Evaluating Three Methods of Assessing Adherence
to an Inhaled Corticosteroid Regimen for Pediatric Asthma

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ABSTRACT

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The effects of nonadherence to treatment regimens for pediatric chronic illnesses are significant. There are several characteristics of asthma therapy that make non-adherence likely. Accurate assessment of adherence is crucial, but difficult. The primary objective of this study was to examine the relationship between three methods of assessing adherence to inhaled corticosteroid treatment for pediatric asthma. This study utilized the baseline data from a randomized controlled trial for improving adherence (Kamps et al., 2008). Participants included 22 males and 25 females with asthma (72% Caucasian, mean age = 10.34 years). Adherence measures included parent and child self-report questionnaires, parent and child 24-hour recall interviews, and electronic monitors (EM). Mean adherence according to EM for this sample (67.21%) was significantly greater than 50%, the typical level for adherence to regimens for chronic pediatric diseases (Rapoff, 2010). Thus, this study provides information about moderate (as opposed to severe) difficulties with nonadherence. Results suggested that self-report methods inflate adherence compared to EM. Sensitivity, specificity, positive predictive value, and negative predictive value were assessed for each method. The self-report methods did not demonstrate sufficient psychometric properties to justify their use as stand-alone measures of adherence. Agreement between parent and child reports was high, but not redundant. These findings call for further research investigating ways that methods of assessment may be effectively combined for an accurate measurement of adherence.

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Dedication

To my family

who lovingly and proudly calls me nerd.

Chapter 1

Introduction

Asthma: Definition and Treatment

As the most common chronic disorder of childhood, asthma is estimated to affect 6.8 million Americans under 18 years old (Bloom & Cohen, 2007). In a classroom of 30 children, an average of three are likely to have this disorder (Centers for Disease Control, 2008). Asthma is a chronic inflammatory disorder of the bronchial airways. In susceptible individuals, inflammation (swelling of the airways) causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning (National Heart Lung and Blood Institute, 2008). These episodes of inflammation are usually associated with extensive, but erratic airflow obstruction and tightening of the muscles around the airways (Bartolome, 2000). Although asthma severity differs across individuals, almost all children with asthma experience a relief from symptoms or reversal, between episodes (American Lung Association, 2008). The American Lung Association identifies several possible causes or triggers of asthma: (a) allergies; (b) viral respiratory infection; (c) exercise; (d) airborne irritants including secondhand smoke and outdoor air pollution; (e) weather factors; and (f) emotional stress.

Episodes of increased asthma symptoms often stabilize either spontaneously or with treatment. The National Asthma Education and Prevention Program Expert Panel Report 3 (Expert Panel Report; NIH, 2007) identifies four components of care necessary to effectively manage asthma: (a) assessment and monitoring; (b) education for the provider, patient, family, and community; (c) control of environmental variables such as

exposure to allergens and comorbid conditions such as obesity that are known to affect asthma; and (d) pharmacologic therapy.

A comprehensive assessment is necessary when establishing an asthma diagnosis. This should include spirometry, as the recommended method for testing pulmonary function. A spirometer is used to measure the amount and speed of air that a patient can inhale and exhale. Spirometry can verify airflow obstruction, its severity, and whether the obstruction may be reversed following inhalation of a quick-relief medication. In addition to the initial assessment of asthma, spirometry should be conducted: (a) after treatment is initiated and symptoms have remained constant; (b) during periods of asthma exacerbation; and (c) at least every one to two years (NIH, 2007). Spirometry is primarily a diagnostic tool used by medical professionals. In contrast, peak expiratory flow (peak flow) meters are designed for monitoring and may be used by patients as part of asthma self-management. Peak flow monitoring is particularly important for patients with any of the following: (a) moderate or severe persistent asthma; (b) history of severe exacerbations; or (c) difficulty perceiving airflow obstruction and worsening asthma (NIH, 2007).

Pharmacologic therapy for asthma is used both to prevent and to control symptoms. When used properly, medications decrease the frequency and severity of asthma exacerbations, and reverse airflow obstruction. Thus, pharmacological interventions improve quality of life for people with asthma (NIH, 2007). The National Heart Lung and Blood Institute classifies asthma medications into two general classes: (a) long-term control medications (also known as long-term preventive, control, or maintenance

medications); and (b) quick-relief medications (also known as reliever or rescue medications).

Long-term control medications are used daily to achieve and maintain control of persistent asthma (NIH, 2007). The term “persistent” is used to distinguish it from intermittent asthma. In intermittent asthma, symptoms occur less than once per week and no control medication is necessary (Yawn, 2008). Long-term control medications also prevent symptoms, often by reducing inflammation. Inhaled corticosteroids (ICS) are the most consistently effective long-term control medications for persistent asthma. Consequently, ICS are the preferred long-term control therapy in children of all ages as well as adults (NIH, 2007). ICS deliver drugs directly into the lungs, thus allowing higher concentrations to be more effectively delivered to the airways. A spacer or valved holding chamber is recommended when using ICS for children under five years of age and as a method for decreasing local side effects (NIH, 2007). Sustained use of ICS reduces the risk of severe worsening of the disease requiring hospitalization or even death from asthma (Suissa & Ernst, 2001). The potential risks of ICS such as oral infection, bronchospasm, and decreased growth, are well balanced by their benefits (NIH, 2007).

Quick-relief medications bring about rapid relief of acute bronchoconstriction by relaxing the smooth muscles of the airway. These medications also decrease the symptoms associated with airflow obstruction such as cough, chest tightness, and wheezing. The therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm is a short-acting β-agonist (SABA). SABAs cause an increase in airflow within three to five minutes of administration. SABAs are not to be used on a regular basis. Individuals who use SABAs more than two days per week for symptom

relief do not have adequate control of their asthma and should ask their physician to initiate or increase long-term control medications (NIH, 2007).

Negative Consequences of Asthma

Childhood asthma has an array of negative consequences such as school absences and high economic burden. Asthma is one of the leading causes of school absence overall, and the most common cause of school absence due to chronic illness (Miller, 1982). In 2003 asthma accounted for an estimated 12.8 million lost school days among the more than 4 million children who reported at least one asthma attack in the preceding year (Akinbami, 2006). As part of a project of the National Coordinating Committee on School Health and Safety, Taras and Potts-Datema (2005) reviewed the literature on the relationship between childhood asthma, school absenteeism, and academic outcomes (achievement and ability). The 66 included studies were published in peer-reviewed journals. Nearly all of them reported a correlation between asthma and high rates of school absence. The association between asthma and academic outcomes is less conclusive. Approximately two thirds of the reviewed studies found no difference between children with asthma and their asthma-free peers on levels of academic achievement or ability. Differences have been reported in a few studies, but cannot be accounted for by asthma presence alone (Fowler, Davenport, & Garg, 1992; Gutstadt et al., 1989).

The economic impact of asthma is substantial. The direct costs of a disease are defined as resources consumed: (a) costs associated with drugs and devices; (b) consultations with physicians; and (c) hospital costs. The indirect costs of a disease are defined as resources lost: (a) time off work as a result of the ill health of the patient; (b)

time spent by people looking after the patient in the home; and (c) premature retirement or death (Barnes, Jonsson, & Klim, 1996). The total direct and indirect costs of asthma per year in the US are estimated to be $18.3 billion (Asthma and Allergy Foundation of America, n.d.).

In general, asthma is considered a mild illness which should be managed by ambulatory care and rarely leads to hospitalization. Nevertheless, research suggests between 33 and 43% of the economic impact of this disease is related to emergency department use, hospitalization, and death (Barnes et al., 1996; Milgrom et al., 1996). According to the National Center for Health Statistics (2006), there were an estimated 754,000 (103 per 10,000 children) pediatric asthma visits to emergency departments and 198,000 (27 per 10,000 children) hospitalizations in 2004.

In 1996 more money was spent on rescue therapy than on prophylactic therapy (Barnes et al., 1996). Likewise, the cost of one admission to the hospital pays for three years of treatment with ICS (Blainey, Lomas, Beale, & Partridge, 1990). Initiation of ICS therapy for children with asthma has been shown to result in monthly health care cost savings of almost 24% (Balkrishnan, Norwood, & Anderson, 1998). A retrospective, matched-cohort study reported a decrease of $28 for average monthly medical care in an ICS group because of reduced clinic visits, emergency department visits, and hospitalizations. However, costs increased to $89 in the non-ICS group (Smith, Rascati, & Johnsrud, 2001). Thus, the initial increase in cost associated with implementing an ICS regimen is offset by the decreased costs of medical care overall.

Asthma-related childhood deaths are rare and have been declining since 1999. Nevertheless, 186 pediatric asthma deaths occurred in 2004 (Akinbami, 2006).

Characteristics of children most at risk for an asthma-related death include: (a) disease that is severe and improperly managed; (b) a near-fatal asthma attack; and (c) history of hospitalization or intubation for asthma (Akinbami, 2006). Failure to appropriately treat episodes of asthma exacerbation is a chief contributing cause of poor outcome (Akinbami, 2006). This suggests that uncontrolled disease may be the result of patients' or guardians' being non-adherent to the treatment regimen. The expense associated with uncontrolled disease makes it worthwhile to examine medication-taking habits prior to conducting costly tests or adding more medication (Cramer, Mattson, Prevey, Scheyer, & Ouellette, 1989).

Treatment Adherence: Definition and Considerations

Treatment adherence has been defined as "the extent to which a person's behavior coincides with medical advice" (Haynes, 1979, p. 2). The term "adherence" is preferred to the historical term, "compliance", because it possesses fewer negative connotations (Horne, 2006). "Adherence" describes medication-taking behavior from the patients's perspective (Farmer, 1999). The term suggests a more active role of patients in their own care (Fish & Lung, 2001). This active role is in direct contradiction to "compliance", which suggests patients are either unable to follow provider instructions or patients are deliberately sabotaging their care (Horne, 2006). Importantly, "adherence" eliminates the notion of blame (Horne, 2006).

Rand & Wise (1994) highlight the fact that adherence does not necessarily have the same meaning in every instance; it is defined by the situation. It is important to explicitly set forth the framework of good adherence for the specific health behavior under study. In addition, it is necessary to specify the timeframe for assessing each regimen

component in order to avoid misrepresentation (Rudd, 1993).

The convention in the field has been to label those participants/patients who take at least 80% of their prescribed medications as “adherent”. This cutoff is based on the work of Haynes and colleagues (1976) in the first randomized controlled intervention study to investigate the adherence to hypertension drug regimens by hypertensive Canadian steelworkers. Following an intervention designed to promote adherence, participants who took at least 80% of their medications experienced positive health results (decrease in blood pressure). This finding certainly has implications for hypertension, but may not be applicable to other diseases (Rapoff, 2010).

The required level of treatment adherence for reaching the desired therapeutic result is unknown for most illnesses (Epstein & Cluss, 1982). Likewise, few clinicians are able to precisely define an adequate amount of adherence (Dirks & Kinsman, 1982). In the absence of convincing data it does not seem appropriate to apply the conventional cutoff of 80% to asthma. Classifying patients as adherent or non-adherent based on non-standardized cutoffs limits our ability to make comparisons across studies and across different aspects of a particular treatment regimen (La Greca, 1990).

Several authors have argued that it is inappropriate to classify patients using only a dichotomous variable (adherent versus non-adherent) (DiMatteo, Giordani, Lepper, & Croghan, 2002; Dirks & Kinsman, 1982; Rudd et al., 1989). Ideally, adherence would be assessed using continuous measures (DiMatteo, et al., 2002), but this has proven to be difficult. The “yes-no fallacy” as described by Dirks & Kinsman (1982) has negatively influenced clinical and research outcomes in multiple ways: (a) actual adherence patterns

are poorly understood; (b) adherence is overestimated; and (c) adherence patterns that increase patients' risk are neglected.

Farmer (1999) asserts that at least three distinct types of non-adherence should be clearly identified: (a) patient takes no medication; (b) the patient stops therapy prematurely; and (c) the patient continues to take the medication, but not as prescribed. Dunbar-Jacob & Schlenk (2001) further delineates possible adherence patterns by emphasizing that patients may continue treatment, but with dosage interval errors.

Patients may take less medication than prescribed because of adverse side effects (Dunbar- Jacob, 2001; Rapoff, 2010; Spector, 1985; Voyles & Menendez, 1983). Patients may also believe that a lower dose of medication is preferable (Dunbar- Jacob, 2001; Horne, 2006). Overdosing may occur because patients miss a dose of medication and "double up" in order to meet the requisite number of doses (Dunbar-Jacob, Schlenk, Baum, Revenson, & Singer, 2001), or patients may feel that their symptoms require extra doses (Dunbar-Jacob, Schlenk, Baum, Revenson, & Singer, 2001). Studies have shown that patients do not consistently exhibit only one type of non-adherence pattern; therefore, variability in adherence may be the most common form of adherence problem (Dunbar-Jacob, Schlenk, Baum, Revenson, & Singer, 2001).

Adherence in Pediatric Asthma

Studies of children with chronic illness consistently report adherence at or below 50% (Dunbar-Jacob & Mortimer-Stephens, 2001; Rapoff, 2010; Rapoff & Barnard, 1991). Rand & Wise (1994) suggest that non-adherence in the treatment of asthma commonly ranges from 30-70%. Negative consequences of non-adherence in the treatment of asthma include increased wheezing, variability in pulmonary function that

limits a child's daily activities (Cluss, Epstein, Galvis, & Friday, 1984), and possibly death (Epstein & Cluss, 1982).

There are several characteristics of asthma therapy that make non-adherence likely (Klingelhofer, 1987). First, asthma is a chronic disease; the pediatric adherence literature has shown that longer disease duration is related to poorer adherence (Lemanek, Kamps, & Chung, 2001; Rapoff, 2010). Second, patients with asthma are likely to experience symptom-free days. Extended periods of remission lead patients to reduce their treatment regimen (Becker et al., 1978; Lemanek et al., 2001; Rapoff, 2010; Smith, Seale, Ley, Shaw, & Bracs, 1986; Voyles & Menendez, 1983). Third, asthma treatment and management is complex and often involves taking multiple medications at different times throughout the day. Research has shown that the more complex the regimen, the more likely non-adherence (Lemanek et al., 2001; Rapoff, 2010; Smith, Seale, & Shaw, 1984; Voyles & Menendez, 1983). Asthma medications, specifically ICS, do not always immediately or obviously affect symptoms (Horne, 2006). Likewise, misunderstanding of the preventive role of ICS is associated with reduced adherence to its daily use (Farber et al., 2003). Fourth, medications are expensive, require close monitoring, and can include undesirable side effects (Spector, 1985).

The method of medication delivery has been shown to affect adherence. Therefore, it is important to consider mode of delivery when comparing rates of adherence. To narrow this comparison, several studies have specifically targeted children's adherence to their ICS regimen.

Coutts, Gibson, & Paton (1992) conducted a study with 14 children 9-16 years old. They defined a "compliant day" as one in which the prescribed number of puffs, or

inhalations, were taken at appropriate times. Adherence to a prophylactic ICS regimen was recorded over one to three months by an EM, the Nebulizer Chronolog (NC; Medtrac Technologies, Inc, Lakewood, Colo.). The EM recorded underuse of medication on 55% of the study days, and overuse on 2% of study days. Seven participants did not take any prophylactic medication on at least one of the study days.

Milgrom and colleagues (1996) studied, for a period of 13 weeks, the adherence of 24 children ages 8-12 years to an ICS regimen. The median actual use was 58.4% as measured by the NC. Bender et al. (2000) studied 27 children ages 7-12 years. Average rate of adherence was 52% after 6 months as recorded by the electronic Doser – Clinical Trials version (Doser-CT; Medtrac Inc, Hudson, Mass.).

Jónasson, Carlsen, & Mowinckel (2000) reported ICS adherence for 122 children ages 7-16 years in a clinical trial of inhaled budesonide or placebo. Adherence was estimated by counting the number of doses remaining in the inhaler. Adherence dropped from 77% at 3 months to 49% at 27 months. Bender, Pedan, & Varasteh (2006) conducted a pharmacy database medication refill study involving 273 children less than 12 years old. Over a period of 12 months, only 19% of the study days were covered by refills.

McQuaid, Kopel, Klein, & Fritz (2003) used the MDILog electronic asthma medication monitor (MDILog; Westmed Technologies Inc, Englewood, Colo.) to measure adherence to ICS by 106 children ages 8-16 years over a period of one month. Mean adherence was 51%. The MDILog was also used by McQuaid, Walders, Kopel, Fritz, & Klinnert (2005) to measure adherence by 53 children ages 7-16 years. Mean adherence was 48% over a period of four to five weeks.

Using various assessment methods, these studies reported adherence from 19 to 77%. EMs consistently reported approximately 50% adherence. Three characteristics are important to consider: (a) length of monitoring period; (b) assessment method; and (c) ICS regimen adherence is similar to other chronic illnesses.

Benefits of Monitoring Adherence

It is crucial for health professionals to have a reliable measure of their patients' adherence to prescriptions. Failure to identify a patient as non-adherent can lead to unnecessary increases in medication dosage, changes among medications including prescription of adjunct medications, and mistakenly labeling a patient as "treatment resistant" (Velligan et al., 2007). Rudd (1993) suggests that up to two-thirds of patients might have their regimens adjusted incorrectly. Incorrect adjustments may be due to: (a) clinician's inability to consider non-adherence as a cause of failure to achieve positive health outcomes, and (b) other clinicians' attributing all treatment failures to patient non-adherence. While non-adherence is probably a significant cause of treatment non-response, other causes include: (a) pharmacokinetic factors; (b) pharmacodynamic factors; and (c) adverse effects or misdiagnosis (Hughes, 2007). Accurate measures of adherence are necessary to correctly identify factors that influence patients's self-treatment (Modi et al., 2006). Identifying non-adherence as the cause of patients's non-response to therapy suggests adherence promotion (as opposed to change in treatment) as the appropriate strategy (Hughes, 2007).

Health care providers need to be able to predict which patients are likely to be non-adherent to prescriptions. Inaccurate predictions may lead to indiscriminate use of costly adherence improvement programs. Such programs may negatively influence those

patients who previously adhered (Finney, Hook, Friman, Rapoff, & Christophersen, 1993; Rapoff, 2010). Since it is known that adherence tends to decrease over the course of chronic diseases, repeated assessment would signal when to introduce intervention to promote adherence.

Progress has been made concerning the development of reliable and valid measures of adherence for pediatric populations. The current recommendation when conducting studies of adherence is to include at least two methods of assessment (Quittner, Modi, Lemanek, Ievers-Landis, & Rapoff, 2008). Following this recommendation, researchers are able to examine the convergence between the measures. However, problems may arise when there are variations in rates of adherence related to method of assessment. Therefore, it is crucial to clearly understand the relationships among measures of pediatric adherence. That is the goal of the present study.

Methods of Assessing Adherence

There is no consensus in the literature as to whether a gold standard for assessing adherence currently exists (Cramer, 1995a; Quittner et al., 2008; Rapoff, 2010). In the absence of a recognized gold standard it is important to consider various methods of assessment and how they may be combined to improve validity. When selecting methods of assessment it is important to pay careful attention to the limitations of each and to have a well-specified definition of adherence (Dunbar-Jacob, Schlenk, Baum, Revenson, & Singer, 2001).

Self-Report Measures

Strengths. Patient or parent self-report is the most common method of assessing adherence (Quittner et al., 2008). Burkhart & Dunbar-Jacob (2002) reported that 21

(36%) of the 58 treatment adherence studies published from 1987 through 1996 relied on self-report alone. This rate is somewhat higher than the approximately 20% reported by Rapoff (2010). Self-report measures are prevalent because they are practical, inexpensive (Modi et al., 2006; Modi & Quittner, 2006a; Rapoff, 2010), and quick and easy to administer (Rand & Wise, 1994).

Matsui & Drotar (2000) recommended that adherence information be collected from multiple sources in an effort to minimize individual bias. Self-report measures facilitate this by using multiple informants (Quittner et al., 2008). This characteristic of self-report measures increases the ease with which reports of adherence may be corroborated. Self-report questionnaires are useful in research because they provide standardized answer categories that simplify the interpretation and processing of data (de Klerk, van der Heijde, van der Tempel, & van der Linden, 1999).

Limitations. Comparisons of self-report versus electronic measures have been reported in a limited number of studies (Gong, Simmons, Clark, & Tashkin, 1988; Milgrom et al., 1996; Spector et al., 1986). They show that subjects overstate their adherence to inhaled medication regimens relative to electronic measures. Klinnert, McQuaid, & Gavin (1997) identified a number of factors which influence self-report accuracy: (a) degree of social desirability or demands (Coutts, et al., 1992; Johnson, 1993; Marhefka, Tepper, Farley, Sleasman, & Mellins, 2006); (b) the relationship between the interviewer and the interviewee; (c) benefits of answering in a particular manner; and (d) the style in which questions are asked. Thus, one is more likely to obtain accurate information from an interviewee in a sympathetic setting that avoids blame and confrontation.

Self-report is susceptible to poor recall accuracy (Rudd, 1993). Rudd (1993) suggests that a one-week interval is ideal for promoting accurate recall; however, most methods ask about adherence over longer intervals. Questionnaires and other self-report methods typically assess global perceptions rather than frequencies of behavior (Quittner et al., 2008). This makes it difficult to target specific behaviors over a certain time period. In addition, it is difficult to use self-report with younger children (Quittner et al., 2008). Another consideration is that there are few validated self-report and interview measures (Quittner et al., 2008).

24-hour Recall Methods

Strengths. Recall methods are useful for assessing observable behaviors and activities. They have substantial ecological validity because they measure behaviors and cognitions as they occur. Recall methods provide crucial information about the processes by which behaviors and interactions unfold. Thus, it is possible to identify reasons underlying poor adherence using recall methods (Modi et al., 2006).

The 24-hour Recall Interview (RI) has been a long-standing method of dietary assessment. Johnson, Silverstein, Rosenbloom, Carter, & Cunningham (1986) were the first to modify the RI to assess all pediatric diabetes management behaviors. The RI is administered via telephone in a conversational format. Participants are informed that investigators are interested in behaviors that the child and family typically does to manage the child's chronic illness. This is in contrast to the family's view of the ideal method of illness management.

Participants are aware that they will be called during a particular time period; however, they do not know in advance on which days the calls will occur. For example, it

is recommended that three (two weekdays and one weekend day) 24-hour RIs take place over a period of two weeks (Johnson, et al., 1986). The child and a caregiver are both interviewed (multiple sources). It is important that these interviews be administered separately (in an attempt to reduce bias) and that the same caregiver be interviewed on each occasion.

The interviewer begins by establishing rapport with the respondent. Respondents are asked to recall the events of the previous day in temporal sequence, beginning with the time the child woke up and ending with bedtime. The interviewer asks questions to promote thinking about the events of the previous day in an unstructured, free-flowing manner. The respondent is encouraged to report all activities of the previous day; however, only adherence-specific behaviors are recorded. If the respondent mentions that an activity relevant to disease management occurred, the interviewer asks for details regarding the behavior. If the necessary information is not voluntarily offered, the interviewer may prompt with questions. The interview requires approximately 20 minutes on the phone.

Some of the advantages of the RI include: (a) target behaviors are not obvious to the respondent; (b) it can show when treatments were done and for how long; and (c) it can provide information about barriers to adherence. By recording a continuous stream of activities and behavior throughout the day and evening, it is possible to identify which activities were performed instead of medical treatments. For example, a child who is scheduled to take medication after school may report visiting a friend after school. A barrier to adherence may thus be identified. A major benefit of the RI is that it reduces biases associated with memory and recall because the assessment is done in real time or

within 24 hours of the targeted activity (Freund, Johnson, Silverstein, & Thomas, 1991). A practical advantage of the RI is that it involves lower cost relative to electronic monitors and can track any number of treatments simultaneously. The relatively unobtrusive nature of the RI may reduce social desirability, hence potentially increases accuracy (Modi et al., 2006).

The initial effort by Johnson and colleagues (1986) to standardize the RI evaluated the management of 168 children with diabetes (6 to 19 years of age) and their parents using the RI described above. Reliability (parent-child agreement) was good to excellent for the majority of the 13 behaviors (mean r = .62). A later study (Freund et al., 1991) consisted of 78 parent-child pairs and reported similar agreement across dyads; however, parent-child agreement was slightly higher on weekdays (mean r = .75) than on weekends (mean r = .65). Reynolds, Johnson, & Silverstein (1990) examined the accuracy of the RI by comparing RI data with direct behavioral observation of 75 children with diabetes (7 to 12 years of age). High observer reliability (r = .95 or higher) indicated observers' data was a reasonable validity standard to compare children's RI data. Observer-child agreement ranged from 73-98% for event occurrence (e.g., insulin injection). Agreement concerning details of events (e.g., time of injection) ranged from 17-98%.

Limitations. In general, the disadvantages of using the RI are practical in nature. It involves an increased time commitment for the patient, family, and interviewer. Conducting phone calls with busy families may prove challenging. Another consideration is that not all families will have ready access to a telephone. In addition, implementing the RI requires research assistants to be trained in conducting interviews.

The RI has been used with children as young as six years. Such young children have been found to have difficulty reporting adherence measures involving timing or duration of events (Johnson et al., 1986; Reynolds et al., 1990). Freund et al. (1991) reported, however, that with practice, young children may become reliable reporters of all adherence behaviors, including those involving time. This potential limitation must be considered in the context of the feasibility of conducting "practice" interviews.

Electronic Monitors (EM)

Strengths. EMs use microprocessors to record automated information on adherence. They record and store the date and time of medication removal from a standard vial or blister package, or actuation of a metered-dose inhaler (MDI). The development of such methods of measuring adherence has provided clinicians and researchers with an increased understanding of behaviors related to individual treatment regimens.

EMs have several advantages over other measures. Therefore, they have become at least the reference standard, if not the gold standard, for adherence measurement (Farmer, 1999). They are objective and unobtrusive (Burke, 2001; Hughes, 2007) and are thought to provide the most accurate and valuable data for assessing adherence to a dosage regimen. This is because they provide unbiased continuous measurement (Hughes, 2007). These data may then be used to assess the appropriateness and effectiveness of an intervention to improve adherence. EMs are also less intrusive than direct observation or biochemical assays.

Falsification of data from an EM would have to occur in real time (Burke, 2001). In order for patients using an EM to "fake good" they would need to maintain a precise and time-consuming pattern of deception (Riekert & Rand, 2002). Studies which utilize an

EM have identified patterns of medication use including “drug holidays” (omitting doses for several days in succession without provider authorization) (Schwed et al., 1999; Urquhart, 1994; Van Wijngaerden et al., 2002), and “toothbrush” or “white coat” compliance (maintaining a façade of adequate adherence by discarding medications or taking them consistently only for the several days immediately before clinic visits) (Podsadecki, Vrijens, Tousset, Rode, & Hanna, 2008; Rapoff, 2010; Urquhart, 1994).

An EM can also help determine whether the absence of a positive health outcome is primarily a problem related to pharmacological non-response or non-adherence (Burke, 2001; Cramer, 1995b; Riekert & Rand, 2002). EMs minimize variance due to measurement error, hence maximization of explanatory power (Rudd, 1993). Knowledge of timing between doses can also help identify and possibly minimize drug-induced side effects (Riekert & Rand, 2002).

Limitations. The major drawback of EMs is that they usually do not confirm ingestion or proper inhalation and may thus overestimate actual adherence (Rapoff, 2010). Therefore, a medication event represents a presumptive dose (Burke, 2001). Unfortunately, EMs are applicable to only a limited number of adherence behaviors. For example, an EM does not currently exist that monitors dietary intake as a necessary treatment for conditions such as diabetes and cystic fibrosis (Quittner, Espelage, Ievers-Landis, & Drotar, 2000).

Although the cost of EMs has decreased since their introduction, their considerable expense remains a disadvantage (Modi & Quittner, 2006b). In order to obtain EM data, one must have access to a computer with the software associated with the EM. Training is required to set up the EM and to interpret the output. This may not be a disadvantage in

the context of research, but may represent a significant limitation in clinical settings. EMs continue to be developed that are more reliable than their predecessors (Apter, Tor, & Feldman, 2001); however, mechanical breakdowns are possible.

Measuring Diagnostic Performance of Tests

Sensitivity and Specificity

When developing a new diagnostic test, it is important to measure how well it performs relative to a gold standard. Sensitivity and specificity are traditionally used for this purpose (Riegelman, 2000). When considering adherence, the "disease" in question is nonadherence. As previously mentioned, adherence researchers do not agree on a gold standard (Cramer, 1995a; Quittner et al., 2008; Rapoff, 2010); thus, EMs are considered a reference standard (Farmer, 1999). Sensitivity measures the percentage of participants who are nonadherent as indicated by the EM who are also labeled as such by the test. Specificity measures the percentage of participants who are adherent by the EM who are also labeled as such by the test. If the sensitivity and specificity of a test are stable, then it may be similarly applied regardless of characteristics unique to the setting and population (Riegelman, 2000). Clinically useful diagnostic tests typically have a sensitivity of 80% and a specificity of 90% (Riegelman, 2000).

Self-report measures of adherence typically demonstrate high specificity (Schafer-Keller, Steiger, Bock, Denhaerynck, & De Geest, 2008; Zeller, Schroeder, & Peters, 2008). This is due to the fact that the majority of patients will report that they are adherent to their treatment regimen. Thus, it is more likely that a number of these patients actually are adherent. It is more challenging to demonstrate high sensitivity in self-report measures. This is due to a relatively high number of false negatives (individuals are

nonadherent by EM, but adherent by self-report). By contrast, self-reports tend to have relatively fewer false positives (individuals adherent by EM, but nonadherent by self-report), and it is thus reasonable to consider a patient's report of poor adherence to be accurate (Farmer, 1999).

Predictive Value

Sensitivity and specificity are of primary concern to researchers who are striving to create measures that correctly identify patients' adherence status. Of particular clinical importance is the likelihood that a patient is actually what he or she claims to be – adherent or nonadherent. This is known as predictive value - the probability of nonadherence being present (or absent) after reviewing the results of the test (Riegelman, 2000). Tests with high positive predictive value assist clinicians in expending valuable resources to those patients with the greatest need.

Pediatric Asthma Studies Utilizing Multiple Methods of Assessment

Milgrom and colleagues (1996) investigated adherence by 24 children ages 8-12 years to β-agonists and ICS over a 13-week period. They compared rates based on MDILog and patient diaries. The median use of ICS reported by patients in their diaries was 95.4%, whereas the median use recorded by the MDILog was 58.4%. More than 90% of patients exaggerated their use of ICS. Adherence by children who experienced exacerbation of disease was markedly lower than by those whose disease did not worsen and did not require oral corticosteroids (Median adherence = 13.7% vs. 68.2%).

Bender and colleagues (2000) compared adherence of 27 children ages 7-12 years as measured by parent and child self-report, canister weighing, and Doser-CT. Adherence was monitored over a period of six months. Both self-report measures yielded adherence

greater than 80%, which was significantly higher than the 69% recorded using canister weight. When adherence recorded by Doser-CT was truncated to no more than 100% of prescribed daily use, average adherence stood at 50%.

Bender, Milgrom, Rand, & Ackerson (1998) investigated adherence of 24 children ages 6-12 years to inhaled β-agonists and ICS. Adherence was measured by MDILog and patient diaries over a period of three months. MDILog showed complete use of drug on a median of 4.9% of study days for ICS and 12.7% of days for β-agonists. By contrast, patients reported complete use on 54% and 30% of days for ICS and β-agonists respectively.

Butz, Donithan, Bollinger, Rand, & Thompson (2005) compared the adherence to ICS by 157 children ages 2-8 years, as measured by the NC and asthma diary cards. Adherence was monitored over a period of 12 weeks. Concordance between diary cards and NC was 85% for use and nonuse. Sensitivity of diary data relative to NC ranged from .80 to .91.

Also using the NC, Gibson, Ferguson, Aitchison, & Paton (1995) investigated the adherence of 29 children (15 months-5 years old) to a prophylactic MDI. Adherence was monitored over a period of two months. Mean daily adherence was 48% as measured by the NC versus 72% based on parent diaries.

Modi & Quittner (2006b) compared EM versus a daily phone diary (DPD) to assess adherence to ICS by 10 children (6-13 years old) with asthma. EM measured adherence for one month. Average adherence for ICS was 70% by EM and 76% according to the DPD. The authors reported a moderate association between the two methods ($r = 0.43$, p

= .22), which indicates the need for further investigation of the convergence between EM and the DPD.

Purpose of Study

A recent review of evidence-based assessment of adherence to medical treatments recommends that studies of adherence include at least two methods of assessment (Quittner et al., 2008). The current study considered this recommendation, and sought to expand the limited data concerning how three measures of adherence relate to one another. The measures were Adherence Questionnaire (AQ), 24-hour Recall Interview (RI), and EM.

Study Hypotheses

Hypothesis 1. In view of the literature which consistently shows that global self-report measures of adherence greatly overestimate adherence, we predicted that the AQ would yield the highest rate of adherence followed by the RI and, lastly, the EM.

Hypothesis 2. Based on published reports of the diagnostic value of self-report tests, we predicted that specificity would be higher than sensitivity on the AQ and RI relative to the EM.

Hypothesis 3. Consistent with the recommendation of using multiple sources of information on adherence, we predicted that on the AQ and RI parent-child agreement about adherence status would be significantly correlated, but not redundant.

Chapter 2

Methods and Procedures

Location of Study

This study focused on the 14-day baseline period of a larger project designed to evaluate the efficacy of a randomized controlled adherence intervention trial for children with moderate to severe asthma (Kamps et al., 2008). The original study took place at two asthma and allergy clinics. The first site was the Pediatric Allergy and Immunology Clinic at the University of Kansas Medical Center (KUMC) located in Kansas City, Kans. The second site was the Asthma and Allergy Clinic, a private practice clinic located in Lawrence, Kans.

Inclusion/Exclusion Criteria

Children were eligible to participate in the original study based on the following entry criteria: (a) age 7 to 12 years; (b) have moderate to severe asthma as determined by their physicians using criteria established by the National Asthma Education Program Expert Panel Report 2 (NIH, 1997); and (c) prescribed once- or twice-daily ICS (beclomethasone or flucticasone). Participants missing any of the following adherence data were considered non-participants for the current study: (a) RI; (b) parent and child self-report adherence questionnaires; and (c) at least seven days of EM data covering the same time period as the other two adherence measures.

Assessment Measures

Adherence Questionnaire (AQ). The AQ (Appendix A) provides data on child's and parent's global perception of the child's adherence. The AQ has a parent and a child form. It consists of four multiple-choice questions, and is written in nonjudgmental

language. The possible range of scores is 0 to 36 with higher scores indicating greater perceived difficulty adhering to the ICS regimen. One question on the AQ asks for the most important reason the ICS is not taken as prescribed. This question was not included in data analyses because it concerns barriers to adherence as opposed to adherence itself. The remaining three questions were given equal weight when considering the sum (see Appendix A for details). The AQ – Parent Form is identical to the AQ – Child Form except that the questions target the respondent's child. The forms were scored identically.

The AQ is a continuous measure, but participants may be categorized as adherent or nonadherent based on their sum. A sum of zero on the AQ signifies that the respondent is reporting perfect adherence. A sum of nine or less on the AQ is considered adherent and a sum greater than nine is considered nonadherent. This allows the respondent to report that the child has "rarely forgotten" to take the ICS in the last two weeks, and that the ICS is not taken as prescribed, but as much as needed for health. The participants and their parent were asked to complete the AQ two times during the study: (a) on the same day they completed the permission/assent forms (Time 1); and (b) approximately 14 days after completing the initial AQ (Time 2).

24-Hour Recall Interview (RI). The parent and child were interviewed separately by phone once during the 14-day baseline period (Appendix B). The RI was conducted by a trained graduate research assistant. Each RI was approximately 20 minutes in length and followed the procedure described by Johnson and colleagues (1986; see details, p. 15). The RI addressed the following areas: (a) nighttime awakenings; (b) medications; (c) peak flow monitoring; (d) exercise; (e) asthma attacks; (f) other problems due to asthma; (g) unusual irritants; and (h) whether this was a typical day for the child. The current

study was concerned only with the information gathered regarding the child's adherence to the ICS regimen. Rate of adherence was calculated by dividing the number of doses reported by the parent or child by the number of doses prescribed. Based on the RI a child prescribed two doses per day was either 0, 50, or 100% adherent, while a child prescribed only one daily dose was either 0 or 100% adherent.

Electronic Monitor. The MDILog is a device used to monitor the use of inhaled medications for the treatment of asthma. The MDILog records the date and time of each actuation of the inhaler. In addition, the MDILog records whether various components of proper inhalation technique occurred: (a) whether the canister is shaken within one minute before actuation; and (b) if the patient's inhalation begins at the time of the actuation of the canister. These are important clinical features because inadequate shaking of the canister or improper inhalation could cause poor response to therapy. If a patient is prescribed multiple puffs per dose (e.g., two puffs 10 seconds apart), recordings from the MDILog can tell if the actuations are spaced correctly. This feature is useful because some asthma patients have been found to consume puffs of inhaled medication too close together to support efficacy (Berg, Dunbar-Jacob, & Rohay, 1998).

Apter and colleagues (2001) conducted an extensive calibration study of the mechanical reliability of the MDILog. The MDILog's most basic feature of clocking the time and date was accurate virtually 100% of the time. More than 1,200 actuations were recorded with each MDILog without battery failure. The accuracy of the MDILog was also assessed when used in conjunction with a spacer. The devices were able to recognize an inhalation when a spacer was used. The authors concluded that the accurate detection of inhalations makes it possible for the MDILog to distinguish true uses from dumping,

and that the MDILog is an accurate and reliable monitor of the adherence patterns for inhaled medication.

The current study calculated daily adherence by dividing the number of doses inhaled, with at least six hours between morning and evening doses as applicable, by the number of doses prescribed. This definition of adherence does not consider whether the medication was shaken properly before administration, the appropriate amount of time elapsed between consecutive puffs, or if the medication was inhaled late. At least 10 seconds should elapse between consecutive puffs. First inhalations are considered late if they occur between 0.9 and 7 seconds after the canister has been actuated.

Mean adherence was calculated by adding all of the daily adherence rates and dividing by the number of days with EM data. For those participants with more than 14 days of EM data, only the 14 days immediately prior to completing the AQ at Time 2 were included in mean adherence calculations. Only days when the participant had the EM for the entire day were considered. Thus, adherence data from the day the EM was given to the participant and the day it was returned to the research assistant were not included. Drug holiday, another measure of adherence, was also calculated. A drug holiday was declared when, according to the EM, no medication was inhaled for three or more consecutive days and then resumed.

Information Forms

Demographic Questionnaire. The Demographic Questionnaire (Appendix C) was created by the researchers of the original study for the purpose of obtaining the following information about each child participant and his/her family: (a) how the person completing the form is related to the child; (b) with whom the child lives most of the

time; (c) marital status of parent; (d) occupation of each parent; (e) level of education of each parent; (f) gender of child participant; (g) age of child; (h) age of both parents; (i) number of children living in the household and number receiving treatment for chronic diseases; and (j) total household income. The questionnaire was completed by the child's parent during the initial recruitment appointment.

Statistical Analysis

All analyses were completed using the Statistical Package for Social Sciences (SPSS, Chicago, Ill.) version 17.0. The data corresponding to participants were reentered into the database in order to check the accuracy of the original database. Data that did not pertain to the current study were not entered. The statistical analyses were conducted following confirmation of a complete and accurate data set.

Analyses were conducted to test whether participants were significantly different from non-participants. Independent-samples *t*-tests were used when considering continuous variables (e.g., child age). Chi-squared analyses were executed to examine categorical variables (e.g., ethnicity), and Yates's correction was applied to chi-square when $df = 1$. Linear-by-linear chi-squared analyses were executed for variables with ordered categories (e.g., household income).

Various characteristics of the AQ were evaluated. Internal consistency was measured using Cronbach's alpha (Cronbach, 1951), a measure of reliability. Cronbach's alpha considers correlations between items on a scale as evidence indicating whether the items measure the same underlying construct. Recommendations differ regarding the alpha levels required to justify the use of a scale. The proposed purpose of the scale does impact the required alpha level: for research, values above 0.7 are considered

satisfactory, whereas clinical applications require 0.9 or higher (Bland & Altman, 1997). Test-retest reliability was analyzed by correlating measures taken at Time 1 and Time 2.

Because multiple interviewers conducted the RI, it was necessary to investigate the extent to which interviewer was associated with reported adherence. Some interviewers conducted very few interviews; thus, a chi-square analysis was not appropriate because multiple cells contained expected values less than five. Each recruitment site (KUMC Pediatric Allergy and Immunology Clinic and Asthma and Allergy Clinic) had a different group of graduate students conducting the RI. The interviewers were collapsed by recruitment site and Fisher's Exact Test was utilized.

Spearman's correlations were calculated to investigate the relationships among the three measures of adherence. Additionally, agreement between adherence measures was examined as follows: The McNemar test for significance of changes for two related samples (McNemar's test; McNemar, 1947) was conducted to examine whether adherence measures significantly disagreed on overall adherence status (Sheskin, 1984).

Differences associated with *p*-values less than .05 were considered statistically significant.

Hypothesis 1. The number of participants classified as adherent based on each assessment tool was recorded. Participants were classified as adherent by the AQ if their sum was less than or equal to nine. Participants were classified as adherent by the RI if the reported adherence was 100%. Participants were classified as adherent by the EM if the mean rate of adherence across days was greater than either 70, 80, or 90%. These three different rates were used in separate analyses because the level of adherence to ICS required for therapeutic benefit is unknown. Following classification, statistically

significant disagreement between pairs of assessment tools was evaluated using McNemar's test.

Hypothesis 2. Sensitivity and specificity evaluate the diagnostic value of an assessment tool (Riegelman, 2000) relative to a reference standard. A sensitivity of 80% and a specificity of 90% are considered clinically useful to diagnose or rule out disease (Riegelman, 2000). In this study the "disease" in question was nonadherence, and EM-derived adherence data served as the reference standard. Sensitivity measures the percentage of participants who are nonadherent by the EM who are also labeled as such by the test (AQ or RI). Specificity measures the percentage of participants who are adherent by the EM who are also labeled as such by the test. This study investigated the sensitivity and specificity of the two self-report measures relative to 70, 80, and 90% adherence as reported by EM. Sensitivity and specificity for the AQ were calculated using separate analyses for each of the three individual items as well as for the sum.

The sensitivity and specificity of the parent and the child forms of the AQ were determined in the following manner:

1. The data obtained from the EM were used to classify participants as nonadherent for three separate analyses based on mean adherence less than 70, 80, or 90%.

2. Participants who responded "yes" to Item 1 were classified as nonadherent. Participants who responded "forgotten to take your [inhaled steroid] 1-3 times a week", "forgotten to take your [inhaled steroid] at least 4 times a week", or "never taken your [inhaled steroid]" to Item 2 were classified as nonadherent. Participants who responded "not as much as you're told to, and not as much as you need it for your health" or "not like you're told to, but as much as you need it for your health" to Item 3 were classified

as nonadherent. Participants whose sum on the AQ was greater than nine were classified as nonadherent.

3. A 2x2 table (see Table 1) was created for each of the three items on the AQ as well as for the total score. Each table reports the number of participants for whom the AQ and EM agreed or disagreed regarding adherence status. Each table also reports sensitivity, specificity, positive and negative predictive values.

4. Values for the sensitivity and specificity of each individual item and the sum of the AQ were calculated as shown in Table 1. These analyses were done separately for the parent and child forms.

Table 1. S*ensitivity and Specificity*

Test	EM Nonadherent	EM Adherent
Nonadherent by self-report	a = Number of participants who are nonadherent by EM & self-report: *true positive*	b = Number of participants who are adherent by EM, but nonadherent by self-report: *false positive*
Adherent by self-report	c = Number of participants who are nonadherent by EM, but adherent by self-report: *false negative*	d = Number of participants who are adherent by EM and adherent by self-report: *true negative*

a + c = Total number of participants who are nonadherent

b + d = Total number of participants who are adherent

Sensitivity = a / (a + c)

Specificity = d / (b + d)

Positive predictive value = a / (a + b)

Negative predictive value = d / (c + d)

The sensitivity and specificity of the parent and the child reports on the RI were determined in the following manner:

1. The EM data corresponding to the day prior to the RI showed the child to be nonadherent if adherence for that specific day was less than 100%.

2. Children were classified as nonadherent based on whether they reported taking their medication as prescribed the day prior to the RI. Those who reported taking less than 100% of the doses prescribed were classified as nonadherent.

3. The number of participants for whom the RI and EM agreed and disagreed were then calculated and organized in a 2x2 table (see Table 1).

4. Values for the sensitivity and specificity of the parent and the child recall were calculated as shown in Table 1.

Positive predictive value was calculated by dividing the number of true positives by the total number of participants who were nonadherent by self-report. Negative predictive values was calculated by dividing the number of true negatives by the total number of participants who were adherent by self-report.

Hypothesis 3. McNemar's test was conducted to examine whether children and adults significantly disagreed in overall nonadherence rate. Kappa, κ, was calculated as a measure of parent-child agreement between parent and child on the two self-report assessments. κ measures the extent of agreement between two raters, adjusting for the amount of agreement expected by chance (Cohen, 1960). The upper limit of κ is +1.00, which occurs only when there is perfect agreement between the judges. When obtained agreement equals chance, $\kappa = 0$. Less than change agreement yields $\kappa < 0$. κs were interpreted using the guidelines established by Landis and Koch (1977): $\kappa \leq 0.20$ is considered "slight" agreement; κ between 0.21 and 0.40 is considered "fair"; κ between 0.41 and 0.60 is considered "moderate"; κ between 0.61 and 0.80 is considered "substantial"; and κ between 0.81 and 1.00 is considered "almost perfect".

Parent-child agreement on the AQ was calculated for each of the three individual items as well as for the sum. According to Fleiss (1971), weighted κ is indicated when some forms of disagreement are more serious than others; serious disagreements have a larger influence on weighted κ than less serious disagreements. Weighted κ was used to

determine agreement for items two and three on the AQ because the responses on these items are ordered. Items two and three have five and three categories, respectively. An online tool offered by Vassar Stats (http://faculty.vassar.edu/lowry/kappa.html) was used to calculate κ for these multi-category measures using quadratic weighting. Figures 1 and 2 display the specific weights used to calculate weighted κ for items two and three of the AQ.

Figure 1. Quadratic Weighting of AQ Item #2

		AQ – Parent Version				
		A	B	C	D	E
AQ – Child Version	A	1	.937	.750	.437	0
	B	.937	1	.937	.750	.437
	C	.750	.937	1	.937	.750
	D	.437	.750	.937	1	.937
	E	0	.437	.750	.937	1

Note. A = never taken; B = forgotten at least 4 times a week; C = forgotten 1-3 times a week; D = rarely forgotten; E = never forgotten

Figure 2. Quadratic Weighting of AQ Item #3

		AQ – Parent Version		
		A	B	C
AQ – Child Version	A	1	.75	0
	B	.75	1	.75
	C	0	.75	1

Note. A = not as prescribed, and not as much as needed for health; B = not as prescribed, but as much as needed for health; C = just as prescribed

Chapter 3

Results

Participants

Over a 3-year study period, 89 children and their parents agreed to participate in the original project. Of these 89 families, 47 (53%) completed all of the measures required for inclusion in this study (see Figure 3).

Study Participants. Of the 47 participants, 80.4% were from married households. The majority of child participants lived at home with approximately two siblings. Twenty-five of the children (53%) were female, and 72% were Caucasian American. Child's age at study entry ranged from 7.04 to 12.62 years (M = 10.34, SD = 1.66). The modal household income was $30,000-$70,000 for 40% of the participant families. The Hollingshead Four-Factor Index of Social Status (HI; see Appendix D) was computed as a measure of socioeconomic status (SES; Hollingshead, 1975). The HI is often cited as one of the best known and most frequently used standard measures of SES (Ensminger & Fothergill, 2003). The HI for the participant families ranged from 6.75 to 38 (M = 21.97, SD = 6.96). The majority of children (70%) were prescribed two doses of ICS per day. Tables 2 and 3 provide additional detailed information about demographic characteristics.

Figure 3. *CONSORT Diagram of Participant Recruitment and Attrition*

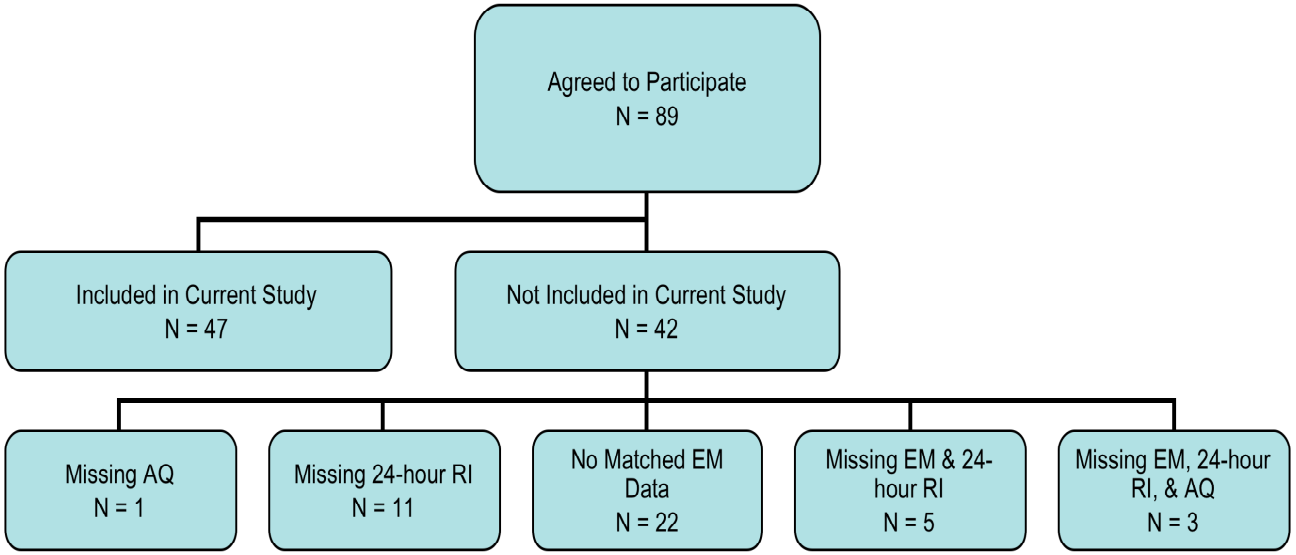

Table 2. *Categorical Demographic Variables n (%)*

Variable	Non-participants	Participants	*p*
Child Gender			.51
Male	23 (56%)	22 (47%)	
Female	18 (44%)	25 (53%)	
n	41	47	
Child Race			.17[a]
Caucasian American	10 (24%)	34 (72%)	
African American	23 (56%)	6 (13%)	
Asian American	0 (0%)	1 (2%)	
Hispanic	5 (12%)	4 (9%)	
Other[b]	3 (7%)	2 (4%)	
n	41	47	
Family Income			.01[c]
$0-$30,000	23 (61%)	12 (29%)	
$30,000-$70,000	8 (21%)	17 (40%)	
Above $70,000	7 (18%)	13 (31%)	
n	38	42	
Marital Status			.08[d]
Married	25 (61%)	37 (80%)	
Single	10 (24%)	5 (11%)	
Divorced	6 (15%)	4 (9%)	
n	41	46	
Number of Doses Prescribed			.09
1	4 (11%)	14 (30%)	
2	31 (89%)	33 (70%)	
n	35	47	
Recruitment Site			< .001
Lawrence	8 (19%)	32 (68%)	
KUMC	34 (81%)	15 (32%)	
n	42	47	

Note. [a]Chi-square analysis computed using Caucasian and Non-Caucasian. [b]The families who selected "Other" for the child's race identified as "Mexican/American", "Native American/East Indian", "Hispanic/African American", "biracial", and "White/Black". [c]Chi-square analysis computed using < $30,000 and > $30,000. [d]Chi-square analysis computed using married and not married.

Table 3. *Continuous Demographic Variables*

	Non-participants		Participants		*p*
Variable	*M*	*SD*	*M*	*SD*	
Child Age	9.72	1.48	10.34	1.66	.07
N	41		47		
Mother Age	34.63	5.86	39.24	5.01	<.001
N	41		45		
Father Age	38.11	8.97	41.70	6.97	.05
N	38		43		
HI[a]	20.74	9.58	21.97	6.96	.501
N	41		44		
Children at Home	2.54	1.33	2.39	1.34	.61
N	41		46		

Note. [a]HI = Hollingshead Index.

Group Differences. Analyses were conducted to test for differences in demographic variables between participants and non-participants. A chi-square test using Yates's Correction showed that participants were more likely to have been recruited from the Lawrence site as opposed to the clinic at KUMC ($\chi^2_{(1)} = 19.62$, $p < .001$). Non-participants were more likely to have a household income below $30,000 ($\chi^2_{(1)} = 7.03$, $p = .01$). The mothers of non-participants were significantly younger than participant mothers ($t = -3.93$, $df = 84$, $p < .001$, two-tailed). The fathers of non-participants were also significantly younger than participant fathers ($t = -2.03$, $df = 81$, $p = .05$, two-tailed). There were no significant differences between participants and non-participants on

child's age at study entry, parent's marital status, number of doses of ICS prescribed per day, gender, race, HI, or number of children at home.

Study Hypotheses

Hypothesis 1. The numbers of participants classified as adherent and nonadherent by each assessment tool may be found in Table 4. The assessment tool which classified the highest number of participants as adherent was the child and parent RI. This is contrary to the hypothesis that the AQ, the more global measure, would yield the highest rate of adherence. As hypothesized, the EM yielded the lowest rates of adherence. Statistically significant disagreements between assessment tools were found using McNemar's test. The child RI did not classify significantly more children as adherent than the AQ – Child Form (p = .057, McNemar's Test); however, the parent RI did classify more children as adherent than the AQ – Parent Form (p = .006, McNemar's Test). Significantly fewer children were classified as adherent by EM corresponding to day of RI than by the child RI (p = .003, McNemar's Test) or the parent RI (p = .001, McNemar's Test).

Table 4. *Frequency and Percent of Participants Classified as Adherent by Each Assessment Tool*

	Frequency	Percent
AQ-Child	32	68.09
AQ-Parent	30	63.83
EM ≥ 70	26	55.32
EM ≥ 80	20	42.55
EM ≥ 90	12	25.53
EM-R	26	55.32
Child-RI[a]	40	86.96
Parent-RI[b]	40	86.96

Note. AQ-Child = Adherence Questionnaire – Child Form, AQ-Parent = Adherence Questionnaire – Parent Form, EM = Mean electronic monitor adherence, EM-R = Electronic monitor adherence for 24-hour Recall Interview, Child-RI = Child 24-hour Recall Interview, Parent-RI = Parent 24-hour Recall Interview. [a] One child did not complete the RI. [b]One parent did not complete the RI.

Hypothesis 2. Specificity was higher than sensitivity for each item on the AQ and the sum score for the parent and the child forms (See Table 5). Specificity was higher than sensitivity for the parent and the child RI (See Table 6). None of the assessment tools reached the levels of sensitivity and specificity necessary to be used as a valid diagnostic tool. Under more stringent adherence criteria (e.g., mean EM-derived adherence of 90%) positive predictive values (PPV) increased while negative predictive values (NPV) decreased.

Table 5. *Sensitivity and Specificity of AQ*

Child Form (*n* = 47)	EM adherence											
	70				80				90			
Item	Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV
1	.29	.65	.40	.53	.24	.59	.40	.41	.31	.67	.73	.25
2	.24	.89	.63	.59	.20	.86	.63	.49	.23	1.00	1.00	.31
3	.24	.92	.71	.60	.20	.91	.71	.50	.17	.92	.86	.28
Sum	.29	.65	.40	.53	.24	.59	.40	.41	.31	.67	.73	.25

Parent Form (*n* = 47)	EM adherence											
	70				80				90			
Item	Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV
1	.48	.81	.67	.66	.44	.82	.73	.56	.40	.92	.93	.34
2	.38	.89	.73	.64	.32	.86	.73	.53	.29	.92	.91	.31
3	.43	.89	.75	.66	.32	.82	.67	.51	.29	.83	.83	.29
Sum	.57	.81	.71	.70	.48	.77	.71	.57	.46	.92	.94	.37

Sen = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value.

Table 6. *Sensitivity and Specificity of RI*

EM adherence = 80%								
Child Recall (*n* = 46)				Parent Recall (*n* = 46)			
Sen	Spec	PPV	NPV	Sen	Spec	PPV	NPV
.15	.89	.50	.58	.15	.89	.50	.58

Sen = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value.

The largest PPV was 1.00 for item two on the AQ – Child Form at 90% EM adherence; thus, 100% of the children classified by this item as nonadherent were actually nonadherent based on the EM data. The largest NPV was .70 for the sum on the AQ – Parent Form at 70% EM adherence. Seventy percent of children classified as adherent based on the total score for the AQ – Parent Form were actually adherent based on the EM data.

Hypothesis 3. McNemar's test may be used to determine that the bias between two raters is approximately equal (Sheskin, 1984). McNemar's test was not significant when comparing parent and child report on the AQ (p = .824, McNemar's Test) nor the RI (p = 1.00, McNemar's Test). The degree of agreement between parent and child on the RI was substantial (κ = .732).

Parent-child agreement on the AQ was calculated for each of the three individual items as well as the sum. Agreement on the first item of the AQ was at chance (κ = .021). Agreement using quadratic weighting for item two was moderate (κ = .437). Item three had fair agreement (κ = .204) using quadratic weighting. When considering the sum of the AQ, parent-child agreement was at chance (κ = .054).

Relationship between EM and Other Measures

AQ – Parent Form and Parent RI. The AQ – Parent Form had several significant correlations with EM-derived adherence (See Table 7). Item 1 was negatively correlated

with mean EM-derived adherence (ρ = −.32, p = .030), such that higher scores on item 1 were associated with a decrease in mean adherence. Drug holidays were correlated with item 1 (ρ = .33, p = .023) and item 3 (ρ = .31, p = .035), such that higher scores on both items were associated with the occurrence of more drug holidays. Item 2 had similar correlations with mean EM-derived adherence (ρ = −.40, p = .006) and drug holidays (ρ = .33, p = .026). The sum of AQ – Parent Form had the highest correlations with EM-derived adherence and drug holidays. Sum was negatively correlated with EM-derived adherence (ρ = −.42, p = .003), such that higher sums on the AQ- Parent Form were associated with lower mean adherence. Sum was positively correlated with drug holidays (ρ = .39, p = .006), such that higher sums were associated with more drug holidays.

The parent RI was not significantly correlated with the EM-derived adherence for RI day (ρ = .18, p = .230). The parent RI was positively correlated with item 1 of the AQ – Parent Form (ρ = .45, p = .002), such that higher adherence reported by the parent during the RI were associated with higher scores (lower adherence) on item 1 of the AQ – Parent Form. This correlation is not in the hypothesized direction. The parent RI was negatively associated with the sum of the AQ – Parent Form (ρ = −.44, p =.002), such that higher adherence reported by the parent during the RI were associated with lower sums (higher adherence) on the AQ – Parent Form.

Table 7. *Summary of Spearman's Correlations between Parent Versions of Assessment Tools*

	M-EM	Holidays	AQ-P 1	AQ-P 2	AQ-P 3	AQ-P Sum	EM-RI	C-RI	P-RI
M-EM									
Holidays	$\rho = -.63^{**}$ ($p < .001$)								
AQ-P 1	$\rho = -.32^{*}$ ($p = .030$)	$\rho = .33^{*}$ ($p = .023$)							
AQ-P 2	$\rho = -.40^{**}$ ($p = .006$)	$\rho = .33^{*}$ ($p = .026$)	$\rho = .46^{**}$ ($p = .001$)						
AQ-P 3	$\rho = -.27$ ($p = .066$)	$\rho = .31^{*}$ ($p = .035$)	$\rho = .27^{*}$ ($p = .072$)	$\rho = .51^{**}$ ($p < .001$)					
AQ-P Sum	$\rho = -.42^{**}$ ($p = .003$)	$\rho = .39^{**}$ ($p = .006$)	$\rho = .81^{**}$ ($p < .001$)	$\rho = .83^{**}$ ($p < .001$)	$\rho = .61^{**}$ ($p < .001$)				
EM-RI	$\rho = .62^{**}$ ($p < .001$)	$\rho = -.38^{**}$ ($p = .009$)	$\rho = -.24$ ($p = .104$)	$\rho = -.17$ ($p = .257$)	$\rho = -.32^{*}$ ($p = .029$)	$\rho = -.32^{*}$ ($p = .029$)			
C-RI	$\rho = .17$ ($p = .258$)	$\rho = -.14$ ($p = .351$)	$\rho = -.30^{*}$ ($p = .040$)	$\rho = -.14$ ($p = .356$)	$\rho = .03$ ($p = .869$)	$\rho = -.22$ ($p = .152$)	$\rho = .02$ ($p = .909$)		
P-RI	$\rho = .23$ ($p = .126$)	$\rho = -.16$ ($p = .299$)	$\rho = .45^{**}$ ($p = .002$)	$\rho = -.24$ ($p = .107$)	$\rho = -.23$ ($p = .123$)	$\rho = -.44^{**}$ ($p = .002$)	$\rho = .18$ ($p = .230$)	$\rho = .85^{**}$ ($p < .001$)	

Note. M-EM = Mean EM adherence without EM-RI, Holidays = Drug holidays, AQ-P 1 = AQ-Parent Item 1, AQ-P 2 = AQ-Parent Item 2, AQ-P 3 = AQ-Parent Item 3, AQ-P Sum = AQ-Parent Sum, EM-RI = EM-derived adherence for RI day, C-RI = Adherence reported in child RI, P-RI = Adherence reported in parent RI, * $p < .05$, ** $p < .001$.

AQ – Child Form and Child RI. The AQ – Child Form had no significant correlations with EM-derived adherence (See Table 8). Likewise, the child RI did not correlate with any of the other measures of adherence.

Table 8. *Summary of Spearman's Correlations between Child Versions of Assessment Tools*

	M-EM	Holidays	AQ-C 1	AQ-C 2	AQ-C 3	AQ-C Sum	EM-RI	C-RI	P-RI
M-EM									
Holidays	$\rho = -.63^{**}$ ($p < .001$)								
AQ-C 1	$\rho = .10$ ($p = .498$)	$\rho = -.01$ ($p = .937$)							
AQ-C 2	$\rho = -.31$ ($p = .037$)	$\rho = .13$ ($p = .387$)	$\rho = .14$ ($p = .348$)						
AQ-C 3	$\rho = -.24$ ($p = .109$)	$\rho = .06$ ($p = .709$)	$\rho = .23$ ($p = .113$)	$\rho = .06$ ($p = .676$)					
AQ-C Sum	$\rho = -.10$ ($p = .485$)	$\rho = .10$ ($p = .527$)	$\rho = .83^{**}$ ($p < .001$)	$\rho = .47^{**}$ ($p = .001$)	$\rho = .465^{**}$ ($p = .001$)				
EM-RI	$\rho = .62^{**}$ ($p < .001$)	$\rho = -.38^{**}$ ($p = .009$)	$\rho = .12$ ($p = .430$)	$\rho = .03$ ($p = .856$)	$\rho = -.08$ ($p = .611$)	$\rho = .09$ ($p = .551$			
C-RI	$\rho = .17$ ($p = .258$)	$\rho = -.14$ ($p = .351$)	$\rho = -.10$ ($p = .513$)	$\rho = -.28$ ($p = .062$)	$\rho = -.03$ ($p = .826$)	$\rho = -.15$ ($p = .317$)	$\rho = .02$ ($p = .909$)		
P-RI	$\rho = .23$ ($p = .126$)	$\rho = -.16$ ($p = .299$)	$\rho = .01$ ($p = .969$)	$\rho = -.22$ ($p = .136$)	$\rho = -.00$ ($p = .979$)	$\rho = -.02$ ($p = .875$)	$\rho = .181$ ($p = .230$)	$\rho = .85^{**}$ ($p < .001$)	

Note. M-EM = Mean EM adherence without EM-RI, Holidays = Drug holidays, AC-P 1 = AQ-Child Item 1, AQ-C 2 = AQ-Child Item 2, AQ-C 3 = AQ-Child Item 3, AQ-C Sum = AQ-Child Sum, EM-RI = EM-derived adherence for RI day, C-RI = Adherence reported in child RI, P-RI = Adherence reported in parent RI, * $p < .05$, ** $p < .01$.

EM-Derived Adherence. EM-derived adherence on the RI day was positively correlated with mean EM-derived adherence ($\rho = .62$, $p < .001$), which suggests that adherence on the RI day is representative of adherence over the entire 14-day period. EM-derived adherence on the RI day was negatively correlated with drug holidays ($\rho = -.38$, $p = .009$), such that higher adherence on the RI day was associated with fewer drug holidays. EM-derived adherence on the RI day was negatively correlated (i.e., agreed with) item 3 ($\rho = -.32$, $p = .029$) and the sum ($\rho = -.32$, $p = .029$) of the AQ – Parent Form respectively.

Additional Information about Assessment Measures

Adherence Questionnaire. Internal consistency for the AQ, measured using Cronbach's alpha, was .403 and .587 for the AQ – Child Form and AQ – Parent Form respectively. The AQ demonstrated poor test-retest reliability for the Child Form ($n = 46$) ($r = .459$, $p < .01$), but good test-retest reliability for the Parent Form ($n = 47$) ($r = .805$, $p < .001$). Descriptive statistics for the AQ at Time 1 and Time 2 are included in Table 9.

Table 9. *Descriptive Statistics for AQ (higher score = poorer adherence)*

	Child Form – Time 1 (*n* = 46)		Child Form – Time 2 (*n* = 47)		Parent Form – Time 1 (*n* = 47)		Parent Form – Time 2 (*n* = 47)	
Item	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
1[a, b]	2.30	4.77	3.83	5.66	3.20	5.37	3.83	5.65
2	3.72	3.30	2.43	2.47	3.51	3.21	3.00	2.26
3	1.83	3.55	1.02	2.60	2.68	4.11	1.91	3.56
Sum	7.89	9.37	7.28	7.83	9.07	0.36	8.74	9.04

Note. [b]One child completed only Item 1 at Time 1. [c]Two parents did not answer Item 1 at Time 1.

24-Hour Recall Interview. Fisher's Exact Test was used to investigate the influence of recruitment site on adherence status (adherent or nonadherent) reported on the RI. Neither parent (p = .157, Fisher's Exact Test) nor child (p = .647, Fisher's Exact Test) adherence rates as reported on the RI differed significantly between recruitment sites.

Analyses were conducted to investigate presence of systematic differences between various RI variables and EM-RI adherence. During the RI respondents reported on the behaviors of the previous day; thus, data from RI may pertain to a weekday or a weekend day. An independent samples t-test examined whether EM-RI adherence differed significantly depending on weekday or weekend day for the RI. No statistically significant difference was found between EM-RI adherence with respect to weekday or weekend day (t = 1.19, df = 45, p = .24, two-tailed). Fisher's Exact Test was conducted to examine the relationship between parent and child RI depending on when the RI occurred during the 14 day monitoring period. A RI that occurred during the first seven days was considered to be in the beginning of the period. No relationship was found between parents (p = .71, Fisher's Exact Test) or children (p = 1.00, Fisher's Exact Test) RI with respect to beginning or end of the monitoring period.

Electronic Monitor. The average of the EM data for each participant was calculated based on the 14 days immediately prior to completing the AQ at Time 2 without including partial days. Participants' adherence was monitored by EM for 10 to 28 days (M = 15.55, SD = 4.41). Nineteen participants had the EM for more than 14 days; their average EM-derived adherence did not differ significantly from that of participants who had 14 or fewer days (t = −.98, df = 45, p = .33, two-tailed). In this study a drug

holiday was declared when EM-derived adherence was zero for three or more consecutive days and then resumed. Thirty-seven of the participants (78.72%) did not take a drug holiday. However, ten participants (21.28%) had at least one drug holiday during the 14-day period.

An independent samples *t*-test examined whether EM-derived adherence differed significantly between the 14 participants prescribed a once daily dose of ICS (M = 75.70, SD = 24.74) and those prescribed twice daily doses of ICS (M = 63.61, SD = 30.22). EM-derived adherence did not differ significantly (t = 1.32, df = 45, p = .097, one-tailed); however, the difference in mean adherence suggests a moderate effect. Thus, it is likely that the small number of participants per group does not yield adequate statistical power for this analysis.

A one sample *t*-test was conducted to test whether the EM-derived adherence rates for the total sample differed significantly from 50% (the rate commonly reported in the literature). The sample distribution of mean adherence did not reject the assumptions of normality as described by Tabachnick & Fidell (1996). The EM-derived mean adherence for the entire sample was 67.21 which is significantly different than 50 (t = 4.07, df = 45, p < .001, two-tailed). Table 10 provides additional descriptive information about the EM-derived adherence for the sample.

Table 10. *Descriptive Statistics of EM-derived Adherence for Sample*

N	47
Minimum	0
Maximum	100
Mean	67.21
Median	76.92
Standard Deviation	28.98
Standard Error of Mean	4.23
Standard Deviation	28.98

A paired-samples *t*-test was conducted to investigate whether mean EM-derived adherence changed significantly from the beginning (Days 1-5) to end (Days 10-14) of the 14-day monitoring period. The difference was marginally significant ($t = 1.83$, $df = 46$, $p = .074$, two-tailed), with EM-derived adherence showing a drop over time (71.06 ± 31.36 vs. 52.34 ± 29.58). This suggests that the children's medication-taking behavior may have been initially influenced by use of the EM. This reactivity appears to have lessened over time; adherence at the end of the 14-day monitoring period may be more representative of the children's typical adherence.

As previously mentioned, the EM used in this study (MDILog) records each actuation of the inhaler and whether various components of proper inhalation technique occurred. The percent of actuations that did not meet the following criteria was recorded: (a) canister was shaken vigorously within one minute before actuation; (b) inhalation occurred within 0.9 seconds of canister actuation (inhalations occurring between 0.9 and

7 seconds after actuation were considered "late" and after 7 seconds the actuation was considered "no inhale"; (c) at least six hours between morning and evening doses; and (d) at least ten seconds between consecutive puffs. Participants had to have the opportunity to correctly administer each component of proper inhalation technique in order for the component to be considered an error. For example, interval between morning and evening doses is not applicable to participants prescribed ICS one time daily; thus, none of the actuations completed by these participants were included in the error rate.

Summary information regarding inhalation technique for the sample may be found in Table 11 and detailed results may be found in Appendix E. These results suggest that inhalation technique is a considerable problem for children in this age range.

Table 11. *Percent of Actuations Not Properly Administered by Error Type*

Error Type	Percent (n = 42)[a]
Canister not shaken	32.86
Late inhalation	23.62
No inhalation	18.62
Less than six hours between morning and evening doses	3.23
Less than ten seconds between consecutive puffs	42.67

Note. [a]Detailed EM data for five participants were not available.

Chapter 4

Discussion

The present study examined relationships among three methods of assessing adherence to ICS treatment for pediatric asthma (RI, AQ, and EM). Results are comparable to similar studies in several ways: (a) a considerable number of children exhibit problematic adherence; (b) limited knowledge and poor mastery of how to properly administer medication is likely a barrier to adherence; (c) self-report tools yield inflated estimates of adherence; (d) parents and children tend to agree on the child's adherence, but also provide unique information about adherence; and (e) multiple methods of assessment are needed for a more accurate representation of adherence.

As previously mentioned, nonadherence is a problem that is financially costly (e.g., unnecessary increases in medication, treatment wrongfully concluded to be ineffective in clinical trial, etc.) and potentially harmful (e.g., exacerbation of disease). Classifying participants according to the conventional cutoff of 80% resulted in 42.55% of this sample being "adherent" based on EM data. Given that the amount of adherence to ICS required for therapeutic benefit in pediatric asthma is unknown, it is important to note that drastically fewer participants (only 25.53%) were classified as "adherent" when a cutoff of 90% was employed.

This study required that an actuation of the ICS must be inhaled (either on time or late) in order to be counted toward adherence. This criterion is more stringent than previous ones because older models of EMs did not have this capability. The relatively large percent of actuations that were not inhaled by this sample (18.62%) suggests that adherence would be considered higher if inhalation was not a required response

component. This result also suggests that a large number of participants in this sample either did not know how or chose not to properly inhale their ICS. Most ICS must be inhaled for therapeutic benefit; thus, the Expert Panel Report recommends regular assessment of ICS technique (NIH, 2007). As EMs become more accurate at confirming inhalation they are likely to be clinically useful for identifying poor inhalation technique that may indicate the need for a spacer or valved holding chamber (NIH, 2007).

It has consistently been reported that simplified treatment regimens are associated with higher adherence (Rapoff, 2010). Fourteen participants in this study were prescribed a once daily dose of ICS. EM adherence for those participants did not differ significantly from participants prescribed two doses per day; however, the difference in mean adherence suggests a moderate effect. Thus, it is likely that the small number of participants per group does not yield adequate statistical power for this analysis.

In accordance with the literature, the self-report measures utilized in this study did inflate estimates of adherence compared to the more objective EM estimates. While clinicians and researchers may not utilize the specific measures used in this study, the findings are likely to be helpful in informing their choice of adherence measure. The extent to which inflated adherence represents a significant hindrance is likely determined by the level of accuracy indicated by one's goal (Bender et al., 2000). For example, clinicians may be satisfied with a quick measure with moderate accuracy while a researcher conducting a clinical trial will require highly accurate adherence measures.

When working with children it is particularly important to obtain data from multiple sources; consequently, it is important to understand the relationship between parents' and children's reports of adherence. As hypothesized, parent-child agreement on

the AQ and on the RI was high but not perfect with regard to adherence status. Results of the present study indicate that children aged 7 to 12 years may not be the most reliable and valid reporters of adherence. This is evident in the lack of significant correlations between the child version of both the AQ and RI with mean EM-derived adherence. Child RI was significantly correlated with drug holidays, suggesting that child report does provide additional information. It may be best for children to report on specific concepts of adherence that do not require detailed information (e.g., number of drug holidays in the past week). Thus, parent report is particularly important when considering children in this age range. When a child reaches adolescence it is likely that they will be as accurate, if not more accurate, reporters of adherence than their parents. This is because parents tend to give more responsibility to the adolescent for executing the treatment regimen than a child of 7 to 12 years.

Neither the AQ nor the RI was found to be sufficient measures of adherence. Consequently, the results of this study support the recommendation made by Quittner and colleagues (2008) that at least two methods of adherence be used in research studies. This study adds to the existing literature by providing additional information about how methods of assessing adherence interrelate.

The relatively large PPV of the AQ, particularly the Parent Form, suggests that it may be useful in a clinical setting. The AQ could be used as a screening tool during medical appointments. Those patients who indicate difficulty with adherence on the AQ would then be given an EM to confirm or deny nonadherence.

Limitations

There are several limitations to this study, the most notable being that data were obtained from a preexisting database. The original study was not designed for the expressed purpose of examining relationships among methods of assessing adherence. Thus, the current study was not conducted under ideal circumstances. The length of the monitoring period in the current study is shorter in comparison to other studies and does not allow for extended examination of adherence. Nevertheless, compared to similar studies, this study included a relatively large number of participants with an extensive amount of information regarding adherence to an ICS regimen over a particular time period.

The significant group differences between participants and non-participants limits the ability to generalize findings. Specifically, participants were more likely to have a higher household income and to be recruited from the private practice site in Lawrence, KS as opposed to the KUMC site. The KUMC site serves an urban population with a high representation of minority children and children from lower income families. In this study, neither household income nor SES was significantly associated with EM adherence. Given the evidence suggesting that lower SES is associated with greater nonadherence (Rapoff, 2010), this null finding is most likely an artifact of small sample size.

The EM-derived mean adherence for all of the participants was significantly greater than 50%. This suggests that as a whole the children in this study had less difficulty with adherence than most of the children reported in other studies. This may have implications for the appropriateness of using the AQ and 24-hour RI with this sample. It is possible

that these measures are not sensitive to moderate problems with adherence, but would be with a more impaired sample.

It is important to mention limitations associated with the specific assessment tools used in this study. The internal consistency for the AQ – Parent and Child Forms was lower than the recommended $\alpha \geq .70$ (Bland & Altman, 1997). This suggests that the AQ is not a pure measure of adherence, which is notable considering that only three questions are on the AQ. Thus, questions that researchers create to examine one concept may be interpreted by participants differently. The AQ – Child Form exhibited poor test-retest reliability, but the AQ – Parent Form was considerably more reliable.

The RI as used in this study possesses several limitations. Most obvious is that data for the current study were available for only one interview. No significant difference was found between adherence reported for a weekday and weekend day on the 24-hour RI. This is an unanticipated finding and is likely an artifact of having only nine interviews inquiring about a weekend day.

The original protocol did include the recommended three recall interviews (two weekdays and one weekend day), but it was determined that the demand on participants and research assistants was too great. This significantly limits our ability to make recommendations concerning the RI procedure. Nevertheless, it is noteworthy that research assistants reported difficulty with contacting busy families and participating families suggested that the interviews were burdensome. This study more closely resembles what would likely occur in a clinical situation.

The large number of participants classified as adherent based on the RI suggests that despite the relatively unobtrusive nature of the RI (Modi et al., 2006), social

desirability may have been a factor in this study. It is possible that respondents are more likely to be influenced by social desirability factors during the first interview. This influence may decrease over time and would need to be accounted for over the recommended three interviews. This study could not investigate this notion because only one interview occurred. Parent-child RI agreement was unexpectedly high. While the interviews are designed to be conducted independently, it is possible that the parent and child were both present during at least some interviews. Overhearing the other person's interview may have influenced responding.

Future Directions

Findings from the current study indicate the continued need for studies investigating optimal methods for obtaining valid and reliable assessments of adherence. As previously mentioned, neither of the self-report tools investigated in this study were found to be accurate stand-alone measures of adherence; thus, it is recommended that at least two methods of adherence be used in research studies (Quittner et al., 2008). Future efforts should be made to report on how to effectively use multiple methods of assessment in clinical and research endeavors. Various suggestions have been made: (a) use EM data to "correct" error associated with self-report (Jasti, Siega-Riz, Cogswell, & Hartzema, 2006); and (b) "triangulate'' methods for a more accurate assessment of adherence (Quittner et al., 2008). However, few studies have reported using such techniques.

Few validated self-report and interview tools are available in the literature; it is likely, however, that additional tools are in fact being used (Quittner et al., 2008). Researchers should be encouraged to evaluate and report the psychometric properties of

the adherence measures utilized in their studies. This will facilitate growth in the assessment of adherence to pediatric chronic illnesses and will help place the results of future studies into context because professionals will be familiar with the measures. Likewise, future studies should include a cost-effectiveness analysis (Muenning, 2008).

There continues to be a need to determine the level of adherence to ICS required for positive health benefits in pediatric asthma. Without this information it is difficult to place adherence findings into the context of health outcomes. Similarly, findings are not as meaningful when we do not fully understand the implications for health benefits of treatments.

Summary and Conclusions

The aim of this study was to examine relationships among three commonly used methods of assessing adherence to ICS treatment for pediatric asthma. This study found that parent and child 24-hour Recall Interviews (RI) inflated adherence estimates to a greater extent than the parent and child Adherence Questionnaires (AQ). This finding was contrary to prediction and must be considered in the context of the study's limitations. This study is one of the few studies that uses indicators (sensitivity, specificity, positive and negative predictive value) traditionally used to evaluate the diagnostic performance of tests. Neither the AQ nor the RI demonstrated psychometric properties which allow for the tools to be used as stand-alone measures of adherence for research or for daily clinical use. Parent-child agreement was high, but not redundant. This finding highlights the shared responsibility for following children's treatment regimens that may be unique to this age group (7 to 12 years old).

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Appendix A

Adherence Questionnaire - Child Form

Participant's Name: _____ Participant Number: _____
Date of Completion: _____

1. Some children have problems taking their medicines the way they were told to. Do you ever have problems taking your [inhaled steroid] the way you were told to?

_12_ yes
__0_ no

2. Some children have trouble remembering to take their medicines. Would you say that in the last 2 weeks you have …

_12_ never taken your [inhaled steroid]
__9_ forgotten to take your [inhaled steroid] at least 4 times a week
__6_ forgotten to take your [inhaled steroid] 1-3 times a week
__3_ rarely forgotten to take your [inhaled steroid]
__0_ never forgotten to take your [inhaled steroid]

3. Would you say that you take your [inhaled steroid]:

__0_ just as you're told to
__6_ not like you're told to, but as much as you need it for your health
_12_ not as much as you're told to, and not as much as you need it for your health

4. What is the most important reason you don't take your [inhaled steroid] as prescribed?

___ forget to take it
___ too busy to take it
___ don't need it
___ side-effects
___ feeling pain/sick/worse
___ other (describe) _____

Adherence Questionnaire - Parent Form

Participant's Name: _____ Participant Number: _____
Date of Completion: _____

1. Some parents have problems reminding their child to take their [inhaled steroid] as prescribed. Do you ever have problems giving your child his/her inhaler as prescribed?

_12_ yes
__0_ no

2. Some parents have trouble reminding their child to use their [inhaled steroid]. Would you say that in the last 2 weeks your child has …

_12_ never taken his/her [inhaled steroid]
__9_ forgotten to take his/her [inhaled steroid] at least 4 times a week
__6_ forgotten to take his/her [inhaled steroid] 1-3 times a week
__3_ rarely forgotten to take his/her [inhaled steroid]
__0_ never forgotten to take his/her [inhaled steroid]

3. Would you say that your child takes his/her [inhaled steroid]:

__0_ just as prescribed
__6_ not as prescribed, but as much as he/she needs it for his/her health
_12_ not as prescribed, and not as much as he/she needs it for his/her health

4. What is the most important reason your child doesn't take his/her [inhaled steroid] as prescribed?

___ forgets to take it
___ too busy to take it
___ doesn't need it
___ side-effects
___ feeling pain/sick/worse
___ other (describe) _____

Appendix B

Interviewer's Name _____
Patient's Name _____ ID # _____
Parent ( ) Child ( )
Today's Date: _____ Yesterday was a Weekday ( ) Weekend ( )

NIGHTLY AWAKENINGS

Time	Time
Parent Obs? YES NO	Parent Obs? YES NO
Activities?	Activities?
Time	Time
Parent Obs? YES NO	Parent Obs? YES NO
Activities?	Activities?

MEDICATIONS

Time am	Time am	Time am	Time am
Amount	Amount	Amount	Amount
Parent Obs? Yes No	Parent Obs? Yes No	Parent Obs? Yes No	Parent Obs? Yes No
On time Late None	On time Late None	On time Late None	On time Late None
Notes:			
Time pm	Time pm	Time pm	Time pm
Amount	Amount	Amount	Amount
Parent Obs? Yes No	Parent Obs? Yes No	Parent Obs? Yes No	Parent Obs? Yes No
On time Late None	On time Late None	On time Late None	On time Late None

PEAK FLOW MONITORING

Morning		Retest	
Time	Zone	Time	Zone
Time	Zone	Time	Zone
Time	Zone	Time	Zone
Behaviors Taken		Behaviors Taken	

PEAK FLOW MONITORING

Evening		Retest	
Time	Zone	Time	Zone
Time	Zone	Time	Zone
Time	Zone	Time	Zone
Behaviors Taken		Behaviors Taken	

Exercise

What type?	What type?	What type?
How Long?	How Long?	How Long?
Take inhaler? YES NO	Take inhaler? YES NO	Take inhaler? YES NO
Asthma attack? YES NO	Asthma attack? YES NO	Asthma attack? YES NO
Comments	Comments	Comments

ACUTE ASTHMA ATTACKS

Time: began:	Time: began:	Time: began:	Time: began:
How long last?	How long last?	How long last?	How long last?
Symptoms	Symptoms	Symptoms	Symptoms
Parent Obs? YES NO	Parent Obs? YES NO	Parent Obs? YES NO	Parent Obs? YES NO
Actions Taken	Actions Taken	Actions Taken	Actions Taken

OTHER PROBLEMS DUE TO ASTHMA

Missed school or other planned activities?	YES NO
Called physician or emergency room?	YES NO
What did physician say, instruct, etc.?	
Visited Doctor?	YES NO
Visited Hospital?	YES NO
Burst of prednisone?	YES NO

UNUSUAL IRRITANTS

1.	YES NO
2.	
3.	
4.	
5.	

COMMENTS:

AREAS TO ADDRESS IF NOT ALREADY DISCUSSED

☐ 1. Nighttime awakenings

☐ 2. Medication

☐ 3. Peak flow monitoring

☐ 4. Exercise

☐ 5. Asthma attacks

☐ 6. Other problems due to asthma (physician, hospital, etc.)

☐ 7. Unusual irritants

☐ 8. Was this a typical day?

☐ 9. Is there anything else related to your child's asthma that you think we should know?

Appendix C

Information Form

Instructions: Please complete the following questions by placing an “x” on the line next to the answer that best describes your family.

How are you related to the child who will be participating in this study?

___ mother

___ father

___ grandparent

___ other (please describe: _____)

With whom does the child live most of the time?

___ mother

___ father

___ grandparent

___ other (please describe: _____)

What is your current marital status?

___ married

___ single

___ divorced

Please describe the occupation of both parents:

mother: _____

father: _____

What is the highest grade level completed by the child’s mother?

___ less than 7th grade

___ junior high school

___ partial high school

___ high school graduate

___ some college or specialized training

___ college graduate

___ graduate/professional training

What is the highest grade level completed by the child's father?

___ less than 7th grade

___ junior high school

___ partial high school

___ high school graduate

___ some college or specialized training

___ college graduate

___ graduate/professional training

Gender of the child participating in the study:

___ male

___ female

Ethnicity of the child participating in the study:

___ African American

___ Asian American

___ Caucasian

___ Hispanic

___ Other (please describe: _____)

Age of the child participating in the study: ___

Age of mother: ___ Age of father: ___

How many children are currently living in the household? ___

What are their ages? _____

How many are receiving treatment for other chronic diseases? ___

Household Income:

___ less than $10,000

___ $10,000-$30,000

___ $30,000-$50,000

___ $50,000-$70,000

___ $70,000-$100,000

___ more than $100,000

Appendix D

Hollingshead Index – as described in Ensminger & Fothergill (2003)

The HI is based on the education and occupation of each employed householder in a home. A householder is defined as a person who has or shares financial responsibility for maintaining the home and supporting the family members living there (Hauser, 1994). Homemakers, students, and unemployed individuals are not included in the calculations, with one exception: If there is no employed adult in the household, the HI is based on the one (unemployed) person most likely to be considered the householder. Occupation is keyed to approximately 450 titles and codes from the 1970 US Census and is graded on a 9-point scale. Education is based on the number of years of school achievement and is scored on a 7-point scale. To determine the HI for an individual, scores on the two scales are weighted and summed; the education score is weighted by 3 and the occupation score is weighted by 5. The sum of the weighted scale scores results in a HI score ranging from 8 to 66. For families with more than one householder, individual HI scores are averaged to obtain a single family HI.

Hollingshead Index of Occupational Status Scale

(1) Farm Laborers/Menial Service Workers
(2) Unskilled Workers
(3) Machine Operators and Semiskilled Workers
(4) Smaller Business Owners, Skilled Manual Workers, Craftsmen, and Tenant Farmers
(5) Clerical and Sales Workers, Small Farm and Business Owners
(6) Technicians, Semiprofessionals, and Small Business Owners
(7) Smaller Business Owners, Farm Owners, Managers, and Minor Professionals
(8) Administrators, Lesser Professionals, and Proprietors of Medium-Sized Businesses
(9) Higher Executives, Proprietors of Large Businesses, and Major Professionals

Hollingshead Index Education Scale

(1) Less than 7th grade
Highest grade completed:
_____
(2) 7th, 8th, or 9th grade
(3) 10th or 11th grade
Which one(s) completed?
_____
(4) High school or GED
Which?
_____
(5) Partial college (at least 1 year completed); or has completed specialized training
Number of years of college completed:
_____
Type of college degree received:
_____
Type of specialized training:
_____
Years of specialized training completed:
_____
(6) Standard college or university graduate
Type of degree received:
_____
(7) Graduate professional training
Type of degree received:
_____

Mean percent of inhaled corticosteroid actuations incorrectly administered for each participant by error type

ID	Doses	No inhale	“Late” inhale	No shake	Dosing interval	Puff interval
1	2	33.33	0	8.33	n/a	67.86
2	2	13.64	0	38.64	12.5	23.81
3	2	4.76	0	4.76	0	21.43
4	2	0	21.82	0	0	3.7
5	2	0	32.14	46.43	0	0
6	2	11.36	18.18	54.55	0	72.73
7	2	56.76	21.62	100.00	0	58.62
8	2	16.42	28.36	25.37	0	23.68
9	2	5.00	20.00	10.00	0	100.00
10	2	20.59	27.94	5.88	0	73.81
11	2	8.00	6.00	12.00	0	14.81
12	1	0	84.21	0	n/a	0

ID	Doses	No inhale	“Late” inhale	No shake	Dosing interval	Puff interval
13	2	0	47.83	0	0	0
14	2	33.33	20.83	0	n/a	85.00
15	1	5.00	5.00	10.00	n/a	30.00
16	2	51.25	11.25	8.75	0	50.00
17	2	31.03	8.62	36.21	0	45.24
18	1	10.64	19.15	0	n/a	33.33
19	1	30.00	20.00	0	n/a	46.15
20	1	23.53	35.29	0	n/a	31.48
21	2	4.00	80.00	6.00	0	16.00
22	1	23.68	50.00	36.84	n/a	26.92
23	2	17.78	57.78	0	0	58.33
24	1	39.68	11.11	63.49	0	57.45
25	1	72.00	10.00	36.00	n/a	87.50
26	2	31.03	34.48	37.93	11.11	37.84

ID	Doses	No inhale	“Late” inhale	No shake	Dosing interval	Puff interval
27	2	9.43	39.62	9.43	10.00	30.00
28	1	0	75.00	100.00	n/a	n/a
29	1	65.31	14.29	73.47	n/a	24.14
30	1	5.00	40.00	100.00	n/a	22.22
31	2	11.54	5.77	15.38	0	41.38
32	2	0	9.62	19.23	0	65.38
33	2	1.75	0	0	0	93.10
34	2	32.08	7.55	0	36.36	44.83
35	2	0	11.11	82.22	11.11	56.52
36	2	11.43	11.43	71.43	0	5.26
37	2	2.04	8.16	85.71	0	86.96
38	2	79.17	4.17	0	12.50	33.33
39	2	1.72	15.52	86.21	0	84.38
40	2	2.33	4.65	95.35	0	10.00

ID	Doses	No inhale	“Late” inhale	No shake	Dosing interval	Puff interval
41	2	4.08	36.73	97.96	0	32.00
42	1	13.16	36.84	2.63	n/a	54.17

Note. No inhale = inhalation did not occur within 7 s of inhalation; “Late” inhale = inhalation occurred between 0.9 and 7s after actuation; No shake = canister was not shaken vigorously within 1 min before actuation; Dosing interval = less than 6 hrs between morning and evening doses; Puff interval = less than 10 s between consecutive puffs; n/a = inhalation technique component is not applicable to participant because he/she never had the opportunity to perform it correctly.