a medication best practice alert in Epic, consultation with a child and adolescent psychiatrist, and extra support for patients and families to improve behavioral health service access. The trial will be conducted in multiple health systems. Each health system will randomize prescribers to one of two study arms, intervention and control. During patient encounters, entering an antipsychotic for a potentially eligible patient will cause either the control or intervention medication alert to fire in the electronic medical record. The control arm medication alert will point prescribing clinicians to relevant *Choosing Wisely®* recommendations. The intervention arm medication alert will inform prescribers that: 1. Antipsychotics are not recommended 1st line treatment for non-psychotic disorders; 2. A child and adolescent psychiatrist (CAP) will review antipsychotic usage by youth; 3. Expedited access to bridging therapy, behavior health navigation, and/or a proactive consultation with a CAP may be ordered. The intervention medication alert will point prescribing clinicians to both *Choosing Wisely®* recommendations and clinical guidelines for SUAY. Analytic data will be collected from automated data sources at the health systems. The primary outcomes are percent of children taking an antipsychotic medication at 6 months of follow up, and total person-months of antipsychotic use among participants during the study period – based on medication order data.
Objectives:	Test the effectiveness of the intervention treatment algorithm vs. usual care control in a practical clinical trial involving several hundred subjects in multiple health systems.
Populations:	Providers authorized to order prescription medications in the health system's electronic medical record. Patients aged ≥ 3 and <18 years without diagnosed psychosis, mania, autism spectrum disorder, or intellectual disability.
Number of Sites:	1. Kaiser Permanente Washington 2. Kaiser Permanente Colorado 3. Nationwide Children's Hospital 4. Kaiser Permanente Northwest

Description of Intervention:	The intervention arm medication alert prompts the prescriber to (a) keep/remove the antipsychotic order, and/or (b) order behavioral health (BH) navigation, and/or (c) order expedited access to psychotherapy (e.g., telemental health bridging) for the patient/family, and/or (d) order a provider-to-provider virtual consult with a child and adolescent psychiatrist (CAP). Case review by a child and adolescent psychiatrist will automatically occur for all eligible intervention arm patients. A provider-to-provider consult will be scheduled if either (a) the prescriber ordered the consult or (b) the CAP needs to discuss the case with the prescriber to complete his/her review. Following review by the CAP, a BH navigator messages the prescriber and reaches out to the eligible intervention arm patient/family to offer extra support (unless actively declined by the prescriber or CAP). The navigator's role is to (a) provide extra support to facilitate access and engagement in appropriate psychosocial therapies; (b) coordinate short-duration bridging therapy sessions for teens/families not engaged in psychotherapy, when appropriate; and (c) keep the prescriber informed of any clinically relevant updates.
Trial Duration:	30 months
Subject Participation Duration:	Up to 30 months for clinicians 6 months for patients
Estimated Time to Complete Enrollment:	24 months

Schematic of Study Design:



1 KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Beginning in the mid 1990's, rates of prescribing antipsychotic medications to children and adolescents grew tremendously (1-6) and remain high in both Medicaid and commercially insured populations (6-9). Most antipsychotic medications prescribed to children are "second generation" or "atypical" antipsychotic medications. We will refer to these simply as antipsychotics. These medications are argued to have milder side effect profiles (e.g., reduced extrapyramidal symptoms) than older "first generation" or "typical" antipsychotic medications. However, the side effects of newer APs can still be severe (10, 11). The side effect profiles of individual medications in the same class differ significantly and their impact on the individual patients who take them are also known to differ (12-14).

The vast majority of antipsychotic use in youth aged 5-17 years is for non-psychotic disorders and is particularly prevalent in youth with a diagnosis of attention deficit hyperactivity disorder (ADHD) with comorbid conduct disorder (CD) or oppositional defiant disorder (ODD) and/or impulsive aggression (7, 15, 16). For example, we analyzed a sample of 562,423 youth prescribed psychotropic medications in our Mental Health Research Network (MHRN), a consortium of 13 health care delivery systems across the U.S., including 11,095 with at least one prescription for an antipsychotic medication, during the year 2011 alone. In this sample, 66% of boys aged 6-11 years that were prescribed an antipsychotic medication had a diagnosis of ADHD and CD or ODD and did not have a psychotic disorder or other FDA-approved indication. (See Penfold *et. al*., 2013 for a detailed breakdown of antipsychotic medication use in MHRN.)

In its *Choosing Wisely®* recommendations, the American Psychiatric Association lists as its 5th recommendation: ***Don't routinely prescribe an antipsychotic medication to treat behavioral and emotional symptoms of childhood mental disorders in the absence of approved or evidence supported indications***(17). However, not all antipsychotic prescribing for emotional and behavioral disturbances is inappropriate. It may be reasonable for clinicians to prescribe antipsychotics when youth are a danger to themselves or others and/or not responding to primary treatments in the absence of a psychotic disorder. Nevertheless, a new and updated algorithm and workflow is needed to guide clinicians regarding when and how to prescribe antipsychotic medications to youth with non-psychotic disorders. Importantly, there are a number of reasonable algorithms for antipsychotic prescribing to youth(18-23); however, there are two fundamental gaps in our understanding of how to implement such guidelines: (a) how to support clinicians most effectively in following the algorithms and (b) how to increase access to psychosocial primary treatments that all of the existing guidelines recommend as part of first line treatment (in addition to non-antipsychotic medications). A new algorithm will be largely ignored unless we address the fundamental issues of implementation(24-31) and long known barriers to changing prescribing practices addressed in the academic detailing literature(32-39).

In phase 1 of SUAY, a sequenced treatment algorithm and clinical workflow were developed. The study is inspired by the highly successful Partnership Access Line (PAL) and Second Opinion program operated for the Washington State Medicaid program. Implementation of this program in Washington resulted in

a 50% reduction in antipsychotic medication use among Medicaid insured youth over its first four years. Second Opinion reviews have previously generated a 51% decrease in outlier ADHD stimulant medication prescribing, coupled with a 10:1 return on investment(40). Similar peer consult programs have been demonstrated effective in other settings.(41, 42) In its current form, this program requires an outpatient pharmacist to hold a prescription awaiting Medicaid authorization for an antipsychotic outside of an established state guideline until there is documentation of a consult between the prescribing provider and a child and adolescent psychiatrist (CAP) at Seattle Children's Hospital. Providers can also electively reach out to the team's consultants via the PAL service line to discuss best practice care in a state-wide rapid access program staffed by 1.5 FTE of CAP time.

Further success and spread into community settings will require understanding and supporting provider, patient and caregiver needs at the point of care when therapies are first being considered and discussed. The core elements of our proposed intervention are: (a) sequenced 'treatment alternatives' algorithm based on best evidence that accommodates diversity of practice; (b) effective clinical decision support (including human consultation) integrated into the flow of practice; (c) behavioral health navigation for psychosocial treatment alternatives that are effective and acceptable to families; and (d) expedited access to evidence-based psychosocial therapy.

2.2 Rationale and Objectives

Antipsychotics are prescribed to children for a number of behavioral health conditions despite lack of FDA approval or evidence of their effectiveness or safety. Such 'off label' use of antipsychotics exposes children to significant health risks. The SUAY trial aims to minimize use of antipsychotics to treat non-psychotic behavioral disturbances in children in four real-world health care systems.

The pragmatic encouragement trial will assess the effectiveness of an intervention aiming to improve patient safety by guiding clinician prescribing behavior of antipsychotics for children ≥ 3 and < 18 years old. The intervention includes a provider-facing medication alert in Epic and case review by a child and adolescent psychiatrist and extra patient-facing support to improve behavioral health service access (e.g., navigation, TMH).

3 OUTCOME MEASURES

Outcome measures will be collected regardless of the extent to which intervention arm clinicians, patients, or families accepted or utilized interventional components. That is, we will follow an intent-to-treat approach and encouragement trial methods.

3.1 Primary

The following primary quantitative outcome measures for the trial will be assessed for the contract deliverable:

- Percent of youth using antipsychotics at 6 months, measured by medication orders placed within the health system during the 180 day follow up period;
- Total person-months of antipsychotic use by youth, measured by medication orders placed within the health system during the 180 day follow up period.

3.2 Secondary

The following secondary quantitative outcome measures for the trial will be assessed:

- Percent of youth using antipsychotics at 6 months, measured by prescription fill data available for the 180 day follow up period;
- Total person-months of antipsychotic use by youth, per prescription fill data available for the 180 day follow up period.
- Emergency department/urgent care visit frequency, both for psychiatric crises and for other reasons;
- Percentage of baseline and follow-up safety assessments (i.e., BMI measurement and laboratory results);
- Percentage of clinicians that follow CAP advice according to algorithm;
- Modal stage at departure from algorithm (first line, second line, third line treatment prior to antipsychotic);
- Percentage of patients with change to psychotropic medication treatment plan following second opinion review;
- Percent of patients that agree to behavioral health (BH) navigation;
- Percentage of patients attending two or more system-provided therapy sessions;
- Percentage of patients attending two or more study-provided therapy sessions;
- Of patients in study therapy, percentage who subsequently attend two or more system-provided therapy sessions.

4 TRIAL DESIGN

We will conduct a two-group pragmatic encouragement clinical trial comparing the intervention and control at multiple sites. The follow up period for the trial will be 6 months.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Prescribing Clinicians: Inclusion and Exclusion Criteria for Provider Subjects

A site programmer will randomly assign providers to one of two study arms prior to fielding. Randomization determines which study medication alert the provider will receive. Intervention arm providers have the ability to order extra support from the study:

- A provider-to-provider consult with a child and adolescent psychiatrist (CAP), and/or;
- Behavioral health navigation for the patient/family , and/or;
- Expedited access to psychotherapy (e.g., telemental health) for the patient/family.

All randomized providers will receive advance notification of the study launch. Providers in the intervention arm will be told about the extra support that may be ordered and given a web-link to the expert clinical guidelines developed for SUAY. The control arm providers will be informed that a research study is being conducted to improve the quality of antipsychotic medication prescribing.

Inclusions:

- Clinician is credentialed to order prescription medications in the health system's electronic medical record (EMR).

Exclusions:

- Clinician practices outside of the delivery system (e.g., external or network provider).

5.2 Patients and Families: Inclusion and Exclusion Criteria for Patient Subjects

Potentially eligible patients are logged for study enrollment at the time the medication alert fires. Patients are assigned to the study arm of the randomized prescribing provider. Local study staff will blindly confirm eligibility via medical record review for all intervention and control arm patients logged for eligibility review and enrollment.

Inclusions:

- Patient is ≥ 3 and < 18 years of age at the time of the encounter at which the study alert fired;
- Study service (BH navigation, bridging therapy, CAP consult) ordered in Epic for the patient;
    - The BPA allows providers to remove the antipsychotic order and still order services.
- Patient is initiating a new episode of outpatient treatment with an antipsychotic medication.
    - New episodes are defined by no record of an antipsychotic medication being ordered within the health system as part of an outpatient care plan in the prior 180 days.

Exclusions:

- Patient has a diagnosed psychotic disorder, mania, autism spectrum disorder, or intellectual disability;

- Patient was enrolled in the SUAY pilot study;
- The antipsychotic entered is prochlorperazine (Comazol®) – which is used to treat nausea;
- An outpatient antipsychotic order is entered by a temporary provider in the health system. For example, a "doc of the day" signing an order initiated by a pharmacist transferring an existing prescription to the health system. This situation may also occur when a temporary provider signs a medication order for a prescription initiated in an inpatient setting as part of a discharge plan.
    - Note that orders placed by temporary providers do not count towards the 180 day medication free period for defining a new episode of care.
- The antipsychotic order was placed within an urgent care, emergency department, or inpatient setting (to avoid intervening during a crisis).
    - Note that orders placed in these settings do not count towards the 180 day medication free period for defining a new episode of care.
- Primary language is not English (e.g., patient requires a translator).

5.3 Provider Randomization Assignment Procedures

5.3.1 Randomization Procedures

Randomization will occur before the trial begins. All eligible providers will be block randomized to ensure comparable numbers of patients enrolled in each study arm. Providers will be categorized according to the expected number of patients for whom they will issue a qualifying prescription during the study period. The expected number of qualifying prescriptions will be determined given past prescribing behavior and department or specialty. Information on past prescribing behavior may vary across study sites based on available provider data but will generally include the absolute number of qualifying prescriptions as well as the rate of qualifying prescriptions (per number of visits billed or number of unique patients seen, as available). Providers in certain departments may also be more likely to write qualifying prescriptions. For example, providers who specialize in mental or behavioral health or providers in clinics focusing on higher risk adolescents. The particular departments associated with more qualifying prescriptions will be identified separately for each health system based on previous prescribing patterns and knowledge of that health system.

Providers in each health system will divided into as few as two randomization blocks (likely and unlikely prescribers) and as many as four randomization blocks (unlikely, likely, high frequency, and very high frequency) based on the total number and distribution of expected number of qualifying prescriptions. For example, KP Washington providers wrote fewer than 100 qualifying prescriptions in the yearlong interval examined and the distribution of qualifying prescriptions per provider had a long right tail indicating that a small number of physicians wrote a large number of qualifying prescriptions. In this

context, we defined four groups for block randomization to protect against a large imbalance in the number of patients enrolled across study arms.

R, an open-source statistical computing software, will be used to generate an even number of control and intervention assignments within each provider block.

Providers hired after initial randomization will be assigned to the unlikely or likely prescribing randomization blocks based on hiring department. Randomization schedules will be generated for unlikely and likely prescribing blocks, and randomization arms will be assigned sequentially as new providers are hired. Providers previously randomized for the phase 2 pilot will remain in the arm assigned for the pilot.

5.3.2 Blinding

Study staff will be blinded to study arm when verifying subject eligibility.

The details of the study design will not be known by clinicians delivering treatment or writing prescriptions or orders (i.e., outcome assessments will be blinded).

Study child and adolescent psychiatrists, behavioral health navigators, and therapists only interact with intervention arm subjects. Group assignment is therefore known to these study staff.

The PI and Site Clinical Investigators will remain blinded to arm assignment until follow-up is complete. Only data coordinating center staff will be un-blinded to arm when preparing harm reports for the DSMB). Investigators will be un-blinded for reporting any intervention arm incidental deaths to the NIMH DSMB, should such events occur during the course of the trial.

5.3.3 Cross-Over Prevention Procedures

Epic coding will ensure control arm providers cannot access intervention components. Periodic checks will be conducted to ensure this remains in place as planned.

If a control arm provider reaches out for a consultation, the CAP may still discuss treatment options and make recommendations as they would as part of their normal role.

The behavioral health navigator will be responsible for ensuring that the services s/he offers and the bridging therapy are only accessible to intervention arm patients and providers.

Patients who change to the panel of a provider assigned to a different arm during the 6 month follow-up period will remain in the arm of their original prescriber for the 6 month follow up period.

5.4 Withdrawals

The algorithm and workflow will be applied to every randomized clinician and eligible patient enrolled at each health system.

Waivers of consent will be obtained from the local Institutional Review Board (IRB) at each site. Neither providers nor patient-subjects may withdraw given the pragmatic design and intent-to-treat analysis

plan. Subjects remain in the study regardless of their acceptability or degree of exposure to interventional components, given the encouragement trial design.

5.5 Opting Out of Study Components

Medication alert: Providers may cancel the medication alert by both de-selecting the antipsychotic in Epic and not ordering any extra support (i.e., CAP consultation, BH navigation, expedited psychotherapy access).

CAP review: Intervention arm prescribers may not opt out of passive CAP reviews. Control arm prescribers are not included in CAP review.

- The CAP is automatically informed of the need for a passive review (i.e., provider did not order a consult) after eligibility is confirmed.
- The CAP is automatically informed of the need for an active review (i.e., provider ordered a consult), prior to eligibility confirmation to avoid any delay.
    - If the patient is deemed ineligible upon review, other study services will not be offered to the patient/family.
- Passive CAP review will still occur if the clinician clicked an exclusion in the BPA (e.g., autism) and the patients is subsequently verified to be eligible. That is, study staff (not the prescriber) determines study eligibility. The prescriber maintains his/her clinical autonomy and may opt not to follow the CAP's treatment recommendations. No treatments or medications are withheld at any time.

CAP consultation: The study CAP may still reach out to an intervention arm prescriber to discuss a case when a CAP consult was not ordered. The prescriber may decide not to respond to or schedule with the CAP. The prescriber maintains his/her clinical autonomy and may opt not to follow the CAP's treatment recommendations. No treatments or medications are withheld at any time. Secondary outcomes include: the percentage of clinicians that follow CAP advice; the percentage of patients with a change to psychotropic medication treatment plan following CAP review; and model stage of departure from the algorithm (first line, second line, third line treatments prior to antipsychotic).

Behavioral health navigation: Intervention arm providers may decline behavioral health navigation for their patient by responding to a staff message from the navigator. Families/teens contacted by the navigator may decline behavioral health navigation at any time. Secondary outcomes include the percentage of patients that agree to behavioral health navigation, and the percent of patient that attend 2 or more face-to-face therapy sessions.

Expedited access to bridging therapy: Intervention arm providers may decline bridging therapy for the patient/family by responding to a staff message from the navigator. Families/teens offered study bridging therapy may decline it at any time. The percent of patients that attend two of more bridging sessions with a study therapist is a secondary outcome of the study.

6 CONTROL ARM

The control arm advance communication and medication alert inform the prescriber of *Choosing Wisely®* recommendations regarding antipsychotic medications in children and adolescents. These guidelines were developed by the American Psychiatric Association (APA). Available at: *http://www.choosingwisely.org/clinician-lists/american-psychiatric-association-antipsychotics-in-children-or-adolescents/*

The firing of the control arm medication alert will add the patient to the study enrollment log as a comparison case. Study staff will confirm eligibility via blinded chart review for all patients logged.

The follow up period is 6 months.

Should a control arm provider find SUAY orders in Epic and attempt to order a study service (e.g., navigation, expedited access to bridging therapy), an alert will fire to inform him/her that the patient is not eligible for the service.

7 INTERVENTION ARM

7.1 Intervention Arm Medication Alert Intervention Description

Randomized providers at each site will be informed in advance of the quality improvement study being conducted. The communication will inform intervention arm providers of the nature of the interventional components (e.g., medication alert, case review by a child and adolescent psychiatrist, behavioral health navigation, bridging therapy).

The medication alert is triggered by entering an antipsychotic in Epic for a target patient. See Appendix B. The patient is added to a study enrollment log at the time of the encounter. The intervention arm medication alert links providers to a document containing *Choosing Wisely®* guidelines, the national expert consensus panel clinical guidelines developed for SUAY, and contextual study information.

Within the alert, the prescriber has the option to:

- keep/remove the medication entered (default = remove)
- keep/remove an order for a provider-to-provider consult with the CAP (default = keep)
- keep/remove an order for BH navigation for the patient (default = keep)
- keep/remove an order for expedited access to bridging therapy for the patient (default = keep)

The study CAP is automatically notified that a review is needed each time an intervention arm provider actively orders a CAP review in the alert and after a patient is verified eligible when a consult is not actively ordered.

7.2 Eligibility Confirmation

Study staff (PI or delegate) blinded to arm assignment will conduct a focused medical record review within 3 business days of the case being logged to the study when the alert fired. The staff person will utilize a checklist of study inclusion and exclusion criteria for this review.

Patients found not to meet criteria will be flagged as ineligible and the reason(s) noted in the study log. Patients found to meet all study criteria will be flagged as eligible. Upon being thus flagged, eligible intervention subjects will be ‘released’ to the CAP and navigator.

7.3 CAP Case Review and Consultation Intervention Description

Expert clinical guidance for safer prescribing of antipsychotics to youth was developed in Phase 1 of the contract. See Appendix C. This will guide the CAP as s/he reviews the clinical scenario around each antipsychotic order (e.g., treatment history, current treatments, diagnoses) to determine the next best step in the treatment plan. If information is missing or the prescription is not in line with expert clinical guidance, the CAP may attempt to contact the prescriber to discuss the appropriateness of proceeding to an antipsychotic for the case and possible revisions to the treatment plan. The CAP will provide the prescriber with a written recommendations summary for every review completed. A standardized template will be used. The CAP’s recommendations may be noted in the medical record.

The prescriber is free to accept or disregard the CAP's recommendations. There are no negative consequences to providers if CAP treatment recommendations are not implemented. That is, the prescriber's clinical autonomy is in no way constrained or diminished.

7.3.1 Administration of CAP Case Review and Consultation

Case review of intervention arm patients will be conducted by a study CAP within 3 business days of receiving notification of the case at each site. If a provider-to-provider discussion is deemed necessary by the CAP and the prescriber did not order a consult directly, a virtual consult between the CAP and prescriber will be arranged within 2 weeks of the visit.

The CAP's review outcomes will be sent to the prescriber and may be noted in the patient's chart. The exact procedure will vary by site. The CAPs may also provide guidance to the navigator (e.g., patient is not a good candidate for telemental health, etc.)

Filling of the script is not delayed by the study while the review occurs. However, existing Washington State law requires antipsychotic scripts for children on Medicaid to be held at the pharmacy until pre-authorization is granted by the State. This process is outside the control of the project at KPWA.

CAP recommendations: A structured template will be used by all study CAPs to convey review outcomes and recommendations to prescribers. Feedback will be shared with the prescriber for every case reviewed. This includes situations where the CAP agrees with the antipsychotic order and/or if the CAP discussed the case with prescriber directly (e.g., by phone, email, or in person).

7.3.2 Procedures for Training Study CAPs and Fidelity Monitoring

Dr. Robert Hilt of Seattle Children's Hospital created and directs both the Second Opinion and Partnership Access Line programs based in Washington State. He will train study CAPs at other clinical sites, as needed, on the study protocol, SUAY guidelines, and CAP consultation best practices.

Site CAPs will meet by regular conference call to discuss fidelity to the SUAY clinical guidelines by anonymously discussing case examples. Recommendations will be periodically quality checked in Epic to ensure CAPs are adhering to and completing the structured recommendations template for the study.

7.4 Behavioral Health Navigation Description

Eligibility will be confirmed via medical record review within 3 business days of the patient being added to the study enrollment log at each site.

Initial provider outreach: The behavioral health navigator will contact intervention arm prescribers via staff message within 2 business days of the CAP providing his/her summary of review outcomes. When a provider actively ordered a study service for their patient, the navigator will send the provider a short message. When a study service was not explicitly ordered for an eligible patient, the navigator will introduce him/herself to the provider in a staff message, briefly describe the extra support the BH navigation can offer the patient, and inform the provider that s/he may respond by staff message to decline the extra support on behalf of the patient, if desired. If a provider contacts a navigator directly

to request a study service, the navigator will request that the provider order the requested service in Epic. Ordering the service in Epic will log the patient for study eligibility review. The navigator will contact the provider if the patient is subsequently deemed ineligible.

Existing guidelines all recommend that psychosocial interventions be tried before prescribing antipsychotic medications. Unless a provider actively declines the extra support, the navigator will contact the teen/family to offer behavioral health navigation.

Initial patient outreach: Waivers of consent/assent are obtained from the reviewing IRBs. BH navigators at each site will administer the equivalent of modified oral consent/assent by phone, as required by the local IRB, when calling to offer up to 6 months of navigation services. BH navigation is offered through the study at no additional cost.

Follow up patient outreach: If the teen/family agree to BH navigation, the navigator will initiate contact at least monthly during the 6 month follow up period to inquire about the child's status and re-evaluate barriers to access. The navigator will use motivational interviewing techniques (e.g., reflective listening, asking open ended questions) with the youth and/or parents to encourage them to engage in psychosocial treatments, attempt to motivate them to continue or restart therapy (as needed), and identify and help problem-solve ways to minimize barriers to starting or continuing therapy. When barriers exist, s/he will offer assistance in identifying behavioral health clinicians that may be a good fit for the family/teen, and further assess appropriateness of short-term bridging therapy.

The navigator will remind teens/families, as appropriate, that laboratory tests are due to be completed 3 months after starting an antipsychotic.

The navigator will note any medication side effect information incidentally reported by the teen/family in the phone note. If a reported side effect is burdensome, the navigator will encourage the patient or parent/guardian to contact their provider about their concern or side effect.

The navigator will follow the study *Safe Practice Protocol* if suicidal ideation is incidentally revealed by a subject during a BH navigation outreach call.

Ad hoc patient outreach: The navigator will reach out to assess barriers and attempt to motivate the teen/family to continue therapy if a BH appointment is missed and not rescheduled within 2 weeks.

Final patient outreach call: The navigator will conclude services with a review of the agreed upon plan for next steps and encouraging continued contact with the clinical care delivery system.

Follow up provider outreach: Following each outreach call, the navigator will secure message the prescriber with relevant updates, as needed.

7.4.1 Administration of BH Navigation Intervention

An Epic reporting workbench will be used to support BH navigation at each site. Navigators will be prompted to follow up with subjects at the appropriate time points, log outreach attempts and

outcomes, note subjects' acceptance or refusal of navigation and (if offered) short term bridging therapy, and track subject adherence to the treatment algorithm.

7.4.2 Procedures for Training of BH Navigators on Intervention

Deborah King, LICSW of Kaiser Permanente Washington will serve as the lead behavioral health navigator and train SUAY behavioral health navigators at other clinical sites.

Navigators will meet regularly by phone to anonymously discuss any difficult cases and ensure fidelity to the protocol between the sites.

7.5 Short-Term Bridging Therapy Description

Either the study CAP or the prescribing clinician may decline bridging therapy for the subject based on the clinical scenario. The BH navigator will use a decision tree to further assess appropriateness of short-term bridging therapy. Any reason that bridging is not offered will be noted in the navigator's reporting workbench (e.g., declined by prescriber, CAP advised against, subject already engaged in therapy, etc.).

The BH navigator will administer modified oral consent/assent for bridging services, as required by the local IRB, schedule the initial session, and note if the teen/family requires a loaner device (e.g., tablet) if bridging visits are to be delivered via telemental health (TMH) video visits.

When TMH is to be delivered, a TMH privacy and safety plan with the subject prior to the first TMH session. The offer of TMH will be suspended if a privacy or safety concern is identified when the form is completed until a clinical decision can be made by the therapist. The plan identifies resources within and outside the home to ensure patient privacy during TMH sessions, and plan for any potential crises, safety concerns, or inability to contact the teen/family.

All bridging visits will be entered in Epic as patient visits. There will be no copays or other charges billed for these study-related visits.

7.5.1 Administration of Bridging Therapy

Each health system will identify 1 or more licensed and credentialed therapists to provide bridging therapy. Study sites will offer clinic-to-home telemental health (TMH) with a study therapist via HIPAA-compliant video visit technology when appropriate for and agreeable to the participant. Phone-based or in-person visits may be offered by sites if technical challenges or patient/family preference prohibit video-teleconferencing visits. If a televideo connection cannot be established, the therapist may reach out by phone to start (or complete) a TMH session without video.

Appointments and set up for TMH: Study staff will provide subjects with instructions for joining telemental health sessions, as appropriate. Appointment reminders will be sent. Appointment reminders for TMH sessions will include a link for the patient to join the next TMH session.

If a suitable personal device is not available for video-visits, study staff will provide an inexpensive, secure loaner device to the subject during their first appointment.

Content: The therapeutic content of bridging sessions is solely determined by the therapists delivering the care as informed by the consensus panel guidelines developed in Phase 1 and established, empirically supported treatments. The study is investigating methods to improve access and use of psychotherapy; not evaluating any specific psychotherapeutic interventions.

Duration and transition: Bridging will conclude after 9 sessions or when the patient can begin long-term, in-person therapy, whichever comes first. The extra support provided by the BH navigators includes helping the patient/family transition from bridging to ongoing psychosocial therapy when appropriate.

7.5.2 Procedures for Training of Therapists in Telemental Health

Kathleen Myers, MD, MPH of Seattle Children's Hospital will train study therapists in telemental health delivery best practices. She will meet by phone regularly with study therapists to discuss technical or other challenges to the telemental health. Protected health information (PHI) will not be shared.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Considerations

We anticipate enrolling as many as 800 eligible patients in the trial (up to 400 per arm), with up to 360 eligible patients in each arm remaining enrolled at 6 months of follow-up (i.e., 10% lost to follow-up).

8.2 Primary Analysis Plan

Data will be collected from project tracking systems, the Epic EMR, and other health system data systems for analysis. Sites will securely transfer limited datasets to the data coordinating center at KPWHRI at defined intervals.

Data validation and quality assurance checks will be undertaken to ensure data collection during the study is sufficiently reliable.

We will use descriptive statistics to summarize adherence to the study algorithm. Specifically, we will summarize the patient characteristics (age, gender, race and ethnicity, diagnoses) of those individuals enrolled in the study and we will summarize clinician adherence to the algorithm protocol by provider specialty. Modal stage at deviation from the protocol will be evaluated among clinicians deviating from the protocol; additionally, modal algorithm stage of drop out among patients in the intervention arm who receive antipsychotic treatment during the 6 month window will be summarized. Our primary outcomes are percent of patients taking antipsychotic medication at 6 months post enrollment and total person-months of antipsychotic use by youth, based on medication order data. As secondary outcomes, we will also compare the percent of patients taking antipsychotic medication at 6 months post enrollment and total person-months of antipsychotic use by youth, based on prescription fill data.

We will also measure: the percentage of patients with a change to psychotropic medication treatment plan following second opinion review; percent of patients that agree to BH navigation; percent of patients that attend 2 or more bridging therapy sessions; and percent of patients that attend 2 or more face-to-face therapy sessions after transitioning from study bridging therapy to standard care.

In order to capture any negative unintended consequences, we will compare the number of emergency department visits, successful and unsuccessful suicide attempts, deaths, and hospital admissions between study arms over the 6 months following the intervention.

8.2.1 Statistical Analysis Plan

All primary analyses will follow an intent-to-treat approach, including all individuals assigned to an intervention arm regardless of the amount of intervention received. Non-inferiority evaluations will also be evaluated in a supplementary “as treated” analysis, comparing outcomes according to treatments actually received by patients during their observed period of follow-up. This supplemental comparison is useful in a non-inferiority assessment due to the fact that the alternative hypothesis of “no effect” is more likely in the presence of protocol violations and therefore the intent to treat approach will be anti-

conservative if many patients in the intervention arm, for example, revert to control. Also, non-inferiority of Emergency Department visit rate in the intervention arm compared to usual care control will only be assessed on final analysis if superiority is shown for the primary endpoint of no antipsychotic use at 6 months.

We will use Poisson regression to estimate (1) the percent of individuals using antipsychotics at 6 months post enrollment and (2) the total number of person-months of antipsychotic use by youth in the six month follow-up period, per provider medication orders, in each of the study arms. We will use generalized estimating equations(43) to estimate the parameters in the Poisson regression model. We will use the robust sandwich estimator to ensure correct standard errors for the intervention effect due to possible violation of the Poisson variance assumption(44); additionally, this will allow us to account for any clustering within clinics(43) and providers. Poisson regression allows comparison of relative incident rates among the intervention arms when outcomes are not rare(45). Additionally, Poisson regression will allow us to control for pre-specified baseline covariates (age, gender, and race) as well as site differences in any antipsychotic use and allow for straightforward estimation of site-specific intervention effects in sensitivity analyses. For a secondary analysis, we will repeat this approach defining antipsychotic use with prescription fill data rather than orders.

Data for our primary outcome of interest, any antipsychotic use, will be collected from electronic health records on provider orders. Electronic health record data on prescription fills will be used to assess the secondary outcome (antipsychotic medication fills). This means that traditional study drop-out due to premature participant withdrawal from the study will not lead to missing data in primary analyses. However, there will be the potential for differential follow-up rates among individuals due to youth disenrolling from their or their parent/guardian's health plan. Death is also a possibility, but unlikely. We will compare those youth for whom we are only able to collect outcome information for a portion of the 6 month follow-up period to those participants for whom we have complete 6 month follow-up information on their demographics, treatment group, and other salient baseline variables. We will account for differential follow-up times due to disenrollment in the Poisson regression model using an offset(46). Because our power calculations are based on excluding all individuals lost-to-follow-up due disenrollment, these estimates are conservative.

The secondary outcome of emergency department visits will be estimated by Poisson regression in each of the arms, again using generalized estimating equations for the reasons listed above for the primary outcome. The intervention will be compared for non-inferiority to control using a margin of M=1.5. This margin of 1.5 for the rate ratio represents a threshold for the relative increase of 50%, beyond which we would consider unacceptable. Sikirica (2014) observed an annual rate of 0.39 per year among adolescents with attention deficit/hyperactivity disorder who were taking antipsychotics(47). Using an estimated rate of emergency department visits of 0.0325 per month on control(47), the non-inferiority margin of 1.5 for the incidence rate ratio would represent a corresponding maximum acceptable rate of 0.0488 per month in the intervention arm. If the rate of emergency department use is greater than expected, say 0.05, then the non-inferiority margin of 1.5 would correspond to a maximum rate of 0.075 in the intervention arm. The estimated treatment effect (emergency department rate on algorithm

divided by the rate on control, estimated by Poisson regression) and 95% two-sided confidence interval (CI) will be compared to the non-inferiority margin (overall: M = 1.5) and non-inferiority of the algorithm approach will be declared if the entire coverage of the 95% CI is less than 1.5.

In safety review reports, the ratio between arms of emergency department visit rates will be accompanied by a confidence interval and by the non-inferiority margin, 1.5, for reference. Confidence intervals will be defined by estimating the rate ratio in 5,000 bootstrap samples. Resampling will be done on the cluster (provider) level and stratified by the presence of any event within each cluster. Quantile-based confidence intervals will be identified using the appropriate percentile corresponding to the Pocock alpha-spending function for interim analyses. Excess harm is observed if the entire coverage of the confidence interval for the rate ratio comparing the greater to the lesser rate of emergency department and urgent care visits is greater than 1.5. (While the final non-inferiority analysis for this safety outcome will use the robust sandwich estimator to ensure correct standard errors, the properties of this estimator are based on asymptotic behavior and small sample size performance may be poor.)

We anticipate initial follow-up of 800 patients, randomized to the two arms, with 720 patients remaining enrolled in the study at 6 months of follow-up (i.e., 10% lost to follow-up). Assuming a $P<0.05$ alpha level, and based on an anticipated 95% of patients in the control arm using antipsychotics at 6 months, this sample will ensure over 95% power to detect a 6% reduction in the percent of participants with any order for antipsychotic medications at 6 months. Furthermore, we expect to have 80% power to detect a 13% reduction in subgroups with exposures occurring with 25% prevalence, and 80% power to detect a 17% reduction in subgroups with exposures occurring with 18% prevalence (e.g., racial/ethnic minorities). A minimal clinically important difference of 10% was pre-specified to allow for evaluation of clinical significance as well as statistical significance as well as statistical significance. We have over 90% power to detect a 10% reduction in antipsychotic use at 6 months for patients in the intervention arm given a rate of 85%, 90%, or 95% use in the control arm.

As these power calculations are based on the assumed percent of participants on any antipsychotic in the control arm and assumed pattern of intervention effects, we provide examples of detectable intervention effects corresponding to alternative scenarios in the table that follows, including varying rates of subgroup prevalence to evaluate power regarding intervention effectiveness in less prevalent minority groups. In summary, at a range of percentages of participants with any antipsychotic use in the control arm, we will have excellent power to detect a variety of clinically meaningful intervention effects within the expected range.

Using an estimated rate of emergency department visits of 0.0325 per month on control(47) and with a one-sided 0.025 alpha level with equal allocation between groups, we estimate 71% power(48) with 400 patients per arm and 67% power with 360 patients per arm (allowing for loss to follow-up) respectively, to detect equality of emergency department visit rates (i.e., a true rate ratio of 1) in a non-inferiority evaluation with a margin of 1.5. With a greater monthly emergency department rate of 0.05, we would have 88% and 84% power with 400 and 360 patients per arm respectively under otherwise equivalent conditions.

Power under varying percentages of participants in each arm taking antipsychotic medication at 6 months (based on medication orders) and under various subgroup prevalence assumptions.

Subgroup prevalence	n per arm*	Intervention	Control	Power
100%	**360**	**89%**	**95%**	**80%**
100%	360	85%	95%	>99%
100%	360	80%	90%	97%
100%	360	75%	85%	92%
25%	**90**	**82%**	**95%**	**80%**
18%	**65**	**78%**	**95%**	**80%**
10%	36	75%	95%	67%
5%	18	65%	95%	62%

8.3 Handling of Missing Data

All outcomes for this trial will be collected from electronic health records, which means traditional study drop out will not result in missing information. It is possible for youth to disenroll from a health care plan in the 6 months following initial randomization. Patients who disenroll from the health system are lost to follow up data collection.

As described above, we will assess the association of baseline characteristics and the probability of remaining enrolled in the same health care plan for the full 6 month follow-up. If there are large differences between the rate of full follow-up by baseline characteristics we will perform sensitivity analyses including these covariates in Poisson regression models to evaluate if missing this missing information has led to biased effect estimates. Our primary analyses will use an offset term(46) in the Poisson regression models in order to include all individuals regardless of the length of follow-up. We have performed conservative power calculations assuming that all individuals without a full 6 months of follow-up will be excluded from analyses. If disenrollment rate is high than anticipate or there is missing information in important baseline characteristics we will use multiple imputation(49) or weighted(50) estimates to ensure that our results are not biased due to missing data.

One study site (NCH) does not have complete prescription fill data because they serve patients in their clinics who are not enrolled in the insurance product for their health plan. Complete capture of prescription fill data does not differ with study arm assignment, thus, we do not expect estimates of the interventions effect to be biased. However, missing prescription fill data could lead to underestimates

of the percentage of youth taking antipsychotics at 6 months and/or the percentage of youth who fill prescriptions for lower risk, first line medications. We will conduct quality assurance checks comparing the number of medication orders and prescription fills by individual across all sites to determine degree to which medication order and prescription fill data differ.

9 PRAGMATIC TRIAL OVERSIGHT

9.1 Data Safety Monitoring

The NIMH Data and Safety Monitoring Board (DSMB) will provide ongoing oversight for the Phase 3 pragmatic trial.

The Board consists of voting members chosen by NIMH for their relevant expertise. The DMSB operates under the rules of an NIMH-approved charter.

The DSMB will advise NIMH of its findings and reports will be shared with site IRBs, as required. We will be responsive to additional specific requests for data reports that may be requested by the DSMB.

Confidentiality will be maintained during all phases of the DSMB review and deliberations.

9.1.1 Schedule and Content of DSMB Reports

The schedule for delivery of the DSMB reports will be determined by the DSMB; three (3) reports per year are expected. DSMB reports will be submitted via email to the COR and DSMB liaison.

Elements that the DSMB needs for the interim and final reports will be clearly defined in advance on a template developed in collaboration with the COR and approved by the DSMB. The report will summarize overall trial progress as well as safety data for each site.

9.2 Premature Termination or Suspension of Trial

This trial may be prematurely terminated if, in the opinion of the PI, NIMH, DSMB or IRB there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the PI and/or NIMH by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Failure to obtain sufficient follow-up data to evaluate the effectiveness of the intervention.

If the project is prematurely terminated or suspended, NIMH will promptly inform the investigators/institutions and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by NIMH or by the investigator/institution, as specified by the applicable regulatory requirement(s).

10 ASSESSMENT OF SAFETY

10.1 Specification of Safety Parameters

It is not feasible to report incidental adverse events (AEs) for this pragmatic trial. Study staff do not have contact with control arm patients. Only intervention arm patients have contact with study staff, resulting in an inability to compare rates of incidental AEs between arms.

We will compare the number and rate of emergency room and urgent care visits, inpatient hospitalizations (psychiatric and non-psychiatric), suicide attempt (fatal and non-fatal), and deaths from all causes to monitor for potential harm to subjects. Comparisons of safety signals between arms will be made and reported to the DSMB 3 times per year. The PI and site investigators will be blinded to the results of these assessments.

10.1.1 Safe Practice Protocols and Tracking

BH navigators will have contact with intervention arm patients/families and will follow safe practice protocol if a patient or parent/guardian voluntarily discloses thoughts of self-harm. Study navigators do not assess suicide risk directly. See Appendix D of this protocol.

Safe practice protocol use, actions taken, and resolution for each event will be tracked and summarized in reports for DSMB. The events will not be considered adverse events because there is no comparison data from the control arm.

The study therapists are members of the local health system workforce and therefore follow their health system's clinical protocols if thoughts of self-harm are reported by a patient.

In addition to safe practice protocols, both navigators and therapists are mandatory reporters. Standard procedures for reporting to Child Protective Services (CPS) will be followed should a subject voluntarily disclose child neglect or abuse. CPS reporting will not be tracked for study purposes.

10.1.2 Adverse Events (AE) / Serious Adverse Events (SAE) and Reporting

As noted above, reporting of incidental adverse events is not feasible for this pragmatic trial.

The number and rate of events will be compared between the two study arms in DSMB reports.

- Emergency room and urgent care visits (SAE)
- Inpatient hospitalizations (psychiatric and non-psychiatric) (SAE)
- Suicide attempt (fatal and non-fatal) (SAE)
- Death from all causes (SAE)

If study staff have contact with a family and discover the patient died, the death will be reported to NIMH within 72 hours of discovery as a serious adverse event. Other SAEs listed above about which study staff gain incidental knowledge will be reported in the next DSMB report.

10.1.3 Unanticipated Problems and Reporting

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all three of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents or events that meet the OHRP criteria for unanticipated problems will be reported to the IRB and the NIMH DSMB. Reporting of Unanticipated Problems to NIMH Program and the NIMH DSMB will be accomplished by submission of an Unanticipated Problem Report via fax or email to the NIMH.

Per HHS regulations 46.103(b)(5), the "appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted". We will apply the following recommended OHRP guidelines to satisfy prompt reporting requirements:

- Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Once submitted, NIMH will send a confirmation email to the investigator within 2 business days. Unanticipated problems will be recorded in the data collection system throughout the trial.

10.2 Halting Rules

Study halting may occur as required by the IRB, NIMH, or the NIMH DSMB. The PI may temporarily suspend enrollment pending review by these authorities if warranted based on significantly more safety events occurring in the intervention arm per safety monitoring results.

The study would not be halted early if the intervention was found to be protective (i.e., significantly lower rates of safety events in the intervention arm).

11 CLINICAL SITE MONITORING

Clinical site monitoring is not planned or budgeted for this project; however, the NIMH reserves the right to conduct independent audits or clinical monitoring as necessary.

See the next section for information about quality control and quality assurance, including quality management.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study Procedures

Standard operating procedures for the study will be detailed in the Manual of Procedures at each site. An overview of procedures is provided in this protocol.

Local staff will be trained on study procedures relevant to their role prior to fielding. Staff training logs will be maintained by the project manager at each study site.

12.2 Quality Management

A Quality Management Plan (QMP) will be created prior to fielding in order to establish the quality management guidelines for tasks related to the study. At a minimum the quality management plan will be reviewed bi-annually by the KP Washington PI and PM.

This QMP will be a living document that will be updated throughout the life of the project, as necessary, in order to document changes in scope or process. The QMP will include a detailed description of quality management activities applicable to the study at each site, including process documents, data collection, study record review, technical issues and resolution, essential documents, and staff training and qualifications. The QMP will include tools and checklists to be used in the quality management process, and describe when and how internal assessments will be summarized and reported to staff.

12.3 Protocol Deviations

Site staff will immediately report protocol deviations to the local PM, who will inform the site Investigator or PI. Any deviations will be considered noncompliance with this protocol or Good Clinical Practice. Protocol deviations will include privacy breaches, and IT-related problems that lead to errors in protocol adherence.

Protocol deviations that may impact patient safety or study data integrity will be immediately reported to the KP Washington PI and PM. The DSMB will be informed within 5 business days of KP Washington becoming aware of a protocol deviation impacting patient safety or study data integrity.

Sites will report other protocol deviations as outlined in the QMP, Site IRBs will be notified of deviations per local reporting requirements. The NIMH Contracting Officer's Representative and NIMH DSMB will review protocol deviations in the tri-annual data reports.

Events not considered protocol deviations: Due to the pragmatic and encouragement design aspects of the study, the failure of a provider or patient to adhere to the protocol (e.g., bypassing medication alert, not responding to request for active CAP consult, not following CAP recommendations, refusal or drop out from BH navigation or bridging, not closing a chart note in time for reviews to be conducted), are not considered protocol deviations. These uncontrolled and expected events are of scientific interest due to the pragmatic nature of the study.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The investigator will ensure that this research study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

13.2 Potential Risks and Benefits

None of the individual interventional components of this study are experimental in nature. All components have been tested and demonstrated effective elsewhere. No medications or other treatments are withheld or delayed. Prescribers are not mandated to accept the CAP's recommendations and remain free to exercise their own clinical judgment. All the participating health systems already offer provider-to-provider consultation, care navigation, and psychosocial therapy.

13.2.1 Potential Risks

Control arm subjects receive no benefit from the study. Potential risks are no different than usual care or usual employment. Breach of confidentiality is a possible risk of this research.

For intervention arm patients, potential risks are no different than those experienced as part of other care navigation or psychosocial therapy offered as part of usual care. Some families/teens may not be comfortable participating in video-based bridging therapy that may be offered by the study. This may be due in some cases to concerns about confidentiality. Information will be provided to ensure families/teens understand these risks. They are free to refuse the video visits offered or to request phone-only visits (no video-conferencing).

For intervention arm providers, potential risks are no different than usual employment insofar as employers are free to implement quality improvement programs and implement medication alerts.

13.2.2 Potential Benefits

Some providers may find study CAP consultations, BH navigation, and bridging therapy to be valuable services. Pediatricians and primary care providers may especially welcome the opportunity to solicit input from a study CAP since they infrequently prescribe antipsychotics.

Youth and families seeing intervention arm providers may have improved access to behavioral health services due to BH navigation and may be offered up to 9 bridging sessions. Both bridging therapy sessions and navigation services are offered at no additional cost to families.

13.3 Institutional Review Board

The protocol and project materials for providers and patients will be submitted to the IRB at each clinical site for local review and approval. IRB approvals and local waivers of consent and assent must be obtained before the research project is initiated at each site. Amendments require review and approval by the IRB before the changes are implemented locally.

13.4 Informed Consent Process

Waivers of informed consent and assent will be obtained for this study at each clinical site, as granted by each local IRB. Written informed consent/assent will not be collected. Providers will be notified of the study via a communication sent prior to fielding. Families/teens are free to refuse navigation or bridging services at any time.

The "Common Rule" for protection of research participants (45 CFR 46.116d) lists specific requirements for waiver of the usual requirement of individual informed consent to participate in research. Those criteria include: The research involves no more than minimal risk to the subjects – According to 45 CFR 46.102: "Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Rationale for waiver of consent:

- We do not believe that any of the components of the intervention expose providers or patients to greater than minimal risk. No treatment or intervention will be restricted or withheld; providers maintain autonomy with respect to clinical decision making;
- No components of the intervention are experimental in nature. Consultation and case review, navigation, psychosocial therapy and medication alerts are all standard health care provisions;
- Engagement in all study activities will be voluntary (e.g., medication alert may be overridden, CAP recommendations may be disregarded, navigation and bridging therapy may be declined);
- For control arm providers and patients, the experience is identical to what would have been delivered had the study not occurred;
- The research is not practicable without a waiver. A trial limited to those who would actively consent to such a study would not be scientifically valid;
- When appropriate, providers and patients are given pertinent information via staff communications (providers) and the BH navigator (patients/families);
- Patients and families are already in the study and randomized prior to being contacted by the navigator. Systematically excluding subjects after randomization would produce invalid research findings. It would be unethical to expose subjects to even minimal risk when such bias is known in advance.

13.5 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals of any gender or racial/ethnic group may participate. Children ≥ 3 and < 18 years of age constitute the population of target patient-subjects. Children diagnosed with psychotic disorders including mania, autism spectrum disorders or intellectual disabilities will be excluded.

13.6 Subject Confidentiality

Appropriate steps will be taken to safeguard participant confidentiality. This includes the following:

- All project data will be maintained on secure, password protected servers at clinical sites. Only project staff needing this information for their work will have access. Members of the study team include Epic programmers from the delivery system;
- Limited data sets from subcontracted clinical sites will be transmitted from to the KPWHRI data coordinating center using a HIPAA-compliant secure FTP site;
- Participants will be identified using only subject ID in any study analytic database(s) at each site;
- The protocol, documentation, data and all other identifying information will be held in strict confidence. No information about the project will be released without prior approval of NIMH per the terms of the contract. Authorized representatives of the NIMH may inspect records, as needed.

13.7 Future Use of Identifiable Data

Identifiable information will be destroyed within 5 years of the end of the contract, consistent with contractual, HIPAA and IRB requirements.

We have no plans to retain identifiable information beyond this period. If this plan changes, we will obtain appropriate IRB approval.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Management Responsibilities

Both institutional and application level access granted by the local information security office and simultaneous knowledge of both a valid user name and password are required to access data collected in electronic records. Any paper records generated with patient identifying information will be kept in locked filing cabinets in secured office buildings.

Data sent to the KPWHRI data coordinating center will be transferred using a secure file transfer protocol (FTP) site. Data coordinating center files will be kept separately from other study files to maintain blinding of study staff working on other aspects of the project.

No participant data shall be overwritten by project staff. As necessary, variables may be recoded into new variables for analyses, so as to preserve the original record. All changes will be documented.

Final datasets will be saved electronically, clearly labeled and stored in a secure project folder on the KPWHRI server accessible only to project staff.

14.2 Data Capture Methods

The majority of data for this pragmatic study is captured electronically in the site EMR, including the study enrollment log. Data entered into the navigator's personal reporting workbench is also in Epic.

TMH administrative metrics are captured by study therapists and entered into a de-identified electronic database.

CAP treatment recommendations will be abstracted from Epic by study staff and meta-data entered into an electronic tracking system.

All electronic records will be kept in a 21 CFR Part-11 compliant data capture system, which includes password protection.

14.3 Study Records Retention

Identifying information and linking files will be destroyed within 5 years of the conclusion of the contract unless consent to retain these files is granted by the IRB. Following this time, no other records will be destroyed without the consent of NIMH. It is the responsibility of NIMH to inform the investigator when these documents no longer need to be retained.

15 PUBLICATION AND NEW SUB-PROJECT POLICIES

The Steering Committee has developed and adopted a policy on publications, presentations and authorship. The most current version of this policy is available on the SUAY web portal site. (*https://www.hcsrn.org/share/page/site/suay/dashboard*). Topics covered by the policy include:

- Policy scope;
- SUAY publication committee;
- Use and confidentiality of data from participating sites;
- Decisions regarding authorship;
- Coordination of the writing process;
- Tracking of publication progress;
- Acknowledgement of SUAY support and federal funding;
- Public access to products of NIH-funded research;
- Publicity regarding SUAY publications.

The Steering Committee has developed and adopted a policy on the proposal and approval of new SUAY sub-projects. The most current version of this policy is available on the SUAY web portal site. (*https://www.hcsrn.org/share/page/site/suay/dashboard*). Topics covered by the policy include:

- Policy scope
- Categories (preparatory or pilot data; affiliated)
- Procedures for proposing and approving preparatory or pilot data activities
- Procedures for proposing and supporting affiliated projects

16 DATA SHARING PLAN

Phase 3 of the SUAY contract is scheduled to last 3.5 years (December 25, 2017 – June 24, 2021). The data sharing plan is incorporated by reference into the contract governing the project. Any changes to the data sharing plan must be pre-approved by the NIH Contracting Officer.

The project is committed to sharing data created by the proposed research, limited only by the need to protect the privacy of potentially identifiable health information. Any datasets for public distribution (including to the National Database for Clinical Trials Related to Mental Illness) will be de-identified in compliance with HIPAA standard for de-identification.

As noted in the contracted statement of work, in Phase 3 a de-identified database of the pragmatic clinical trial will be delivered to the government, along with a statistical report addressing the research questions of the study, and a cost-benefit analysis of the intervention.

17 LITERATURE

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PROTOCOL APPENDICES

These documents are relevant to, but not considered part of, the protocol. Each clinical site will modify, store, and obtain IRB approval for the documents locally.

Modifications to the protocol appendices by any clinical site do not constitute a protocol amendment.

APPENDIX A: SCHEDULE OF EVENTS

Event	Description	Timing
Medication Alert and Enrollment Log Entry	The medication alerts fire in Epic during routine clinical encounters at which an antipsychotic is entered in Epic for a target patient. The patient is automatically added to the study enrollment log when the alert fires.	Day 0
Alternatively: Active Order Entered in Epic and Enrollment Log Entry	The intervention arm provider directly orders a study service (i.e., navigation, bridging therapy, CAP consult) in Epic outside of the medication alert. The patient is automatically added to the study enrollment log when the order is entered.	Day 0
Eligibility Validation	Study eligibility will be validated by chart review for all patients logged.	Target: Day 0-3
Child and Adolescent Psychiatrist Review and Recommendations	The study CAP will complete case reviews and send the prescriber recommendations within 3 business days of receiving notification of an eligible case. Consultation will be scheduled to occur within 10 business day when the study CAP requires more information and a consult wasn't ordered.	Target: Day 0-6 (review only or consult ordered) Target: Day 0-13 (consult not ordered, discussion needed)
Behavioral Health Navigator Outreach to Prescriber	The BH navigator will outreach the prescriber following CAP review. The navigator will also send periodic clinically relevant updates while his/her patient is receiving behavioral health navigation support.	Target: Day 3-180 *(i.e., after the CAP's review is completed)*
Behavioral Health Navigation for Patient/Teen	The navigator will contact families/teens to offer up to 6 months of BH navigation. Outreach will occur within 2 business days following CAP review. Teens/families accepting this extra support will be contacted at least monthly. Ad hoc contacts may be made if psychotherapy appointments are missed and not rescheduled.	Target: Day 6-180 *(i.e., after BNH outreach to provider is complete)*
Bridging Therapy	Some teens/families will be offered bridging sessions with a study therapist. Up to 9 sessions may be offered.	(variable)

6 Month Follow Up Period	Data will be collected for the 6 month period after each eligible patient is added to the enrollment log. Analytic data will be derived from the EMR and other health plan data systems and study tracking systems.	Day 0-180

APPENDIX B: PROVIDER ADVANCE COMMUNICATIONS AND MEDICATION ALERTS

- Advance communication to intervention arm providers
- Advance communication to control arm providers
- Example text of intervention and control arm medication alerts

APPENDIX C: SUAY CLINICAL GUIDANCE

- Expert clinical guidance for the safer prescribing of antipsychotics to youth

APPENDIX D: BH NAVIGATION

- Behavioral health navigator script(s) for introductory calls
- Behavioral health navigator script(s) for ongoing and final calls
- Example staff messages to prescriber from behavioral health navigator
- Example staff message to transition patient from bridging to ongoing psychotherapy
- Behavioral health navigation safe practice protocol

APPENDIX E: TELEMENTAL HEALTH BRIDGING

These items apply only to study therapy sessions delivered via the telemental health modality. They do not apply to in-person sessions provided by a study therapist at the clinic.

- Telemental health privacy and safety planning form for video visits
- Patient telemental health introductory and appointment reminder emails
- Reminder telephone script for patient to return loaner device for video visits