THE ROLE OF ADHERENCE ON HEALTH OUTCOMES IN PEDIATRIC CHRONIC CONDITIONS: A META-ANALYSIS

BY

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Abstract

Increased adherence to medical regimens has been suggested to lead to improved health outcomes. It is unknown what level of adherence is necessary to achieve improved health in different pediatric chronic conditions. In this study, a meta-analysis was carried out to explore the relationship between adherence and health outcomes across pediatric chronic conditions. Twenty-six studies utilizing correlational data were included in the meta-analysis. Results indicated a relationship between adherence and health outcomes, in that lower levels of adherence are related to negative health outcomes (overall effect size d=-0.47). There was significant heterogeneity across studies in the meta-analysis (Q=465.82) and all potential moderators demonstrated significant heterogeneity (i.e. disease, health outcome measurement, and adherence measurement method). The meta-analysis did not determine cut-points for specific pediatric chronic conditions and this should be an area of future research as it could assist physicians in more effective treatment planning. The use of intervention studies is encouraged as these provide a more powerful demonstration of the relationship between adherence and health outcomes.

Keywords: medication adherence, health outcome, pediatric

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Introduction

Adherence: Definition and Importance

The term adherence has been defined consistently in the literature over the past 30 years as: "the extent to which a person's behavior (in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice" (Haynes, 1979, pp. 1-2). The term adherence is preferred to "compliance" because it suggests a more active role for patients in making a choice to follow their treatment regimen (Lutfey & Wishner, 1999).

The improvement of adherence to pediatric treatment regimens is important because it is a major public health concern (La Greca & Mackey, 2009). Nonadherence is common with around 50% of those with regimens for chronic diseases failing to adhere (Rapoff, 2010). Nonadherence can also be an important factor in high rates of unnecessary health care utilization (McGrady & Hommel, 2013; Peicoro, Potoski, Talbert, & Doherty, 2001). The annual health care costs due to nonadherence may be as high as $300 billion per year in the United States (DiMatteo, 2004). Pediatric nonadherence will likely continue to be a health concern as more complex treatments are developed in the future (La Greca & Mackey, 2009). As medical treatments become more complex and the prevalence of chronic conditions increases, the assessment and treatment of adherence becomes more important to improving health outcomes (Quittner, Lemanek, levers-Landis, & Rapoff, 2008).

Nonadherence and Health Outcomes

There is the potential for poor health outcomes due to a lack of adherence (Rapoff, 2010). Nonadherence may contribute to increased disease activity, complications, unnecessary health care utilization, and limitations in quality of life for patients and their families (Drotar, 2000). Nonadherence has been linked to more emergency department visits and hospitalizations due to

children and adolescents experiencing exacerbations and complications requiring medical attention (McGrady & Hommel, 2013).

Nonadherence in HIV disease may result in viral rebound, subsequent reduction in HIV treatment options, development of genotypically resistant mutations, and diminished treatment efficacy (Malee et al., 2009). Higher active joints for children with juvenile idiopathic arthritis has been linked to lower adherence to anti-inflammatory medications (Feldman et al., 2007). Heart, kidney, and liver transplant failures are correlated with incomplete adherence to immunosuppressive drugs (Rapoff, 2010). Adherence has also been shown to decrease in adolescence as the responsibility for following treatment regimens falls to the patient (Bucks et al., 2009). In order to document the relationship between adherence and health outcomes, reliable and valid methods of assessing adherence are needed.

Assessing Adherence

The assessment of adherence is more complex in a pediatric population compared to adults mainly because of parental involvement. There are several methods to assessing adherence and the choice of assessment methods will often depend on the specific medical regimen of the patient (Rapoff, 2010). These can include pill counts, assays, observations, electronic monitors, parent report, child report, and provider estimates (Quittner, Espelage, Ievers-Landis, & Drotar, 2000). All of these strategies have strengths and limitations that are important to consider when assessing adherence. Since there are limitations to all strategies, it is recommended to use multiple methods of adherence assessment along with multiple informants (Hilker, Jordan, Jensen, Elkin, & Iyer, 2006; Quittner et al., 2000).

Pill Counts. Pill counts have long been used in the assessment of adherence and are a straightforward assessment (Rapoff, 2010). The number of pill counts in a day will depend both

on the patient and the dosage. Specific medication is also a factor since medications can be pills, liquids, or involve inhalation of medicine. Strengths of pill counts are that they are relatively feasible. Pill counts have often been used in the assessment of adherence making comparison across studies simpler (Rapoff, 2010). A limitation of pill counts is that they can often lead to an overestimate of adherence because they cannot confirm ingestion. Another limitation is that they provide little information about drug administration, including overdosing, underdosing, and the timing of dosing. Due to the evidence that pill counts overestimate adherence, it is recommended that another method be used along with pill counts. (Bond & Hussar, 1991).

Drug Assays. Laboratory assays can provide measurements of drug levels in bodily fluids such as urine, saliva, and serum (Roth, 1987). There are several strengths of assays when assessing adherence, one being that they are quantifiable and clinically useful. One of the most important strengths is that assays confirm that medications have been ingested (Rapoff, 2010). There are serious limitations to assays. They measure adherence over short time intervals. They can also be expensive and invasive making them less feasible in pediatric populations. Finally, pharmacokinetic variations depending on the drug's absorption, how it is metabolized, and excreted can account for drug levels that may or may not reflect adherence (Rapoff, 2010).

Observations. Observational measures, typically in the form of behavior checklists, have been used to measure adherence, however, direct observation of patient adherence is rare (Rapoff & Barnard, 1991). A strength of observational measures is that they are automatically valid in that they measure what they intend to measure (Johnston & Pennypacker, 1993). Further strengths of observational measures are that they avoid subjective judgments that may be seen in patient, parent, or provider ratings of adherence and they assess other important dimensions of adherence (i.e. frequency, duration, interresponse time) (Rapoff, 2010). The major limitation

with observational measures is accessibility. Clinicians and researchers do not have the access to measure a patient's behavior in a consistent manner. A general limitation with observational methods across all research is the possibility of reactivity where patients behave in ways that are not typical when they are being observed (Rapoff, 2010).

Electronic Monitors. Electronic monitors are being called the new "gold standard" by some for measuring adherence (Cramer, 1995). Electronic monitors have the capability to record and store the date and time of when certain medications have been removed from their respective containers. This information can be stored for several months and downloaded into data files for analysis (Rapoff, 2010) . Strengths of electronic monitors are that they provide a long-term measurement of adherence in real-time, they can reveal several adherence problems (i.e. underdosing, overdosing, delayed dosing), and they can help identify drug reactions. The main limitation of electronic monitors is that they do not confirm ingestion and may overestimate actual adherence (Rapoff, 2010). Consequently, a medication event denotes a presumptive dose (Burke, 2001). Another limitation of electronic monitors is that being a mechanical device, they are capable of breaking down or malfunctioning (Rapoff, 2010). Although the costs of electronic monitors has decreased since their introduction, their costs are generally too high for clinical use (Modi & Quittner, 2006a).

Patient/Parental Report. Patient and/or family reports are the most common method for assessing adherence (Quittner et al., 2008) and include several formats such as global ratings, structured interviews and questionnaires, and daily diaries (Rapoff, 2010). Global ratings ask patients or parents to report adherence over unspecified or varying time intervals. There has been considerable advancement in the development of structured interviews and questionnaires for assessing adherence. Self-report measures, often with both patient and parent versions, have

been developed for assessing adherence for asthma, cystic fibrosis, diabetes, HIV, spina bifida, and transplantation (Rapoff, 2010). Daily diaries involve the patient or parent recording specific adherence behaviors over varying lengths of time either through standard written forms, via phone interviews, or online websites (Rapoff, 2010). Diary methods provide important information about the processes by which behaviors unfold, thus making it possible to identify reasons underlying poor adherence (Modi et al., 2006). A strength of patient and/or parent reports is that they are generally simple, convenient, inexpensive, and clinically feasible (Bond & Hussar, 1991). Additional strengths are that they provide detailed information of a patient's adherence patterns and are less labor-intensive for patients and families (Rapoff, 2010). There are several limitations to patient and parent reports. The most notable is that these tend to overestimate adherence by minimizing doses that have been missed (Quittner et al., 2008). These self-report measures are also prone to issues with accurate recall (Rudd, 1993), and they are difficult to use with younger children (Quittner et al., 2008).

Provider Estimates. Provider estimates involve physicians and/or nurses making global ratings of the degree to which their patients are adherent to a medical regimen. A strength of provider estimates is that they are fast, simple, and inexpensive (Rapoff, 2010). There is also some evidence that provider estimates do better at assessing adherence compared to global estimates obtained from the patient or family (Rapoff & Chrisophersen, 1982). A limitation of provider estimates is that they are generally not as accurate as other measures, such as assays (Rudd, 1993). Another limitation is that providers are inaccurate in a specific way; they are generally good at identifying adherent patients, but not at identifying nonadherent patients (Rapoff, 2010). A further limitation involves the general inaccuracy of clinical judgments,

which are often biased and may be inferior to actuarial or statistical methods (Dawes, Faust, & Meehl, 1989).

Assessing Health Outcomes

The initial diagnosis of a disease involves the monitoring of certain health-status parameters, and once the diagnosis is made, these parameters continue to be monitored to track a patient's health status (see Table 1). Clinical signs and symptoms and laboratory and diagnostic studies are typical medical outcomes (Rapoff, 2010).

The assessment of health outcomes will vary depending on the illness. In asthma management, physicians monitor frequency of asthma symptoms, frequency of nocturnal awakenings, level of lung function, and the use of quick-relief medications. Another important component to assess is the probability of asthma exacerbations (Martinez, 2009). Disease monitoring for pediatric patients with HIV infection may vary depending on the progression of the illness. Regular measurement of plasma HIV RNA levels and $CD4^+$ T-cell counts are conducted to determine the risk of disease progression and when to start or adjust antiretroviral treatments (Working Group on Antiretroviral Therapy and Medical Management of Infants, 1998).

Cystic fibrosis (CF) affects multiple systems (i.e. respiratory, digestive, endocrine, reproductive) and presents a complex treatment regimen (Barker, Driscoll, Modi, Light, & Quittner, 2012). Daily treatments involve the use of aerosol medication, airway clearance, pancreatic enzyme supplements (Modi & Quittner, 2006b) along with making lifestyle alterations such as caloric increases and monitoring pulmonary exacerbations (Barker et al., 2012).

Sickle cell disease (SCD) requires specific physical, laboratory and other evaluations to monitor children with the disease. The typical routine clinical laboratory evaluations include CBC with WBC differential, reticulocyte count, percent Hb F, renal function, hepatobiliary function, and pulmonary function. These evaluations vary depending on age and necessary frequency. It is also important to evaluate growth and development in children with SCD along with optimizing nutrition. Other recommended health behaviors include avoiding strenuous exercise, avoiding extreme temperatures, maintaining adequate hydration, and getting enough rest (National Heart, Lung, & Blood Institute, 2002).

Diabetes type 1 treatment requires setting realistic and individualized goals for each child or adolescent (Jain, 2013). Jain (2013) discusses five goals of contemporary diabetes management in children. These involve preventing diabetic ketoacidosis and severe hypoglycemia, establishing realistic glycemic targets and regimens adapted for a child's specific circumstances, maintaining near-normal blood glucose and hemoglobin A1c levels, maintaining a reasonable quality of life, and accomplishing normal growth, development and psychological maturation (Jain, 2013).

Juvenile arthritis (JA) has several outcome measures currently in use (Giannini et al., 1997). Traditional outcome measures utilized include physician assessment of disease severity, pain, and the number of involved joints (Brunner et al., 2004). Although these are important, Brunner et al. (2004) describe the importance of health-related quality of life measures in JA because traditional outcome measures do not capture the child's overall sense of well-being.

Cancer is the leading cause of disease-related death in children and adolescents (Levine et al., 2013). This diagnosis not only presents challenging treatment, but also several sources of stress for children and their parents (Kupst & Bingen, 2006). Quality of life in children and

adolescents with cancer has been recognized as an important outcome indicator in clinical trials (Hinds et al., 2004). Treatment and management in pediatric cancer will vary dependent on several factors (i.e. tumor location, affected organs, stage of cancer). Management will also depend on if the individual is in treatment or in remission.

The above-discussed chronic illnesses are not the only conditions that will be included in this study. These are the more common diagnoses in pediatrics and are discussed to demonstrate the vast differences in treatment and monitoring of childhood chronic conditions.

Quality of Life Measures

Quality of life (QOL) is described as "the individual's perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (Schipper, Clinch, & Olweny, 1996). QOL measures can provide value in several areas of research such as comparing outcomes in clinical trials, evaluation of interventions, and assessing the outcomes of new treatments (Eiser & Morse, 2001a). Parent respondents are often utilized to assess a child's QOL, however, children and parents may not have the same views on the impact of illness (Eiser & Kopel, 1997). Due to this, measures have been developed to assess QOL with children who have a chronic illness (Eiser & Morse, 2001b).

Health-related quality of life (HRQOL) allows patients and their families to identify how chronic illness personally affects their lives (Johnson, 1994). HRQOL measures are becoming more appreciated by medical providers because they aide in identifying not only the physical, but also the psychosocial consequences of chronic illness (Rapoff, 2010). HRQOL is considered to be a multidimensional construct that includes at least four core domains: (1) physical symptoms, (2) functional status, (3) psychological functioning, and (4) social functioning (Palermo et al.,

2008). HRQOL measures for children and adolescents are becoming more prevalent (C. Eiser & Morse, 2001b).

There are both "well-established" generic HRQOL measures as well as disease-specific HRQOL measures for children and adolescents (Palermo et al., 2008). A commonly used HRQOL measure used in medical settings is the Pediatric Quality of Life Inventory (PedsQL) (Varni, Seid, & Rode, 1999). The PedsQL is a generic measure of HRQOL making it possible to compare children with chronic illness to healthy children (Rapoff, 2010). Other generic HRQOL measures include the Youth Quality of Life (Patrick, Edwards, & Topolski, 2002), the Child Health Questionnaire (CHQ; (Landgraf, Abetz, & Ware, 1996), and the Child Health and Illness Profile (CHIP; (Starfield, Riley, & Green, 1999). Disease-specific HRQOL measures allow insight into illness-specific difficulties and may have greater clinical relevance for patients (Palermo et al., 2008).

Current Study

A meta-analysis reviewing the efficacy of adherence interventions suggested that adherence interventions not only increase adherence, but also lead to improved health outcomes (Graves, Roberts, Rapoff, & Boyer, 2010). However, it is unknown to what level of adherence is necessary for there to be improvement in a patient's health. The degree of adherence required for positive outcomes most likely varies from one regimen to another (Sackett & Snow, 1979). Gordis (1979) reported that children taking as little as 30% of their prescribed prophylactic penicillin would experience considerable safety from recurrences of rheumatic fever. However, individuals with hypertension need to take at least 80% of their medications to exhibit systematic decreases in their blood pressure (Sackett & Snow, 1979). Highly active antiretroviral therapy

(HAART) requires strict adherence for long-term effectiveness and is suggested that 90-95% is the minimum standard for complete viral suppression in individuals with AIDS (Wagner, 2003).

Sackett and Snow (1979) suggested that the relationship between adherence levels and the achievement of the treatment goals should be described when reporting on an adherence study. Yet, this is rarely done. Researchers report average adherence rates to specific medical regimens, but these rates are not considered the necessary level to generate positive health outcomes. The literature currently focuses on how adherent patients are to medical regimens, but not what that adherence means in relation to health outcomes (i.e. was the patient adherent enough?).

Knowledge of adherence levels could also be helpful to inform physicians about the effectiveness of the medical regimen. Rapoff (2013) assembled the table below to illustrate important considerations regarding the relationship between health outcomes and adherence.

Health/Disease/Quality of Life Outcomes

Adherence	GOOD	POOR
GOOD	Best possible outcome. Patient is sufficiently adherent to achieve favorable outcomes with minimal or no negative side effects of treatment. Action: Continue to encourage good adherence.	Patient is sufficiently adherent but the treatment is not effective or is not potent enough. Action: Change treatment or add additional elements.
POOR	Patient is nonadherent but has good outcomes because of spontaneous remission, they are adherent enough to achieve good outcomes, or other factors (outside of the prescribed treatment) are helping to obtain good outcomes. Action: Investigate what factors may be contributing to positive health outcomes.	Patient is nonadherent and has poor outcomes, presumably due to lack of adherence or some other factors (like the lack of efficacy of the prescribed treatment). Action: Addressing nonadherence should be a prime target to improve outcomes.

The scenarios under "poor health" are what are concerning for those in healthcare. It is essential for a physician to differentiate between lack of adherence and an ineffective treatment regimen. This is why it is important to not only assess adherence, but know to what extent adherence plays a role in the health outcomes of the patient. Having the knowledge of the necessary level of adherence for positive health outcomes in certain illnesses could provide a new way for physicians to evaluate the effectiveness of medical interventions as well as patient progress.

The current study involved a meta-analysis of the current literature on the relationship between adherence and health outcomes for children and adolescents with a chronic illness. In the hopes of building on the findings of Graves et al. (2010), this study focused on health outcomes and how those are moderated by patient adherence. Another study aim was to be able

to draw disease-specific conclusions related to both adherence levels and positive health outcomes.

Method

Literature Search

Computerized and manual methods were utilized to locate studies to be included in the meta-analysis. The comprehensive literature search involved both psychological and medical databases such as PsycINFO and PubMed. The search also incorporated psychology dissertations. The searches included all years in the databases up to August 2014. Each database was completed using a 2 x 7 x 3 search pattern similar to the Graves et al. (2010) meta-analysis. This involved the following key terms: "adherence" or "compliance" and "health outcome" or "health status" or "disease monitoring" or "disease management" "health care utilization" "pain ratings" or "quality of life" and "child" or "pediatric" or "adolescent." Should the keywords around an individual's health status not warrant many studies due to the generality of the words, disease-specific health outcomes will be applied to the search (i.e. pulmonary functioning for cystic fibrosis, blood glucose monitoring for diabetes).

Inclusion and Exclusion Criteria. Several criteria were used to determine if a study was included in the meta-analysis. To be included in the study, participants must be diagnosed with a chronic illness. The study must report on both adherence and some form of a health outcome. Both adherence outcomes and health outcomes must be measured quantitatively to allow determination of the statistical effect. Quality of life was also included as a health outcome. Lastly, the study participants had to be under the age of 21. Should studies include both children and adults, outcomes had to be reported separately for children to include the study.

Coding. The coding process involved two independent raters for the selected studies. Interrater reliability was calculated by having both raters code the first 30% of the selected studies. This was done first in the coding process to determine that the measure of agreement was at an appropriate level. Level of agreement needed to be at a minimum of 0.80, or 80% agreement. The raters coded all variables on a coding template (See Appendix).

Coded Variables. Each study included in the meta-analysis was coded for several methodological and sample characteristics. Adherence outcome measures were be coded into four different categories. These included direct measures (i.e. laboratory assays that identify medication levels), indirect measures (i.e. pill counts and electronic monitors), subjective measures (i.e. self-report measures, provider estimates, and diary methods), and pharmacy refill. Health outcome data were coded into six different categories. These included laboratory tests used to determine health status (i.e. disease-specific outcome measures mentioned under "assessing health outcomes" in the introduction), pain-related measures, quality of life measures (i.e. disease specific measures or generic health-related quality of life measures), health care utilization, disease activity, and mortality.

Methodological information was collected to gather additional relevant information that could affect study outcomes. Methodological variables that were coded included year of publication, the type of publication (i.e. journal article, dissertation), methodological design (i.e. single subject, randomized control trial, pre-post design), sample size, and comparison group (i.e. control group, alternative treatment). Demographic information collected included gender, age, ethnicity, and socioeconomic status (SES).

Analysis Strategy

Effect Size Estimates. This study included both studies with a comparison group (involving differences in means) as well as studies with one group (correlational data). Selected studies utilized different measures or scales. Due to this, the recommended effect size estimate involves dividing the mean difference in each study by that study's standard deviation. This creates an index that is comparable across studies, known as the standardized mean difference, or the *d* statistic (Borenstein, Hedges, Higgins, & Rothstein, 2009). For correlational studies, the correlation (*r*) was first converted to the Fisher's *z* scale, which will be utilized in all analyses. The effect size "*r*" represents both the direction and strength of the relationship between adherence and health outcomes. A negative *r* represents that poorer health is associated with poor adherence, while a positive *r* indicates that better adherence is associated with better health.

To convert to a common metric, the transformed values from correlational studies were converted to the standardized mean difference, or the *d* statistic (Borenstein et al., 2009). Cohen's d effect size values are generally interpreted as .2 for small, .5 for medium, and .8 for large effects (Cohen, 1988).

Due to the low number of studies meeting criteria that reported means and standard deviations, only correlational studies were included in the meta-analysis. Studies reporting means and standard deviations reported separate statistics and were thus ruled out of the larger analysis. Results from these studies were reported separately to demonstrate the relationship between adherence and health outcomes in a more qualitative manner.

Homogeneity Testing. To determine whether the effect sizes that are averaged into a mean value are estimating the same population effect size, the *Q* statistic was calculated (Lipsey & Wilson, 2001). The *Q* statistic is distributed as a chi-square with $k - 1$ degrees of freedom, where *k* is the number of effect sizes (Hedges & Olkin, 1985). Significant *Q* statistics indicate

heterogeneity in outcomes, which would be expected when averaging all ESs from the collected studies (Durlak, 2003). From here, possible moderator variables can be selected to group the studies into different categories. This was done in the hopes of yielding a nonsignificant *Q* (Durlak, 2003).

Results

Meta-Analysis of Correlational Studies

Interrater Reliability. Two independent raters were trained to code the required information from included articles. Interrater reliability was calculated by having both raters code the first 30% of studies included in the analysis. Kappa was calculated for categorical data to assess measure of agreement. Kappas ranged from 0.95 to 1.0, with a mean kappa of 0.99, which indicates a high level of rater agreement (Orwin, 1994).

Study Characteristics. A total of 26 articles and dissertations were included in the meta-analysis. A flowchart (Figure 1) of article selection is included in the appendix. Of the 26 included studies, 19 (73.1%) were published articles and seven (26.9%) were dissertations. All 26 studies reported correlational data. The majority of the studies involved a diagnosis of type-1 diabetes (73.1%). Other diagnoses included were three studies that involved a diagnosis of HIV/AIDS (11.5%), two with asthma (7.7%), and two with sickle cell disease (7.7%). The total N across all the included studies was 3925 (M=150, SD=231.4).

Demographic Characteristics. The mean age of individuals included in each study ranged from 5.2 to 17.1 years (M=12.5, SD=2.5). One study included individuals outside of the inclusion age range, however, the study reported outcomes by age ranges and only outcomes within the inclusion criteria age range were included in the analysis (Haberer et al., 2012). Twenty-four studies (92%) reported information about child gender. The percentage of males

ranged from 37% to 59.6% (*M*=50.4, *SD*=7.1) and the percentage of females ranged from 40% to 60% (*M*=49.6, *SD* = 7.1). Nineteen (73%) studies reported information regarding ethnicity of participants. Of these studies, the majority reported a predominantly Caucasian sample (74%) while the remaining 26% had a predominantly African American sample. The percentage of minority group participants ranged from 6% to 98.7%. Eleven (42%) studies reported quantifiable information related to SES, which was classified by predominant household income. Of these studies, five (45.5%) reported a predominant household income between $50,000 and $74,999. Other indices related to SES were reported by studies (i.e. parental education), however, these were not coded.

Methodological Characteristics. All 26 studies included in the meta-analysis utilized correlational data. Twenty-three of these studies were cross-sectional designs (88.5%). The other three studies were longitudinal designs.

Eleven of the included studies (42.3%) utilized multiple methods of assessing adherence. Of these 11 studies, nine (81.8%) assessed adherence through collecting child and parent report. Only one study utilized a method for assessing adherence outside of child, parent, and provider report. Twenty-one studies (80.8%) included a laboratory test to provide a health outcome measure (i.e. HbA1c, RNA viral load). Quality of life was assessed in eight (30.8%) of the included studies. Other methods of assessing a health outcome included hospitalizations, pain, and disease severity/activity.

Adherence and Health Outcomes. Across the 26 studies, a total of 53 effect sizes (i.e. study outcomes) were reported. The majority of the studies (61.5%) reported multiple outcomes on the relationship between adherence and health outcomes. The results of the meta-analysis are provided in Table 2. Across the 26 studies, the relationship between adherence and health

outcomes was significant ($P<0.001$) with a random effects test. Cohen's *d* across all studies was 0.47 indicating a small to medium effect (Cohen, 1988). However, there was a significant amount of heterogeneity in this analysis ($Q=465.82$). Due to this significant amount of heterogeneity, the data was divided into groups in an effort to find potential moderators.

Illness. Due to the studies including primarily children with a type-1 diabetes diagnosis, illness was divided into two sub groups for analyses: diabetes and other illnesses. The relationship between adherence and health outcomes was significant for both diabetes ($P<0.001$) and the other illnesses ($P<0.05$). Studies of diabetes yielded an effect in the medium range ($d=0.53$) and studies of other illnesses in the small to medium range ($d=0.21$). Both diabetes studies and other illness studies demonstrated significant amounts of heterogeneity ($Q=386.87$ and $Q=56.61$, respectively).

Health Measures. The studies were then divided by method of assessing health outcomes, which resulted in three groups for analyses: studies utilizing QOL measures, lab tests, and all other measures. The relationship between adherence and health was significant with the use of a lab test ($P<0.001$). This analysis still yielded a medium effect ($d=0.70$) and a significant amount of heterogeneity ($Q=73.37$). Studies utilizing QOL measures or another measure of health other than a direct lab test did not demonstrate a significant relationship.

Adherence Measures. The studies were also divided by method of assessing adherence, which were resulted in three groups for analyses: studies utilizing self-report, parent report, and all other adherence measures. The relationship between adherence and health was significant with the use of self-report adherence measures ($P<0.001$) and parent-report measures ($P<0.05$). The use of self-report and parent-report both yielded effects within the medium range ($d=0.51$ and $d=0.40$, respectively), however, both analyses also demonstrated a significant amount of

heterogeneity (Q=188.93 and Q=235.80, respectively). Other methods for assessing adherence, when grouped together, did not yield a significant relationship between adherence and health.

Summary of Non-Correlational Studies

Study Characteristics. Ten additional studies met inclusion criteria; however, the statistics provided did not lend themselves to be included in the meta-analysis (see Table 3). The studies do provide additional information related to the relationship between adherence and health, and thus results will be discussed in a qualitative nature with effect sizes reported for each study separately. Of the 10 studies, five were randomized controlled trials (RCTs), four were intervention studies without a control group, and one was a longitudinal study. Of the ten studies, eight were specifically targeting changes in adherence or disease management but measured both. Five of the studies included a sample of children with diabetes, three studies included children with asthma, one study included children with end-stage renal disease (ESRD), and one study with a sample of children with arthritis.

Adherence and Health Outcomes. Results from these 10 studies were mixed. Of the five RCT studies, only one reported a within study effect in the medium effect size range (Ellis et al., 2005) while all other effect sizes ranged from no effect to small effects. Ellis and colleagues (2005) utilized multisystemic therapy to improve adherence in adolescents with diabetes and found significant changes in HbA1c (d=0.64). They did not find significant changes in insulin adherence, however, significant increases in frequency of blood glucose testing was observed in this sample (Ellis et al., 2005). Glaser et al. (2004) observed the effects of an insulin dosage calculation device (IDC) on health and adherence in a sample of adolescents with diabetes. Significant group differences were observed for adherence (d=0.17), but not for either health measure (d_{HbA1c}=0.00, d_{QOL}=0.12). Jan and colleagues (2007) implemented an internet-based

interactive telemonitoring system to improve outcomes in children with asthma. Jan et al. (2007) observed decreases in adherence, however, the treatment group was statistically higher in adherence compared to the control group at study completion and there was not a significant change in peak expiratory flow (PEF; d=0.14). In a study utilizing regular standardized telephone contact for adolescents with diabetes, authors reported significant differences between the treatment group and control group regarding QOL (d=0.20) at study completion (Lawson et al., 2005). They observed differences between treatment regarding adherence (d=0.35), however this was not a significant difference. There was also no significant change in HbA1c (d=0.14; Lawson et al., 2005). Wysocki and colleagues (2000) carried out a trial of behavior therapy for adolescent with diabetes and their families. This study did not demonstrate significant differences between treatment and control groups on adherence (d_{recall}=0.21, $d_{\text{self-report}}$=0.28) or HbA1c (d=0.20).

The remaining five studies reported changes in one or both domains of adherence and health over time. Two of the studies demonstrated improvements in both adherence and health outcomes. Smith and colleagues (1994) reported significant changes in self-reported adherence (p=0.001) and peak expiratory flow (PEF; p=0.05) in a sample of children with asthma. Stranger and colleagues (2013) found significant changes in a sample of children with diabetes for both adolescent reported (p=0.04) and parent reported (p<0.001) adherence as well as a significant change in HbA1c (p<0.001). . Hashim et al. (2013) reported statistically significant change in adherence (p<0.001) and showed a trend in QOL improvement (p=0.13); however this was not statistically significant. In a study of adolescents with asthma, Riekert and colleagues (2011) demonstrated significant changes in caregiver reports of adherence, but not adolescent report. This study also demonstrated a statistically significant improvement of QOL over time, but not

in asthma symptom reports (i.e. symptom free days). In the one longitudinal study on adherence and health in children with JIA, authors reported that moderate adherence to medication was related to lower active joint count (Feldman et al., 2007).

Discussion

The meta-analysis described here demonstrated that there is a relationship between adherence and health outcomes, in that lower levels of adherence are related to negative health outcomes (overall effect size d=0.47). This outcome is consistent with the meta-analysis of a*d*herence studies carried out by Graves et al. (2010). They reported a significant effect for health outcomes in both group designs (d=0.40) and single-subject designs (d=0.74) following an adherence intervention. However, the research utilized in the current meta-analysis did not provide information regarding the optimal level of adherence needed to affect positive health outcomes across diseases and regimens. Thus, one of the two study questions was not answered through this meta-analysis.

There was significant heterogeneity across studies included in the meta-analysis as demonstrated by a significant Q for all included studies (Q=465.82). Studies were divided into groups based on possible moderators (i.e. disease, health outcome measurement, and adherence measurement method), and all potential moderators demonstrated significant heterogeneity. Due to the low number of studies included in the meta-analyses as well as little variability in demographics, there were no other moderators in high enough quantity across studies for further homogeneity testing.

The support for the relationship between adherence and health outcomes is an important one. This is an assumption by most that the more adherent one is to a medical regimen, the more likely that health will improve. However, physician method of analyzing adherence heavily relies

on self-report methods, which are known to overestimate adherence (Rapoff, 2010). Even though electronic monitors are considered the "gold standard" for assessing adherence, the cost likely affects the utility of their use within a clinical setting (Riekert & Rand, 2002).

Quality of Life (QOL) has become a popular method for assessing self-perceived health status. The meta-analysis results demonstrated that higher levels of adherence are not significantly related to higher reports of QOL. This has a few possible interpretations. One possibility is that higher adherence may be taxing on children, and thus affecting QOL outcomes in a negative direction. This is plausible as certain medical interventions are uncomfortable and painful. Most of the studies utilized in this analysis involved children with diabetes, which often involves following a complex medical regimen including daily injections of insulin. A second interpretation could be that self-perceptions of health may differ from more "technical" assessments of health (i.e. blood tests). Another study considered coping strategies to be a strong predictor of HRQOL (Petersen et al., 2006), however coping strategies were not required for inclusion in this study thus leaving out a possible important variable related to QOL. There is considerable debate as to the best way to define health, and because of this, there are likely several interpretations of how individuals perceive their personal health status. It is also possible that a significant relationship was not found between adherence and quality of life due to the low number of studies within this analysis.

It is an interesting consideration as to whether quality of life should be used as an outcome measure in adherence studies. On one hand, it makes sense because for certain chronic illnesses, quality of life is a better measurement of overall health because there is no laboratory or blood tests to measure health. Alternatively, health outcomes that can be more readily

assessed via laboratory tests (i.e. diabetes and HIV) are directly related to important health measures such as blood glucose levels and viral load.

Intervention studies provide a more powerful demonstration of the relationship between adherence and health outcomes. Due to the low number of intervention studies included and the different approaches in each study design, it is difficult to draw overall conclusions from these studies. However, across these studies, it was demonstrated that interventions targeting adherence are beneficial in improving adherence. This is consistent with previous findings (Graves et al., 2010). Changes in corresponding health outcomes were demonstrated in certain studies, but not across all intervention studies. This relationship warrants further investigation to understand the association between adherence and health outcomes, as well as what level of adherence across chronic illnesses and medical regimens is necessary to achieve positive health outcomes.

Limitations

There are several limitations to note from this study. First, all studies included in the meta-analysis utilized correlational data. The use of correlational data lends to possible limitations in the interpretation and meaning of the data. One should proceed with caution when drawing causal inferences from correlational data (DiMatteo et al., 2007). Also, a meta-analysis may not be appropriate when utilizing a small number of studies (Field, 2001).

Second, the majority of the studies reported cross-sectional data and only three studies utilized data at multiple time points. It is difficult to draw strong conclusions from a single time point, especially when assessing an individual's health. The outcomes of this study do not provide information regarding adherence, health, or the relationship between the two over time.

The lack of intervention studies in the analysis is a limitation. Not utilizing the RCTs and other longitudinal studies in the analysis presents a limitation. Specifically not including the intervention studies takes out some important data. These studies show a strong relationship between the two variables of interest due to observing what happens when one variable is manipulated. These studies also utilized different types of interventions. Not all interventions were targeted at improving adherence. Outcomes may have varied had all studies focused on adherence, specifically medication adherence.

Search criteria may have been too broad. The initial search yielded almost 5,000 studies, and yet only 36 met the study criteria. Several studies were excluded due to not assessing medication adherence specifically. Several treatment regimens involved non-medication treatments, such as dietary restrictions or exercise, which are often important aspects of treatment regimens and high adherence to these recommendations likely contribute to positive health outcomes along with medication adherence.

Future Research

Adherence methods outside of self-report and parent report (i.e. electronic monitors, diary methods) are not being utilized outside of intervention research. There could be a number of reasons for this, such as finances and accessibility (Rapoff, 2010). However, without more direct measures of adherence, we rely on self-report of patients and their caregivers which often overestimates adherence (Rapoff, 2010). Implementing more direct adherence measures in clinical practice may be challenging due to time constraints of physician consultations. However, physicians need to accurately evaluate adherence because it can inform them as to the effectiveness of the treatment regimen.

Intervention studies targeting adherence were ruled out of this study due to not assessing a health outcome along with assessing change in adherence. Studies should incorporate some measure of health, be that QOL or a more direct measure at not only baseline, but also across time to allow for analysis of health outcome change over time. This would lend to a better understanding of the relationship between adherence and health, and also be a powerful clinical tool to demonstrate to patients how health does improve when adherence is high.

There is a need to determine "cutpoints," or the minimum necessary level of adherence to have positive health outcomes. This meta-analysis aimed to investigate cutpoints, however, they appear to be sparse in the literature. Cutpoints would allow for a more efficient way of categorizing patients as "adherent" or "nonadherent" (Rapoff, 2010). To develop these cutpoints, more data is necessary. The previous standard of 80% for medication adherence does not apply across all medical regiments, for instance, HAART treatment of HIV (Rapoff, 2010). These cut-points will likely vary dependent on the chronic illness and the regiment being implemented.

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Note: * indicates the publication was included in the meta-analysis

Table 1.

Chronic Illnesses Included in Study

Chronic Illness	**Symptoms & Health Consequences**	**Health Outcome Assessments**
AIDS/HIV	Loss of immune function, high viral loads, opportunistic infections	Plasma HIV RNA levels, CD4+ T-cell counts
Arthritis	Synovitis, rash, fever, joint symptoms, pericarditis, laboratory abnormalities	Pain assessments, joint counts, functional disability
Asthma	Airway obstruction, chronic inflammation, airway hyperresponsiveness, bronchoconstriction, swelling of the airways, mucus production	Peak expiratory flow rate (PEF), number of asthma attacks in a given period of time, lung functioning, frequency of noctural awakenings, symptom free days (SFD)
Diabetes	Impaired glucose metabolism, insulin deficiency, risk of heart, kindey, eye, and nerve disease	Hemoglobin A1c test (HbA1c), blood glucose monitoring frequency of severe hypoglycemia, evaluating growth and development
End-Stage Renal Disease (ESDR)	Kidney failure, risk of cardiovascular disease, bone disorders, body alterations, and sexual problems	Graft loss, rejection of transplant, kidney function
Sickle-Cell Disease	Pain, anemia, high white blood cell count	CBC with WBC differential, reticulocyte count, percent Hb F, renal function, hepatobiliary function, pulmonary function, evaluating growth and development

(Brunner et al., 2004; Giannini et al., 1997; Hashim et al., 2013; Jain, 2013; Kasapcopur & Barut, 2015; Martinez, 2009; National Heart, Lung, & Blood Institute, 2002; Working Group on Antiretroviral Therapy and Medical Management of Infants, 1998).

Table 2.
Summary of Meta-Analysis Results

Measures	ESs[a]	N[b]	Median r (Range)	Unweighted Mean *r* (95% CI)[c]	Fisher's Z[d]	d[e]	Z-value[f]	Q-value[g]
All studies	53	3925	-0.31 (-0.56-0.49)	-0.21 (-0.29 to -0.14)	-0.24	0.47	-5.68***	465.82***
Illness								
Diabetes	38	3310	-0.33 (-0.56-0.49)	-0.24 (-0.32 to -0.15)	-0.27	0.53	-5.30***	386.87***
Other Illnesses[h]	15	572	-0.20 (-0.50-0.42)	-0.15 (-0.27 to -0.03)	-0.11	0.21	-2.36*	56.61***
Health Outcomes								
QOL	13	849	0.06 (-0.56-0.49)	-0.00 (-0.18 to 0.18)	0.10	0.22	-0.02	129.20***
Lab Tests (Health)	34	3383	-0.34 (-0.55-0.14)	-0.33 (-037 to -0.28)	-0.35	0.70	-14.30***	73.37***
Other Health Measures[i]	6	399	0.00 (-0.48-0.42)	-0.03 (-0.26 to 0.21)	-0.08	0.15	-0.22	28.52***
Adherence								
Self-Report Adherence	27	3443	-0.31 (-0.56-0.32)	-0.26 (-0.34 to -0.17)	-0.26	0.51	-5.18***	188.93***
Parent Report Adherence	20	1586	-0.35 (-0.55-0.49)	-0.18 (-0.32 to -0.03)	-0.22	0.40	-2.34*	235.80***
Other Adherence Measures[j]	6	263	-0.29 (-0.50-0.28)	-0.17 (-0.39 to 0.06)	-0.18	0.34	-1.44	20.45**

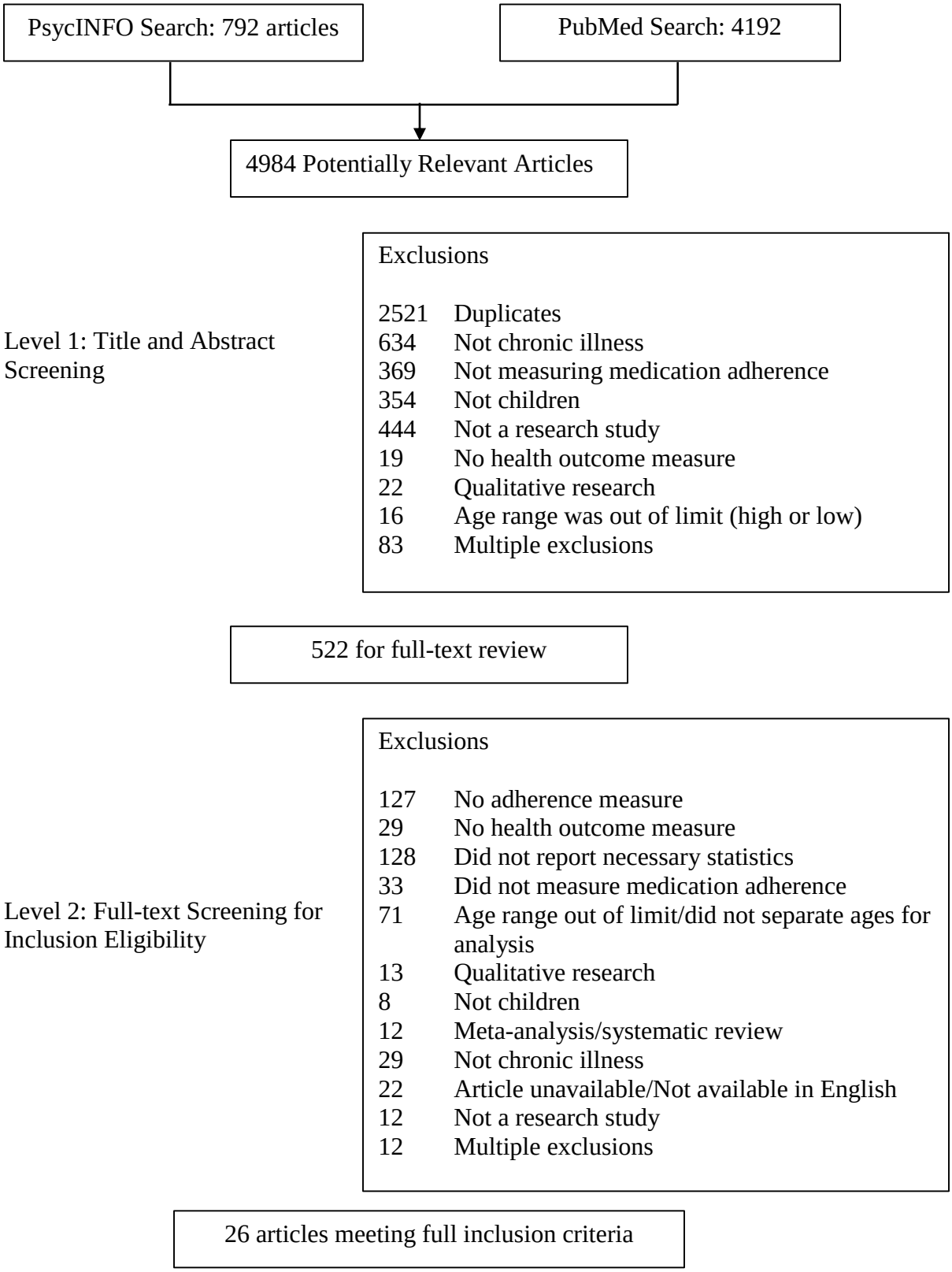
****P*<0.001, ***P*<0.01, **P*<0.05
[a]Number of effect sizes in analysis.
[b]Total N across all samples.
[c]Random-effects analysis.
[d]Fisher's Z statistic was calculated to provide Cohen's d.
[e]Cohen's d is presented as a another, and more familiar, effect size.
[f]Z-test of whether correlation differs from 0.
[g]Test of homogeity. A significant Q indicates a heterogenous sample.
[h]Other illnesses included: AIDS/HIV, asthma, and sickle-cell disease.
[i]Other health measures included: hospitalizations, pain, and disease activity/severity.
[j]Other adherence measures included: provider estimate, pill count, and electronic monitor.

Table 3.
Non-Correlational Studies

Randomized Controlled Trials	**Chronic Illness**	**Adherence Method**	**d (Adherence)**	**Health Assessment**	**d (Health)**
Ellis et al. (2005)	Diabetes	Recall Interview	NA	HbA1c	0.64
				ER Visits	NA
Glaser et al. (2004)	Diabetes	Self-Report	0.17	HbA1c	0.00
				QOL	0.12
Jan et al. (2007)	Asthma	Self-Report	NA	PEF	0.14
Lawson et al. (2007)	Diabetes	Self-Report	0.35	HbA1c	0.14
				QOL	0.2
Wysocki et al. (2000)	Diabetes	Recall Interview	0.21	HbA1c	0.20
		SCI	0.28		
Longitudinal Studies	**Chronic Illness**	**Adherence Method**	**p (Adherence)**	**Health Assessment**	**p (Health)**
Feldman et al. (2007)	Arthritis	Parent Report	0.37	QOL	0.03
				Active joint count	0.08
				Pain	0.20
Hashim et al. (2013)	End-Stage Renal Disease	Provider estimate	< 0.001	QOL	0.13
Riekert et al. (2011)	Asthma	Self-Report	0.17	SFD	NA
		Parent Report	0.02		
Smith et al. (1994)	Asthma	Self-Report	0.001	PEF	0.05
Stranger et al. (2013)	Diabetes	Self-Report	0.04	HbA1c	< 0.001
		Parent Report	< 0.001		

NA - authors did not provide this statistic or not enough data was provided to calculate the statistic

Figure 1.
Flow Diagram of Article Selection



Appendix A

CODING MANUAL

The Role of Adherence on Health Outcomes in Pediatric Chronic Conditions:
A Meta-Analysis

This document instructs coders on (1) what information to pull from selected articles and (2) how to code that information. Any information in *italics* is how a coded item is labeled in the excel coding sheet where all data will be initially entered.

The Coding Manual is divided into three sections:

1. Demographic & Methodological Variables
2. Adherence & Health Outcomes Measures
3. Effect Size Information

Section 1: Demographic/Methodological Variables

1. Bibliographic reference

    - Study ID Number. (*StudyID*)
        - Assign next number in sequence from excel coding spreadsheet.

    - Author (*Author*)
        - If one or two authors, type out name or both names (ex: Smith and Jones)
        - If more than two authors, type out first author and "et al." (ex: Smith et al.)

    - Publication year (*PubYear*)
        - Type out four-digit year.

    - Type of publication. (*TypePub*)
      Enter the below codes for each article dependent on the type of publication.
      1 – journal article
      2 – dissertation

2. Sample Descriptors

    - Age.
        - Mean age of sample (*AgeMean*)
            - Enter reported age value.
            - If not reported, enter 99.
        - Age range. Indicate the youngest age and oldest age included in the study.
            - Report lowest end of range (*AgeLow*)
            - Report highest end of range (*AgeHigh*)
            - Note: If it goes outside of the age range for inclusion, but reports separate data for an appropriate age range, only state the age range that will be used for reporting outcomes)
        - Did study include adults/infants or larger age range than inclusion criteria? (*OutRange*)
            - 1 – Yes
            - 0 – No

    - Gender
        - Predominant sex of sample (*Sex*)
          1 – male
          2 – female
          3 – unclear
        - Percentage of sample male *(%Male*)

If not reported, do a quick calculation. Round to the nearest percentage.

Type out percentage
99 - unknown

- Percentage of sample female *(%Female*)
  If not reported, do a quick calculation. Round to the nearest percentage.

  Type out percentage
  99 – unknown

- Ethnicity
  - Percentage of White individuals *(%White*)

    Type out percentage
    999 - unknown
  - Percentage of Black individuals *(%Black*)

    Type out percentage
    999 - unknown
  - Percentage of Hispanic individuals *(%Hispanic*)

    Type out percentage
    999 - unknown
  - Percentage of Asian individuals (*%Asian*)

    Type out percentage
    999 - unknown
  - Percentage of Other Ethnicities report *(%Other*)

    Type out percentage
    999 – unknown
  - If "Other" is reported – type out what ethnicities are included in this group (*OtherEthSpec*)
    - If "Other" is not reported, leave this box blank

- SES (*SES*)
  - Predominant household income.
    - 1 – less than $24,999
    - 2 - $25-$49,999
    - 3 - $50-$74,999
    - 4 - $75,000 +
    - 5 – Unknown

- Chronic Illness (*ChronIll*)

  1 - AIDS/HIV
  2 - Arthritis
  3 - Asthma
  4 - Cancer
  5 - Cystic Fibrosis

6 – Diabetes
7 - Epilepsy
8 - Hemophilia
9 – Irritable Bowel Syndrome
10 – Renal Disease
11 - Sickle Cell Disease
12 – Transplant
13 - Multiple
99 - Other
If "Multiple" or "Other" – type out illness(es) (*IllOther*)

- If classified as one of the above illness, leave this box blank

Section 2: Adherence Measure and Health Outcome Measures

1. Adherence Measure

    - Laboratory assays (*LabAssay*)
        1 – Yes
        0 – No
        If "Yes," type out the adherence measure, if "no" leave *LabAssaySpec* box blank
    - Pill counts (*Pillcount*)
        1 – Yes
        0 - No
    - Electronic monitors (*ElecMon*)
        1 – Yes
        0 - No
    - Self-report (*SelfReport*)
        1 – Yes
        0 – No
    - Parent report (*ParReport*)
        1 - Yes
        0 - No
    - Provider estimates (*ProvEst*)
        1 – Yes
        0 - No
    - Diary methods (*Diaries*)
        1 – Yes
        0 - No
    - Pharmacy refill (*Pharm*)
        1 – Yes
        0 - No
    - 9 – Other (*OtherAdh*)
    - If "Other" – type out the adherence measurement method in *OtherName* box
        i. If classified as one of the above adherence measures, leave this box blank

2. Health Outcome Measure

    - Laboratory tests [disease-specific outcome measures] (*LabTest*)
        1 – Yes
        0 – No
        If "Yes," type out the disease-specific outcome measure in *LabTestName*, if "no" leave this box blank
    - Pain-related measure (*Pain*)
        1 – Yes
        O - No
    - Quality of Life measure (*QOL*)

1 – Yes
0 – No
If "Yes," code further specifier in *QOLSpec* box
1 – General QOL
2 – Health-related QOL (HRQOL)
3 – Disease-specific QOL measure

- Health Care Utilization (*HCU*)
  1 – Yes
  0 – No
  1. If "Yes," type out how this was measured in *HCUSpec* box
- Disease activity (*DisAct*)
  i. 1 – Yes
  ii. 0 – No
  1. If "Yes," type out how this was measured in *DisActSpec* box
- Mortality (*Mortality*)
  1 – Yes
  0 – No
- Other (*OtherHealth*)
  i. 1 – Yes
  ii. 0 – No
  1. If "Yes," type out the measurement method in *OtherSpec* box

Section 3: Effect Size

1. Type of Data (*ESspec*)
    a. 1 - Effect Sizes based Means
    b. 0 - Effect Sizes based on Correlations

- If you coded "1" for effect sizes based on means, continue coding thru the next section "ES based on Means." If you coded "2," skip down to section titled," ES based on Correlations."

2. Effect Sizes based on Means

    - Mean of Treatment Group (*TreatMean*)
        Enter in reported value for the mean of the treatment group only in this cell

    - Standard Deviation of Treatment Group (*TreatSD*)
        Enter in the reported value for the Standard Deviation of the treatment group in this cell

    - N, or number of individuals, of the Treatment Group included in the calculations for the mean and standard deviations of that group (*TreatN*)
        Enter number of individuals

    - Mean of Control Group (*ControlMean*)
        Enter in reported value for the mean of the control group only in this cell

    - Standard Deviation of Control Group (*ControlSD*)
        Enter in reported value fro the Standard Deviation of the control group in this cell

    - N, or number of individuals, of the Control Group included in the calculations for the mean and standard deviation of that group (*ControlN*)
        Enter number of individuals

3. Effect Sizes based on Correlations

    - Correlation Variables
        Variable 1 (Corr*Var1*)
            1 – Continuous
            0 – Dichotomous

        Variable 2 (Corr*Var2*)
            1 – Continuous
            0 – Dichotomous

- Type of Correlation (*CorrType*) Enter code for corresponding correlation
  - 1 - Product-moment Correlation
    - Computed with 2 continuous variables
  - 2 – Point-biserial Correlation
    - Computed with 1 dichotomous and 1 continuous variable
  - 3 – Phi Coefficient
    - Computed with 2 dichotomous variables

- N, or number of individuals included in analysis (CorrN)
  - Enter number of individuals

- r, or correlation (*r*)
  - Enter reported r value

- p-value (*p*)
  - Enter reported p-value for correlation
- Was correlation significant? (*Sig*)
  - 1 – Yes
  - 0 – No

- Significance level (*SigLevel*)
  - Type in significance level
  - Note – This is usually written out in articles as "<0.05" or "<0.001" but you do not need to use the "<" sign because this will be assumed.