Path 2 Purpose Study Protocol

Background and Significance:

- Depression: Given the high rates of youth depression and the long-term impairment associated with depression, efforts to prevent depressive disorders in adolescents have tremendous implications for population health.
- Mental, Emotional, and Behavioral (MEB) Disorders in Adolescents: One in five young people have at least one MEB disorder at any point. Nearly 50% of children with an MEB disorder also have significant impairment in their social, cognitive, or emotional development, which is associated with poorer physical health. We have no strategy to deliver evidence-based depression prevention approaches to the adolescent population, nor do we have data on their acceptability. The challenge is to widely implement effective evidenced-based mental health interventions in primary care, which are sustainable past the study phase, and make them successfully adaptable in diverse communities.

Study Aims:

- Aim 1: Evaluate the willingness and ability of our community partners to implement two depression early intervention/prevention models in primary care: TEAMS and CATCH-IT
- Aim 2: Evaluate the efficacy of each intervention in decreasing symptoms of depression in adolescents ages 13-19 identified through primary care, and decrease the percentage of individuals falling above an accepted clinical diagnostic threshold on the scales that measure these illnesses.
- Aim 3: Evaluate the comparative effectiveness of each intervention for African Americans, Latinos, sexual/gender minority youth, males and females, rural youth and for individuals above and below the accepted diagnostic thresholds for these illnesses.
- Secondary Aim 1: Evaluate the efficacy of each intervention in decreasing symptoms of substance abuse, anxiety disorder, and conduct disorders in adolescents ages 13-18.
- Secondary Aim 2: Examine possible mediators and moderators of intervention response, including demographic variables, family history, treatment expectations, life events, and trauma history.

Study Design:

- This study is a two-arm comparative effectiveness randomized clinical trial to evaluate each intervention's ability to intervene early to prevent depressive illness, and teens', parents' and providers' experiences with each intervention approach. Using cluster randomization, participants will be offered the program assigned to their site. Inclusion: ages 13-19 years, all genders, English speaking, and have elevated symptoms of depression, as indicated by PHQ-9 score. Recruitment sites will be diverse in socio-economic status and racial/ethnic representation. Exclusion: Currently engaged in individual treatment for a mood disorder; currently engaged in a cognitive-behavioral group or therapy; any past psychiatric hospitalizations; or any past self-harm attempt with moderate or greater lethality.

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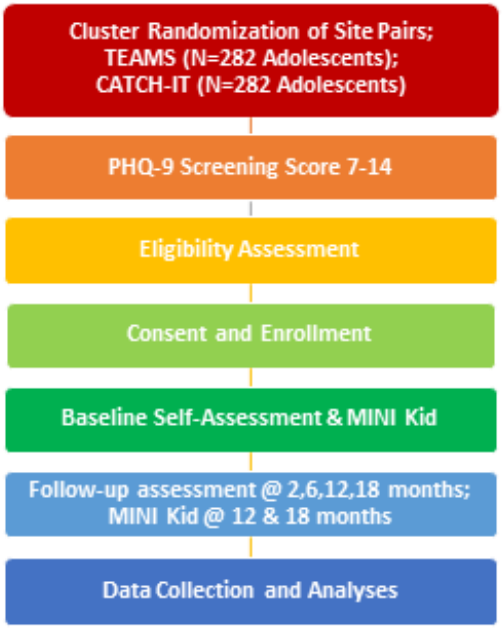

Analysis:

We will conduct both main effect and moderation analyses to examine whether POD and CATCH-IT are equivalent. The experimental design is a 2 Groups (POD *vs.* CATCH-IT) 5 Times of measurement (0 baseline, 2, 6, 12, and 18 months) *repeated measures* design. The design allows main effect tests of Group mean differences combining Times (1 d.f. G), Time mean differences combining Groups (4 d.f. T), scientific interest centers on the G T *interactions* (4 d.f.) which permit testing differences in *trend lines* (linear, quadratic) between groups and group differences in change from baseline or between times. Moreover, by introducing patient subgroups (S), it is possible to examine 3-way interactions (G T S) to study heterogeneity of treatment effects (HTE).

- **Aim 1:** We will use standard t-tests, or as appropriate, non-parametric tests to compare POD and CATCH-IT regarding domains of stakeholder experience (time, cultural acceptability, and implementation cost).
- **Aim 2:** We will estimate incidence rates by calculating the number of depressive episodes per 10,000 person-weeks by 18 months. Kaplan-Meier curves will be used to estimate the time to first episode according to each intervention and will be compared with the log-rank test. We will use linear mixed effect growth models to examine (1) individual level changes in CES-D and other MEB.
- **(Secondary Aim 1)** symptoms over time and (2) whether this association differs between intervention groups. All linear mixed models will be adjusted for the covariates listed under Aim 3.
- **Aim 3 (and Secondary Aim 2):** We will examine possible moderating effects of risk factors, geographic location, ethnicity, gender, sexual/gender minority status, race, baseline parent CES-D, baseline teen CES-D by including interaction terms in the Cox models (depressive disorder only) and growth curve models. Analyses will be conducted using R, version 3.3.1 (cran.r-project.org), SAS, version 9.4 (SAS Institute, Cary, NC), and Mplus version 8 (statmodel.com). To maximize power in this comparative effectiveness study, we will follow procedures developed

from a recent individual level synthesis project involving multiple randomized preventive trials for adolescent depression that we have conducted.

Outcomes

All measures have been found to have strong psychometric properties and measure domains repeatedly stated by adolescents and families to be personally relevant – including resiliency, quality of life and we expect a relatively small difference in the average trajectories on depressive symptoms as the primary outcome IT standard deviation of the slopes. We used the RMASS program and verified this with a simulation using R program to compute power based on this design with unequal spacing. We defined non-inferiority as absolute risk of depressive episodes within 8.48 % of the estimated prevalence the TEAMS trial arm of 32.1% after 18 months, that is, CATCH-IT achieving 50% of the risk reduction of TEAMS based on its low burden and cost. We will conduct cox proportional hazards models with covariates and frailty models (time to depressive episode) and growth curve (depression and functional status). Assuming 5% loss to follow-up at each time point, we require N = 564 for the 2-arm study. We will also examine variation in impact, emphasizing a test of moderation by baseline level of symptoms as well as membership in key demographic groups such as AA, Latino, LGBTQ youth and rural whites (Aim 2). To examine differential benefit of one intervention versus the other, we will test for an interaction between intervention, time, and initial level of symptoms, conducted with Mplus.