1) Protocol name: Reducing Duration of Untreated Psychosis

2) Author of Protocol

X UC Davis Researcher

3) IRB Review History

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4) Objectives

Delays in treatment for first episode psychosis (FEP) are associated with worse long-term patient outcomes [1, 2]. While international consensus recommends duration of untreated psychosis (DUP) of less than three months for optimal outcomes [3], the US average is estimated at one to three years [1]. Recent evidence indicates that extended DUP is largely due to *mental health care system delays* [4] in identifying and engaging patients, which limit the impact of public education campaigns on DUP. Therefore, any major reduction in DUP must include service system changes at multiple levels.

We observed these same delays in the "supply side" of treatment within our own evidence-based FEP specialty clinic at the University of California at Davis, the Early Diagnosis and Preventive Treatment (EDAPT) clinic. Since 2012, the mean time between psychosis onset and initial contact with the 633 individuals referred to EDAPT was 615 days. Consistent with previous observations [2], this was highly variable (SD=916 days), with a median delay of just under one year (245 days). Analysis of referral pathways and intake procedures revealed two primary "bottlenecks": (1) ***delays in identification*** and referral of patients from first healthcare contact within the community to first EDAPT contact (mean 325 days) accounting for 53% of overall DUP; and (2) ***failure of engagement*** in FEP specialty care (once determined to be eligible for EDAPT, 19% did not attend initial clinic appointments). It is clear that these two components - identification *and* engagement in FEP services - must be addressed to effectively reduce DUP, defined in this proposal as time from first onset of psychotic symptoms to engagement in FEP specialty care at EDAPT, in accordance with the RFA.

To address these two bottlenecks in the pathway to FEP care, this proposal will use a two phase cluster randomized controlled trial (RCT) design to consecutively test two specific strategies to reduce DUP through: 1) more rapid *case identification* by referral sources (secondary mental health and primary health care referral sources and schools); and 2) more timely enrollment and retention in care by *improving initial engagement* in FEP outpatient services. Twenty community partner sites will be enrolled and randomized to one of two intervention arms in each of two phases, with stratification by type of site (i.e. schools/universities, ER/inpatient hospital, outpatient mental health, or primary care) to ensure equal diversity of referral sources across arms. In Phase 1, we will assess the comparative effectiveness of two approaches to rapid **identification**: (1) our present standard targeted provider education [5] on signs and symptoms of early psychosis to motivate referrals to EDAPT FEP services, versus (2) standard targeted provider education plus electronic screening during referral site intake with automatic referral of patients to EDAPT FEP services when they exceed screening cut-offs. Next, the Phase 1 identification intervention with the lowest DUP will be provided to all sites, and sites will be re-randomized to one of two **engagement** interventions for Phase 2: (1) our present standard clinic-based engagement program within EDAPT, versus (2) a community-based engagement approach using a multidisciplinary EDAPT mobile team and a telemedicine link to a prescribing EDAPT psychiatrist. In so doing, we will address the following aims:

Aim 1: To compare the effectiveness of targeted provider education alone versus the addition of electronic screening in improving the speed of accurate case identification. We will test the following hypotheses: H1) The DUP of patients identified through the targeted education plus electronic screening arm will be lower than the DUP of those referred following standard targeted provider education alone; and H2) the electronic screening procedure combined with standard targeted provider education, relative to targeted provider education alone, will lead to identification of more FEP cases.

Aim 2: To determine the effectiveness of clinic-based engagement versus community-based mobile telepsychiatry-enhanced engagement in FEP care following case identification, in increasing FEP enrollment and reducing DUP. We will test the following primary hypotheses: H1) The community-based mobile team will lead to higher rates of FEP enrollment than standard clinic-based engagement services; and H2) The mobile team will lead to shorter time from screening/referral to enrollment than clinic-based engagement.

Secondary analyses in each phase will compare the satisfaction of referral sources, identified patients and family members with each approach. Exploratory analyses will also test whether mobile engagement will result in higher enrollment rates and reduced time from referral to enrollment for underserved populations, specifically individuals with more severe symptoms, lower socioeconomic status and ethnic/racial minorities.

5) Background

5.1) AIM 1 RATIONALE

The Problem: Education of Healthcare Providers Is Not Adequate For Early Identification of FEP. Standard practice for most FEP clinics involves education of the public and referral sources as well as advertising to "recruit" early psychosis patients to their clinics, where patients then receive extensive diagnostic assessments [6]. However, public health interventions often employ simple, fast and relatively inexpensive screening methods to indicate the need for more costly diagnostic procedures, such as Pap tests for cervical cancer [7]. Therefore, it is not surprising that studies of pathways to care for individuals with psychotic disorders have identified the delay between first health care contact and accurate identification to be a primary contributor to DUP[4, 8, 9]. Similarly, in our experience in California, accurate and efficient case identification of FEP patients is challenging for both primary care and general mental health care providers, as well as schools and other "first identifiers."

Surprisingly, one of the greatest contributors to DUP is the delay in referring individuals who *were already engaged in the mental health system* to specialty FEP care. Our findings are consistent with results from other FEP clinics around the world, demonstrating that psychotic disorders may be under-detected in general mental health care settings. In a chart review of all available medical files for patients ages 18-45 first presenting to mental health services in a catchment area of approximately 400,000 inhabitants in the Netherlands, only 33% of patients reporting psychotic symptoms were diagnosed with psychotic disorders[10]. Of those with 2 or more psychotic symptoms who received a diagnosis of non-psychotic disorders, other psychotic disorders (e.g. substance-induced psychosis) or no diagnosis at all, 53% were later diagnosed with a non-affective psychotic disorder during the two-year follow-up period. While some of these patients may have been accurately diagnosed at intake and later transitioned to a non-affective psychotic disorder, it is unlikely to be true of all patients. The authors conclude that "Systematic examination of psychotic experiences at first contact with mental

health services may serve as a useful measure to overcome this limitation of … clinical practice."

In addition to these structural factors, a primary social barrier to engagement in mental health services is the social stigma attached to a mental illness diagnosis[11, 12]. This problem was identified by the World Health Organization as one of the greatest remaining obstacles to mental illness treatment[13]. Stigma refers to the negative attitudes and beliefs that cause the public to fear, avoid and discriminate against individuals with mental illness, which leads to documented losses in educational, occupational, and social opportunities[14]. It is, therefore, understandable that individuals and their families often avoid mental health services to avoid stigmatizing labels[15], and often do not engage in services until the individual has become a danger to self or others and requires emergency care. This is particularly relevant for FEP patients and family members, who have cited stigma as a reason they delayed seeking care[16]. In a qualitative study utilizing a series of semi-structured interviews with family members of FEP individuals, Franz and colleagues[17] documented these negative societal and self-beliefs, and used interview results to create a "grounded theory model" for the ways in which stigma presents a barrier to engagement in FEP care, leading to increased DUP. In this model, anticipation of negative societal reactions contributes to social withdrawal and a withholding of clinical symptoms, thereby raising the threshold for engagement in treatment services and contributing to increased DUP. Although this may be a "demand-side" barrier, "supply-side" solutions may be helpful. Unfortunately, the same non-traditional services where FEP individuals may feel more comfortable and less stigmatized (e.g. primary care and school-based mental health services), are less skilled in detecting FEP.

The Solution: Psychosis Screening at Points of Entry to Healthcare. In order to address this "supply-side" delay in identification for FEP treatment, we propose to test a simple self-report screening measure administered via handheld android device at intake to all patients in primary health care, secondary health care and school-based mental health settings in approximately 20 clinics and schools in Sacramento County. Growing evidence suggests that this is a feasible, efficient and effective strategy for improving detection of FEP patients, although it has yet to be tested across a catchment area in the United States.

Screening in Secondary Mental Healthcare Settings. Two prior studies, both in the Netherlands, tested screening strategies for psychosis at first contact to mental health services. In the first study[18], a random sample of 246 patients completed a screening questionnaire, received a standard clinician diagnosis, and also a structured diagnostic interview with a research psychologist or psychiatrist. Twenty-six patients (11%) received psychotic disorder diagnoses on the structured interview, but clinician diagnosis matched for only 10 (39%) of these patients. Upon case discussion, clinicians agreed with the research diagnoses for all 26 patients. The questionnaire showed good concurrent validity with the structured interview diagnoses, and the authors suggest that when patients do not show overt signs of psychosis at clinic intake, clinicians often do not thoroughly investigate,

but that routine screening would assist this process. A second study[19] directly compared two ascertainment strategies for full and attenuated (at-risk) psychosis in two large catchment areas: (1) self-report screening of all secondary mental health care referrals using the Prodromal Questionnaire followed by clinical interview for high scorers (the method proposed for the current study) versus (2) direct clinician referral to specialty FEP care. Not only did the screening identify more total patients than referral alone, it also identified 52 fully psychotic patients who had not been previously identified as such by their clinicians (12% of screen positives and 1.4% of all screens). Similarly, 60 patients referred as "at-risk for psychosis" were actually fully psychotic (34%), suggesting that these patients with psychosis would not have been identified as psychotic and been referred to FEP care without screening. The authors conclude that "screening, as well as referral options, should play a more prominent part in the general secondary mental health care." These studies clearly illustrate the ways that FEP patients are under-detected even in mental health care systems that have access to specialty FEP clinics.

Screening in Primary Health Care Settings. Primary care clinicians are often the first contact for a teen or young adult with psychosis [20], but primary care providers may not have sufficient training or experience to identify FEP accurately, with many individuals going undetected [21]. Contacts with primary care are second in number only to emergency care contacts for FEP patients prior to specialty care [22], further supporting the importance of this group as "first identifiers." In a study of 42 patients with schizophrenia [23], longer DUP was related to fewer appointments with their general practitioner prior to receiving mental health care, suggesting that primary care clinicians must seize the opportunity to assess patients for FEP. However, a recent pathways study of 324 FEP patients [24] revealed that patients in contact with primary care had a referral delay to FEP services that was *twice as long* as those not seen in primary care. Other studies report similar DUP delays when contact is with a non-psychiatric healthcare professional [25]. Given that the average length of a primary care visit in the US is 32 minutes for a new patient appointment and 18 minutes for a routine visit [26], it is clear that education of primary care referral sources may not be enough. Accordingly, an early psychosis checklist using clinical ratings has been developed for primary care referral sources who cannot be assumed to have specialist knowledge of FEP, and who are often pressed for time in visits [27]. Our screening method utilizes an alternative technology-based solution that requires even less time from primary care providers.

Screening in School-Based Mental Health Settings. The top 5 most commonly reported disabilities in US children are mental health conditions [28]. A number of research funding opportunities and legislation proposals have emerged recently as a result of a federal priority to identify adolescents and young adults with serious mental illness and, in particular, psychosis [29]. While school-based identification of mental health problems has been promoted as effective when embedded within prevention and treatment services [30], no screening instruments to date in the U.S. have focused on psychosis. Including school-based mental health clinics (high schools and universities) as referral sites within the proposed project will allow us to reach transition-age-youth where they are most likely to reach out for services,

but where counselors may have insufficient experience or expertise in identifying psychosis.

Electronic Screening. Electronic screening for health indicators is becoming increasingly common in healthcare settings, with the near-universal use of electronic health records and intake "kiosks" where new patients can complete intake forms via a desktop or mobile computer in the clinic waiting room. This methodology addresses several obstacles to efficient care, including providers' lack of time and training, and is well-accepted by patients [31]. Electronic screening for mental health problems in pediatric primary care effectively increases psychiatric care referral [32] and is well-matched to the preferences of adolescents and young adults, who are quite familiar with mobile computing devices. In a study that screened over 4,000 ninth grade students for suicide risk, 19.6% of students were identified and 77% of those completed at least one follow-up mental health visit [33]. Electronic screening is, in fact, the method of choice for behavioral healthcare screening in primary care settings for the Veterans Health Affairs roll-out of Patient-Centered Medical Homes, which utilize far more extensive screening than the brief questionnaire proposed for this study. Additionally, electronic administration of our screening questionnaire allows for simpler presentation of items, as the questions regarding distress and impairment related to specific items are skipped when that item is not endorsed.

5.2) AIM 1 PRELIMINARY DATA

Screener Development. Previously, we developed a self-report screening measure to improve identification of patients with early psychosis, the Prodromal Questionnaire-Brief (PQ-B). While structured interviews remain the gold-standard instruments for diagnosing psychosis syndromes, they require specialized training to administer and several hours of clinician and patient time. The PQ-B is intended to be the first step in a two-step screening and diagnostic process, and was developed over a series of studies[34-36] in clinic-referred and general population samples. The original Prodromal Questionnaire (PQ [34]), was a 92-item version including positive, negative, disorganized and general/affective symptoms. The PQ showed moderate concurrent validity against a diagnosis of clinical-high-risk (CHR)/psychotic syndromes on the Structured Interview for Prodromal Syndromes (SIPS [37]) in a clinic-referred sample, but very high rates of item endorsement in a general population university sample [35]. Those rates dropped significantly once criteria regarding distress and impairment were added. Distress about psychotic-like experiences predicts later psychotic disorder in the general population [38, 39]. Finally, the measure was reduced to positive symptoms only, as that is the primary basis for CHR and FEP diagnoses, and items were selected that had the highest agreement with SIPS diagnosis in the original sample. The PQ-B Distress Score (positive symptoms endorsed as distressing or impairing) of 6 or more demonstrated 88% sensitivity and 68% specificity in a sample of 141 patients referred for CHR and FEP syndromes to one of two university-based FEP clinics [36]. As a result, the PQ and PQ-B have been translated into over a dozen languages and are used in FEP clinics around the world. Although the PQ-B produces too high a rate of false-positives to be used alone, it is quite effective as a first stage screen, followed by

phone evaluation and/or face-to-face interview-based diagnosis to increase specificity.

Electronic Screening. To increase public access to early psychosis screening, a web-based version of the PQ-B was developed at UCSF for community-based FEP clinics. Over the past 9 months, 91 of 492 (18.5%) calls to that FEP clinic (PREP) were self-referred from this website. Many more completed the PQ-B online after receiving information about PREP from their referring clinician, prior to their first contact with us.

5.3) AIM 2 RATIONALE

The Problem: Clinic Based Services are Not Sufficient to Engage all Patients. Rapid case identification (**Aim 1**) will not impact DUP if patients do not successfully engage in FEP services following referral. A study in the United Kingdom[8] found that delays in engagement in mental health assessment and treatment services were over seven times longer than delays in referral processes, accounting for 35% of overall variance in DUP. These delays were attributed to long wait lists for initial appointments, and to patients failing to attend scheduled clinic appointments, leading to discharge and a lengthy re-referral process [8]. At EDAPT, one in five patients fails to attend initial appointments and engage in FEP care. Thus, the goal of Aim 2 is to reduce barriers to engagement in specialty care FEP services, thereby reducing DUP.

Barriers to engagement in FEP services can be broadly classified into two primary categories; structural (largely economic) and sociocultural. Structural barriers that delay engagement in FEP services both in EDAPT and in other clinics include unavailable or inefficient transportation[40], inability of family member(s) and patients to leave work or school to attend scheduled appointments[41, 42], and unavailability of child care during scheduled appointments. Not surprisingly, these barriers are felt most acutely by families with limited financial resources, and these structural barriers may contribute to the finding that DUP is most protracted for FEP patients from urban and minority populations[43-46], including African Americans and recent immigrants from Asian Pacific Islander (API) communities[47-49].

As described previously in Aim 1, a primary social barrier to engagement in mental health services for FEP patients and families is the social stigma attached to a mental illness diagnosis[11, 12, 16]. In a qualitative study employing a family interview approach[50], investigators studying a clinical high risk population found that these stigmatizing beliefs were less prominent earlier in the illness process, *with the exception of ethnic minority families* who endorsed feelings of shame and a resulting desire to conceal clinical symptoms. This is consistent with our own experience, as Asian Pacific Islander (API) and Slavic patients were the most likely to mention social stigma (or "loss of face") as the reason why they hesitated to engage with our FEP services. Moreover, 35% of patients who failed to engage in FEP services were from minority groups, whereas only 20% of drop-outs were

Caucasian. Thus, as with the structural barriers discussed above, these social roadblocks appear to be experienced most acutely by minority populations.

The Solution: Mobile Assessment and Engagement into FEP Specialty Care
To identify best practices for reducing these structural and societal barriers to rapid engagement, we propose to contrast our current clinic-based engagement services against a community-based mobile engagement model. Our standard clinic-based services, in place since 2004, employ a Family-Aided Assertive Community Treatment (FACT) evidence-based model developed by the PIER Program at Maine Medical Center [51]. Like other Assertive Community Treatment (ACT) models[52], this approach emphasizes a rapid response to incoming referrals.

Despite the relative speed of our initial FACT intervention, almost 1 in 5 patients did not attend initial clinic appointments and never successfully engaged in FEP services. To directly address the structural and stigma-related barriers outlined above, we hypothesize that we can increase the number of patients enrolled in FEP services and reduce time from identification to enrollment through a community-based mobile engagement procedure (**Aim 2, Hypothesis 1**). Mobile assessment and engagement approaches have been popularized outside of the United States, through studies in Australia[53], Switzerland[6] and Norway[54]. In this model, a multi-disciplinary team of nurses or social workers meet with the client in a convenient community setting (home, school, community center) as soon as possible following case identification to conduct an initial diagnostic assessment. If indicated, a consulting psychiatrist is contacted during this initial appointment to confirm diagnosis and initiate treatment. Research on this mobile assessment approach reveals that it can reduce inpatient hospitalization rates by 8% [55] and, when combined with comprehensive public education, reduced DUP by 1.5 years[54]. We predict that it will similarly reduce time to engagement in FEP services in the current study by eliminating transportation barriers and providing contact outside of regular office hours, which reduces conflicts with school, work, and childcare responsibilities. Community-based engagement has been most effective at increasing initial clinic attendance and ongoing service engagement [56]. Moreover, this approach reduces the potential stigma of an initial visit to a mental health clinic, which we predict will be particularly important for individuals with more severe symptoms, ethnic minorities and those with a lower SES (**Aim 2, Hypothesis 2**).

6) Inclusion and Exclusion Criteria

Participants will be help-seeking children, teenagers, and adults, age 12-30, referred from 20 randomized referral sites within Sacramento County. Ten of these sites are already identified with another 10 sites being actively recruited. These individuals will be identified by their referring clinician, physician or counselor as needing mental health care for attenuated or threshold psychotic symptoms. Participants will

be eligible for EDAPT treatment if they meet criteria for a diagnosis of affective or nonaffective psychosis with onset in the past 2 years.

Exclusion criteria (assessed at initial phone evaluation): Participants will be excluded from EDAPT if the duration of psychosis is greater than 2 years, although their DUP will be documented for the purposes of the study analyses and they will be referred elsewhere for care. Patients will also be excluded for 1) current substance dependence, as determined by clinical interview and patient records, or 2) neurological illness or injury leading to psychotic symptoms, or only substance induced psychotic symptoms. Clinics will be asked to exclude patients from PQ-B screening or referral if they have a documented IQ < 70 or do not speak English. Adults unable to consent and prisoners will also be excluded from this study.

7) Number of Subjects

In Phase 1 (years 1 to 2), 150 subjects are anticipated. For Phase 2 (years 3 to 4), we anticipate enrolling an additional 200 participants. Due to supplemental funding obtained in 2017, an additional 50 participants will be enrolled during Phase 2 at WellSpace Integrated Behavioral Health Center. In the event of screen failures, additional subjects will be enrolled to attempt to meet these numbers.

8) Recruitment Methods

Subjects will be recruited for participation in the proposed study based upon referrals from sites in the community. Sites selected for participation in the proposed study are based upon an analysis of previous referral sources for FEP care at the EDAPT clinic. Of the referrals received by EDAPT in the past 2 years, eligible FEP patients were most often identified by ER/inpatient hospitals (100%), followed by schools/universities (64%) and community mental health providers (70%). Primary care referrals had the lowest success rate, with 42% excluded due to long duration of illness and 58% lost to follow up after initial referral. We will target sites from 4 strata (schools/universities, ER/inpatient hospitals, community mental health, and primary care) in order to capture all possible points of first contact for individuals eligible for FEP care.

Sites will identify individuals at the point of contact for mental health care, such as requesting mental health services at the student counseling center, presenting with a mental health concern during a regular medical visit in a primary care clinic, presenting with any mental health concern at an ER/inpatient setting, or all individuals initiating care in a community mental health clinic. We have obtained letters of support for sites within Sacramento County Behavioral Health (community mental health, ER/inpatient), UC Davis Health System (community mental health, ER/inpatient, primary care, pediatrics), Sierra Vista Hospital (inpatient), WellSpace Health (community mental health, primary care), Community Psychiatry, Sacramento City Unified School District, Twin Rivers Unified School District, Sacramento Job Corps (school). All referral sites will be asked to track their total number of new contacts for services during the study period to record the baseline number of cases at each site. Screening sites will also

track the number of cases that were not eligible for the screen due to basic criteria (see Inclusion/Exclusion criteria above).

HIPAA Considerations:

Individuals presenting to sites in the Targeted Education and Screening Arm of the study will complete an informed consent process on the android tablet (see Electronic Tablet Screening Form attached). Patients will be asked to give their name, date of birth, race, ethnicity, and gender at the time of the screening. Name and date of birth are automatically scrambled on the device in order to generate a non-identifying unique string of alphanumeric characters. Using this information to generate a unique ID plays several roles: 1) allows study staff to identify PQ-B data for patients who enroll in the study, 2) prevents any breach of privacy if the handheld is lost, 3) flags individuals who may complete the screening questionnaire more than once at different sites. Without this unique identifier, a participant could fill out several questionnaires at different clinics over the duration of the study and invalidate the data collected. Race, ethnicity, and gender are tied to this unique identifier and encrypted on the handheld device. This additional demographic data is critical to collect at screening to insure that randomization of sites was successful (i.e., electronic screeners are being equally distributed across clinics with all races and gender represented). This data also insures that samples are representative of the local population. Patients will complete the self-report survey in 3-5 minutes and the PQ-B will be automatically scored. A feedback screen will indicate the patient's unique study identifier and indicate whether the patient is eligible for the next screening phase of the study (i.e., phone evaluation). Patients' PQ-B scores will not be shown, but will be recorded on the handheld. Referral site staff will follow the device instructions and will invite patients scoring above the PQ-B threshold to complete a brief phone evaluation with study staff at that time, or at another time that is convenient to them. De-identified data will be downloaded monthly from each screening tablet at each site by study staff to allow tracking of the number of PQ-B screens completed. While the majority of patients will be referred based on PQ-B screening results, referral sources in the active intervention arm will also be instructed that they can still refer patients for phone evaluation in the presence of negative PQ-B screening results if they believe the client is appropriate for EDAPT services based upon other information. In routine clinical practice, screening would be used in addition to clinician referral, not in place of it. Sites may choose complete their own internal consent procedures as part of their internal documentation process. These site-specific internal documentation procedures are in addition to documentation of consent already obtained via the electronic tablet. Natomas Unified School District will be internally documenting that appropriate parental consent was obtained using the "NUSD psychosis screener consent form.docx".

Several study sites with high patient throughput may need additional accommodations in order to minimize participant burden and the impact of the study on direct patient care. In order to facilitate screening, research staff will work with site staff on prioritizing administration of screening to those individuals

presenting with mental health complaints. To prioritize these individuals for screening, limited access will be granted to specific PHI (age and chief complaint/presenting problem) via the patient tracking system or initial evaluation note in EMR. This information will be used to prioritize subjects to receive the screening tablet, and will be destroyed immediately after screening.

Individuals presenting to sites in the Targeted Education Arm of the study would simply be referred for the phone evaluation directly by their counselor, doctor or clinician. Participants may also identified by visiting our website and completing a web-based version of the screening consent and PQ-B that uses the same language as the electronic tablet screen. Providers that are part of the Active Arm and use the web-based screening option will ask permission of potentially eligible participants to share their contact information with the research team, who will direct the participant to complete the web-based screening. As with the android tablet version, only name, date of birth, race, ethnicity, and gender would be recorded and assigned a unique identifier. The participant will not receive their PQ-B score, but will be assigned a unique identifier upon completing the web-based version of the screen and be provided with the phone number of the EDAPT clinic in the event of a positive screen. The participant can only be linked to the screening PQ-B score if a) the provider asks a patient if they are willing to complete the web screening form (and phone interview if screening reveals a score above the cutoff), b) the patient is willing to be screened and gives permission for the provider to share their contact information with the research team, and b) the patient successfully completes the web screening form (and phone interview if screening reveals a score above the cutoff).

Positive screens/referrals received by all intervention arms will be asked to consent to and complete a brief phone evaluation (see attached phone evaluation form). When screening potential subjects, basic contact information (i.e., name, gender, age, race/ethnicity, symptom onset date, and phone number) will need to be obtained in order to schedule an appointment for the subject to undergo the full informed consent procedure and provide HIPAA authorization. The PHI obtained at this time will consist of the subject's responses to the questions on our telephone evaluation form. Because this initial screening is done by telephone, it will not be possible to obtain written HIPAA authorization prior to collecting this information. However, written HIPAA authorization will be requested at the beginning of the participant's first visit to the research facility. All protected health information used to recruit subjects will be kept in a locked filing cabinet. Each subject will be given a unique identifier corresponding to their participation in the study which will not contain any identifying information. These unique identifiers will be kept in a separate filing cabinet, which will not contain any protected health information. This protected health information will not be used for any purpose other than recruitment for this study, nor will it be disclosed to any other person or entity. All protected health information used to recruit subjects will be destroyed using the confidential paper and shredding system provided by the UC Davis Health System

within one month of their participation or immediately if the subject proves to be ineligible for or declines to participate in the study.

For participants who were screened using the PQ-B at WellSpace Health, complete a phone evaluation, and are enrolled in the supplemental study at WellSpace Health in Phase 2 (details presented below on pages 18-19, health records will not be accessed or appended to, so no HIPAA authorization form will be obtained for these subjects. A full informed consent will be signed using Docusign.

9) Compensation to the Subjects

Participants will be compensated $25 for their participation in the intake appointments and completing the satisfaction surveys.

Participants in Phase 2 who are screened at a primary care setting will also have the opportunity to participate in an additional interview where questions will be asked about the feasibility of the screening process. Participants will be compensated and additional $30 for this optional interview.

Additionally in Phase 2, up to 50 participants screened at WellSpace Health who score below the PQ-B cutoff score will be compensated $50 for completing an assessment over the phone. Similarly, up to 150 participants screened at WellSpace Health who exceed a total PQ-B distress score of 20 or higher will be compensated $50 for completing an assessment over the phone.

10) Study Timelines

Subjects will participate in each phase of the study for up to six months in order to determine whether the participant has successfully engaged in treatment.

The anticipated duration to enroll all study subjects is 4 years.

We anticipate completing the primary Phase 1 analyses by the end of Year 2 and Phase 2 analyses by the end of Year 5.

Subjects participating in the WellSpace Health supplement who scored below the PQ-B cutoff will participate for only the duration of time needed to complete the phone assessment, approximately 1-2 hours.

11) Study Endpoints

The primary endpoints of the study for Phase 1 will be an examination of the duration of untreated psychosis for individuals in the active versus TAU treatment identification arms. The total number of patients recruited through each arm will also be examined. Secondary endpoints of the study for Phase 1 will be an

examination of the satisfaction ratings of referral sources, patients, and family members in each arm of the study.

The primary endpoints of the study for Phase 2 will be an examination of the rates of enrollment in FEP care in the community-based mobile arm versus the standard clinic-based engagement arm. We will also examine the duration of time from screening to enrollment across the two arms. Secondary endpoints for Phase 2 will be an examination of the satisfaction ratings of patients and family members with the screening procedure compared to the targeted provider education alone. Finally, we hope to examine the severity of symptoms, minority and socioeconomic status of individuals in the two arms, with the anticipation that minority, low-SES, and more severe patients will be better served by mobile engagement.

12) Procedures Involved

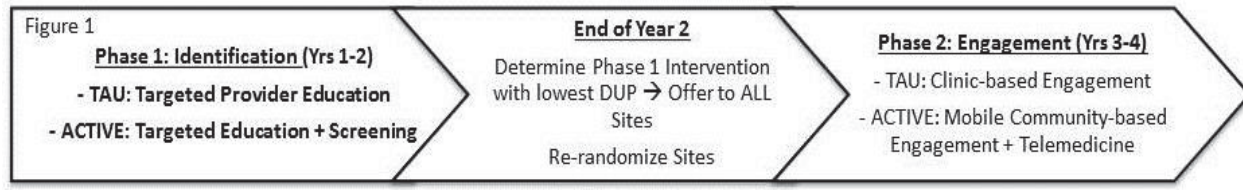

Figure 1. Overview of Study Design

Phase 1 Summary: Shown in Figure 1, the proposed study to test Aim 1 is a cluster randomized controlled trial (RCT) utilizing two approaches to rapid identification: (1) standard targeted provider education [5] to motivate client referrals to FEP services, versus (2) standard targeted provider education plus electronic self-report screening using PQ-B, with automatic referral of patients to EDAPT FEP care when they exceed a Distress threshold score of 6 or more.

As shown in Figure 2 below, all standard referrals and screen-positives will receive a brief phone evaluation from the research study staff, followed by in-person structured clinical interview to establish diagnosis and eligibility for the FEP service and date of psychosis onset. We will compare the number of FEP patients and the length of DUP (defined as time from onset of first full threshold positive symptom to enrollment in treatment in EDAPT, which occurs immediately following completion of the clinician assessment for eligible clients) via each method.

Phase 1 Procedures: Research staff located within the EDAPT Clinic, located in the Wong Building at UCDMC will be the coordinating site for receiving first episode psychosis patient referrals from 20 community referral sites. These 20 referral sites will be randomized to one of two intervention arms arms [Treatment as Usual (TAU) = Education Alone; Active = Education + Screening] and the sites will participate in the assigned intervention for Years 1 and 2 of the proposed study (Phase 1). Ten sites are already committed, with another 10 sites being actively recruited.

Sites assigned to TAU will receive the EDAPT standard targeted provider education, which focuses on increasing awareness about the signs of early psychosis and building collaborative relationships with community members so they see EDAPT as a rapid and effective source of help. It consists of a 2-hour workshop describing: 1) how to identify specific early symptoms and changes associated with the onset of psychotic illness, 2) the benefits of early intervention on treatment outcomes in psychosis, 3) the structure, philosophy and treatment model of the EDAPT Clinic, and 4) procedures for expeditious referral to our program. Case-based vignettes are reviewed to ensure understanding of the key symptoms. During this workshop, we empower community referral sources to seek our help if they have a suspicion that an individual or family may be struggling with psychosis. We provide written materials (informational booklets, handouts, brochures in multiple languages) and show videos that can be adapted to the needs of various audiences, from mental health or primary care providers to consumers and their families. In the past 7 years, EDAPT has given 267 presentations for local schools, hospitals, mental health providers, primary care providers and community programs, directly educating over 15,000 individuals in the Sacramento community.

Sites assigned to the Active intervention will receive the same standard targeted education as described above. In addition, the PQ-B will be administered to all patients at their first visit to the referral sites (e.g. intake) via an android tablet provided to the site for ease of administration and scoring. The android version of the PQ-B will be identical to the web-based version described above. We will provide multiple tablets per site so that the screening is available for more than one individual simultaneously and can be completed in any appropriate location.

Prior to completing the PQ-B, patients will complete an informed consent process on the android tablet (see Electronic Tablet Screening Form attached). Patients will be asked to give only their name, date of birth, race, ethnicity, and gender at the time of the screening and will be assigned a unique study identifier to 1) allow study staff to identify PQ-B data for patients, and 2) prevent any breach of privacy if the handheld is lost. Patients will complete the self-report survey in 3-5 minutes and the PQ-B will be automatically scored. A feedback screen will indicate the patient's unique study identifier and further instructions for the referrer. Patients' PQ-B scores will not be shown, but will be recorded on the handheld. Referral site staff will follow the device instructions and will invite patients scoring above the PQ-B threshold to complete a brief phone evaluation with EDAPT staff at that time, or at another time that is convenient to them. De-identified data will be downloaded monthly from each screening tablet at each site by study staff to allow tracking of the number of PQ-B screens completed. While the majority of patients will be referred based on PQ-B screening results, referral sources in the active intervention arm will also be instructed that they can still refer patients for phone evaluation in the presence of negative PQ-B screening results if they believe the client is appropriate for EDAPT services based upon other information. In routine clinical practice, screening would be used in addition to clinician referral, not in place of it.

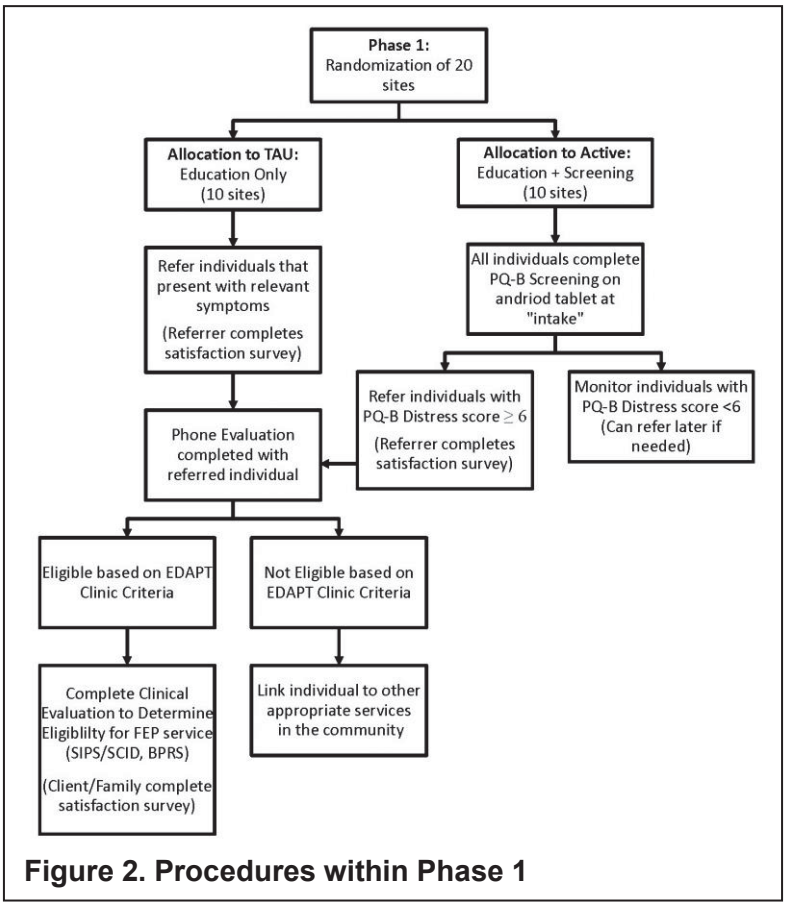

Figure 2. Procedures within Phase 1

Electronic administration is especially useful for the PQ-B; each endorsed symptom item is followed by a question regarding distress and impairment related to the symptom which can be skipped if the symptom is denied, shortening administration time, without requiring hand-scoring. Clinical directors for most sites agreed that electronic administration of the PQ-B would be easy to incorporate. However, in feedback from some Sacramento County clinics, such as the Emergency Department, the option to use a paper-and-pencil method was requested for specific cases where safety is a concern or clients refuse to use any electronic equipment (e.g. due to delusional beliefs). Therefore, screening by android tablets will be the primary mode of administration, but we will allow paper-and-pencil administration for situations where it is more appropriate. Use of the paper-and-pencil version will

be tracked and associated data will be collected to provide information on feasibility of electronic screening in various settings.

Assessment to Determine Eligibility for FEP services: Positive screens/referrals received by both intervention arms will be asked to consent to and complete a brief phone evaluation (see attached phone evaluation form). In addition to phone calls, research staff will use Google Voice texting software to send text reminders to study participants to coordinate study reminders and to schedule phone evaluations. Texts sent by research staff will not include any protected health information and will be sent through a Google Voice generated phone number. If they meet basic inclusion criteria (see below) for EDAPT services based on phone evaluation they will be asked to complete a 1-2 hour clinic-based assessment at EDAPT to determine diagnosis and eligibility. Prior to assessment, the study will be discussed with patients and/or their legal guardians and consent and assent will be received in accordance with U.C. Davis IRB policies. At clinic assessment, patients will complete the Psychosis, Mood and Substance Use modules of the SCID-IV-TR [57], SIPS, or K-SADS [58], to determine diagnosis and date of onset of psychotic symptoms. Symptom severity will also be rated on the 24-item Brief Psychiatric Rating Scale (BPRS [59]) and Clinical Global Impression Scale (CGI). Social and occupational functioning will be assessed with the Global Assessment of Functioning Scale and Global Functioning Scales (see Measures). Information on family history, psychosocial functioning, number of prior mental health contacts, previous use of psychiatric medications and psychological treatments will be collected. In cases where patients do not qualify, clinicians will provide appropriate referrals. Interpretive services will be provided to allow participation by family members who do not speak English proficiently. If deemed eligible for the study, participants will be admitted into the EDAPT clinic and proceed with treatment as usual.

Measures (self-report):

- Prodromal Questionnaire- Brief (PQ-B) Screening: The PQ-B is a 21-item self-report measure that assesses positive symptoms of psychosis and impairment/distress related to each symptom. As described earlier, a threshold of 6 or higher on the PQ-B Distress score will be used in this study, as recommended from the validation study [36] and confirmed in our pilot work in Sacramento County.
- Satisfaction Surveys: Patients in both intervention arms will complete standardized satisfaction questionnaires[66] adapted for this study (Hypothesis 3, Aims 1 and 2). These questionnaires are based upon results of a qualitative focus group study of issues important to patient satisfaction[66], which revealed 3 central themes (ease of access to service, clarity of information provided, usefulness of service). Item responses utilize a 7 or 5-point Likert scale (from “strongly agree” to “strongly disagree”). The total score provides an overall satisfaction index. Additionally, EDAPT providers will complete standardized satisfaction questionnaires adapted for this study. These Provider Satisfaction Questionnaires (PSQ) were developed

from the *Telehealth Usability Questionnaire*[67]. Item responses utilize a 7-point Likert scale (from "strongly agree" to "strongly disagree). If study participants do not complete the satisfaction survey during their in-person study appointment, the satisfaction survey will be emailed to the participant through REDCap survey mode. REDCap survey mode is a feature of REDCap, our data collection system, which allows study participants to fill out a public version of a data form in the REDCap project without logging into REDCap. Once the participant completes the satisfaction survey, the data will automatically be entered back into the data form and will be visible only to research personnel with access to the REDcap project. We will email the REDCap survey to the participants' email addresses that we have on file from when we emailed consent forms using Docusign.

Measures (administered):

- Structured Clinical Interview for Diagnosis for DSM-IV-TR (SCID-IV-I/P [57]) and Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS [58]): At EDAPT intake, individuals age 16 and older will be administered the Psychosis, Mood and Substance Use modules from SCID-IV-I/P while patients 15 years and younger will be administered the K-SADS to determine the appropriate DSM-IV diagnoses for the FEP group. The Structured Interview for Prodromal Sydromes (SIPS [37]) will be used to determine psychosis risk state for those individuals who present with attenuated psychotic symptomatology. Onset of psychosis will be established as the date of onset of first full threshold positive psychotic symptom from the A criteria of DSM-IV TR. Diagnosis and date of psychosis onset will be confirmed by team review of all data.
- Brief Psychiatric Rating Scale (BPRS [59]): The interviewer will complete the 24-item BPRS at EDAPT intake which contains detailed anchor points, probe questions, and a rating of Total Symptom severity at. Symptom severity will also be calculated across four domains (positive, negative, agitation/mania, depression/anxiety) according to the factor analysis by Kopelowicz and colleagues[60].
- The Global Functioning Scale: Social (GFS: Social; Auther et al., 2006) and Global Functioning Scale: Role (GFS: Role; Niendam et al., 2006) provide ratings of functioning in social and role domains, respectively, on two separate 10-point Likert scales, which are scored independently of symptom severity. The GFR and GFS will be administered at the initial study enrollment appointment following informed consent and at follow-up.
- Global Assessment of Functioning-Modified (GAF) A modified version of the GAF, which includes detailed anchors to improve reliability, will be used to determine participants level of global functioning on a 0-100 point scale, where higher scores indicate better functioning.
- The Clinical Global Impression Scale [CGI; (Haro et al., 2003] is[61] a brief 12-item scale assessing illness severity and degree of improvement over follow-up that is appropriate for use in clinical or research settings. This measure will be administered at the initial study enrollment appointment following informed consent, and at follow-up.

Masters- or Doctoral-level clinicians trained to reliability standards will complete diagnostic interviews and symptom ratings. Research staff training to reliability standards will complete phone follow up evaluations. Consensus diagnoses will be made between examiners, who will maintain at least an average intra-class correlation of .80 for symptom ratings and an average kappa value of .80 for diagnostic agreement.

Site Staff/Administrator Debriefing Interview: In order to better understand why individuals may choose to not pursue additional clinical evaluations for services after taking the tablet screening measure, we will interview site administrators, clinicians, and staff who conduct evaluations at partner sites (see DUP Admin-Staff Qualitative Interview.docx). The purpose of the interview is to consult with members of each site to understand strengths and weaknesses of the electronic tablet screening procedure in general (with no reference to individual patients), with hopes of identifying areas that can be improved in preparation for starting Phase 2 of the study. These interviews would not involve any additional contact with or sharing of PHI from any past, current, or potential participants. In lieu of an in person interview, participating primary care staff will also be given an online survey, accessible through Qualtrics, with the same goals in mind (see DUP_PCN_Survey.docx).We are offering to bring each primary care site coffee and snacks if we receive their feedback.

Phase 2 Summary: After Phase 1, we will select the identification method that yielded the lowest DUP and then provide this identification method to all 20 participating sites in Phase 2. Individuals identified by the tablet screening will be randomized (at the individual level) within site to either standard clinic-based engagement [TAU: treatment as usual] or telemedicine-enhanced mobile engagement [Active]. Additionally, to determine the validity and feasibility of screening for psychosis in primary care, we will evaluate the sensitivity and specificity of the PQ-B relative to diagnosis by clinical interview for participants screened at the WellSpace behavioral health intake. To address this goal, 50 participants who score below the PQ-B cutoff score will proceed through the study procedures in a manner similar to high scoring participants, to evaluate whether the PQ-B score was accurate in screening psychotic symptoms.

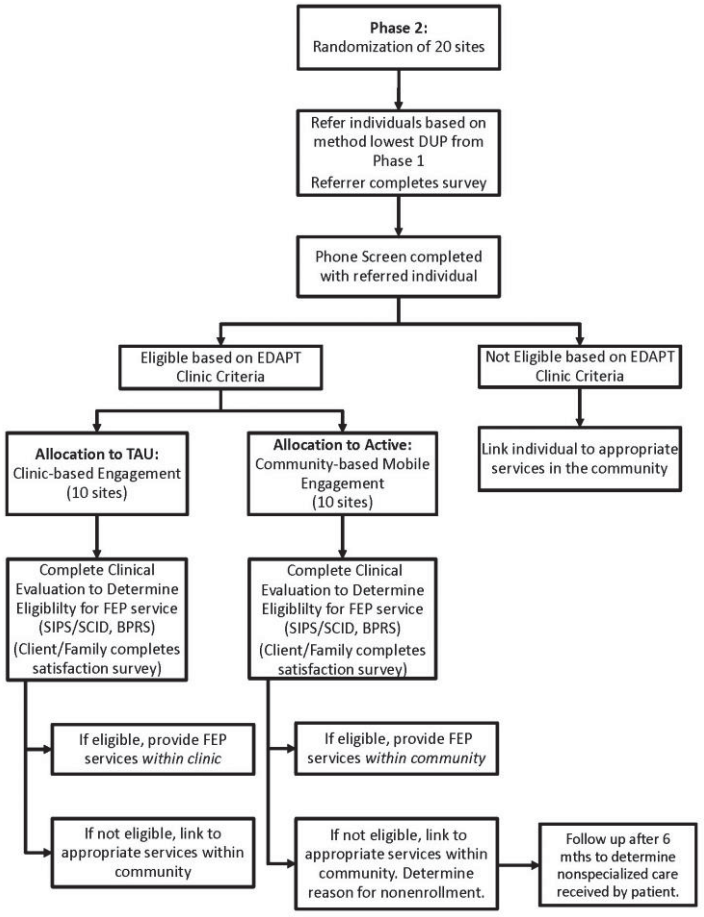

Figure 3. Procedures within Phase 2

Phase 2 Procedures: The same 20 sites will participate in Years 3 and 4 of the proposed study (Phase 2). If an individual is deemed appropriate for the study after the phone evaluation, individuals will be randomized (at the individual level) within site to either standard clinic-based engagement at EDAPT [TAU: treatment as usual] or telemedicine-enhanced mobile engagement at a secure site within the community [Active]. (Figure 3).

Both arms: Prior to the initial clinical assessment, the study will be discussed with patients and/or their legal guardians and consent and assent will be received in accordance with U.C. Davis IRB policies (see consent procedures outlined below). As in Phase 1, the clinical assessment will be completed by a Masters- or Doctoral-level clinician trained to reliability in the diagnostic and symptom measures (SCID/K-SADS, BPRS – see previous Measures section). The clinician will complete the assessment with the individual and collateral informants to determine a diagnosis and eligibility for EDAPT care (see Inclusion/ Exclusion criteria section). If the individual does not enroll in FEP services at EDAPT, project staff will follow up with the referral source and individual to determine the reasons for non-enrollment. Project staff will attempt to contact the individual and/or family six months later to determine what type of services the individual received in lieu of FEP specialty care and their clinical outcome.

TAU (Clinic-based Engagement): The clinical assessment appointment will be completed within the EDAPT clinic. If deemed eligible for EDAPT services, the individual will be scheduled for a clinic-based appointment with the EDAPT psychiatrist for an evaluation within 5 days. The EDAPT

clinician will follow up with the individual within 5 days of the psychiatric evaluation (by phone or in the clinic) to assess early treatment compliance.

Active (Community-based Mobile Engagement): Clinical assessment appointments will take place at the EDAPT clinic or within the community, wherever the individual would prefer. With patients deemed eligible for EDAPT services, the EDAPT clinician will contact the EDAPT psychiatrist with a telemedicine-enabled laptop to complete the psychiatric evaluation remotely. The EDAPT clinician will follow up with the individual within 5 days to assess early treatment compliance.

Telemedicine-enabled Laptop: For individuals deemed eligible for FEP care and assigned to community-based mobile engagement, a portable laptop computer will be used to establish a telemedicine link with the prescribing psychiatrist during the a mobile engagement session. During this session, the psychiatrist will perform a comprehensive psychiatric evaluation. The laptop will be equipped with a built-in high definition camera to facilitate teleconferencing using Zoom video conferencing software, which is HIPPA approved and supported by the UC Davis Center for Health Technology.

WellSpace Integrated Behavioral Health: All primary care patients, ages 18-30, who are directed to Integrated Behavioral Health (IBH) services will be asked to complete the PQ-B screener on an android tablet at their first IBH appointment identically to other sites. Additionally, participants who score below the PQ-B threshold will be offered the opportunity to participate in the study in a manner similar to the high scoring participants, with the goal of evaluating the efficacy of the PQ-B screening measure. After the participant completes the screener and scores below the cutoff, the IBH clinician will follow the device instructions and propose the additional research opportunity with the research request form (see Negative Screen Research Request Fax Form.doc). If the participant declines further participation, the person proceeds with the usual care provided by WellSpace Health. If the participant is interested in further participation, the care coordinator will give an informational flyer about the study (see WellSpace DUP Flyer.docx) and ask the person to complete the form, which contains information about the study and basic contact information. After completing the form, the WellSpace Health clinician will fax the form to the study coordinator using WellSpace approved standard operating procedures for sending protected information. Once study staff receive either the standard referral form for those who have scored above the PQ-B threshold or the Negative Screen Research Request fax form for those who have scored below the PQ-B threshold, the participant will be contacted and fully consented electronically (see WellSpace DUP Supplement Consent.doc) using Docusign and complete the assessment with the interviewer blinded to their PQ-B score. The assessment procedure will use previously approved assessment measures implemented for other study participants, except that the assessment is conducted over the phone rather than in person. Research

activities taking place in county facilities will be reviewed by the Sacramento County DHHS Research Review Committee.

Phase 2 Primary Care Provider and Participant Qualitative Interview: Use of screening tools to assess psychotic disorders are not frequently utilized in primary care settings. Given that this study has five primary care sites in which screening is taking place, it is of interest to understand how well the screening process is functioning both at the level of the provider and the patient. Approximately 10 primary care providers will be interviewed (see Primary Care Provider Interview.docx) to assess advantages, disadvantages, and areas of improvement for the electronic screening process in the primary care setting. Providers will be offered $30 to participate in this interview. This will not occur during their working hours. Additionally, approximately 10 research participants will be also be interviewed (see Primary Care Participant Interview.docx) to obtain this perspective from the patient. Former and current research participants referred from a primary care setting will sign an additional consent form if participating in this interview portion. Research participants will be compensated an additional $30 for participating in this interview.

Phase 2 EDAPT Provider Satisfaction Questionnaires: In order to understand and assess the advantages and disadvantages for providers who are conducting initial evaluations with clients through telehealth compared to standard clinic-based appointments, EDAPT providers will be asked to complete standardized satisfaction ratings (see Provider Satisfaction Questionnaire Clinic.docx and Provider Satisfaction Questionnaire Telehealth.docx) after they have completed an intake evaluation with a DUP participant through either a telemedicine-enabled laptop or through a standard clinic-based appointment. Approximately 5-10 providers will complete the satisfaction ratings, and they will repeat the ratings for each DUP client who presents for an initial evaluation. The Provider Satisfaction Questionnaire (PSQ) contains four self-report questions in the clinic version and two additional questions in the telehealth version.

13) Data and Specimen Banking

No data or specimens will be stored for future use.

14) Data Management and Confidentiality

Data Analysis Plan for Phase 1:

Key Variables: For the proposed analysis, DUP will be defined as the number of days between the onset of first psychotic symptoms (as determined by the SCID/KSADS and clinic records) and the date of the first in-person EDAPT clinical interview (at clinic or in community). Program enrollment is defined as a patient who agrees to EDAPT FEP services and completes the in-person clinical interview. Enrollment rate is defined as the number of patients who enroll in the program divided by the total number of patients referred to EDAPT within the study period.

Preliminary Analyses: We will run standard diagnostic statistics and graphical analysis for all variables to check for outliers and out-of-range values and to

confirm that distributions meet assumptions of the statistical tests to be used. The psychometric properties of measures with scale scores will be examined for internal consistency and factor structure to ensure the measures are operating as desired with this diverse sample. Many of the measures have been widely used, so problems are not anticipated. As recruitment is projected to occur over many months, preliminary analyses will test the correlation between order of study entry and outcome. Dropout rates will be examined by condition. If differences for any of these variables are noted, they will be statistically controlled as a covariate in model testing or as a stratification variable.

Missing Data: Every effort will be made to limit the amount of missing data. When possible, patients will be re-contacted to obtain missing information. Most missing data will likely result from drop out between referral and phone evaluation, and between phone evaluation to first clinical appointment. While a certain amount of this is inevitable, our design and tracking procedures will limit this loss. To date, we have completed phone evaluations on 79% of potentially eligible referrals, and 69% of individuals who are eligible complete the first clinical appointment. To minimize patient loss, we reach out to all available contacts, including the referring provider if applicable, and will continue to do so as part of this project. Prior to analysis, we will examine baseline predictors of enrollment. If it appears missingness is related to a measured aspect of the patients, we will include those measures as covariates in the hypothesis-testing models. The modeling strategy (see C.6.3) will allow us to use all collected data in our estimation. Sensitivity analyses will check that methods of dealing with missing data do not have a major impact on study conclusions.

Primary Analyses: The general approach to hypothesis testing will involve the estimation and testing of mixed-effects models of the outcomes which will include a term to directly test the hypothesis. All analytic models will account for the design effects of cluster randomization 47 and randomization strata 48. Statistical models will all include randomization strata as a fixed variable to allow testing of strata-by-condition interactions. The use of these statistical techniques will be taken into account in interpretation of the outcome. Models will be estimated using maximum likelihood methods under SAS v9.3 which will allow us to include all collected data in the analysis. At all stages of the analysis, statistical assumption will be tested and analysis methods will be adapted accordingly.

As the Poisson model assumes that all patients within a covariate group have the same underlying outcome rate, we will also estimate and test parallel models based on the negative binomial distribution which relaxes this assumption. While our experience indicates there are often minimal differences between these models, a comparison of the fit statistics will indicate which is the preferred result to base our conclusions on. The general model in common in many areas of research and can be summarized as: $\lambda(y) = \exp(\beta 0 + \beta 1x1, \beta 2x2, \ldots, \beta kxk)$, for k covariates where λ = is the population rate parameter and xk = covariate k.

- H1: DUP will be lower for FEP patients identified through the provider education plus screening procedure, compared to the DUP of FEP patients identified by targeted provider education alone. Analysis: As the outcome for this hypothesis is a count of number of days, it will be tested using the general approach described above in the form of a Poisson or negative binomial model including a term for condition (i.e., how identified) and baseline covariates identified in preliminary analysis. The test of the coefficient on the condition term will directly test this hypothesis.
- H2: A greater number of FEP patients will be identified through the targeted provider education plus screening procedure, compared to the number of FEP patients identified by targeted provider education alone. Analysis: While also a count, this outcome—mean number of patients—is anticipated to have a greater range with a less skewed distribution and can best be modeled as a continuous variable. This hypothesis will be tested using a standard linear model in a fashion parallel to the model testing H1 including the same covariates. A term for condition will again directly test the hypothesis. A Poisson or negative binomial model as used for H1 will be used should the observed distribution of the outcome differ from what is anticipated and be deemed more appropriate.
- H3: Referral sources, patients and family members will report at least equal (non-inferior) satisfaction with the screening procedure as compared to the targeted provider education procedure alone. Analysis: This hypothesis will be tested using a one-tailed test following procedures for non-inferiority trials outlined in the literature 49, 50. Modeling will account for repeated measures by referral sources and the non-independence of patients and family members.

Sample Size and Power for Phase 1: The sample size for Phase 1 is based on several factors including site availability and census, timeframe and estimated effect sizes. Based on pilot data, we anticipate the design effect (clustering by site) to be minimal - approximately .01. Sample sizes were estimated, however, using a range of intra-class correlations. With randomization by site, for H1, we anticipate being able to detect an effect in number of days ranging from .35 to .37 with an N of 150 patients [63, 64]. Based on our current DUP at EDAPT of 296 days (± 516) as the estimated DUP in the control arm, a DUP of 148 days (± 258) in the screening arm would result in an effect size of approximately .36, within our detectable range. For the modeling of counts (H2), we will have approximately 80% power to detect a response ratio of 1.28 [65]. For H3, we will consider satisfaction of the 2 groups to be "equivalent" if the effect size, as measured by Cohen's d, to be <0.5 for which we will have 80% power to detect.

Data Analysis Plan for Phase 2:
Statistical procedures used to test the hypotheses under Phase 2 will largely follow those described for Phase 1.

- H1: The community-based mobile team will lead to higher rates of enrollment in FEP care than standard clinic-based engagement services. Analysis: This hypothesis will be tested by estimating and testing a logistic

regression model of the proportion of patients who made it from phone evaluation to treatment. As with other models, we will account for clustering by site.

- H2: The community-based mobile team will lead to shorter time from screening to engagement than standard clinic-based engagement services. Analysis: Using procedures similar to those used in the Phase 1 analysis, mean number of days will be compared between conditions using a negative binomial model including a term for condition (i.e., how identified) and baseline covariates identified in preliminary analysis.
- H3: Patients and family members will report at least equal (non-inferior) satisfaction with the screening procedure as compared to the targeted provider education procedure alone. Analysis: This hypothesis will be tested using a one-tailed test following procedures for non-inferiority trials outlined in the literature 49, 50. Modeling will account for repeated measures by referral sources and the non-independence of patients and family members.
- H4: Mobile FEP engagement will enroll individuals with more severe symptoms, minority status and lower socioeconomic status (SES) into FEP services than individuals enrolled via clinic-based FEP engagement. Analysis: To examine relationships with symptom severity, minority status and socioeconomic status, we will add terms for these measures into the models used for hypothesis testing. Interaction terms will test whether the treatment effects varied as a function of these indicators.
- H5: The electronic screener will demonstrate good concurrent validity with a significant Area Under the Curve (AUC) of at least .50 when compared to phone screen diagnosis for individuals identified in primary care settings.

Sample Size and Power for Phase 2: Sample size for Phase 2 was estimated in a similar fashion as for Phase 1. Factors included the site size, timeframe, estimated effect sizes and level of intraclass correlation are based on pilot work. Based on our estimate of a mean of 148 (+/- 258) days DUP in the active arm of Phase 1, a reduction to the target of less than 90 (+/- 30) days for the active arm (mobile engagement) in Phase 2 would be equivalent to an effect size of .32, within our detectable range. Randomizing by site in Phase 2, we anticipate being able to detect an effect ranging from .30 - .32 with N=200 patients and a response ratio as low as 1.24 with 80% power. For H3, we will consider satisfaction of the 2 groups to be "equivalent" if the effect size, as measured by Cohen's d, is <0.5, which we will have 80% power to detect.

Steps Taken to Secure the Data:
De-identified data will be stored in locked cabinets. Furthermore, only individuals on the research team who have a specific need to access subject information (i.e., to evaluate demographic data) will be permitted such access. All study personnel will have passed required courses on privacy and confidentiality. Records containing identifying information and the data code key will be stored in locked cabinets or in

password-protected computer files with access controlled by the study coordinator and study physicians.

Steps Taken to Ensure Quality Control of Data:
The Biomedical Informatics Program of the UC Davis Clinical and Translational Science Center will be used as a central location for data management. Vanderbilt University, with collaboration from a consortium of institutional partners, has developed a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from the Biomedical Informatics Program. The iterative development and testing process results in a well-planned data collection strategy for individual studies. The REDCap system provides secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus) REDCap servers are housed in a local data center at UC Davis Health System and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org).

Access to REDCap is limited to research personnel who are on the IRB-approved study personnel list. Additionally, data that is encrypted and not easily stored in REDCap (android tablet results) will be stored de-identified on password-protected servers at the Imaging Research Center that are protected by an institutional firewall. All data entered into REDCap or password-protected databases will be double-entered by trained staff to ensure data integrity.

Data-transmission:
De-identified data will be downloaded monthly from each screening tablet at each site by study staff to allow tracking of the number of PQ-B screens completed. Electronic administration is especially useful for the PQ-B; each endorsed symptom item is followed by a question regarding distress and impairment related to the symptom which can be skipped if the symptom is denied, shortening administration time, without requiring hand-scoring. Clinical directors for most sites agreed that electronic administration of the PQ-B would be easy to incorporate. However, in feedback from some Sacramento County clinics, such as the Emergency Department, the option to use a paper-and-pencil method was requested for specific cases where safety is a concern or clients refuse to use any electronic equipment (e.g. due to delusional beliefs). Therefore, screening by android tablets will be the primary mode of administration, but we will allow paper-and-pencil administration

for situations where it is more appropriate. Use of the paper-and-pencil version will be tracked and associated data will be collected monthly by study staff to provide information on feasibility of electronic screening in various settings.

15) Provisions to Monitor the Data to Ensure the Safety of Subjects

The participant's information will be held in a locked filing cabinet. Interviews and assessments will be conducted by experienced staff that is trained to notice any cause of concern that is decided to be severe and in need of attention by the investigators. A referral to a psychiatrist or other health professional will be made if needed, and if the researchers learn that that the individual or someone with whom the individual is involved is in serious danger or harm, we will inform the appropriate agencies. Data collected during phone evaluation and clinical interviews will be reviewed weekly and staff will be supervised by a licensed clinical supervisor.

16) Withdrawal of Subjects

A subject may withdraw his/her consent even after giving permission, and may withdraw from the study without prejudice at any time. Investigators may choose to withdraw subjects from the study without regard to their consent under circumstances where newly disclosed information indicates that the subject meets one or more exclusion criteria.

Examples of subject discontinuation criteria include:

- Clinical judgment of the investigator or at request of subject, sponsor, or regulatory authority
- Withdrawal of consent and/or patient decision
- Evidence of current substance dependence

If the subject chooses to withdraw from the study, but is eligible and willing to continue to participate in some continuing aspect of the study (i.e., partial withdrawal), data will be collected for procedures the subject is willing to complete. If the subject is withdrawn or chooses to withdraw fully, data collected up to that point will be preserved for data analysis.

17) Risks to Subjects

Some participants may experience psychological discomfort in discussing the symptoms of their first episode or other diagnostic conditions. There are no other known risks associated with any of the clinical interview or survey procedures to be used in the proposed study. There are no alternative procedures or methods available with less risk or cost that provide comparable information to that obtained by the procedures described in this proposal.

Risks will be minimized in the following manner. All interviewers conducting phone evaluations and diagnostic clinical interviews will be trained to be sensitive to participant distress, and in procedures to minimize this distress. All of the data

collected for these studies will be kept strictly confidential. Under no circumstances will individually identifiable data be released to anyone without the written consent of the subject. Results will be reported as group findings only. Results will be discussed with the subject (or with the patient's physician) at their request.

No adverse events are contemplated for this study. We do not expect significant emotional distress as we emphasize breaks in the clinical interviews should there be any difficulty. The subject also may choose to stop at any time as participation is voluntary. In the extremely unlikely event that there is a serious adverse event – we would first make sure that the subject was medically evaluated in the UC Davis emergency center or other appropriate site. After taking care to ensure that the subject was being clinically evaluated and treated if necessary we would report the incident to the IRB without name of the subject. This would be done within twenty-four hours of the incident.

18) Potential Benefits to Subjects

Participants who the screening measure identifies as needing evaluation to determine the presence of psychotic symptoms will be compensated $25 for their participation. Additionally, all study procedures aim to link them with appropriate clinical services and will be for their benefit. Participants recruited from WellSpace Integrated Behavioral Health will be compensated $50 for their participation. Patients will receive a thorough diagnostic evaluation (in person for the majority of participants and over the phone for WellSpace low-PQ-B scoring participants), which will be available to their physician upon request. Patients' participation will contribute to the improvement of evidence-based methods of identifying and engaging early psychosis patients, without known risk.

19) Vulnerable Populations

Children and teenagers aged 12-30 will be included in the proposed study. All study procedures are appropriate and validated for this age range. The research staff working with the children will have extensive experience in interacting with individuals in this age range and their families. They will be carefully trained and closely supervised by the P.I., who is a psychiatrist with 20 years of experience working with adolescents and young adults with psychotic disorders. The Co-Is are also licensed clinical psychologists and psychiatrists with experience working in clinical and research contexts with youth at risk for psychosis as well as individuals with schizophrenia and their families.

If a child is identified as a ward of the court, an advocate will be appointed at the time of full consent for the study to act in the best interests of the child. Examples of appropriate advocates include a court-appointed advocate, foster parent, the child's attorney, case manager, or social worker. The family advocate at the EDAPT clinic may also act as an advocate to wards of the court. Any appointed advocate will have an appropriate background, and will agree to act in, the best interests of the child for the duration of the child's participation in this research

protocol. The advocate will not be associated in any way with the research, investigator, or guardian organization. The name and agreement of the advocate will be documented at the time of full consent. Wards of the court can still be referred for clinical services if they choose not to participate in the study. Wards of the California Youth Authority will not be recruited for participation in this study.

Several sites (particularly emergency departments and psychiatric hospitals) see patients who may need to be placed on an involuntary hold (5150), typically for 72 hours. This research can benefit these individuals because it provides rapid referral to outpatient mental health services after hospitalization, which may mean that the patient is provided with treatment more quickly than the norm. Although patients are typically linked with outpatient mental health services upon release from the hospital, these services are not specific to their needs and, for individuals with early psychosis, only represents the type of "usual care" that is associated with poor outcomes. Unfortunately, this means that patients will often spend weeks or months within "usual care" before they are ultimately referred to our specialty psychosis clinic, if they are referred at all. By including these individuals in our screening protocol, we may be able to receive a referral for services while the patient is still in the hospital and can then see the patient very quickly after discharge, maintaining excellent continuity of care. We feel that these potential benefits outweigh the risks of the study, which are minimal (i.e., psychological discomfort answering questions about participants symptoms). We propose the following to adequately protect the interests of these subjects. The mental capacity of potential participants will be evaluated by a clinician that is not a member of the research staff. If a potential participant under a 5150 is deemed fit to consent by the clinician and is willing to participate in the study, they may sign the consent form. If a potential participant is deemed unfit to consent, they may be included in the study only if surrogate consent is obtained from a legally authorized representative. Additionally, it will be stressed that completion of the screening questionnaire is completely voluntary and is not related to his or her stay in the hospital. The electronic consent already documents that choosing to not participate does not affect the patient's treatment in any way. Staff will also be instructed to discontinue the screen if the participant shows any increased distress or discomfort. The participant's consent will be documented on the electronic screening tablet as with all other participants. Such patients can still be referred to our clinic through the usual methods.

20) Multi-Site Research

N/A

21) Community-Based Participatory Research

N/A

22) Sharing of Results with Subjects

Study results will not be shared with subjects as standard practice. Results of the clinical interview or questionnaires will be discussed with the subject (or the

patient's physician) at their request. When this information is requested, only individuals competent to provide feedback to participants (i.e., study psychologists and psychiatrists) will discuss these results.

23) Setting

Initial screenings involving a brief electronic consent/assent and survey will take place at the 20 randomized referral sites within Sacramento County. Ten sites have already been identified with another 10 sites being actively recruited. Phone evaluations will be conducted at the Imaging Research Center and the Wong Building on University of California Davis's Medical Center campus in Sacramento, CA. Clinical evaluations will be conducted at the EDAPT Clinic in the Wong Building on University of California Davis's Medical Center campus in Sacramento, CA. Community-based mobile engagement sessions will take place at the patient's home using a telemedicine-enabled laptop connected to a clinician at the Wong Building.

24) Resources Available

This project will be funded by university start up funds for Dr. Cameron Carter. (MED: PSYCH: CARTER SEED FUNDS S-IMAG900) as well as a grant that is pending funding from the National Institute of Mental Health. Dr. Carter and experienced staff members will be conducting the interviews and assessments.

Early Diagnosis and Preventative Treatment (EDAPT) Clinic: The EDAPT clinic provides FEP outpatient services for individuals ages 12-30 across the spectrum of early psychosis, including first episode of affective and nonaffective psychosis (FEP) and clinical high risk (CHR), regardless of whether clients have Medi-care, private insurance or are uninsured. Founded in 2004 by Cameron Carter, M.D., EDAPT is nationally recognized as a leading provider of early psychosis care. Our program has a strong and diverse interdisciplinary team of physicians, clinicians, supported education/employment specialists, consumer and family advocates with unique expertise in state of the art assessments and evidence based practices for early identification and intervention for psychotic disorders. Our clinic provides individual and family therapy, multi-family group, age-appropriate peer symptom management groups, and targeted treatment for substance use. In addition, EDAPT provides targeted education to community members free of charge. EDAPT serves individuals from across the Central Valley of California and, while the bulk of patients are from Sacramento County, many referrals also come from surrounding counties, including the Sierra Nevada foothills and the San Francisco Bay Area. Annually, EDAPT serves approximately 90 FEP and 30 CHR individuals. We typically receive 36 referrals and identify 5 eligible FEP and 2 eligible CHR individuals per month. It is closely affiliated with the Translational Cognitive and Affective Neuroscience Laboratory and is a major source of referrals for the research programs in schizophrenia and related disorders conducted by that group.

UC Davis Imaging Research Center

This 6500 square foot building is an air conditioned, research laboratory for imaging and psychological studies located on the campus of the UC Davis Medical Center. The laboratory has subject waiting areas, ample restrooms and water fountains, as well as lockable offices where interviews and assessments can be done in private to insure the subject's confidentiality. The center has several lockable filing cabinets, where subject information will be stored.

Qualifications of Investigators at UC Davis

Dr. Cameron Carter, M.D., has 20 years of experience using functional imaging to investigate functional brain circuitry in healthy subjects during pharmacological challenge as well as individuals with schizophrenia and other serious mental disorders and focused on imaging biomarker development to enhance translational research. He will be PI of the UC Davis site as well as coordinate the multi-site fMRI elements of the project.

Dr. Tara A. Niendam, Ph.D., is a licensed clinical psychologist with over 15 years of experience using clinical, functional and cognitive assessments to examine predictors of outcome in youth in the earliest stages of psychotic illness. Dr. Niendam will assist Dr. Carter in overseeing the project, managing staff in day-to-day activities, recruiting participants, managing data collection and analysis. She will participate in interpretation of the results as well as in presenting the results of the research and preparing manuscripts for publication. She will be co-investigator at the UC Davis site.

Roles and Responsibilities of Personnel

Project Scientist: will be assisting in several aspects of the study, including consenting, clinical assessment, MRI procedures, and supervision of junior specialists.

Clinical Psychologists: will be assisting in multiple aspects of the study, including consenting, clinical assessment, and supervision of junior specialists.

Clinical Social Worker (LCSW): will assist in subject diagnostic assessments and telemedicine evaluations as part of clinic intake procedures.

Marriage and Family Therapist (LMFT): will assist in subject diagnostic assessments and telemedicine evaluations as part of clinic intake procedures.

Psychiatrist (MD): will assist in subject diagnostic assessments and telemedicine evaluations as part of clinic intake procedures.

Junior Specialists: will serve as study coordinators and assist in subject recruitment, phone evaluations, scheduling, consenting, and satisfaction and follow up (6 and 12 month) assessments.

All individuals assisting with this research project at UC Davis will be familiar with the Investigator's Protocol for this study and will participate in weekly research meetings with the PI to monitor the progress of the research and review their duties and functions.

25) Prior Approvals

Approvals will be obtained from each community site director indicating that they wish to participate and agree to abide by the procedures outlined in this protocol.

26) Provisions to Protect the Privacy Interests of Subjects

All study personnel will have passed required courses on privacy and confidentiality. Subjects will be informed that their de-identified data will be stored in locked cabinets. Furthermore, only individuals on the research team who have a specific need to access subject information (i.e., to evaluate demographic data) will be permitted such access. Records containing identifying information and the data code key will be stored in locked cabinets or in password-protected computer files with access controlled by the study coordinator and study physicians. As part of the screening, consent, and initial interview stages, subjects will be reminded that they need only share personal information that they feel comfortable disclosing. Finally, subjects may request an alternative staff member to perform study procedures (or withdraw from the procedure) if they do not feel at ease with that staff member.

In accordance with CA law protecting pregnant minors, any minor who is found to be pregnant, through verbal disclosure or testing, will be asked permission to disclose the information to their parents if deemed necessary.

No identifiers shall be disclosed to a third party except as required by law or for authorized oversight of the research project.

27) Compensation for Research-Related Injury

The research does not involve more than Minimal Risk.

28) Economic Burden to Subjects

The only costs or economic burden that participants may bear is the commitment of their time for the research procedures (i.e., brief questionnaire, phone evaluation, and clinical interview). Notably, all of these procedures except for the brief screening questionnaire would be typically administered (outside of a research context) to anyone presenting for treatment into the EDAPT clinic.

29) Consent Process

All subjects who are suitable and agree to enroll in the study will have the procedures to be performed explained in full to them and their parents or legal guardians (minors) and any questions they have will be answered.

The consent process for Phase 1 is as follows:

1) A brief assent/consent for PQ-B screening will be obtained via the android tablet from subjects and their parents (if a minor) at the time of screening for those in the Active Arm. Subjects recruited from the Treatment as Usual arm do not receive this screening and their consent process begins with the phone evaluation (step 2).

- Documents presented: Electronic Screening Form, PQ-B

2) Verbal assent/consent to complete the phone evaluation will be obtained from all patients/parents prior to gathering information to determine eligibility. Prior to children engaging in the phone evaluation, parental consent will be provided verbally to the interviewer, as well as verbal assent from the child. At the time of the phone evaluation, participants will be asked for their verbal consent to match the phone evaluation data with the PQ-B e-screening survey identifier. Potential risk and benefits from this research will be reviewed.

- Documents presented: Phone Evaluation Form

3) Full written informed assent/consent following Standard Operating Procedures (SOP: Informed Consent Process for Research [HRP-090] attached) will be obtained from patients/parents prior to completion of the in-person clinical interview. Written informed consent will take place at the EDAPT clinic (Wong Building). Given that parents will be asked to complete questionnaires and participate in the initial interview, parents will complete a consent form that stipulates they are both consenting for their own participation and for their child's participation. As part of the consent process, each participant will sign a HIPAA Authorization for Research form.

- Documents presented: Phase 1 Adult Consent Form, Phase 1 Parent Consent Form, Phase 1 Child Assent Form, HIPAA Authorization for Research Form

The consent process for Phase 2 is as follows:

1) If the electronic screening was found to be the most successful intervention in Phase 1, Phase 2 will similarly involve obtaining a brief assent/consent for PQ-B via the android tablet from subjects and their parents (if a minor) at the time of screening. Alternatively, if Treatment as Usual was identified as the most successful intervention in Phase 1, the Phase 2 consent process will begin with the phone evaluation (step 2).

- Documents presented: Electronic Screening Form, PQ-B

2) Verbal assent/consent to complete the phone evaluation will be obtained from all patients/parents prior to gathering information to determine eligibility. Prior to children engaging in the phone evaluation, parental consent will be provided

verbally to the interviewer, as well as verbal assent from the child. At the time of the phone evaluation, participants will be asked for their verbal consent to match the phone evaluation data with the PQ-B e-screening survey identifier. Potential risk and benefits from this research will be reviewed.

- Documents presented: Phone Evaluation Form

3) Full written informed assent/consent following Standard Operating Procedures (SOP: Informed Consent Process for Research [HRP-090] attached) will be obtained from patients/parents prior to completion of the in-person clinical interview. Written informed consent will take place at the EDAPT clinic (Wong Building) or electronically using Docusign. Given that parents will be asked to complete questionnaires and participate in the initial interview, parents will complete a consent form that stipulates they are both consenting for their own participation and for their child's participation. Monolingual Spanish-speaking parents of English-speaking participants will be provided a translated copy of the consent form that has been certified by University of California, Davis Medical Interpreting Services. As part of the consent process, each participant will sign a HIPAA Authorization for Research form.

- Documents presented: Phase 2 Adult Consent Form, Phase 2 Parent Consent Form, Phase 2 Child Assent Form, Phase 2 Parent Consent Form Spanish, Spanish Translation Certification Letter, HIPAA Authorization for Research Form

4) For participants who were screened using the PQ-B at WellSpace Health in Phase 2, full written informed consent will be obtained electronically using Docusign from patients prior to completion of the phone evaluation. Health records will not be accessed or appended to, so no HIPAA Authorization form will be obtained for these supplemental subjects. WellSpace Health only serves clients over the age of 18, so only the adult consent form is presented.

- Documents presented: WellSpace DUP Supplement Consent

Only patients who give their informed assent/consent will take part in these studies. This will be obtained by Dr. Carter, or the clinical evaluators associated with the project. A subject may withdraw his/her consent even after giving permission, and may withdraw from the study without prejudice at any time. If a parent or participant ever appears hesitant about the research process, the investigator will inquire whether the subject still consents to research or wishes to withdraw.

Children are classified as individuals under age 18 years and according to the guidelines of HRP-013. Due to a determination of minimal risk, permission of one parent is sufficient even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

Assent will be obtained from all children and documented in the written consent form.

30) Process to Document Consent in Writing

The investigators will follow "SOP: Written Documentation of Consent (HRP-091)," and these documents (separate for Phase 1 and 2) are attached with this submission.

31) Drugs or Devices

No drugs or devices will be used in this study.

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