PREDICTING HETEROGENEITY OF TREATMENT RESPONSE IN A CLINICAL SAMPLE OF SUICIDAL ADOLESCENTS

by

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This thesis is dedicated to those lost to suicide, to their family and friends who will miss them forever, and to my best friend, Sam, whose memory holds my past and inspires my future.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

During the past two decades, several treatments specifically targeting youth suicide have been developed. Although most of these treatments have been shown to be more effective than treatment as usual, research has consistently indicated substantial variation in adolescents' response to these treatments. The current study employed Growth Mixture Modeling (GMM) to categorize trajectories of symptoms over the course of a sixteen-week comparative efficacy trial for suicidal adolescents. One hundred and twenty adolescents (ages 12-18) were randomly assigned to receive either Attachment Based Family Therapy (ABFT) or Family-Enhanced Non-Directive Supportive Therapy (FE-NST). GMM identified three distinct classes of adolescents' trajectories of depressive and suicidal symptoms: a) Non-Responders (15.8%), b) Good Responders (57.5%), and c) Slow Responders (26.7%). Well-established risk factors for suicide, as well as baseline sociodemographic variables were then tested as predictors of class membership. Results showed that baseline levels of suicide ideation, MDD diagnosis, pessimism, NSSI, and perceived burdensomeness distinguished class membership and predicted poorer response to treatment. These results point to baseline variables that predict lower likelihood of benefitting from treatment (ABFT and FE-NST) and add to the growing literature on individualized treatment planning.

Chapter 1

INTRODUCTION

Suicide is a serious health concern, especially in adolescence. Recent data from the U.S. National Vital Statistics System identified suicide as the third leading cause of death in those aged 10 to 14 and as the second leading cause of death in those aged 15 to 24 (CDC, 2013). In a 2013 nationwide survey, 17% of high school students reported having seriously considered suicide in the past year, 13% made a plan, and 8% made an attempt (CDC, 2013). One-hundred and fifty-seven thousand adolescents between the ages of 10 and 24 years old seek emergency care for self-inflicted injuries and 4,600 adolescents die by suicide each year. In response to these high and historically stable suicide rates in adolescents, the past decades have demonstrated a sharp increase in interventions targeting suicidal youth, and a recent review of the current evidence base identified several treatments as "probably efficacious" (Glenn, Franklin, & Nock, 2015). These treatments were categorized as (1) family-based therapy (e.g. Attachment-Based Family Therapy; Diamond et al, 2010); (2) family enhanced individual therapy (e.g. Integrated CBT; Esposito-Smythers, Spirito, Kahler, Hunt, & Monti, 2011); and (3) individual therapy (e.g. Skills-Based Treatment; Donaldson, Spirito, & Esposito-Smythers, 2005). The current study examined adolescents' treatment response to Attachment-Based Family Therapy (ABFT) and Family-Enhanced Non-Directive Supportive Therapy (FE-NST; N=129). Our study had two primary aims: first, to categorize subgroups of adolescents with distinct

profiles of change in their depressive and suicidal symptoms over the course of treatment, and, second, to explore baseline sociodemographic and psychosocial risk predictors of class membership.

Heterogeneous Trajectories of Treatment Response

Despite the growing evidence base supporting the effectiveness of treatments for suicidal adolescents, there remains substantial heterogeneity in treatment response and outcomes among adolescents who receive these treatments. Evaluations of evidence-based treatments are frequently based on group averages in randomized clinical trials that often rely on treatment as usual as the comparison group. Relatively few RCTs show significant treatment effects when comparing two active treatments (Spirito, Stanton, Donaldson, & Boergers, 2002). As a result, we have little evidence that any one of these treatments will be effective for a given client (Ng & Weisz, 2016; DeRubeis et al., 2014). Additionally, there remain a substantial number of adolescents who fail to respond to treatment at all (Brent, et al., 1997; Weisz et al., 1995). More research is needed on this variability in treatment response (especially subsamples of adolescents who respond poorly or not at all) to inform clinical decisions and move closer to personalized treatment.

Most research on differential treatment response has employed variable centered, regression-based moderation analyses to identify variables that facilitate or reduce the magnitude of treatment benefit (Connell, Stormshak, Dishion, Fosco, & Van Ryzin, 2015). While this approach of identifying effect sizes as indicators of

treatment response has yielded useful information, these average effects do not help predict likelihood that a particular individual will benefit from a treatment (Westen, Novotny, & Thompson-Brenner, 2004; Beidas et al., 2014; Lindheim, Kolko, & Cheng, 2012). In order to make predictions using probabilities, outcomes must be dichotomous. The dichotomization of treatment response has been debated in the literature for some time and has been defined in different ways across treatment research. For example, in studies on "treatment non-response" for depressed and suicidal adolescents alone, "non-response" has been defined as meeting criteria for MDD at the end of treatment (Brent et al., 1998), remaining above a clinical cutoff (>= 31 on the BDI) at the end of treatment (Koenig et al., 2014), making a suicide attempt during follow up (Huey et al., 2005), showing less than 50% improvement on a validated scale (Asarnow et al., 2009), and not demonstrating change greater than what might be expected from random variation (Reliable Change Index (RCI); Reuter et al., 2016). While dichotomizing variables allows for probabilistic predictions, there is a need to better define "non-response" and acknowledge the distinction between treatment response (i.e. magnitude of change from pre- to post-treatment) and treatment outcome (i.e. clinical status post-treatment; Beidas et al., 2014; Lindheim, Kolko, & Cheng, 2012). For example, adolescents with severe baseline symptomatology may have a higher probability of responding to treatment but a lower probability of a positive outcome (Beidas et al., 2014). In other words, an adolescent could demonstrate significant improvement in symptoms, but still have remain clinically elevated. While the distinction between response and outcome is an

important one, there is still room for improvement on how to evaluate response and outcome to get a better sense of overall treatment benefit.

Growth mixture modeling (GMM) allows us to identify subpopulations characterized by a cluster of variables and has the potential to more parsimoniously address both treatment response and treatment outcome in a single model. In particular, mixture modeling approaches to intervention research have allowed researchers to identify distinct groups of clients based on trajectories of symptomatology over the course of treatment as a function of individual intercepts and slopes. GMM then provides categorical latent variables allowing us to predict the probability of class membership based on baseline variables. For example, Connell and colleagues (2015) identified a group of adolescents in a family-focused school-based preventative intervention who did not respond to the intervention. This group of non-responders was more likely to be male, to have lower antisocial behavior, and to have higher levels of baseline depression. In a similar approach, Birmaher, Brent, and colleagues (2000) identified a group of non-responders in short-term therapy for depressed adolescents that were characterized by higher baseline levels of depression and parent-child conflict. These studies illustrate the potential benefits of GMM for identifying and exploring subpopulations of adolescents who do not respond well to an otherwise effective treatment.

Predictors of Poor Treatment Response/ Risk Factors for Depression and Suicide Ideation

At least 40% of depressed adolescents do not respond adequately to psychotherapy alone or in combination with medications (Brent et al., 1998). Brent and colleagues (2008) have pioneered the study of depressed adolescents who fail to respond to psychopharmacological treatments using selective serotonin reuptake inhibitors (SSRI). In their randomized control trial, Treatment of Resistant Depression in Adolescents (TORDIA), these investigators identified baseline depression, overall impairment, suicidal ideation, hopelessness, non-suicidal self-injury (NSSI), and family conflict as factors that increase the likelihood of non-response to SSRIs (Asarnow et al., 2009). Similar or related factors accounted for treatment non-response in a clinical trial comparing three psychosocial interventions for depressed adolescents. In this study, comorbid anxiety, cognitive distortion, and hopelessness all increased the probability of treatment non-response (Brent et al., 1998). Birmaher, Brent, and colleagues (2000) reported that non-responders to short-term therapy for depressed adolescents had higher baseline depression and higher reported conflict. Another large trial, Treatment for Adolescents with Depression Study (TADS), identified older age, more chronic depression, lower functioning, more hopelessness, and more comorbidity as predictors of poorer treatment response (Curry et al., 2006). Other studies of depressed adolescents' treatment response have produced similar findings, indicating that baseline symptom severity (Mufson et al., 2004; Rohde et al.,

1994) and parent-child conflict (Rengasamy et al., 2013) increase the likelihood of poor response to treatment.

These studies of poor treatment response have identified risk for depressed adolescents. However, less is known about poor response to treatments that specifically target adolescent suicidality. In a sample of 70 suicidal youth who had attempted suicide, depressive affect and parental control predicted non-response (defined as a suicide attempt within period of treatment follow-up) to either multisystemic therapy or inpatient hospitalization (Huey et al., 2005). In a separate intervention trial, Berona and colleagues (2017) identified 4 subpopulations of acutely suicidal, hospitalized adolescents: subclinical, primarily internalizing, moderately dysregulated and severely dysregulated. They found that being categorized as internalizing (e.g. elevated depression, anxiety, hopelessness) predicted suicide attempts and rehospitalization three and 12-months post-discharge, and the dysregulation profiles (e.g. elevated depression, anxiety, attention problems, and aggression) predicted suicide attempts at three months. Although these studies have begun to identify predictors of response to treatments targeting suicidality specifically, they define "non-response" as the presence of suicidal behavior during follow up. More research is needed on predictors of non-response defined as changes in symptomology over the course of treatment.

Studies that have identified predictors of suicidal adolescents' non-response to treatment tend to converge with general risk factors for suicidality. For instance, previous suicide attempts and NSSI have been repeatedly identified as predictors of

future suicidal behavior among adolescents (Nock, Joiner, Gordon, Lloyd-Richardson, & Prinstein, 2006). Difficulties with emotion regulation (Neacsie, Fang, Rodriguez, & Rosenthal, 2017; Pisani et al., 2013) and comorbid psychopathologies have also been identified as risk factors for adult and youth suicide (Rapp, Lau, & Chavira, 2017; Nock et al., 2013). Additionally, the Interpersonal Theory of Suicide (ITS; Joiner, 2005; Van Orden et al., 2010), which focuses on thwarted belongingness (i.e. feeling socially disconnected/ isolated) and perceived burdensomeness (i.e. feeling like one's loved ones/ society would be better off without him/her), has been found to increase risk for adolescent suicidality. Yet, to our knowledge, prior suicide attempts, NSSI, difficulties with emotion regulation, and ITS measures have not been examined as predictors of differential treatment response for suicidal ideation in adolescents. These factors may play an important role in helping clinicians anticipate poor response to particular treatments and adjust their treatment plans accordingly.

The Current Study

Despite the emergence of several promising treatments for suicidal adolescents, very little is known about which particular treatments would work best for which adolescent/family. Further, even efficacious treatments consistently produce subpopulations of adolescents who do not respond to treatment and remain largely unstudied. "The classic question of 'What works for whom?' might fruitfully be reframed as 'What doesn't work for whom?'" (Pelham, Dishion, Tein, Shaw, & Wilson, 2017, p. 10). The current study utilizes data from a RCT comparing ABFT to

FE-NST (NCT01537419: Attachment Based Family Therapy for Suicidal Adolescents, PI: Diamond & Kobak). We used latent growth mixture modeling to identify heterogeneous trajectories of suicidal ideation and depressive symptoms over the course of 16-weeks of treatment.

Our primary aim was to identify distinct classes of adolescents based on their trajectories of depressive and suicidal symptoms over the course of treatment. We were particularly interested in identifying a group of adolescents who responded poorly to treatment. Our secondary aim was to investigate baseline predictors of poor treatment response by testing previously established risk factors for adolescent depression and suicide ideation. More specifically, we expected that symptom severity, comorbid psychopathology, pessimism, parent-child conflict, and emotion dysregulation would account for poorer treatment response.

Chapter 2

METHODS

Participants

The participants for this study were 129 adolescents who participated in a randomized clinical trial for suicidal adolescents (NCT01537419: Attachment Based Family Therapy for Suicidal Adolescents, PI: Diamond & Kobak). Adolescents were referred from multiple sites throughout the greater Philadelphia area. Of the 253 adolescents who were screened for the study, 129 (51%) met inclusion criteria by endorsing severe suicidal ideation (defined as a score of 31 or above on the Suicidal-Ideation-Questionnaire (SIQ)), clinically significant depression (defined as a score on the Beck Depression Inventory (BDI; above 20)), and at least one primary parent or caregiver agreeing to participate. Twenty-seven (11%) of the screened adolescents declined to participate and 97 (38%) did not meet study criteria. Exclusionary criteria included requiring a higher level of care (i.e. evidence of imminent risk of harm to self or others, psychotic symptoms, or severe cognitive impairment), non-English speaking participating parent, and initiation of medication within three weeks of the initial pre-treatment assessment. Most adolescents (37.9%) were recruited through emergency departments, 23.5% were self or community clinician referred, 20.9% were recruited through mental health or primary care service centers, 10.8% through schools, and 6.9% via referrals from inpatient psychiatric hospitals. A quarter (25%) of adolescents

had a history of hospitalization, 39.3% reported a history of suicide attempts, and 56.4% reported a history of non-suicidal self-injury (NSSI).

At the time of baseline assessment, the average age of the participants was 14.96 (*SD*=1.66), with the adolescents ranging in age from 12 to 18 years old. Eighty-three percent of the participants were female. Fifty-six percent of adolescents identified as black/African American, 31% as white, 6% as American Indian/Alaska Native, 2% as Asian, 1% as Native Hawaiian/Pacific Islander, and 12% as other. Sixteen percent of adolescents identified as being Hispanic. Most adolescents (88%) identified as being heterosexual, 10% as lesbian/gay, 22% as bisexual, and 9% as being unsure. The average number of people living in the household as reported by the adolescent was 4.4 (*SD*=1.7). The average income-to-needs ratio for this sample was 2.07 (*SD*=1.45) with 31.3% reporting living below the poverty line. Forty-three percent of adolescents reported living with both of their parents (intact two-parent household), 43% reported living in a single parent household, 7% reported living with a single parent and that parent's partner, and 5% reported another living situation (e.g., living with kin, living alone, etc.).

Procedure

This study was approved by the Institutional Review Boards of the Children Hospital of Philadelphia, Drexel University, the University of Delaware, and the School District of Philadelphia. After being screened as eligible, participants were interviewed at the study center and completed a battery of baseline assessments

including a full diagnostic interview. Following this baseline assessment, the 129 adolescents were then randomized into two treatment groups (ABFT or FE-NST). One-hundred and twenty adolescents began treatment. Symptoms of depression and suicide ideation were collected at weeks 0 (baseline), 4, 8, 12, and 16 (post-treatment) by an outcomes study team who was blind to adolescents' treatment assignment.

Measures

Primary Outcome Measures

Suicidal Ideation Questionnaire-Junior (SIQ-JR Monthly; Reynolds & Mazza, 1999). The SIQ-JR is a 15-item measure assessing how often subjects had thoughts about suicide (e.g., thoughts about death, suicidal plans) in the past month. Example items include "I thought about killing myself" and "I wished I were dead." Each item was scored on a 7-point Likert scale ranging from 0 ("I never had this thought") to 6 ("Almost every day") with total scores ranging from 0 to 90. Raw scores of 31 or above indicate a high level of suicidal ideation. Clinical and school-based samples utilizing the SIQ-JR reported high internal consistency (α = .93-.96) (Reynolds & Mazza, 1999). In this sample, the scale demonstrated good internal consistency (α = .86).

Beck Depression Inventory-II (BDI-II; Beck, Steer & Brown, 1996). The BDI is a widely-used, 21-item self-report instrument designed to assess the severity of depressive symptoms in adults and adolescents. Each of the 21 items is composed of

four statements representing increasing increments of depression severity for a specific symptom. The score for each item on the scale ranges from 0-3, with the total score ranging from 0 to 63. Scores above a 20 indicate moderate depression. Example items include Loss of Pleasure (0- "I get as much pleasure as I ever did from the things I enjoy" to 3- "I can't get any pleasure from the things I used to enjoy") and Sadness (0- "I do not feel sad" to 3- "I am so sad or unhappy that I can't stand it"). The BDI-II has high internal consistency (α = .91) and is highly and positively correlated with other measures of depression. In this sample, the scale demonstrated internal consistency of α = .85.

Baseline Variables

Sociodemographic variables. Adolescents completed demographic surveys including information such as age, gender, race/ethnicity, LGBTQ status, and socioeconomic status.

Treatment condition. Attachment-Based Family Therapy (ABFT) is a 16-week family therapy designed for adolescents aged 12 to 18 (Diamond, Russon & Levy; 2016). ABFT is rooted in attachment theory, using an interpersonal, process-oriented approach to repair ruptures in the parent-adolescent relationship and increase the adolescent's confidence in the parent's availability. Key mechanisms in ABFT include coaching reparative conversations and increasing positive parenting skills (e.g. validation, warmth, and tolerance of vulnerable emotions). ABFT entails both

adolescent-only and parent-adolescent sessions to treat adolescents and has been found to be particularly helpful in treating depression and suicidal ideation.

Family-Enhanced Non-Directive Supportive Therapy (FE-NST; Levy & Diamond, 2010) is a modified version of the Supportive Relationship Treatment Manual (Brent & Kolko, 1991). FE-NST is a 16-week treatment aimed at developing a supportive relationship between the adolescent client and his/her clinician. Clinicians employ evidence-based practices including attending, reflective listening, empathy, validation, and responding to clients' direct concerns. NST was modified to add parent psychoeducation sessions (suicide risk assessment, understanding depression, advocacy/resource development, and problem solving) to supplement the adolescents' treatment sessions.

Psychiatric diagnoses. The computerized Diagnostic Interview Schedule for Children (C-DISC; Shaffer et al., 2000) is a structured psychiatric diagnostic interview for children and adolescents aged 6 to 18 that covers 36 psychiatric diagnoses that occur in children and adolescents based on DSM-IV criteria. It was developed primarily for epidemiological research but is also useful in clinical settings. For the current study the C-DISC modules for various anxiety disorders, mood disorders, oppositional defiant disorder, and substance abuse were administered to participating adolescents.

Life Orientation Test- Revised (LOT; Scheier, Carver, & Bridges, 1994). The LOT is a 12-item self-report measure examining outlook on life and orientation towards the future. Items include "Things never work out the way I want them to"

(reverse coded) and "I always look on the bright side of things." Items were rated on a 5-point Likert-scale ranging from 1 (strongly agree) to 5 (strongly disagree). Scores were averaged across the 12 items with higher scores indicating a more optimistic outlook and lower scores more pessimistic. These items in this sample demonstrated acceptable internal consistency (α=0.73).

The Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004). The DERS is a 36-item self-report measure assessing emotion regulation. Items include "I experience my emotions as overwhelming and out of control" and "When I am upset, I can still get things done" (reverse scored). Items were scored on a 5-point Likert-scale ranging from 1 (almost never (0-10%)) to 5 (almost always (91-100%)). Scores were averaged across the 36 items and the measure demonstrated good internal consistency (α=0.89).

The Self-Report of Family Functioning (SRFF; Bloom, 1985). The SRFF consists of 10 items selected from the Family Environment Scale. The SRFF is composed of two 5-item scales (conflict and cohesion) with Cronbach's alphas ranging from .63 to .91, with most in the .70 to .85 range. These items have yielded highly reliable and stable factors (Stark et al., 1990). An example conflict item is "We fight a lot in our family" and a cohesion item is "We feel close to each other in our family." In this sample, internal consistency for the conflict scale and cohesion scales were α = .66 and .79, respectively.

Interpersonal Needs Questionnaire (INQ; Van Orden, Cukrowicz, Witte, & Joiner, 2012). The INQ is a self-report measure consisting of 15 items rated on a 7-point Likert scale from 1 (Not at all true for me) to 7 (Very true for me). Nine of these items measure thwarted belongingness, or feeling disconnected from meaningful social relationships. Items include "other people care about me" and "I feel like I belong." This construct demonstrated acceptable internal consistency with $\alpha = .76$. The remaining 6 items measure perceived burdensomeness, or feeling like loved ones would be better off without you. Items include "the people in my life would be happier without me" and "I think I am a burden on society." These items demonstrated good internal consistency ($\alpha = .92$).

Data Analytic Plan

Data were first analyzed using Mplus version 7 (Muthén & Muthén, 2013). Growth mixture modeling (GMM) was used to identify latent classes in trajectories of depressive and suicidal symptoms (intercept and slope; SIQ and BDI measured at weeks 0 (baseline), 4, 8, 12, and 16). GMM is exploratory and relies on an iterative process to find the optimal number of classes. The optimal solution for the number of classes was examined using Bayesian Information Criterion (BIC), Sample Size Adjusted Bayesian Information Criterion (SSBIC), Akaike Information Criterion (AIC), and entropy. Lower BIC, SSBIC, and AIC values indicate better fit (Nylund, Asparouhov, & Muthén, 2007). Entropy with values approaching 1 indicate clear delineation of classes (Celeux & Soromenho, 1996). Additionally, simulation studies

have purported that when entropy values are high (greater than 0.8), using most likely class membership is the best method to identify relationships between the latent class variables and auxiliary variables (Clark & Muthén, 2009).

SPSS version 21 was used to evaluate and test predictors of class membership. First, one-way ANOVA and Chi Square analyses identified baseline variables that independently differentiated class membership (see Table 1). Although all C-DISC diagnoses were tested, only significant diagnoses are reported in Table 1. Next, all baseline variables with significant associations with class membership were entered as predictors in multinomial regression analyses. An iterative process of reducing the model (through individually excluding non-significant predictors) was then used to identify baseline variables that remained significant predictors of class membership, above and beyond the other variables.

Chapter 3

RESULTS

Missing Data

GMM was applied to the growth trajectories of the 120 adolescents who started treatment. Most participants (69.9%) completed all five repeated measures of suicidal ideation and depressive symptoms, 20.4% completed four measures, and 9.7% completed three or fewer. The number of completed repeated measures was not related to either baseline depression (r = -.13, p = .16) or baseline suicidal ideation (r = 0.22, p = .82). Therefore, missing data was assumed to be missing at random and restricted maximum likelihood estimation was used to determine class membership. Due to missing between-subject baseline variables that are not able to be estimated, 19 participants were excluded list-wise in multinomial logistic regression analyses. Therefore, final logistic regressions are based on 101 participants who were not missing any predictor variables. Missingness was due to late addition of measures, and adolescents missing baseline data did not differ on any variables of interest.

Growth Mixture Models

GMM was used to model adolescents' symptom trajectories over 16 weeks of treatment. Fit indices for 2, 3 and 4 class models are presented in Table 1. A 4-class model yielded better fit (lower BIC and AIC values) than a 3-class model. However, the 4-class model included a class with very few cases (n = 9) and had lower entropy.

The 2 and 3-class models had higher entropy than the 4-class model, indicating that, in this sample, classes were more distinct in the 2 and 3-class models. Using this information together, the 3-class model was chosen for all subsequent analyses. Further, because the entropy for the 3-class model was high (0.93), class membership was used as a categorical variable.

Describing Three Patterns of Treatment Response

Class 1 (n=19) captured the most severe adolescents. This class had significantly higher starting levels of suicide ideation than Class 2 and Class 3 and had significantly higher depression than Class 2 (see Table 4 for Wald χ^2 significance tests). The slopes for Class 1 were not significantly different from zero, indicating that, on average, these 19 adolescents did not show statistically significant changes in symptoms over time. Additionally, this class had significantly higher depression and suicide ideation scores at the end of treatment than Classes 2 and 3. On average, this group did not show significant decline in symptom severity over the course of treatment and remained in the clinically significant ranges for depression and suicide ideation (Week 16 BDI score: 40.3; Week 16 SIQ score: 52.1). Due to its overall flat slope and clinically elevated post-treatment symptomatology, we have labeled Class 1 as treatment "Non-Responders." To further describe this class and acknowledge that there is individual variation even within classes, we examined this group of adolescents using previous methods of identifying treatment non-response. When using the reliable change index, 44% of these adolescents showed significant improvement on the BDI and 50% on the SIQ. However, none of them met criteria

for remission using clinical cutoff scores for depression (< 9 on the BDI) or suicide ideation (< 12 on the SIQ). In fact, all (100%) adolescents in the Non-Responders class remained in the moderate to severe range for depression and suicide ideation at the end of treatment.

Class 2 (n=69) characterizes the lowest risk and best responding adolescents. This class had significantly lower starting levels of depression and suicide ideation than the Non-Responders and Class 3. Class 2 showed the most improvement in symptoms over the course of treatment indicating that, on average, these adolescents had a decrease of 1.43 points on the BDI and 1.97 points on the SIQ per week. Additionally, Class 2 had significantly lower ending levels of depression and suicide ideation: on average, these adolescents ended the 16-week treatment below the clinical cutoff for remission (Week 16 BDI score: 6.3; Week 16 SIQ score: 7.2). Due to significant decrease in symptomatology and reaching the threshold for remission, this class was labelled "Good Responders."

Class 3 (n=32) captured adolescents who responded better than the Non-Responders but not as well as the Good Responders. Class 3 had significantly higher depression and suicide ideation than the Good Responders and had lower initial levels of suicide ideation than the Non-Responders. Unlike the Non-Responders, this class did demonstrate a significant reduction in symptoms over the course of treatment indicating that, on average, adolescents in this class experienced a reduction of 0.74 points on the BDI and 1.43 points on the SIQ every week. However, these slopes were significantly flatter than those of the Good Responders. When considering post-

treatment outcomes, Class 3 ended lower than the Non-Responders and higher than the Good Responders, meeting the clinical cutoff for remission for suicide ideation (SIQ score = 24.9) but not for depression (BDI score = 26.4). Therefore, because Class 3 had less change over the course of treatment, we labeled them "Slow Responders."

Baseline Predictors of Treatment Response

Univariate Predictors of Treatment Response

Baseline variables including socio-demographic variables, symptom severity, comorbid psychopathology (all DISC diagnoses), pessimism (LOT), difficulty with emotion regulation (DERS), family conflict and cohesion, perceived burdensomeness and thwarted belongingness, history of NSSI, and history of suicide attempt were explored as baseline predictors of the three classes of treatment response (see Table 4). Several of these baseline variables differentiated the three patterns of treatment response. Good Responders were, on average, younger than both the Slow and Non-Responders groups. The Non-Responders, on average, had higher baseline depressive and suicide ideation symptoms, had more pessimism, more difficulty with emotion regulation, more feelings of burdensomeness and were more likely to have MDD, GAD, and have endorsed NSSI than did the Good Responders. Non-Responders also had higher suicide ideation and depressive symptoms, lower LOT, and were more likely to have a diagnosis of GAD and endorse NSSI than the Slow Responders. The Good Responders were younger, had lower baseline depressive severity, and were less likely to be diagnosed with MDD than the Slow Responders.

Multinomial Regression Analyses

A series of multinomial regression analyses were then conducted using baseline variables that distinguished between patterns of treatment response to predict class membership (see Table 5 for Full Model). Non-significant variables were dropped from the analysis until a reduced model emerged (see Table 6). When comparing Non-Responders to Slow Responders, odds ratios indicated that for each point increase in suicide ideation, adolescents were 2.67 times more likely to be Non-Responders. For each one point decrease in optimism, adolescents were 16.5 times more likely to be Non-Responders. Those who endorsed NSSI were 21.85 times more likely to be Non-Responders. When using Good Responders as the comparison group, for each one point decrease in optimism, adolescents were 13.7 times more likely to be Non-Responders, and those with a MDD diagnosis were 8.1 times more likely to be Non-Responders. Additionally, there may be an increased probability of membership in the Non-Responders class based on higher suicide ideation scores and history of NSSI. However, these odds ratios should not be interpreted as they are outside the bounds of statistical significance (p=.092 and .058, respectively). When comparing Slow and Good Responders, for every point increase in perceived burdensomeness, adolescents were 1.6 times less likely to be Good Responders, and those with a MDD diagnosis were 10.9 times less likely to be Good Responders.

Table 1. *Fit indices for the best fitting Growth Mixture Modeling model (n=120).*

Model Tested	AIC	BIC	SSABIC	Entropy
1 class model	9162.5	9201.5	9157.3	
2 class model	8742.8	9785.8	8735.7	0.935
3 class model	8630.5	8697.4	8621.5	0.903
4 class model	8591.7	8672.6	8580.9	0.861

Table 2. *Describing the three latent classes (n=120).*

	n	SIQ Intercept @ Week 0	SIQ Intercept @ Week 16	SIQ Slope	BDI Intercept @ Week 0	BDI Intercept @ Week 16	BDI Slope
Non-Responders	19	63.1**	52.1**	-0.67	44.6**	40.3**	-0.27
Good Responders	69	38.8**	7.2**	-1.97**	29.2**	6.3**	-1.43**
Slow responders	32	47.8**	24.9**	-1.43**	38.2**	26.4**	-0.74**

Table 3. *Comparing differences in three patterns of treatment response (df=1).*

		Intercept @ Week 0		Intercept @ Week 16		Slope	
		Wald χ^2	*p*	Wald χ^2	*p*	Wald χ^2	*p*
Class 1 (Non-Responders) vs. Class 2 (Good Responders)	SIQ	27.98	<.001	33.93	<.001	13.64	<.001
	BDI	31.12	<.001	136.49	<.001	17.79	<.001
Class 1 (Non-Responders) vs. Class 3 (Slow Responders)	SIQ	10.07	<.001	85.70	<.001	3.11	.078
	BDI	2.42	.120	109.00	<.001	1.69	.190
Class 2 (Good Responders) vs. Class 3 (Slow Responders)	SIQ	5.37	.021	38.92	<.001	4.80	.028
	BDI	12.58	<.001	19.31	<.001	15.34	<.001

Table 4. *Socio-demographic and depression/suicide related baseline variables by group membership (n=120).*

	Total Sample	Class 1 Non-Responders	Class 2 Good Responders	Class 3 Slow Responders	Univariate Significance Test
Demographic Variables					
Age (M(*SD*))	14.98 (1.67)	15.42 (1.30)	14.61 (1.58)	15.50 (1.83)	F (2, 119)= 4.19, *p*=.017*
Income to Needs	2.08 (1.40)	2.68 (1.59)	1.90 (1.37)	2.23 (1.46)	F (2, 119)= 1.56, *p*=.098
Gender (% men)	18.3%	15.8%	20.3%	15.6%	χ^2 (2)=0.42, *p*=.812
White (% white)	30.8%	27.5%	25%	57.1%	χ^2 (2)=5.24, *p*=.073
LGBQ (% endorsed)	29.9%	27.6%	18.8%	42.9%	χ^2 (2)=2.07, *p*=.355
Treatment Condition (% ABFT)	50.4%	50.6%	37.5%	64.3%	χ^2 (2)=2.15, *p*=.342
Depression/ Suicide Related Baseline Variables					
SIQ (M(*SD*))	49.94 (15.12)	61.26 (12.61)	47.62 (15.55)	48.94 (12.68)	F (2, 119)= 6.98, *p*=.001***
BDI (M(*SD*))	35.44 (9.12)	43.46 (8.05)	32.18 (8.35)	37.71 (7.75)	F (2, 119)= 15.94, *p*<.001***
LOT (M(*SD*))	1.47 (0.57)	0.87 (0.48)	1.64 (0.47)	1.44 (0.58)	F (2, 119)= 17.55, *p*<.001***
DERS (M(*SD*))	3.11 (0.56)	3.44 (0.49)	2.97 (0.57)	3.21 (0.48)	F (2, 119)= 6.69, *p*=.002**
PB (M(*SD*))[a]	3.95 (1.57)	5.07 (1.50)	3.57 (1.51)	4.21 (1.44)	F (2, 112)= 7.36, *p*=.001**
TB (M(*SD*))[a]	3.99 (1.06)	4.37 (0.88)	3.80 (1.10)	4.16 (1.00)	F (2, 112)= 2.62, *p*=.077
Family Conflict	2.17 (0.68)	2.32 (0.63)	2.17 (0.67)	2.10 (0.73)	F (2, 119)= 0.59, *p*=.555
Family Cohesion	2.90 (0.67)	2.63 (0.64)	2.92 (0.71)	2.94 (0.60)	F (2, 119)= 1.54, *p*=.220
MDD dx [b]	38.7%	70.6%	18.2%	67.9%	χ^2 (2)= 12.00, *p*=.002**
GAD dx [b]	8.1%	23.5%	6.1%	3.5%	χ^2 (2)=11.25, *p*=.004**
NSSI [c]	58.1%	89.5%	52.9%	50%	χ^2 (2)=6.77, *p*=.034*
Past suicide attempt	39.2%	42.1%	40.6%	34.4%	χ^2 (2)=0.54, *p*=.763

[a]n=113, [b]n=111, [c]n=117

Treatment condition was dummy coded 0 for NST, 1 for ABFT; Gender was dummy coded 0 for male, 1 for female; Race was dummy coded 0 for non-White, 1 for White; LGBQ was dummy coded 0 for heterosexual, 1 for LGBQ

Table 5. *Predictors of Class Membership: Multinomial Logistic Regression Full Model (n=101).*

	Full Model					
	Non-Responders vs. Slow Responders		Good Responders vs. Slow Responders		Good Responders vs. Non-Responders	
Predictors	OR	95% CI	OR	95% CI	OR	95% CI
Age	.93	[.52-1.66]	.75[t]	[.53-1.05]	.80	[.46-1.41]
SIQ	1.06[t]	[.10-1.14]	1.02	[.98-1.06]	.96	[.90-1.02]
BDI	1.00	[.89-1.12]	.96	[.98-1.04]	.96	[.87-1.07]
LOT	.03**	[.00-.30]	.51	[.14-1.91]	18.33*	[1.9-178.3]
DERS	.85	[.11-6.39]	.89	[.25-3.21]	1.05	[.16-7.09]
Burden	.59	[.26-1.30]	.64[t]	[.38-1.07]	1.10	[.53-2.25]
MDD dx	.56	[.08-3.82]	.10***	[.03-.35]	.17*	[.03-.99]
GAD dx	12.26[t]	[.69-216.7]	2.20	[.14-33.8]	.18	[.01-2.25]
NSSI	58.16*	[1.5-2303.5]	1.74	[.55-5.57]	.03[t]	[.001-1.16]

***p<.001, **p<.01, *p<.05, [t] p<.10

Table 6. *Predictors of Class Membership: Multinomial Logistic Regression Reduced Model (n=101).*

	Reduced Model					
	Non-Responders vs. Slow Responders		Good Responders vs. Slow Responders		Good Responders vs. Non-Responders	
Predictors	OR	95% CI	OR	95% CI	OR	95% CI
Age						
SIQ	1.07*	[1.05-6.80]	1.01	[.68-2.39]	.95[t]	[.20-1.13]
BDI						
LOT	.06**	[.01-.45]	.83	[.27-2.58]	13.71**	[1.99-94.3]
DERS						
Burden	.71	[.37-1.38]	.64*	[.42-.99]	.90	[.49-1.65]
MDD dx	.74	[.13-4.30]	.09***	[.03-.29]	.12*	[.03-.62]
GAD dx						
NSSI	21.85*	[1.5-323.5]	1.61	[.55-4.72]	.07[t]	[.01-1.10]

***p<.001, **p<.01, *p<.05, [t] p<.10

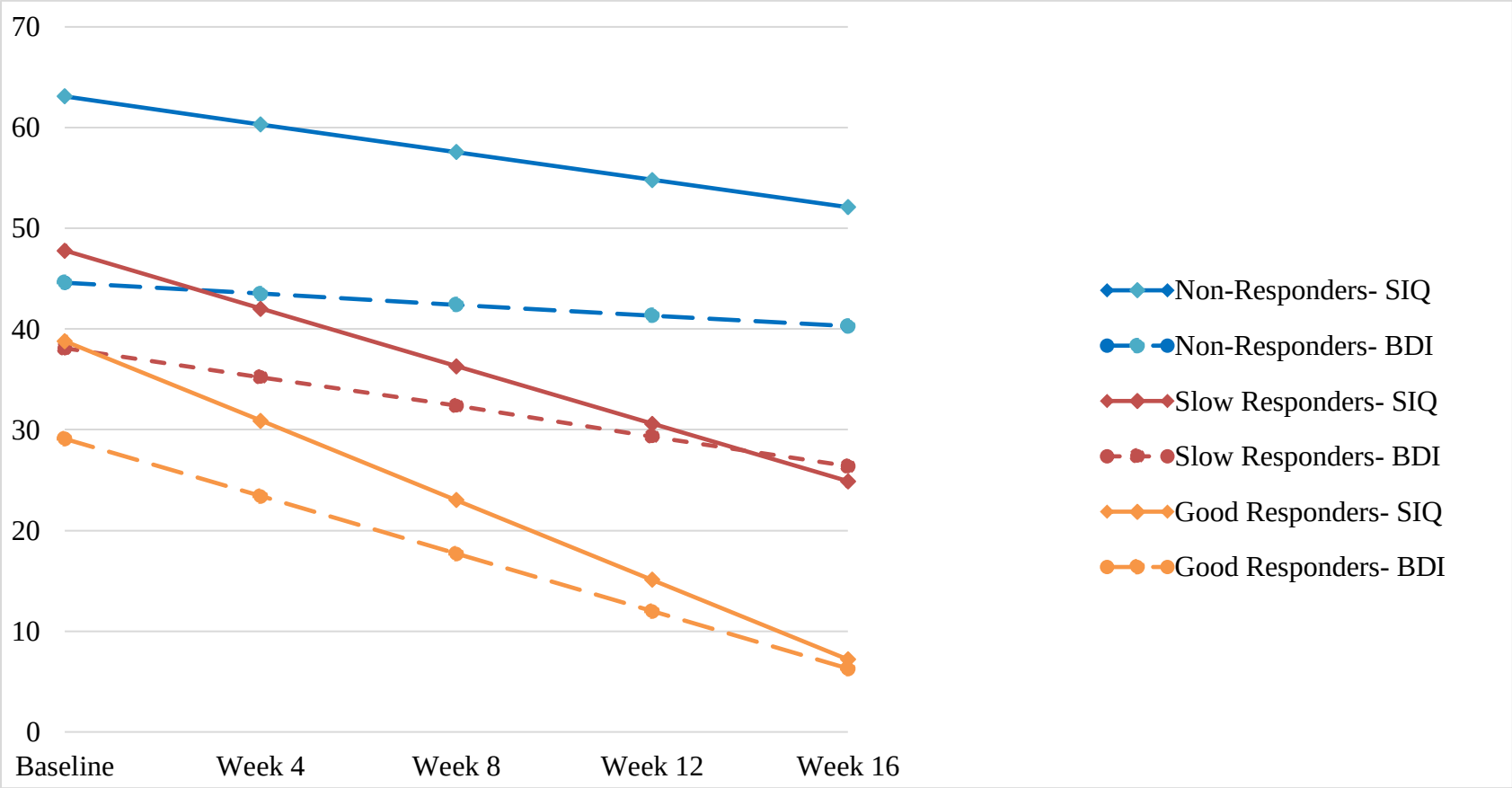

Figure 1. Growth Mixture Modeling for suicide ideation and depressive symptoms over the course of 16 weeks of treatment.

Chapter 4

DISCUSSION

Growth mixture modeling identified three distinct groups of adolescents' responses to 16-weeks of treatment: Non-Responders, Good Responders, and Slow Responders. The majority of adolescents were identified as Good Responders, a class characterized by significant reduction of depressive and suicidal symptoms and full remission by the end of treatment. However, the Non-Responders and Slow Responders, who did not demonstrate as much treatment benefit, encompassed a significant proportion of the adolescents. Adolescents in the Non-Responder group are of particular concern. These adolescents had the highest baseline levels of severity of suicidal ideation, higher levels of pessimism, and more NSSI behaviors compared to adolescents in the Slow Responder group. These adolescents also had higher rates of MDD diagnoses than adolescents who were in the Good Responders group.

In the current study, baseline levels of suicidal ideation predicted treatment non-response. Baseline symptom severity has been identified as one of the most robust predictors of poorer treatment response in samples of clinically depressed adolescents (Asarnow et al., 2009; Brent et al., 1998; Birmaher et al., 2000; Curry et al., 2006). However, this is the first study, to our knowledge, to extend on this research by examining this relationship as a function of trajectories of symptomatology in treatments specifically targeting suicidality. Our results also showed that a history of NSSI also predicted non-response to treatment in the current sample. Similarly, this

aligns with existing literature on non-response to SSRIs in treatment resistant depression (Asarnow et al., 2009), yet is a novel addition to the literature on suicide specific treatments. NSSI is likely an indication of severity of depressive and suicidal symptoms. However, it predicted non-response above and beyond baseline SIQ scores, indicating that NSSI is a unique contributing risk factor. NSSI has been conceptualized as a maladaptive coping mechanism used to relieve distressing negative emotions that not only causes bodily harm and danger, but has been theorized to be part of a habituation process to pain that can lead to increased capacity for suicidal behavior (Joiner, 2005). Additionally, NSSI can be a barrier to therapeutic alliance (Peterson, Freedenthal, Sheldon, & Andersen, 2008) and can be addictive in nature (Nixon, Cloutier, & Aggarwal, 2002), which can both interfere with the adolescent's ability to benefit from treatment and replace maladaptive coping mechanisms with adaptive strategies.

Feelings of hopelessness and pessimism were also identified as a predictor of poor treatment response, consistent with findings in the adult and adolescent literatures across treatment modalities and psychopathologies. It is likely that adolescents who are generally pessimistic about the future are more severely depressed and suicidal and may be pessimistic about treatment as well. Hopelessness may be particularly salient for adolescents who have less control over their participation in therapy, may not have sought therapy on their own, and, as a result, may not be as engaged or hopeful for remarkable change in their functioning. Taken together, the current study found that symptom severity, NSSI, and hopelessness each

uniquely predicted treatment non-response. This supports past research on treating depressed adolescents and builds upon it by extending the relationships to suicidal adolescents in treatment specifically targeting suicidality, whether ABFT or FE-NST.

In addition to predicting Non-Response, results from this study also differentiated Slow from Good treatment response. Slow Responders reported higher baseline levels of perceived burdensomeness and were more likely to have a diagnosis of MDD. There is robust support of the relationship between perceived burdensomeness and suicide ideation in the existing suicide literature, yet we believe this is the first study that has identified burdensomeness as a predictor of differential treatment response (Ma, Batterham, Calear, & Han, 2016). In the current study, perceived burdensomeness distinguished Good Responders from Slow Responders, but it did not predict treatment non-response. One possible explanation of this somewhat surprising findings could be that perceived burdensomeness may interfere with an adolescent's ability to gain support from parents, which could explain its prediction of slower treatment response. However, burdensomeness could also be a targetable factor that could act as a mechanism of change in treatments focused on building secure adult-adolescent relationships, such as ABFT and FE-NST. This could be one possible explanation for why such a potent risk factor predicted slow versus good response but not non-response. Further research is needed on the ITS measures and their possible utility as mechanisms of change in suicidal adolescents. Adolescents who entered treatment with a diagnosis of MDD were around 8 and 11 times more likely to be in the Slow and Non-Responder groups, respectively, than in

the Good Responder group. Again, this finding aligns with previous symptom severity research and is not surprising given that these treatments (ABFT and FE-NST) did not target depressive symptoms specifically. Therefore, these results suggest that these treatments may not be sufficient for suicidal adolescents who meet full criteria for MDD at the initiation of treatment.

One prominent debate in the psychotherapy literature is the definition and operationalization of treatment response and outcome; this distinction is especially unclear in treatment research of suicidal adolescents. Many different methods have been used to identify dichotomous outcome variables, including the reliable change index, clinical cut-offs, diagnostic thresholds, and other dichotomous variables (i.e. suicidal behavior- present or absent). One strength of GMM is that groups are identified by profiles of trajectories over time that account for intercepts and slopes, rather than cutoffs or change indices that only use pre-post or just post data. GMM's use of multiple time points accounts for the inherent correlation between repeated measures. Another strength of GMM is its ability to account for missing data. If a participant did not complete treatment, GMM can predict a trajectory using multiple time points and include this individual in the analyses, unlike methods using cutoff or change scores. For example, in our study, we were only able to calculate RCI/cutoff scores for 108 adolescents (versus classifying all 120 in GMM).

Limitations

Although GMM was a useful method of identifying treatment non-response in this study, it is not without its limitations. For instance, some reliable change was

evidenced within the Non-Responders group. Similar to other studies of treatment non-response, the threshold for which we categorize participants is not as clear as we would like. However, we believe the classification of the Non-Responder group is justified based on its significantly flat slope and that this class had an average SIQ score of 52.1 and BDI score of 40.3 at the end of treatment. Therefore, even though a substantial proportion of adolescents in the Non-Responders group showed clinically significant change, they remained, on average, clinically elevated for both depressive and suicide ideation symptoms at the end of treatment. One large trade-off of GMM is its exploratory nature. While this methodology allows us to identify distinct classes based on observed variables in our data, it can limit the study's generalizability to other samples. In other words, it remains unclear if similar trajectories of symptoms and classes would emerge in a different sample.

Another important limitation of this study is sample size. Because GMM separates participants into categories, sample size may have limited our findings. It is possible, if not likely, that more than 3 distinct classes would emerge in a class analysis of a much larger sample. In the current study, both the Non-Responders and Slow Responders classes had relatively small cell sizes (n = 19 and n = 32, respectively). Consequently, we are limited by low statistical power to detect significant effects in our multinomial logistic regression analyses. For example, it is likely that small cell size explains why we did not detect a significant difference between the BDI slope for the Non-Responders and Slow Responders even though the Non-Responders' slope was not significantly different from zero and the Slow

Responders' was. Lastly, it is possible that one or more classes would be best represented by a non-linear trend (Hayes, Laurenceau, Feldman, Strauss, & Cardaciotto, 2007). However, the relatively small sample size limits the number of parameters we can adequately test in GMM.

Future Directions

The use of GMM to analyze future clinical trial data has implications for useful and adaptive clinical decision making (Lei, Nahum-Shani, Lynch, Oslin, & Murphy, 2012). Our findings are the first to employ GMM to differentiate trajectories of treatment response to ABFT and FE-NST. It is important to note that class membership was not related to treatment condition. Future research in this area should explore interactions between treatment modality and risk factors on treatment response. Additionally, our findings did not replicate any of the established relationships between family functioning and treatment response. It is possible baseline self-reports of conflict may play a different role in response to treatments like ABFT and FE-NST, which aim to improve the parent-child relationship (either through direct intervention in ABFT or psychoeducation in FE-NST). In general, more research is needed to identify the mechanisms of change employed by these efficacious treatments for suicidal and depressed adolescents. Another area of possible future research is the maintenance of treatment gains or non-response over longer periods of time post-treatment. An interesting continuation of this study would be to identify classes of piece-wise analyses to explore if there are patterns in how adolescents respond during treatment and throughout follow-up.

Conclusions

The results from the present study identified three trajectory classes of depressive and suicidal symptom course across 16-weeks of treatment in a clinical sample of adolescents. First, findings suggest that first, heterogeneous trajectories can be identified by distinct classes. To our knowledge, this study is the first to identify probabilities of differential trajectories of symptomatology in treatments specifically targeting suicidality in a clinical sample of adolescents. Second, known risk factors for suicide and depression can be used to predict class membership and therefore likelihood of treatment response. In line with research on treatment of adolescent depression, symptom severity, NSSI, and hopelessness predicted also non-response. Additionally, this is the first study to our knowledge to identify predictive validity of thwarted belongingness on response to treatment in suicidal adolescents. Researchers and clinicians should be aware of possible heterogeneous symptom trajectories, especially treatment non-response, and continue to explore variables that predict differential response to the growing number of evidence-based treatments. Future research is needed to continue to inform clinical work and treatment decision-making in terms of choosing the treatment with the highest probability of benefitting a given adolescent client.

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Appendix

IRB APPROVAL LETTER

RESEARCH OFFICE

210 Hullihen Hall
University of Delaware
Newark, Delaware 19716-1551
Ph: 302/831-2136
Fax: 302/831-2828

DATE:	May 12, 2017
TO:	Roger Kobak, Ph.D.
FROM:	University of Delaware IRB
STUDY TITLE:	[261940-7] Attachment Based Family Therapy for Suicidal Adolescents
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	May 12, 2017
EXPIRATION DATE:	May 5, 2018
REVIEW TYPE:	Administrative Review
REVIEW CATEGORY:	Administrative Review

Thank you for your submission of Continuing Review/Progress Report materials for this research study. The University of Delaware IRB (HUMANS) has APPROVED your submission. This approval is based on an appropriate risk/benefit ratio and a study design wherein the risks have been minimized. All research must be conducted in accordance with this approved submission.

This submission has received Administrative Review based on the applicable federal regulation.

Please remember that informed consent is a process beginning with a description of the study and insurance of participant understanding followed by a signed consent form. Informed consent must continue throughout the study via a dialogue between the researcher and research participant. Federal regulations require each participant receive a copy of the signed consent document.

Please note that any revision to previously approved materials must be approved by this office prior to initiation. Please use the appropriate revision forms for this procedure.

All SERIOUS and UNEXPECTED adverse events must be reported to this office. Please use the appropriate adverse event forms for this procedure. All sponsor reporting requirements should also be followed.

Please report all NON-COMPLIANCE issues or COMPLAINTS regarding this study to this office.

Please note that all research records must be retained for a minimum of three years.

Based on the risks, this project requires Continuing Review by this office on an annual basis. Please use the appropriate renewal forms for this procedure.

If you have any questions, please contact Nicole Farnese-McFarlane at (302) 831-1119 or nicolefm@udel.edu. Please include your study title and reference number in all correspondence with this office.