STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: As Safe As Possible (ASAP): A BALANCED, 2X2 DESIGN TO TEST CONJOINT AND UNIQUE EFFICACY OF AN INPATIENT INTERVENTION AND AN EMOTION REGULATION/SAFETY PLANNING APP IN PREVENTING SUICIDE ATTEMPTS POST-DISCHARGE.

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As Safe As Possible (ASAP): A BALANCED, 2X2 DESIGN TO TEST CONJOINT AND UNIQUE EFFICACY OF AN INPATIENT INTERVENTION AND AN EMOTION REGULATION/SAFETY PLANNING APP IN PREVENTING SUICIDE ATTEMPTS POST-DISCHARGE.

Abstract

Aims: One of the highest risk periods for suicidal behavior is in the first 6 months after discharge from psychiatric hospital. In this 2-site study (University of Texas Southwestern Medical Center; UTSW and Western Psychiatric Institute and Clinic; WPIC), we propose to conduct a randomized clinical trial (RCT) in 250 hospitalized suicidal adolescents, examining the single and additive effects of two components of an inpatient unit intervention for suicidal adolescents, As Safe As Possible (ASAP), which focuses on emotion regulation and safety planning, and an emotion regulation/safety plan phone app (BRITE). In a recently completed pilot RCT of 65 suicidal adolescent inpatients, ASAP + BRITE reduced the hazard of suicide attempts over the subsequent 6 months compared to treatment as usual (AU) substantially (adjusted HR=0.22, p=0.03), especially in youth with a previous history of a suicide attempt (HR=0.12, p<.05). **Methods:** We will randomize 250 hospitalized suicidal adolescents with a history of a suicide attempt or ideation with plan to one of 4 conditions in a 2 by 2 design: (1) ASAP + BRITE + TAU; (2) BRITE + TAU; (3) ASAP + TAU; or (4) TAU alone to determine the single and additive effects of ASAP and BRITE on suicide attempts in the subsequent six months. **Expected Outcomes:** We hypothesize that ASAP and BRITE will each effectively reduce suicide risk post-discharge compared to TAU and that the combination will be superior and more cost effective relative to each individual intervention as well as to TAU.

Project Description

I. SPECIFIC AIMS/HYPOTHESES

The transition from inpatient to outpatient care is a time of extremely high risk for suicidal behavior and suicide and accounts for a significant proportion of suicides that occur while patients are in mental health care (Appleby, Dennehy, Thomas, Faragher, & Lewis, 1999; Appleby, Shaw, et al., 1999). There are currently no established interventions for suicidal teens transitioning from inpatient to outpatient care. By implementing a treatment that can be delivered on an inpatient unit prior to the transition to outpatient treatment, we anticipate being able to lower suicidal risk during this critical high-risk period, which can contribute to reversing the more than decade-long increase in adolescent suicide (Curtin, Warner, & Hedegaard, 2016). To address this issue, we developed brief, 3-hour intervention for adolescents who were psychiatrically hospitalized for suicide risk, termed ASAP (As Safe As Possible). ASAP focuses on the development of a safety plan, teaching emotion regulation and distress tolerance skills, along with 1-2 post-discharge follow-up calls to encourage adherence to use of the safety plan and to outpatient treatment. ASAP was supplemented by a smartphone app (BRITE) that supported daily emotion regulation and a safety plan that was personalized to the needs and preferences of each adolescent. We conducted a two-site clinical trial in 65 psychiatrically hospitalized suicidal adolescents, randomized to ASAP + BRITE + TAU or treatment as usual (TAU) alone. ASAP showed a reduced hazard for post-discharge suicide attempt over the subsequent six months (adjusted hazard ratio (HR) = 0.22, p=0.03), and ASAP effects were even stronger in those participants (n=52, 80%) who had a history of a suicide attempt (HR=0.12; p=0.04). BRITE appears to contribute to this effect, insofar as declines in suicidal ideation and emotion dysregulation, and, increases in reasons for living, were proportional to the frequency of use of the app(r's=0.37). We believe that ASAP and BRITE have the potential to be widely disseminated because: (1) 64% of eligible participants enrolled in the study; (2) the interventions are brief and inexpensive; and (3) patients and families gave very positive feedback with regard to both ASAP and BRITE.

In order to identify the most cost-effective component of this intervention, we propose to build on our pilot work by: (1) recruiting a larger, more demographically diverse sample to replicate these findings; (2) disaggregating the effects of ASAP and BRITE through the use of a 2 by 2 design; (3) testing for mediators of treatment outcome; and (4) determining which treatment arm is most cost-effective, and therefore most likely to be acceptable to payers and providers.

Therefore, we aim to randomize 250 adolescents hospitalized, either in a psychiatric unit or a medical unit for a suicide attempt, to one of four treatment arms: (1) ASAP + BRITE + TAU; (2) BRITE + TAU; (3) ASAP + TAU; and (4) TAU alone and assess suicidal ideation and behavior at 1, 3, and 6 months post-intake, in order to:

1. Assess the relative efficacy of ASAP, BRITE and the combination on suicidal ideation, non-suicidal self-injury (NSSI), and suicide attempts, and re-hospitalizations.

H1: Both ASAP and BRITE will be superior to TAU alone, and ASAP + BRITE + TAU will be superior to BRITE or ASAP alone.

2. Examine mediators and moderators of treatment outcome

H2: The effects of ASAP and BRITE will be mediated by increases in reasons for living, decreases in dysfunctional emotional regulation, increases in functional emotional regulation, and decreases in implicit associations with death, and will be moderated by previous history of an attempt, and family engagement in treatment. In addition, the impact of BRITE will be proportional to the frequency of use.

3. To examine the costs and cost efficacy of ASAP and BRITE and the combination.

H3: Both ASAP and BRITE will be more cost-effective than TAU, and the combination of ASAP and BRITE will be more cost-effective than either individual component alone.

II. BACKGROUND AND SIGNIFICANCE

Background. Adolescent suicidal behavior is common, with more than 2,000,000 adolescents presenting to emergency departments (EDs) each year with suicidal behavior. Nearly 7% of adolescents in any one year make a suicide attempt, and an equal number have clinically significant suicidal ideation with a plan (Lewinsohn, Rohde, & Seeley, 1996). Suicide is the 2nd leading cause of death among 12-17 year olds, and suicidal behavior is associated with functional impairment and significant costs to the health care system, other service systems, and families (Centers for Disease Control and Prevention, 2010; Curtin et al., 2016; Florence, Haegerich, Simon, Zhou, & Luo, 2015; Shepard, Gurewich, Lwin, Reed, & Silverman, 2015). Short-term costs include costs of medical care for youth with suicide attempts, lost productivity for youth who die, and costs to families such as lost productivity for family members caring for youth in crisis. While Healthy People 2020 has as its objective to reduce suicide and suicide attempts in adolescents, trends for more than a decade have shown an increase in teen suicide (Curtin et al., 2016).

Focus early in treatment. In clinical populations, one of the times of greatest risk for recurrent suicidal behavior and completed suicide is during transition of care (transition between inpatient and outpatient care; prior to or at the onset of outpatient care), and quality improvements in this window of time have been shown to decrease the suicide rate in adults (Appleby, Dennehy, et al., 1999; Appleby, Shaw, et al., 1999; While, et al., 2012). The window of greatest risk is in the 1-4 weeks after the initial suicide attempt, with 25-50% of all suicidal events (defined as a suicide attempt or an increase in suicidal ideation) occurred within the first 4 weeks of treatment (Brent, Greenhill, et al., 2009; Vitiello, Silva et al., 2009; Wilkinson, Kelvin, Roberts, Dubicka, & Goodyer, 2011). *Thus, providing a brief, targeted intervention prior to discharge that protects against acting on suicidal urges in early outpatient*

treatment could make a substantial contribution towards reducing the incidence of youth suicidal behavior.

Early-onset of suicide event, even in high-quality treatment of suicidal ideation. In clinical studies of adolescents with treatment resistant depression, in which participants received close monitoring and either medication management alone, or in combination with CBT, the rate of suicidal events was 28% in the first 12 weeks of treatment, with a median time to event of 3 weeks (Brent, Emslie, et al., 2009). In an open trial of a CBT intervention especially designed to reduce suicide attempts in depressed adolescent suicide attempters, 40% of all suicidal events took place within the first 3 weeks of treatment (Brent, Greenhill, et al., 2009). Moreover, one of the most potent predictors of an eventual attempt or suicidal event is high baseline suicidal ideation (Brent, Emslie, et al., 2009; Brent, Greenhill, et al., 2009; Vitiello, Silva, et al., 2009; Wilkinson et al., 2011). In community samples, 56% and 29% of adolescents with suicidal ideation with or without a plan, respectively, will make a suicide attempt within a year of assessment (Nock et al., 2013).

Safety Planning. The safety plan, a structured set of coping strategies that a suicidal individual can deploy to de-escalate suicidal risk in the face of suicidal urges or identified precursors thereof (e.g., anger, sadness) is considered best practice for the management of high risk patients. The plan, developed with a mental health clinician, consists of: (1) activities the suicidal individual can do independently or alone (e.g. distraction, deep breathing); (2) reaching out to supportive individuals; and (3) finally, seeking clinical attention (Samra & Bilsker, 2007; Stanley et al., 2009). A safety plan is developed in the context of treatment, in which a chain analysis of the events leading up to the suicidal episode is conducted, a more comprehensive treatment plan to reduce suicidal risk is developed, and motivational techniques are deployed to enhance use of the safety plan and follow-up with treatment.

While safety plans have become a mainstay of clinical care, methods to facilitate their implementation have not yet been critically evaluated, nor has the efficacy of safety plans in preventing future suicidal acts been carefully evaluated (Knox et al., 2012). In order for a youth in crisis to deploy his or her safety plan, the plan has to be accessible. Youth at high risk for suicide who are being treated for suicidality may have a written safety plan as part of their treatment; however, this plan may not always be accessible when they experience suicidal urges. Therefore, identifying an alternative mechanism to increase accessibility and utility of safety plans could be quite helpful.

A precursor of the modern safety plan was developed by Rotheram-Borus and Bradley (1991), in which youth in a shelter for homeless runaways were taught a 5-step program for coping with suicidal ideation: 1. Identify 3 positive compliments about self; 2. Identify 3 people to go to for support; 3. Learn how to monitor and regulate emotion using an “emotion thermometer” in order to cope with suicidal urges; 4. Develop a concrete alternative to acting on suicidal impulses; and 5. Make a commitment to refrain from engaging in suicidal behavior. The number of suicide attempts in these shelters prior to implementation of the program was 9 in the previous 3 months, compared to 2 in the subsequent 18 months, which, when corrected for the period of observation, is a 27-fold decrease in the incidence of suicide attempts (assuming a similar number of youth in both conditions). This suggests that a brief intervention using emotion regulation techniques and mobilization of social support to cope with suicidal urges can be effective in reducing the probability that an adolescent will act on his or her suicidal ideation. However, to our knowledge, other than this study, the efficacy of safety planning has never been critically evaluated, particularly in adolescents.

ASAP is designed to target known protective and risk factors for suicidal behavior, namely reasons for living (Bagge, Lamis, Nardoff, & Osman, 2013; Bakhiyi, Calati, Guillaume, & Courtet, 2016) and adaptive emotion regulation (Zlotnick, Donaldson, Spirito, & Pearlstein,1997; Polanco-Roman, Jurska, Quinones, & Miranda, 2014), and to decrease the frequency of maladaptive emotion regulation. We

found that ASAP + BRITE + TAU, compared to TAU, increased reasons for living and adaptive emotion regulation, and decreased dysfunctional emotion regulation, as described in more detail below.

Utilizing technology for improving distress tolerance and safety planning. Approximately 73% of American youth have or have access to smart phones (Lenhart, 2015). Close to 80% of homes have internet access, and for 21% of teens (up to 44% of minority teens), a cell phone is the teen's *sole means* of access to the Internet (Lenhart, 2010). Consequently, use of technology in this population to extend treatment is logical and timely. There are no empirically tested phone apps for safety planning, especially for teens, but there is a randomized trial to evaluate a safety planning app in adults currently underway (Andreasson et al., 2017). While there are cell phone applications related to safety planning in adults with suicidal behavior (Emory News, 2013; De la Torre, Castillo, Arambarri, Lopez-Coronado, & Franco, 2017; Larsen, Nicholas, & Christensen, 2016; Stanley & Brown, 2012;). We propose to supplement standard care by evaluating a safety plan smartphone application (which has been developed with promising outcomes; Kennard et al., 2015) that teens can easily access to provide tools to cope with suicidal urges and preserve safety.

Significance. Adolescent suicide is the second-leading cause of mortality in adolescents, and adolescent suicidal behavior is a common cause of morbidity associated with significant functional impairment. The rates of both adolescent suicide and suicidal behavior has been increasing. This proposal aims to reduce the likelihood of a suicide attempt during a very high-risk period of time, which is the transition from inpatient to outpatient care. Currently, even with high quality treatment, there is a high incidence of early suicidal events in outpatient care.

Innovation: In our previous pilot RCT, we found that the combination of BRITE and ASAP with TAU resulted in a significant reduction in the hazard for suicide attempts. This is novel, as there are no established interventions to prevent suicidal behavior during the transition from inpatient to outpatient care for hospitalized suicidal adolescents. . This study would provide a replication of these findings in a larger, and more demographically diverse sample (larger minority recruitment and higher proportion of males). This is important, as ethnicity may moderate the impact of psychosocial interventions (Weersing et al., 2017) and risk factors for suicidal behavior differ between adolescent males and females (Brent, Baugher, Bridge, Chen, & Chiappetta, 1999; King, Jiang, Czyz, & Kerr, 2014). Moreover, this new study will disaggregate the effects of ASAP and BRITE. With respect to BRITE, this would be one of the first studies to evaluate the added value of a structured safety plan. Finally, we will evaluate the cost-efficacy of BRITE, ASAP, and the combination. While there are an increasing number of suicide prevention apps, almost none are geared to adolescents, and none have been critically evaluated. Moreover, this study also aims to assess the incremental costs and benefits of these brief interventions, which is critical to widespread dissemination of these interventions. Moreover, the cost analysis will include costs to the families of youth who attempt suicide, and these costs have rarely been studied.

Impact: This study will identify the most cost-effective components of ASAP + BRITE + TAU (i.e. BRITE, ASAP, or BRITE + ASAP) to prevent suicidal behavior in adolescents after discharge from the hospital, which can lead to larger scale dissemination studies. In our initial pilot studies, ASAP + BRITE + TAU cut the suicide attempt rate 2.5 fold and reduced re-hospitalizations as well. Hence, this intervention has the potential to reduce suicidal behavior and to prevent rehospitalization, which could in turn prevent future pain and suffering and save costs to health systems and families as well.

There are no established interventions to prevent the recurrence of adolescent suicidal behavior after discharge from psychiatric hospital. This proposal has the potential to assess and improve upon a major component of best clinical care for suicidal teens, which is the transition from inpatient to outpatient care. By focusing on the time-period of greatest risk for recurrence—the transition from a higher level of care to outpatient treatment, this project directly aligns with the mission of the recently convened National Action

Alliance for Suicide Prevention Research Prioritization Task Force that calls for the development and testing of interventions that will reduce the rate of suicide and suicide attempts, particularly among high-risk groups (National Action Alliance for Suicide Prevention Research Prioritization Task Force, 2014).

The addition of the BRITE app could potentially improve suicidal adolescents' ability to resist acting upon suicidal urges, be easily and widely deployed, and save lives. Since many suicides in this population are impulsive, the BRITE app could be an easily accessible tool to manage suicidal urges that could foster greater resiliency among youth at high risk for suicide. As such, the proposed work is expected to have a significant impact on high risk children, their families, and clinicians.

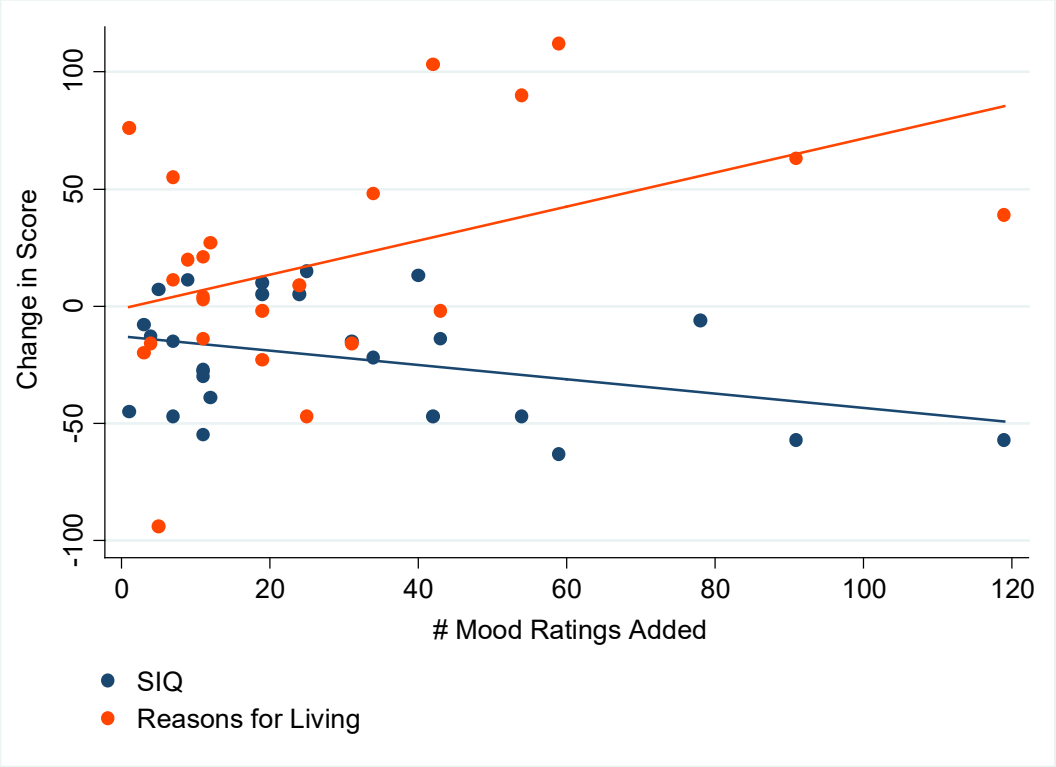
Feasibility: The investigators have worked productively together in the past through collaborations on 2 multisite trials (the Treatment of SSRI-Resistant Depression in Adolescents (TORDIA) and the Treatment of Adolescent Suicidal Adolescents TASA), resulting in several publications that inform this proposal (Brent et al., 2008; Brent, Emslie, et al., 2009; Brent, Greenhill, et al,. 2009; Emslie et al., 2010; Kennard et al., 2009; Lynch, Dickerson, Clarke, et al., 2011; McMakin et al., 2012; Stanley et al., 2009; Vitiello, Brent, et al., 2009; Vitiello et al., 2011).

Additionally, the investigators worked together to successfully complete a two-site NIMH funded treatment development trial for the ASAP intervention (Kennard et al., 2017). Both sites are very familiar with the management of suicidal adolescents and proper rescue procedures in the contexts of both research and clinical care. Both groups also have experience in treatment development, with Kennard (2014) developing a wellness-oriented cognitive behavior therapy (CBT) that effectively prevents depressive relapse (HR = 0.31, p = .01). Both groups have met or exceeded recruitment targets for multiple adolescent treatment trials. Both sites see at least 200 new suicidal adolescent inpatients per year, with an average length of stay of 5 to 7 days. Retention in previous studies of similar populations has been in excess of 85% for the year.

Previous work informing this study: The motivation for this study is that, despite delivering "state of the art" psychosocial interventions in TORDIA and TASA, a high proportion of the suicidal events that occurred in these studies happened within 3-4 weeks of intake (Brent, Emslie, et al., 2009; Brent, Greenhill, et al., 2009). Hence, some additional intervention is needed early in treatment to protect against suicidal urges. The investigators conducted focus groups with patients, parents, and clinicians, which informed the development of the ASAP intervention and BRITE phone application for this proposal (Kennard et al., 2015). The phone app has been developed and piloted with good preliminary outcomes (see below).

Preliminary Data: The pilot study (N=65) for ASAP/BRITE was conducted by these two sites. Adolescents (ages 12 to 17) who were hospitalized with recent ideation with plan or intent and/or a recent suicide attempt were randomized to receive ASAP + BRITE + TAU or TAU alone. Participants were balanced both within and across sites on age (12-15 vs. 16-17.11), gender, and past attempt. Suicidal ideation (Suicidal Ideation Questionnaire – Junior) and behavior (Columbia Suicide Severity Rating Scale, C-SSRS) were assessed at weeks 4, 12, and 24 by independent evaluators. The intervention was accepted by a high proportion of those patients who were eligible (65%). Those in the ASAP group, compared to those in TAU had fewer attempts over time (13.3% vs. 31.0%, p=.10, Hedge's g = .44), and a longer time from baseline to attempt than TAU (adjusted HR=0.22, 95% CI: 0.05, 0.85, z=-2.19, p = 0.03). Prior attempts moderated treatment, such that those who had a prior attempt (2/3 of the sample) and received ASAP had a much lower hazard of time to reattempt (HR=0.12, 95% CI: 0.01, 0.94, z=-2.02, p=0.04). There was a non-significant trend for those assigned to ASAP to be less likely to be re-hospitalized (10.0% vs. 24.1%, χ^2_1=2.09, p=0.15, *g*=-0.38). Also, ASAP + BRITE + TAU, in moderator analyses, reduced suicidal ideation in those with lower reasons for living and more dysfunction emotion regulation., Participants whose families participated in the intervention showed slightly lower rates of attempt during the study (11.1% vs. 14.3%, p>0.99), lower

hazard of attempt (HR=0.72, 95%CI: 0.07, 6.88, p=0.77) and more decreasing SIQ scores over time (β=-0.61, 95%CI: -1.12, -0.11, p=0.02). Of those participants who received the phone app, 72.7% viewed the app, and of these 75% added content with an average use of almost 30 times. More frequent response to prompts from the app for mood check-in, was associated with improvement on reasons for living (ρ=0.37, p=0.08) and declines in suicidal ideation (rho=-0.37) over the 24- week follow-up period (see figure below).



Using the Client Satisfaction Questionnaire, CSQ, where higher scores indicate more satisfaction with their treatment (range 8 to 32), the ASAP group showed greater satisfaction than the TAU group ([N=26], M=26.6, SD=3.8 vs. [N=20], M=24.1, SD=5.2, z = 1.57, p =0.12, *g* = 0.56). The satisfaction scores on the app using the Post-Study Satisfaction and Usability Questionnaire (PSSUQ; where lower scores indicate more satisfaction, range 10 to 70) were as follows: week 4: M = 17.6, SD = 7.1, N=21; week 12: M = 18.6, SD = 10.4, N=24; week 24: M = 18.4, SD = 8.0, N=25.

Our data demonstrate that the intervention is feasible, acceptable, and effective. We propose to build on the pilot RCT to include a larger sample. This will allow us to test each aspect of the intervention separately, as well to test the additive effects of the combined intervention, against treatment as usual (TAU).

Previous studies related to cost-effectiveness analysis. The long-term goal of this study is to develop and implement evidence based care for youth with suicidal behavior and ideation into health systems that serve such youth. To this end, it is critical that we provide practical information about the cost of running the interventions, and the longer-term impact of the interventions on health care and other costs. This type of information could be critical to the future adoption of these interventions into routine practice. In order to achieve this aim, we have added Frances Lynch, a health economist to our

study team. Dr. Lynch has extensive experience in designing and leading cost-effectiveness analyses in the context of randomized controlled trials (Lynch, Dickerson, Pears, & Fisher, 2017; Lynch, Dickerson, Clarke, et al., 2011; Lynch, Dickerson, Garber, et al., 2011; Beardslee et al., 2013), and she has previously worked with the lead investigators in the proposed study (Kennard, Brent) in examining the cost effectiveness of interventions for youth with treatment resistant depression (Lynch, Dickerson, Clarke, et al., 2011; Lynch, Dickerson, Garber, et al., 2011). Dr. Lynch has particular expertise in the economics of youth mental health conditions (Lynch & Dickerson, 2017), and suicide prevention (Lynch, 2014).

III. RESEARCH METHODS

Overview of Study Design.

Participants

Participants will include adolescents 12-17.11 years of age (N=250) who either 1) present to the inpatient psychiatry unit with recent suicidal ideation with plan or intent and/or a recent suicide attempt, or 2) are hospitalized on a medical floor for a suicide attempt. Participants must be English speaking because the treatment is not validated in any language other than English. Additionally, adolescents must own a smartphone, tablet, or device on which the Brite app can be utilized. Exclusion criteria include current (i.e., within the past two weeks) psychosis, mania, <85% of ideal body weight, and any cognitive disabilities necessitating additional testing (e.g., IQ <70, recent concussions with ongoing symptoms, etc.), as these conditions may require more intensive interventions or limit comprehension of the intervention components. Additionally, we will exclude participants being discharged to a residential treatment facility due to the level of supervision by professional adults in those facilities. The idea of the study is that the youth will return to his/her environment and will have the ability/need to use her/her safety plan while facing her/her real life problems. Residential treatment is very similar to the inpatient setting in that it is very treatment oriented and there are numerous restrictions about electronics. Lastly, youth who does not have a responsible adult who has the ability/authority to consent for research participation (e.g., youth in the custody of child protective services) will be excluded. We will oversample males and ethnic minorities so that each group constitutes at least 25% and 35% of the total sample, respectively.

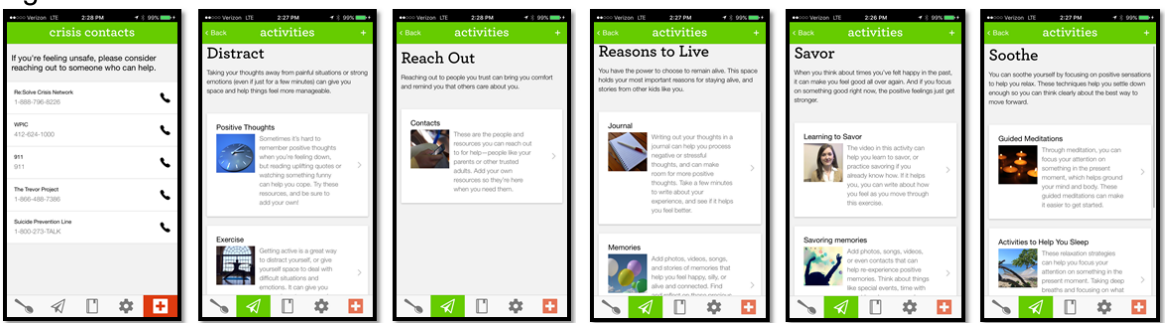
Treatment Intervention (ASAP)

The ASAP intervention model is designed to increase protection against adolescents acting on their suicidal urges and attempting suicide. We use a motivational interviewing (MI) framework for the intervention. The four modules are as follows: 1. treatment overview and psychoeducation about suicidal behavior, chain analysis, reasons for living, and safety planning; 2. distress tolerance techniques 3. savoring techniques for the maintenance of positive mood by reminiscing on recent positive events are taught, along with the practice of “switching” strategies designed to build resilience to stressors that may destabilize mood (29); and 4. review of the ASAP skills and safety plan with the teens and their family members (as available). Quality assurance ratings will be obtained on a random sample of 20% of ASAP sessions. Up to two bridging calls (2) to the participant will be made at 1 and 2 weeks after discharge to review use of safety plan and ASAP components, and assess adherence to follow-up care.

Phone App/BRITE (See also description about how app is personalized below)
A HIPAA-compliant web-based phone application (Fig 1) provides the participants with guidance, social support, and convenient access to distress tolerance strategies and their safety plan via the patients’

phone. The app is compatible with both IOS and Android platforms. The study therapist will have access to a setup interface and web interface in order to customize the content of the participant's view usage. Participants get daily text reminders to rate their level of emotional distress (1-5, 5 the most upsetting) and on the basis of their level of distress, they are offered distress tolerance and emotion regulation skills, and support material that they have chosen. For participants at a high level of distress, the app offers the safety plan, including individual, interpersonal, and clinical contact options. The therapist, with the patient, will have the capacity to input hypertext links to offsite techniques such as videos, images, sound memos, and support systems. For example, if a standard safety plan might recommend distraction or review of reasons for staying alive, we can link these recommendations to a video or text that might outline reasons for living, reasons to be hopeful, or an image that would serve as a distraction or a cue to savoring that is personalized for that individual. If initial "personal strategies" do not work, and the patient wanted to contact a parent, friend, or professional, the app provides a direct link (call or text) to the supportive or professional contacts developed as per the safety plan. Up to two bridging calls (2) to the participant will be made at 1 and 2 weeks after discharge to review use of safety plan and ASAP components, and assess adherence to follow-up care.

Figure 1.



<u>BRITE ALONE</u>

The BRITE only condition will consist of a one session (1 hour) visit with a study therapist who will conduct safety planning, specifically identifying the triggers of the suicide attempt/event using a chain analysis approach. In addition, the therapist will assist the patient in recognizing existing coping skills. The BRITE ALONE intervention will also include up to two bridging calls (2) to the participant that will be made at 1 and 2 weeks after discharge to review use of BRITE, and assess adherence to follow-up care.

The BRITE app intervention will include using an emotional thermometer to identify markers of "point of no return" and ask the participant to identify strategies that could be used to de-escalate (avoid triggers, distraction, calling family support/ professionals, reasons for living, deep breathing, mindfulness, emergency contacts). Information from the chain analysis, coping skills assessment, and emotional thermometer discussion will assist the therapist and patient in populating the BRITE app. Finally the therapist and patient will identify barriers that might interfere with the patient's ability to use their plan. The Safety Plan will include: (1) a family component that includes the following: asking the patient to explain the safety plan to the parents, getting parental feedback, asking both parents and patient what might get in the way of implementing the plan, considering either ways to overcome those barriers or revising the plan, and (2) removing/securing lethal agents. The patient should be referred for emergency evaluation if they clearly express suicidal intent and are unwilling to commit to the safety plan. Clinical conditions that would impede ability to adhere to a safety plan include: psychosis, bipolar disorder (rapid cycling or mixed state), alcohol and drug abuse, and a traumatic brain injury.

ASAP + BRITE + TAU:

In this treatment condition, we will combine treatment as usual with ASAP and the phone app as we did in the pilot study (N = 65). The study therapist will provide the ASAP components that are described above, and assist the patient in populating the app with the ASAP strategies (safety plan, reasons for living, distress tolerance, savoring, supportive and professional contacts). The family will be included in the treatment to review ASAP skills and the phone app.

Treatment as Usual. The focus of inpatient care across sites is on diagnosis, safety assessment, development of a safety plan, stabilization, initiation or adjustment of pharmacotherapy, psychoeducation for patients and families, and disposition. Clinical referrals for outpatient treatment will be provided prior to discharge. Unit therapists develop a safety plan with the patient and family, although there is no standard protocol for doing so. For participants in the ASAP only group, BRITE only group, and ASAP + BRITE + TAU, therapists will expand on the inpatient safety plan to include emotion regulation and distress tolerance strategies.

The ASAP + TAU, BRITE + TAU, and ASAP + BRITE + TAU treatment will be front-loaded, meaning that each will either precede discharge or commence within one week of discharge to recommended outpatient psychiatric treatment. Study therapists will be trained to deliver all three active treatment arms. TAU will be provided by inpatient staff. Researchers will also send a letter regarding participation in the study to the subject's outpatient therapist.

*Randomization***.** Participants will be randomized centrally at WPIC by a web-based computer program that has been used successfully in other studies (Brent et al., 2008; Garber et al., 2009).The study coordinator at each site will complete a Randomization Request form on the secure website. Once the form is completed, a database trigger will run the randomization program to determine the group assignment. The program will automatically generate and send an email to the study coordinator and the data coordinating center to notify them of the assignment. Participants will be balanced both within and across sites on age (12-15 vs. 16-17.11), and past attempt vs. high ideation. To increase the gender and ethnic diversity in the overall sample, we will oversample males and individuals from minority groups to include 25% males and 35% minority groups.

Assessments (see Table 1):

Follow-up assessments using independent evaluators blind to treatment condition will be conducted at Weeks 4, 12, and 24. TAU or standard care on the inpatient unit includes diagnosis, safety assessment and stabilization, initiation or adjustment of pharmacotherapy, psychoeducation of patients and families, and disposition. It is standard care for the inpatient units to provide clinical referrals for outpatient treatment and typically a follow-up appointment occurs about 1 week after discharge. We will also directly measure TAU services post hospitalization using a service use assessment instrument (CASA – see measures section).

Demographics, including gender identity and sexual orientation (as per requirements by AFSP research grants) will be collected at baseline. We will compare the four treatment conditions with respect to three main sets of outcomes: (1) efficacy at reducing suicidal ideation, and increasing time to suicidal attempt and (2) moderators and mediators related to suicidal outcomes, (3) cost effectiveness of each intervention alone and combined compared to TAU.

To shorten the diagnostic assessment, dimensional measures of psychopathology will be obtained from the parent, using the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) and the corresponding Youth Self Report (YSR) from the participant (Achenbach, 1991) at intake. Diagnostic assessment will include dimensional measures of anxiety (the Screen for Anxiety Related Disorders [SCARED, 5 item scale]) (Birmaher et al., 1999), depression (Patient Health Questionnaire [PHQ-9]) (Johnson, Harris, Spitzer, & Williams, 2002; Richardson et al., 2010), alcohol and drug use (CRAFFT-self report substance use screening tool) (Knight et al., 1999), and sleep disturbance (Pittsburgh Sleep Quality Index [PSQ]; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). These measures will be obtained at each follow up, since these are often targets of group and individual treatment and because these may be potential moderators of use of the safety plan and of suicidal ideation change.

Outcome measures:

*Suicidal ideation and behavior***.** Information about past and current suicidal behavior and non-suicidal self-injury will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2011). NSSI, while not a primary outcome of this study, is important because of recent findings that NSSI is an even stronger predictor of eventual suicidal behavior than past suicidal behavior (Asarnow et al., 2011; Wilkinson et al., 2011; Cox, Stanley, et al., 2012). Factors related to the risk of suicide attempt or completion will also be measured using the Concise Health Risk Tracking scale (CHRT; Trivedi et al., 2011). As a secondary outcome, we will track reasons for living, using the Reasons for Living Inventory questionnaire, with the expectation that over time, as a result of treatment and the safety plan, that adolescents will show an increased score on this scale, which has been shown to be protective against future suicidal behavior (Osman et al., 1998).

*Assessment of Moderators and Mediators***.** We will be comparing the efficacy of ASAP, BRITE, and the combination of both on change in suicidal ideation, suicidal behavior free days, and time to suicide attempts. It is important to assess those variables most likely to contribute to differences in outcome, or that may moderate the effects of the intervention. Based on our preliminary results, we anticipate that the effects of ASAP and BRITE will be mediated by changes in emotion regulation (Difficulties in Emotion Regulation Scale [DERS]; Gratz & Roemer, 2004), distress tolerance (Distress Tolerance Scale; Simons & Gaher, 2005), reasons for living (RFL-A; Osman et al., 1998), and motivation (Readiness, Importance, & Confidence Ruler [RICTC]; Moyers et al., 2009).

Possible moderators of outcome include history of child maltreatment (Childhood Trauma Questionnaire [CTQ]; Bernstein, Fink, Handelsman, & Foote, 1997), social support (Multidimensional Scale of Perceived Social Support [MSPSS]; Zimet, Dahlem, Zimet, & Farley, 1988), and family climate (Family Adaptability and Cohesion Evaluation Scale [FACES-IV]; Marsac & Alderfer, 2011). As noted above, we will also test whether history of a suicidal attempt moderates treatment response, as it did in our pilot study.

Client Satisfaction. Client satisfaction will be obtained from the patient and caretaking parent using an adaptation of the Computer System Usability Questionnaire (CSUQ) to assess satisfaction with the phone app. The PSSUQ will be filled out by the participant, and is based on earlier measures designed to predict the adoption of technology, based on two main factors: ease of use (easy to learn, access, flexibility, quality of sound, quality of visual display) and usefulness (able to access when needed, helpful when used), which are scored along a 7-point Likert Scales with good psychometric properties (Davis, 1989; Lucas & Spitler, 1999). Exit interviews will also take place to measure satisfaction. Participants who are randomly selected to complete an Exit interview assessment will be given an additional $25 payment. Participants will only be paid after completion of the assessment.

Treatment Utilization. Treatment history will be obtained at baseline, including services received for psychiatric complaints and medications taken. History will also be obtained at baseline and recent use during all follow-up assessment calls using the Child and Adolescent Services Assessment [CASA] (Ascher & Farmer, 1996).

Suicide Free Days. The adolescent version of the Longitudinal Interval Follow-Up Evaluation (A-LIFE): Psychiatric Status Ratings (PSR) score sheet (Keller et al,, 1987) will be used to evaluate suicide free days. This measure is used to record symptom variations that have occurred since the last assessment. The extent of the subject's recovery from previous episodes of DSM-IV disorders as well as the occurrence and degree of severity of any new disorders is recorded using a 4-point rating over monthly intervals on the PSR score sheet.

Table 1. Assessments

	Completed By:	**Assessment Of:**	**Baseline**	**Wk 4**	**Wk 12**	**Wk 24**
SDQ	P	Symptoms	X			
YSR	SR	Symptoms	X			
C-SSRS	C, IE	Suicidal behavior	X	X	X	X
CASA	C, IE	Service Use	X	X	X	X
Trauma *(2-items)*	SR	Trauma	X			
PHQ-9	SR	Depression	X	X	X	X
SCARED *(5 item)*	SR	Anxiety	X	X	X	X
DERS	SR	Emotional Regulation	X	X	X	X
DTS	SR	Distress Tolerance	X	X	X	X
RICTC	C, IE	Motivation	X	X	X	X
MSPSS	SR	Social Support	X	X	X	X
FACES-IV	SR	Family Support	X			
CRAFFT	SR	Substance	X	X	X	X
PSQI	SR	Sleep	X	X	X	X
RFL-A	SR	Reasons for Living	X	X	X	X
CSUQ	SR (*app users*)	Satisfaction with app		X		
PedsQL	SR, P	Quality of Life	X	X	X	X
FEII-E	P	Parent missed time from work	X	X	X	X
ALIFE	IE	Suicide free days		X	X	X
CHRT	SR	Suicide Risk	X	X	X	X
Exit interview	SR	Satisfaction		X		
GENINFO	C	Demographics	X			

IE: Independent Evaluator; C: Clinician/Therapist; SR: Self-Report; P: Parent; B: Behavioral Marker completed by patient

Rescue procedures and disclosure of suicidal ideation on interview. Upon entry into the study, we obtain permission to discuss the patient's care with one of three supportive individuals nominated by the participant who can help the participant to obtain emergency treatment, if he or she is judged to be

a high suicidal risk during the follow-up period, after discharge from inpatient care. If the patient endorses suicidal ideation on a clinical assessment, we ask if the participant can keep him- or herself safe, and assess the degree of intent and planning related to suicidal ideation. Participants judged to be at high risk will be discussed with either Drs. Kennard or Brent. If upon discharge, during the follow-up period, the patient is judged to be at high risk, participants and/or their parents will be referred for emergency care. Both sites have access to 24-hour psychiatric emergency care.

Removal from the study. The main reason to be removed from the intervention is if the participant develops a condition that makes it impossible to cooperate with case management (e.g., acute psychosis, mania). However, we will follow-up all participants at their scheduled assessments.

Personalization of the App: A HIPAA-compliant web-based application has been designed to provide the participants with guidance, social support, and convenient access to their safety plan via the patients' phone. If a participant does not have a cell phone or a device that can access the application, the study will supply the participant with one for the duration of the study (24 weeks). Phones that are provided to the participants will have all data removed prior to reassigning to a new participant. All phones will be password protected in case it is lost or stolen. The research coordinator and PIs will have access to a setup interface and web interface in order to customize the content of the participant's app and view usage. The app goes beyond the current practice of writing a safety plan that the patient can carry with them. Instead, the app will not only list the steps in the plan, but has the capacity to support these steps through hypertext links to offsite techniques such as videos, images, sound memos, and support systems.

The BRITE App includes the following components, which are in accordance with accepted best practice for developing and implementing such plans: *Personal Strategies:* Distraction (take a walk), listen to music (link to audio), think about a favorite spot (beach picture), reasons for living (link to family picture, picture of pet, image of a college s/he wants to attend, friend talking about how important the patient is to them), or other techniques (exercise, self-talk, savoring). *Reaching out:* Talking with friends, family and other supports; (participant clicks on one and autodials or autotexts). *Professional help:* therapist, guidance counselor, family physician, psychiatrist, emergency numbers; (list of contacts, the patient clicks on one, and autodials).

Clinical studies and real-time analyses of contributors to suicidal behavior find that the following are contributors to the decision to make a suicide attempt in the face of suicidal urges: (1) inability to generate alternative solutions; (2) inability to manage or cope with negative affect; (3) hopelessness and inability to consider reasons for living; and (4) perception of being a burden, and hence not reaching out for support (Joiner, Pfaff, & Acres, 2002). The app provides technological aids to combat these common characteristics of suicidal adolescents. The application has a list of alternative solutions to suicide which the adolescent has generated when calm. By having such a list handy and stored on the phone, the teen does not have to re-generate this list when under duress. In addition to poor problem-solving, youth who are at risk for suicidal behavior show difficulty with emotion regulation: they experience more subjectively distress, and are less adept at coping and attenuating negative emotion (Nock et al., 2013). The first step in the safety plan is to review techniques, chosen by the teen that can be effective in achieving emotional de-escalation. Joiner has articulated a model of suicidal behavior that includes perceived burdensomeness (Joiner et al., 2002). The dangerous part of this perception is that support can be protective against suicidal risk, but a person who perceives her/himself to be a burden will not reach out. Thus, we have the capacity to include, when appropriate, short videos of a person in the patient's social network who says how important s/he is to them. The second and third tier of interventions are to reach out to other people in his/her social network, and to seek clinical attention—either from the therapist, ED, or 24-hour hotline that is programmed into the app. All these techniques serve to help the participant cope with suicidal urges and defuse the suicidal crisis. Since

the phone will record the patient's response to, and use of, the different techniques of the safety plan, this provides a framework for the therapist to evaluate the efficacy of the plan and to make changes accordingly.

Treatment blinding. During the RCT, the independent evaluator (IE) will be blinded to the assigned condition and will take the following steps to preserve the blind: participants and families are asked not to share with the IE which condition they are assigned to; at staff meetings when cases are reviewed, IEs are not present; IEs are asked to guess what the treatment assignment is at the end of each interview, and they will notify the project coordinator if they become unblinded. Also, we obtain complementary self-report forms that will not be influenced by interviewer bias.

Research Clinician dashboard: The study therapist whose patient is assigned to BRITE and ASAP + BRITE + TAU will have a dashboard for that patient set up that will display information gathered from use of the app, namely frequency of use. The BRITE clinician dashboard contains information about each individual participant's activity on the app. From the dashboard, research and clinical staff are able to view the date and time participants downloaded and registered the app onto their phone. Study staff are also able to view other app activities including how many times they log in, how they rate their mood at each login (on a 1-5 scale) and which activities they viewed, modified to make more personal, or deleted. The duration of time in which the app remains open and any navigation the participant does within the app is logged and time stamped. After completing an activity, participants are also prompted to submit if they feel better, worse, or the same after the activity and are offered a chance to re-rate their mood post activity. We will, with the permission of the participant and family, provide their outpatient clinician with regular updates about app use and efficacy of different strategies.

Quality Assurance.
Assessments. IEs will be supervised by trained and experienced evaluators on the C-SSRS. All assessments will be taped, and 20% will be reviewed by the supervisors at each site. IEs must maintain at least 80% agreement with the supervisors in order to continue in this role.

Safety planning. There are three aspects to quality assurance for case management. First, each assessment will be staffed at each site by the PIs or co-Is (Drs. Brent, Goldstein, or Douaihy or Drs. Kennard, Foxwell, Stone). Second, after the chain analysis, assigned site investigators will review the chain analysis and subsequent safety plan that is developed at their respective sites. Third, the quality of the safety planning will be reviewed using the Safety Plan Rating Scale (SPRS) (Kennard et al., submitted).

Treatment. Therapists will have at least a master's level training or will be currently enrolled in a doctoral program with experience and expertise in treating suicidal youth. ASAP therapists will have a 2-day training (by Skype or ooVoo) on the components of treatment prior to beginning formal intervention and will also attend a day-long training in MI principles, skills and strategies with study with Co-I Dr. Douaihy, an experienced member of the MI Network of Trainers (MINT) and Dr. Tina Goldstein, who has expertise in the application of MI principles. Dr. Dana McMakin (Co-I) will provide training in savoring, switching strategies for improving access to positive mood. Therapists will record all of their sessions; all sessions will be reviewed for the open trial, and then a random 20% of sessions will be reviewed in the RCT for adherence and competence. Therapists will also receive training on BRITE during the 2 day training. Study therapists will be able to provide ASAP only, BRITE only, and ASAP + BRITE + TAU.

Statistical analysis.
We will begin with a preliminary analysis of data, for example to examine missingness patterns, outliers, and consider transformations and dimension reduction methods. Next, we will compare the four groups on demographic and clinical variables to identify any differences between groups. In the regression analyses below, we will include those variables that are related to the main outcomes of the

study. We will also assess site effects and control for them if indicated. Our initial analysis for each hypothesis will be a test of equality of the two or four cells without covariates, using the appropriate (t or F, chi-square, Kaplan-Meier) test for continuous, discrete, and time-to-event data. We will then use appropriate (GLM) regression methods developed by Hedeker and colleagues (Hedeker, Mermelstein, & Demirtas, 2008; Hedeker, Mermelstein, & Demirtas, 2009) for both continuous and discrete data. We will also use the Cox models to study the time to suicidal event, with appropriate modifications if the proportional hazards assumption is in doubt. We will try to ascertain the reason(s) for any missing data in order to decide on how to deal with missingness. We adopt the general approach of Little and Rubin (2002): we will do sensitivity analyses, comparing the results of completers only, last value carried forward, and multiple imputation by chained equations (MICE) and report inferences that are well supported by those analyses. Next, we will address the three secondary aims: our approach to mediation and moderation analysis, and cost-effectiveness analysis are described below. We will also do extensive exploratory analyses to assess the potential effects of other covariates we measure, such as adherence, gender identity, emotion regulation, and sexual orientation. Finally, for all regression analyses, we will use standard regression diagnostics (residual plots, influence measures) to assess the fits of our models, and refine them if indicated by the data.

Primary aims.

Hypothesis 1. Both ASAP and BRITE will be superior to TAU alone, and ASAP + BRITE + TAU will be superior to BRITE or ASAP alone.

Our main analysis will be the use of two-way ANOVA with an interaction term. We will use the assessments from the instruments listed in Table 1 to study the three main outcomes. For SI severity, we will use a linear model; for NSSI and suicide attempts, we will use a Poisson model; and for the time to attempt, we will use the Cox model. We will include as covariates the following: site, the three covariates we balanced on in our randomization, and any covariates we find in our preliminary analyses to be associated with the outcome; we will consider mixed effects models if they provide a better fit. We do not expect a strong interaction term; if so, our inferences will be based on the main effects. As additional analyses, we will use post-hoc tests for the four main comparisons: the combination vs. each component, and each component vs. TAU.

H2: The effects of ASAP and BRITE will be mediated by increases in reasons for living, decreases in dysfunctional emotional regulation, increases in functional emotional regulation, and decreases in implicit associations with death, and will be moderated by previous history of an attempt, and family engagement in treatment. In addition, the impact of BRITE will be proportional to the frequency of use.

For moderator and mediator analyses, we use the standard approach of Baron and Kenney (1986) and later explicated by Kraemer and colleagues (2002) and Kraemer (2008) for moderators. The search for moderators is typically an exploratory analysis because it involves the testing of interaction terms, for which power is usually limited. Thus, we will use the recent optimal weighted moderator profiles developed by Wallace, Frank, and Kraemer (2013) that combine potential (weaker) moderators. For mediator analyses, we will follow the approach of Preacher and Hayes (2008) for handling multiple mediators. In particular, we will begin by including the candidate mediators listed above in a single model and test their significance using both standard errors using the Gaussian model or the bootstrap if the Gaussian model is not a good fit.

H3: Cost per outcome achieved will by will be lower for each of the interventions (ASAP + BRITE + TAU; ASAP alone; BRITE alone) compared to TAU at Week 24 Weeks follow-up. Cost per outcome achieved will be most advantageous for ASAP + BRITE + TAU. We will adopt a societal perspective on costs, assessing the cost of all usual health services, costs of services in other sectors (e.g., school),

and costs to the families (e.g., out-of-pocket costs, missed time from work). This perspective will provide the type of data relevant to health care managers and health policy makers who would make decisions about whether or not to adopt these interventions. We will conduct a series of incremental cost-effectiveness analyses (CEA) comparing ASAP + BRITE + TAU, ASAP, BRITE, and TAU.

Cost effectiveness ratio (CE ratio). Below, we provide a sample computation of a CE ratio, comparing ASAP to TAU and using change in *quality-adjusted life years (QALYs)* as the clinical outcome metric.

$$\textit{Incremental Cost-Effectiveness} = \frac{\text{(Direct ASAP Intervention Costs) + (Total Service \& Family Cost}_{ASAP} - \text{Total Service \& Family Costs }_{TAU})}{[\Delta\text{Mean QALY}_{ASAP} - \Delta\text{Mean QALY}_{TAUl}]}$$

Experts have noted that there are numerous empirical challenges to accurately estimating incremental cost-effectiveness ratios (Gold et al., 1996). We next describe our procedures for assessing each component of the CE ratio, namely, the CE clinical metric and the costs of the ASAP and BRITE interventions, other services and family costs.

Clinical metrics. We will conduct cost-effectiveness analyses using several clinical metrics that may be useful to decision-makers. First, we will calculate CE ratios using QALYs, this is the recommended metric by experts (Gold, Siegel, Russell, & Weinstein, 1996). Specifically, we will calculate QALYs using the PEDSQL (Varni, Seid, & Rode, 1999). However, this may not be the most meaningful outcome to clinical decision-makers. For this reason, we will also calculate CE ratios using an additional clinical metric, number of days free from suicide attempt and/or ideation (SFD). We will follow methods used in studies of the cost-effectiveness of depression treatment (Lave, Frank, Schulberg, & Kamlet, 1998; Lynch et al., 2017; Lynch, Dickerson, Clarke, et al., 2011). We will calculate S*FD*s using data from our suicide attempt and ideation outcome measures. Total S*FD*s will be calculated by summing estimated daily S*FD* values over the 6-month study period.

Overall approach to measurement of cost. In our analysis, costs will be assessed with the following general strategy: (a) calculate direct costs of ASAP and BRITE, including intervention (labor, equipment, supplies, facilities, management); (b) calculate total other service use and expense for each participant, in each arm of the study (ASAP, BRITE, ASAP+BRITE+TAU, TAU) using the CASA; and (c) family costs (out-of-pocket expenses, parent missed time from work). Note that this approach includes all services as "costs" for youths in each arm, not simply the cost of the new intervention programs. This methodology will allow us to capture any cost-offset of participation in the ASAP, BRITE, or ASAP + BRITE + TAU programs or, conversely, any increase in costs associated with additional service utilization by youths in these arms. This same strategy will be used for determining costs of the TAU arm (counting all service utilization as a cost associated TAU).

Measurement of direct intervention costs. An intervention "input" will be defined as any service provided to the intervention groups that is not provided to the TAU control group by the research team. We will not include research-specific inputs on either side of this calculation, such as time spent conducting baseline assessments. The direct costs of the intervention programs are the salary and fringe benefits for labor inputs (e.g., therapists, appointments clerks); costs of medical office space to

conduct the intervention meetings; costs of treatment manuals and materials and therapy supplies; and general administration and overhead. Purchased inputs (e.g., manual printing) will be valued at their invoiced cost. Professional labor inputs will be valued using unit cost estimates developed from a national database (see costing algorithm).

Measurement of utilization of services (Total Service Costs). Comprehensive service use profiles will be developed on every participant. We will obtain data on utilization with the CASA, Child Health Services Screen. The CASA collects comprehensive data on all types of health services received by the participant in any health care setting, associated with treatment for the target conditions of the study (i.e., internalizing symptoms). We will also collect family out-of-pocket expenses from the CASA. Parent time missed from work will be assessed using the Family Economic Impact Interview, Employment module (FEII-E) (Lynch & Dickerson, 2012).

Costing algorithm. To assign costs to the utilization data and the mental health professional services used in the interventions, we will develop a set of unit cost coefficients using the Medical Expenditure Panel Study (MEPS), a nationally representative survey of health care utilization and cost that includes comprehensive assessment of health care services including mental health services (Agency for Healthcare Research and Quality, 2004). Similar approaches have been used by other investigators conducting CEA of mental health interventions (Schoenbaum et al., 2001). Health care costs will be converted to constant dollars by using the cost conversion coefficients for a year in the middle of the study period. This approach eliminates the effects of inflation on expenses and removes the burden of adjusting for inflation from the cost and cost-effectiveness models.

Model fitting. We will collect detailed data to minimize the need to estimate resource consumption. This will not alleviate all uncertainty in measurement of the CEA, however. To address the remaining uncertainty, we will conduct sensitivity analyses to ascertain the effects of variations in the key parameters. If these analyses indicate considerable uncertainty, we will use simulation modeling such as bootstrapped estimates to reduce uncertainty. We have used these methods successfully in previous studies (Lynch et al., 2017; Lynch, Dickerson, Clarke, et al., 2011; Lynch et al., 2005). The CEA will be conducted by Dr. Lynch in coordination with the lead investigators (Kennard, Brent).

Power Analyses

All power calculations assume size alpha= 0.05 two-sided tests and requiring power 0.80, and assuming 85% retention (we had 92% retention in our pilot study), so we have 51 subjects per cell. For Hypothesis 1, with a total of 204 patients, we can detect a small effect size of approximately $f^2 = 0.06$ for the two-way models with an interaction term. For post-hoc direct comparisons involving only the cells of size 51 we have power to detect medium effects of size approximately d=0.55. For Hypothesis 2, the results of Hedges and Pigott (2004) show that we have power to detect large effects for individual cells. It is well known that tests for moderation can have low power; however, we do expect that our use of optimally combined moderators will enhance our ability to identify key moderators. Finally, for testing potential mediators, previous simulation studies indicate that we have power to detect medium to large effects sizes for the individual cells (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

Strengths, Limitations, and Future Plans.

To our knowledge, this is the first attempt to establish the efficacy of brief interventions to prevent post-discharge suicide attempts in psychiatrically hospitalized suicidal adolescents, the first to establish the

efficacy of safety planning as an intervention, and the first to test the efficacy of a smartphone intervention to reduce suicidal behavior. However, we cannot control the duration and types of treatments that the participants experience while on the inpatient unit and thereafter, although we can document and adjust for the effects of differences to pre- and post-discharge intervention. For example, we can conduct analyses stratified by length of hospitalization as a sensitivity check. In addition, there may be differences with respect the type, intensity, and duration of outpatient care, although we will gather this information and covary its impact on outcome.

Based on our cost-effectiveness analyses, we will identify the most cost-effective component of our intervention for future dissemination studies, by training inpatient staff on the intervention, and evaluating the effectiveness of this intervention as delivered by inpatient clinicians.

HUMAN SUBJECTS RESEARCH

Human Subjects Issues. A full IRB application has been submitted and will be modified to include this increased sample size. We are aware that any study of suicidal patients requires special attention to issues of participant safety and confidentiality. All participants will be in inpatient treatment with close monitoring by the treatment staff. However, we will take several steps to ensure participant safety. We will include provision of rescue procedures for patients at high suicidal risk, including involvement of significant others and involvement of emergency mental health services if necessary.

Protection Against Risk. The risks due to interview are three-fold: discussion of potentially upsetting information, loss of confidentiality, and assessment burden. The interviewers will all be trained and skilled interviewers who can assess and monitor the reaction to questioning about sensitive topics; interviewees will be given the option of not responding or ending the interview. We will provide the patient and family with emergency contact numbers regardless of treatment assignment. If upon follow-up, participants are not in treatment and we identify serious psychopathology and/or suicidal risk, we will provide referral information to the participant and parents. If at any of these points, we perceive that the patient is in imminent suicidal risk and the parent/patient is not willing to address this issue, then we will contact emergency mental health services to initiate an emergency assessment. To protect against violations of privacy, we try to have the respondent take the phone call in a private place. To protect the adolescent who may be suicidal, we only conduct phone interviews when know we will be able to reach the participant's parent. In particular, teens will be evaluated at weeks 4, 12, and 24 to assess suicidal ideation and behaviors, as well as specific psychiatric illnesses, and may be given recommendations for additional treatment options should concerns arise during the evaluation. The risk of lack of improvement or worsening of psychiatric illness will be addressed by monitoring subjects closely during assessments. For all groups at 4, 12, and 24 weeks, if we detect untreated psychiatric disorder, or non-adherence, and there is not imminent risk, then we will pass this information to the parent and provide recommendations.

Because of the sensitive nature of the phone app, the phone application will follow HIPAA compliance best practices to ensure the privacy of the users' information at all times. Security will be integrated throughout the app, and accomplished with device login timeouts; ensuring all sensitive information is encrypted when stored and transmitted; two-factor authentication, which is an approach to authentication that requires the presentation of "two or more" factors (e.g., phone UID and login password); and ensuring that no sensitive data is stored on the device itself. Most of these features will prevent loss of confidentiality in the event that the phone is lost; however, we will also ensure that the app can be remotely deactivated to make sure all information remains confidential.

We will convene an independent Data Safety Monitoring Board (DSMB) to review adverse events across the study and within each intervention arm. Prior to any clinical interview confidentiality is discussed with the patient and family during the consent process. This includes state guidelines for reporting abuse. All research personnel are trained and certified in ethical conduct of research, all information stored securely and separately from identifying information, phones will contain no identifying data and the phone app will be password protected, and communication between participant and research staff will be encrypted. Because its sensitive nature, the phone application will follow HIPAA compliance best practices to ensure the privacy of the users' information at all times.

Project Timeline

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<tr><td colspan="5">Year 1</td><td colspan="4">Year 2</td><td colspan="4">Year 3</td><td colspan="4">Year 4</td></tr>
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<tr><td colspan="15">Technical support, app training</td><td></td></tr>
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<tr><td></td><td colspan="14">Recruitment, consent, and enroll patients to RCT</td><td></td><td></td></tr>
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Months 1 – 3 (June 1, 2018 – August 31, 2018)

Study implementation preparations
- Training in ASAP intervention and BRITE
- Meet with inpatient staff

Months 3-43 (September 1, 2018 – December 1, 2021)
- Recruitment of participants for RCT
- Data entry

Months 44 – 48 (December 1, 2022 – May 31, 2021)

- Data entry continued
- Data cleaning on completed participants
- Write primary outcome paper

MULTIPLE PI LEADERSHIP PLAN

Drs. Kennard and Brent will jointly provide oversight of the entire project and development and implementation of all policies, procedures, and processes, including the scientific agenda, specific aims, study design, and training of personnel. In addition, both will oversee the study procedures to

ensure that systems are in place and function in a way so as to remain in compliance with local IRB policies, US laws, DHHS and AFSP policies including human research, data and facilities.

Governance: We will operate on consensus whenever possible. The process will be to encourage all to have a voice in decisions and to move the group toward consensus. In the multi-site TORDIA project, for which WPIC and UTSW were the two largest sites, we were always able to achieve consensus. If we cannot come to consensus, will consult with other senior colleagues and reconvene.

Executive Committee (EC): The EC will have a weekly conference call to discuss the status of the study, recruitment, intervention, adherence, and adverse events. The EC will consist of each of the PIs and 1 Co-I from each site (Brent, Kennard, Goldstein, Foxwell), and Dr. Kennard will serve as the chair. The EC will make all decisions regarding the protocol, budget, and publication policy.

Publication Policy: The EC will establish a publication policy at the start of the study. The core papers are listed under the products at the end of the application will include papers on the description of the model and feasibility, the utility of the phone app, and the results of the RCT with respect to proximal (e.g., positive affect) and more distal (suicidal events) outcomes. Additional papers will be proposed by individual authors at the sites, and the EC will review and approve all papers. Each site will be represented on all outcome papers.

Study Coordinator Conference Calls: The study coordinators, research assistants, and data manager (WPIC) from each site will have a biweekly conference call to discuss day-to-day study procedures, patient management, reliability of assessments, and review for data completeness and data management.

Dispute resolution. As noted above, we strive to make all decisions by consensus, and in the past decade of working together, always have been able to do that. However, should we not be able to reach consensus, we will turn to our respective chairpersons who will confer and decide.

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