PREDICTORS OF NON-ADHERENCE TO ORAL CHEMOTHERAPY IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Abstract

Overall survival for pediatric patients with acute lymphoblastic leukemia (A.L.L.) treated with contemporary therapy now exceeds 85%; however, approximately 20% will experience relapse. Since A.L.L. is the most common malignancy in children, relapsed patients comprise a large proportion of the total number of children with cancer. The prognosis for long-term survival following relapse is generally poor; thus, relapsed A.L.L. is a significant contributor to cancer-related mortality in children.

Poor adherence to oral medication is a substantial problem in contemporary health care and may contribute to unexplained relapses in children with A.L.L. Therapy for pediatric A.L.L. includes a prolonged "maintenance" phase that requires daily 6-mercaptopurine (6MP), a self- or parent/caregiver-administered oral chemotherapy agent given for approximately two years. 6MP has been shown to be a critical component of the curative regimen for A.L.L.; thus, children with A.L.L. who fail to adhere to oral 6MP chemotherapy as prescribed may be at increased risk of leukemia relapse.

This study used extant questionnaire data from a cohort of children with A.L.L enrolled on a Children's Oncology Group study (AALL03N1) to determine the prevalence of self/parent-reported non-adherence to oral 6MP during the maintenance phase of A.L.L. therapy, and to identify sociodemographic and behavioral predictors of non-adherence to oral 6MP.

Twenty-two percent of children in the cohort were non-adherent to oral chemotherapy, defined as missing more than one dose of 6MP for non-medical reasons over the 112-day observation period. The risk of non-adherence was significantly

increased for those who failed to perceive the severity of the child's illness (Odds ratio [OR] 1.89, 95% Confidence Interval [CI] 1.00-3.55, P=0.049) or the benefits of treatment with oral 6MP (OR 1.78, 95%CI 1.07-2.94, P=0.025). Vulnerable subgroups included Hispanic ethnicity (OR 2.25, 95%CI 1.30-3.90, P=0.004) and older age (OR 1.07 per year, 95%CI 1.02-1.12, P=0.005).

Study findings suggest that even occasional reports of missed 6MP doses may herald a significant adherence problem; that patients and their parents may need ongoing reminders regarding the subclinical and asymptomatic nature of leukemia in remission; and that frequent review with families regarding the purpose, function, and proper administration of oral 6MP is imperative.

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List of Abbreviations

Abbreviation	Term
6MP	6-mercaptopurine
6TGN	6-thioguanine nucleotide
A.L.L.	Acute lymphoblastic leukemia
AQ	Adherence Questionnaire
CNS	Central nervous system
DHEA-S	Dehydroepiandrosterone sulfate
DOB	Date of birth
DQ	Demographics Questionnaire
HBM	Health Belief Model
HCPR	Healthcare Provider Report
HPRT	Hypoxanthine-guanine phosphoribosyltransferase
MethylTIMP	6-methylthioinosine monophosphate
MMP	Methylated mercaptopurine
MRW	Maintenance Report Worksheet
NCI	National Cancer Institute
PCR	Parent/Caregiver Report
RBC	Red blood cell
SCT	Social Cognitive Theory
SR	Self Report
SPSS	Statistical Program for the Social Sciences
TPMT	Thiopurine methyltransferase
WBC	White blood count
XO	Xanthine oxidase

Chapter 1: Introduction

1.1. Childhood Acute Lymphoblastic Leukemia (A.L.L.)

Acute lymphoblastic leukemia (A.L.L.), a malignant disorder of lymphoid hematopoiesis, is the most common malignancy of childhood, accounting for nearly 25% of all cancer diagnosed in children less than 15 years of age (Horner, et al., 2009). Childhood A.L.L. occurs at an annual rate of 38.0 per million (Spector, Ross, Robison, & Bhatia, 2006), and approximately 2,400 children under the age of 15 are diagnosed with A.L.L. in the United States each year (Jemal, et al., 2009; Spector, et al., 2006). Common symptoms of childhood A.L.L. include pallor, fatigue, fever, bruising, bleeding, and bone and joint pain. Clinical manifestations are generally related to impaired hematopoiesis and extramedullary spread of the disease (Pui, 2006a).

Prior to the advent of modern leukemic therapy in the latter half of the twentieth century, childhood A.L.L. had a rapidly fatal course, and most children succumbed to the disease within a matter of months (Simone, 2006). However, with contemporary therapy, survival rates have steadily improved, particularly over the past four decades, such that current 5-year survival rates now exceed 85% (Jemal, et al., 2009).

1.2. Relapse in Childhood A.L.L.

Even with contemporary therapy, approximately 1 in 5 children with A.L.L. will experience relapse (recurrence) of their disease (Nguyen, et al., 2008). Since A.L.L. is the most common malignancy in children, those who experience relapse comprise a large proportion of the total number of children with cancer. In fact, relapsed A.L.L. occurs more frequently than newly diagnosed acute myeloid leukemia and most solid tumors of

childhood (Harned & Gaynon, 2008). Once relapse has occurred, the prognosis for long-term survival is generally poor; thus, relapsed A.L.L. is a significant contributor to cancer-related mortality in children (Nguyen, et al., 2008).

1.3. Treatment of Childhood A.L.L.

Childhood A.L.L. is typically treated in four distinct phases. Each phase plays a specific role in achieving the overall goal of cure of the child's leukemia. The intensity of each phase and the agents employed for treatment vary based on prognostic features of the disease, which are generally determined at or near the time of diagnosis. The process of determining treatment based on prognostic features of the disease is known as "risk-directed therapy." Using a risk-directed strategy for treatment assignment, patients with the most unfavorable prognoses (and hence, the highest risk of relapse) receive the most intensive therapies, while patients whose predicted outcomes are more favorable (and whose risk of relapse is therefore lower) receive less intensive therapies. The overall goal is to maximize the potential for successful outcomes while limiting both immediate and long-term toxicities through a process that reserves the most intensive and toxic therapies for those children who stand to benefit most from their use.

Prognostic features in childhood A.L.L. include the child's age, white blood count at diagnosis, leukemic cell lineage (immunophenotype), rapidity of response to therapy, and cytogenetic characteristics of the leukemic cells (Pui, 2006a). Major factors known to have prognostic implications in childhood A.L.L. are listed in Table 1.1 on the next page. Higher intensity therapy, if required, is generally delivered during the initial phases of leukemic therapy, and the vast majority of patients receive similar therapy during the

final and longest phase of treatment, known as "maintenance," a period during which daily oral chemotherapy is prescribed.

Table 1.1 Major prognostic features in childhood A.L.L. [Adapted from Pui (2006b)].

Factor	**Favorable**	**Unfavorable**
Age at diagnosis	1 to 9 years	<1 year or ≥10 years
WBC at diagnosis	<50,000/μL	≥50,000/μL
Gender	Female	Male
Response to therapy	Rapid early response	Slow early response
Immunophenotype	Precursor-B cell	T-cell
Cytogenetic features	t(12;21) *TEL-AML1*	t(4;11) – *MLL* (11q23)
	Trisomy 4, 10	t(9;22) – *BCR/ABL*
	Hyperdiploidy	Hypodiploidy

Abbreviation: WBC = White blood cell count

1.3.1. Phases of therapy in childhood A.L.L. Treatment for childhood A.L.L. generally spans a two to three year time period. The initial intense phases of therapy (Induction, Consolidation, and Intensification), are followed by a final prolonged low-intensity "Maintenance" phase of therapy that generally lasts about two years. All phases of therapy include treatment directed to the central nervous system (CNS). The phases of treatment for childhood A.L.L. are illustrated in Figure 1.1 on the next page.

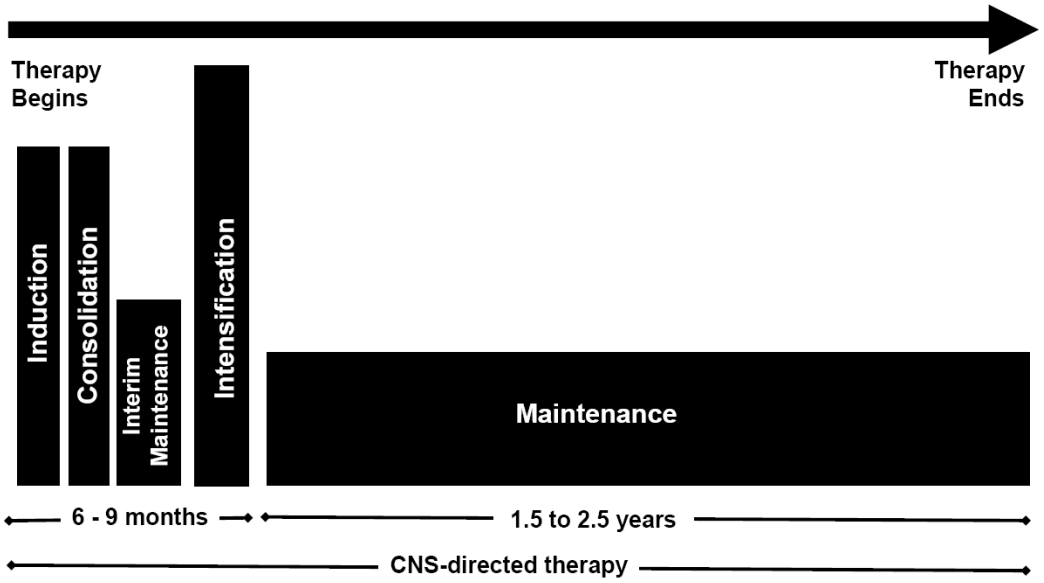


Figure 1.1. Phases of therapy for childhood A.L.L. [Adapted from Landier & Wallace (2003)]

1.3.1.1. ***Induction.*** The initial phase of therapy, known as "Induction" is designed to induce a rapid remission of the leukemia and to eradicate more than 99% of the initial disease burden (Pui & Evans, 2006). The Induction phase generally lasts for 4 weeks and involves administration of both parenteral (intravenous, intramuscular, and intrathecal) chemotherapy and oral corticosteroids (dexamethasone or prednisone). Induction therapy renders approximately 98% of children free of clinical or morphologic evidence of leukemia ("remission") by the end of this phase. However, despite achievement of remission, subclinical disease remains (Borowitz, et al., 2008), and further therapy to eradicate the residual leukemia is always required (Pui & Evans, 2006).

1.3.1.2. ***Consolidation.*** The "Consolidation" phase follows Induction and is designed to strengthen the remission by eradicating a sizable portion of the remaining subclinical disease. This phase also employs parenteral chemotherapy; however, the

selected antineoplastic agents often differ from those used during the Induction phase. Oral chemotherapy is often introduced during this phase.

1.3.1.3. ***Intensification.*** The "Intensification" phase is generally the most taxing phase of treatment and often recapitulates elements of the Induction and Consolidation phases. The goal of Intensification is to eliminate as much residual leukemia as possible, along with any resistant leukemic clones.

1.3.1.4. ***Maintenance.*** The "Maintenance" phase is the final portion of therapy for childhood A.L.L. and is a critical component of the curative regimen (Koren, Ferrazini, et al., 1990; Relling, Hancock, Boyett, Pui, & Evans, 1999). The goal of the maintenance phase is to maintain remission and to eradicate any remaining subclinical leukemia. This phase relies heavily on 6-Mercaptopurine (6MP), a self- or parent/ caregiver-administered oral chemotherapy that is taken at home on a daily basis for approximately two years (Gale & Butturini, 1991). During the maintenance phase, patients must also take an additional oral chemotherapy agent (Methotrexate) on a weekly basis, along with a monthly dose of intravenous chemotherapy (Vincristine), five-day "pulses" of oral corticosteroids (dexamethasone or prednisone) administered every four weeks, and periodic doses of intrathecal chemotherapy.

1.3.2. 6-Mercaptopurine (6MP). Systemic exposure to 6MP plays a critical role during the maintenance phase of A.L.L. therapy; low systemic exposure to 6MP has been shown to adversely affect prognosis (Koren, Ferrazini, et al., 1990; Lilleyman & Lennard, 1994; Relling, et al., 1999). Significant inter-patient variability in systemic exposure to 6MP has been demonstrated (Lennard, Welch, & Lilleyman, 1995); potential

reasons for this variability in systemic 6MP exposure include genetic differences (polymorphisms) in drug metabolizing enzymes, transporters, or targets (pharmacogenomics) (Evans & Relling, 1999), bioavailability (Rivard, Lin, Leclerc, & David, 1989), or adherence to daily oral administration (Lennard, et al., 1995).

1.3.2.1. ***6MP metabolism.*** The antileukemic effect of 6MP occurs as a result of metabolic conversion into its active metabolites, followed by subsequent incorporation of these metabolites into leukemic cellular DNA (Dervieux, et al., 2002). The metabolic conversion of 6MP occurs via several competing pathways and is dependent on the activity of several drug metabolizing enzymes, including xanthine oxidase (XO), thiopurine methyltransferase (TPMT) and hypoxanthine-guanine phosphoribosyl-transferase (HPRT). The metabolic pathways involved in conversion of 6MP to its active metabolites are illustrated in Figure 1.2 on the next page.

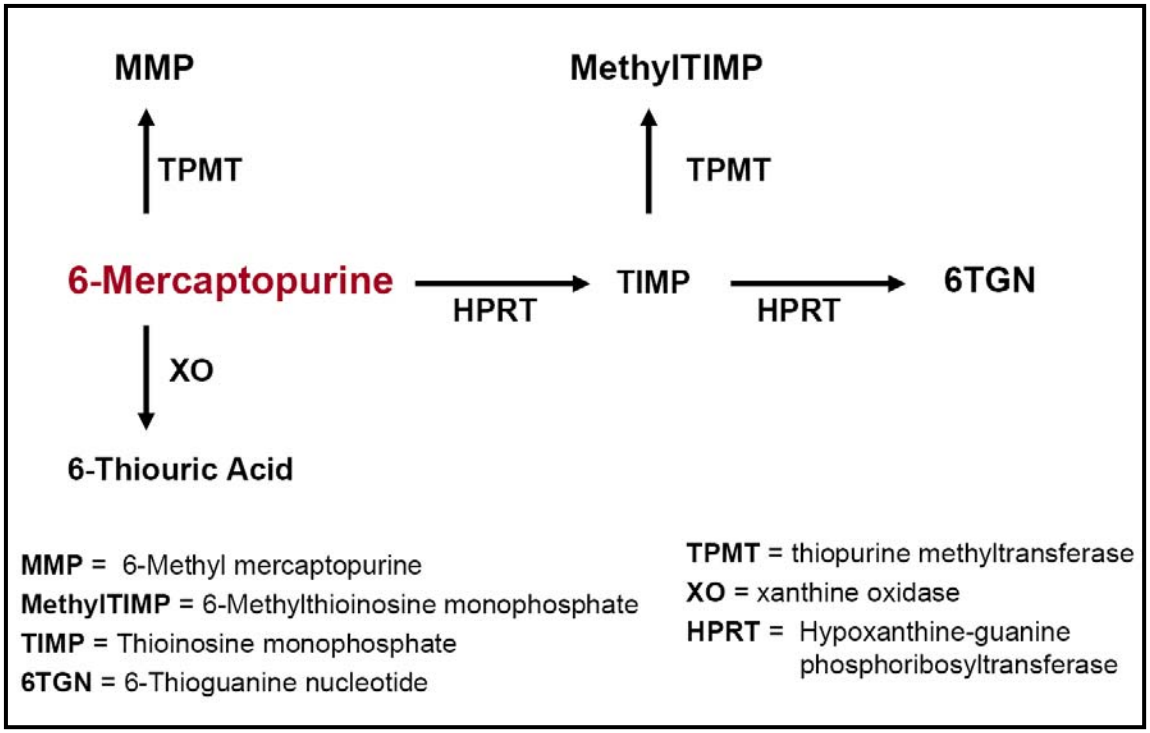


Figure 1.2. 6MP metabolism [Adapted from Dervieux et al. (2001, p. 5811)].

1.3.2.2. ***Bioavailability of 6MP.*** Systemic exposure to 6MP may be affected by its bioavailability, particularly in regard to the time of day that the agent is administered. In a study of 118 children with A.L.L. who received treatment on a standard-risk protocol, patients who received 6MP in the evening had superior disease-free survival compared to those who received morning 6MP dosing, with risk of relapse 4.6 times greater for morning compared to evening scheduling (Rivard, Infante-Rivard, Hoyoux, & Champagne, 1985). This finding was confirmed in a study of 294 patients with A.L.L. taking 6MP during the maintenance phase; 42 patients took 6MP on a morning schedule, 219 on an evening schedule, and 33 had varied schedules. Patients on the evening schedule had a superior outcome [probability of event-free survival (pEFS) = 0.82 +/-

0.03 vs. 0.57 +/- 0.08; $P = 0.0002$] (Schmiegelow, et al., 1997). The importance of timing of 6MP doses may be related to diurnal variation in 6MP kinetics. Koren, Langevin et al. (1990) demonstrated a significantly longer elimination half-life of 6MP in children with A.L.L. when the drug was administered in the evening compared to morning dosing (423 +/- 142 minutes vs. 176 +/- 22 minutes).

6MP bioavailability may also be affected by differences in drug absorption related to ingestion of food or milk (Schmidt & Dalhoff, 2002). Cow's milk contains high levels of xanthine oxidase (XO). Since 6MP is inactivated by XO (Figure 1.2), intake of cow's milk may reduce the bioavailability of 6MP (de Lemos, Hamata, Jennings, & Leduc, 2007; Rivard, et al., 1989; Sofianou-Katsoulis, Khakoo, & Kaczmarski, 2006). Administration of 6MP with food has also been shown to result in a reduction of peak plasma levels as compared to administration in a fasting state (Burton, et al., 1986; Riccardi, et al., 1986). Thus, patients are generally advised to refrain from intake of food, milk, or dairy products for 1 hour before or 2 hours after 6MP administration.

1.4. Adherence to Medication

Adherence to medication is not a single event, but a process that occurs over time. Non-adherence occurs on a continuum that may range from never filling the prescription or never taking any of the prescribed medication, to occasional or frequent missed doses, to over-adherence (taking more medication than is prescribed) (Partridge, Avorn, Wang, & Winer, 2002). Additionally, incorrect administration (e.g., incorrect dose, frequency, or timing of the medication), and/or not following instructions associated with the medication (e.g., dietary restrictions or timing of dose in relationship to food) may

influence drug absorption or efficacy and are therefore important considerations when assessing adherence (Schmidt & Dalhoff, 2002).

1.4.1. Clinical implications of non-adherence in childhood A.L.L. Despite the life-threatening nature of pediatric A.L.L, reported non-adherence rates to oral 6MP range from 10% to 33% (Davies, Lennard, & Lilleyman, 1993; Lancaster, Lennard, & Lilleyman, 1997; Lau, Matsui, Greenberg, & Koren, 1998; Lennard, et al., 1995; Macdougall, McElligott, Ross, Greeff, & Poole, 1992; Traore, et al., 2006). The potential consequences of non-adherence to prescribed oral 6MP chemotherapy may include an increased likelihood of leukemia relapse and potential death from leukemia (Davies & Lilleyman, 1995; Dibenedetto, et al., 1994; Hale & Lilleyman, 1991; Koren, Ferrazini, et al., 1990; Lilleyman & Lennard, 1996).

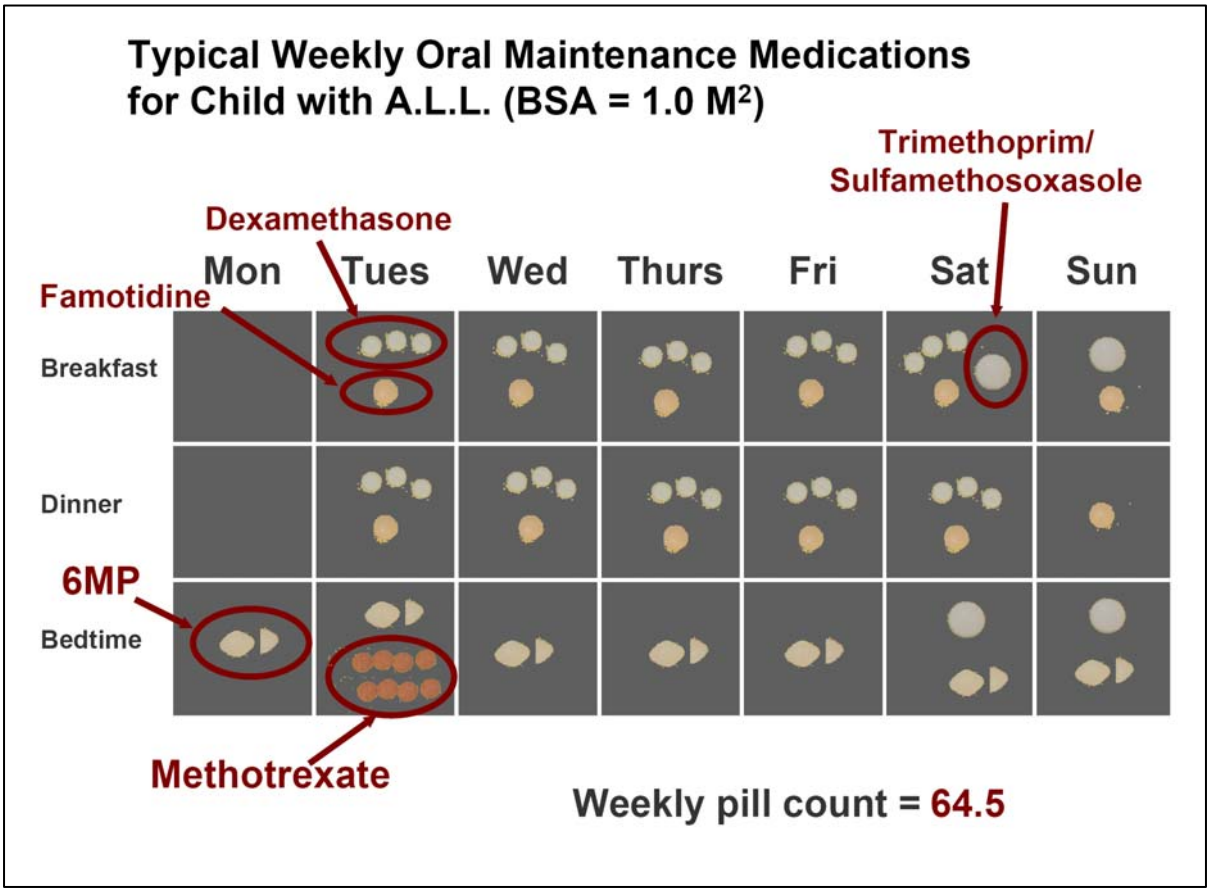
1.4.2. Treatment-related factors relevant to adherence in childhood A.L.L. Contemporary protocols for treatment of childhood A.L.L. are typically complex in design, a treatment-related characteristic that has been shown to negatively correlate with adherence (Claxton, Cramer, & Pierce, 2001). During the maintenance phase of A.L.L. treatment, children receive parenterally-administered medications given in the clinic, along with multiple oral medications at home, including oral chemotherapy (daily 6MP and weekly methotrexate, administered during the maintenance phase for approximately 2 years), corticosteroids (typically administered in 5-day "pulses" every month and associated with poor palatability), and oral antibiotic prophylaxis for pneumocystis pneumonia (usually administered 2 to 3 days per week). Many children also require additional supportive care medications, such as antiemetics, stool softeners, histamine

type-2 receptor antagonists (for control of steroid-related gastrointestinal symptoms), and oral care regimens (including mouthwashes and antifungal agents) for prevention of oral candidiasis. Table 1.2 identifies some of the medications commonly prescribed for children with A.L.L. during the maintenance phase of therapy.

Table 1.2. Oral medications for A.L.L. during the maintenance phase of therapy
[Adapted from Landier, Toomey et al. (2009)]

Oral Medication	**Purpose**	**Status**
Corticosteroid	Leukemia treatment	Required in most regimens
Methotrexate	Leukemia treatment	Required in most regimens
6-Mercaptopurine	Leukemia treatment	Required in most regimens
Trimethoprim/ sulfamethosoxasole (or similar drug)	Pneumocystis prophylaxis	Supportive care – required
Antacid and/or histamine type-2 blocker	Treatment/prevention of corticosteroid-related gastrointestinal symptoms	Supportive care – often prescribed
Stool softener	Prevention of constipation	Supportive care – often prescribed
Laxative	Treatment of constipation	Supportive care – prescribed as indicated
Antiemetic	Prevention/treatment of nausea	Supportive care – prescribed as indicated
Antifungal	Prevention of oral candidiasis	Supportive care – prescribed as indicated
Prescription mouthwash/ oral care regimen	Prevention of opportunistic oral infections	Supportive care – prescribed as indicated

A sample of typical weekly medications prescribed for a hypothetical 7-year-old child receiving maintenance chemotherapy for A.L.L. is depicted below in Figure 1.3.



*Based on standard dosing for a hypothetical 7-year-old child who is 129 centimeters in height (4 feet, 2-1/2 inches), weighs 28 kilograms (61.5 pounds), and has a body surface area of 1.0 square meters.

Figure 1.3. Exemplar of weekly medications for A.L.L. [From Landier, Toomey et al. (2009)].

Scheduling and dosing of these medications may vary depending on the patient's clinical status, blood counts, and symptoms. Frequent changes of dose and scheduling of prescribed medications are not unusual, and may occur due to intercurrent infections or changes in the child's blood counts or body surface area. In addition, the required medications may present significant challenges in administration due to regimen

complexity, pill size, number of pills required per dose, adverse taste and/or palatability of the medications, lack of availability of liquid formulations of some medications, dietary restrictions (such as requirements to avoid milk and dairy products 1 hour before or 2 hours after taking 6MP or methotrexate), medication side effects, and specific scheduling requirements (e.g., dosing at specific intervals before or after meals or at bedtime) (Landier, Toomey, et al., 2009).

1.5. Theoretical Framework

Establishing a theoretical framework is an important aspect of study design that is useful in understanding and conceptualizing the process (e.g., health behavior) under study, and in determining the relevant study questions, measures, and analytic procedures (Munro, Lewin, Swart, & Volmink, 2007; Rapoff, 1999). Theoretical frameworks frequently employed in adherence-related research include the Behavioral Learning Theory (Skinner, 1953), the Theory of Reasoned Action and Planned Behavior (Ajzen & Fishbein, 1980), the Transtheoretical Model (Prochaska & DiClemente, 1983), Protection Motivation Theory (Rogers, 1975), Social Cognitive Theory (Bandura, 1986), and the Health Belief Model (Becker, 1974).

1.5.1. Behavioral Learning Theory. Behavioral learning theory, first developed by B. F. Skinner in the 1950's, is characterized by use of antecedents (cues) and consequences (rewards/punishment). In this model, antecedents may be internal (thoughts) or external (environmental cues, e.g., reminders), and consequences are external (rewards or punishments) in order to reinforce the behavior. The focus is on change of overt behavior, which is accomplished by teaching skills to manage adherence.

Limitations of the theory include its lack of incorporation of other potential influences on adherence (e.g., habits, past behaviors, understanding of diagnosis), and its focus on external behavior (Munro, et al., 2007).

1.5.2. The Theory of Reasoned Action and Planned Behavior. The Theory of Reasoned Action and Planned Behavior combines two models developed by Ajzen and Fishbein (1980). The Theory of Reasoned Action postulates that behaviors are under volitional control, and that intent to perform an action (which is influenced by attitudes, beliefs, subjective norms, and expected outcomes) is the best predictor of that behavior. This model was found to be limited in its application because behavior is not always under volitional control; therefore, the model was extended to include the Theory of Planned Behavior, which represents the perceived ease or difficulty in performing the targeted behavior ("behavioral control"), a construct similar to self-efficacy (Munro, et al., 2007). The combined theory incorporates attitudes, beliefs, relevant skills, emotions, past experience, and external circumstances. In this model, behavioral control is assumed to have a direct effect on intention.

1.5.3. The Transtheoretical Model. The Transtheoretical Model purports that behavioral change occurs as individuals move through five distinct stages (precontemplation, contemplation, preparation, action, and maintance) (Prochaska & DiClemente, 1983). The model is used widely to guide behaviorly-based interventions, such as smoking cessation (Prochaska, Velicer, DiClemente, & Fava, 1988) and weight control (Marshall & Biddle, 2001), and has also been applied to studies of medication adherence (Cook & Perri, 2004). Limitations include the often substantial time required

for individuals to move through the stages within the model, a serious obstacle to application of the theory when rapid behavior change in required (Munro, et al., 2007), as is the case in childhood leukemia therapy.

1.5.4. Protection Motivation Theory. Protection Motivation Theory, developed by R. W. Rogers, is based on adaptive and maladaptive coping that occurs in response to fear arousal. There are three main components of the model: (1) perceived severity of the health threat, (2) perceived susceptibility to the health threat, and (3) perceived efficacy of the response. These three components combine to determine the intensity of the response; an adaptive response is motivated as a result of desire to obtain protection from the perceived danger (protection motivation) (Rogers, 1975). The Protection Motivation Theory is closely related to the Health Belief Model (HBM), and builds on several HBM components; however, the HBM includes some additional elements (Barriers, Benefits, and Cues to Action) that may be particularly useful in studying adherence.

1.5.5. The Health Belief Model. The HBM is the theoretical framework selected to guide this study. The HBM is one of the oldest and most widely applied models in health psychology (Becker, 1974). The HBM was originally developed in the 1950's to assist researchers in understanding why people did or did not take advantage of preventive health services (Hochbaum, 1958). Since the 1970's, the HBM has been used to guide research aimed at understanding adherence to prescribed medical regimens (Rapoff, 1999). The HBM was chosen for this study because it has been shown to have construct validity in adherence studies and has been proven as a means for exploring and

reducing non-adherence (Abraham, Clift, & Grabowski, 1999; Elliott, Morgan, Day, Mollerup, & Wang, 2001; Soliday & Hoeksel, 2000).

Six major categories of variables are identified as predictors of adherence in the HBM, as follows: (1) *Perceived susceptibility* (e.g., the risk of contracting or re-contracting a health condition); (2) *Perceived severity* (e.g., the person's evaluation of the consequences of not taking the prescribed treatment); (3) *Perceived benefits* (e.g., the person's evaluation of the benefits of taking the prescribed treatment); (4) *Perceived barriers* (e.g., the person's perception of the difficulties related to taking the prescribed treatment) and (5) *Cues to action* (e.g., internal cues, such as disease symptoms, or external cues, such as reminders, that trigger the person to take the prescribed treatment). These first five components are all part of the original model (Becker, 1974). More recently, a sixth component, (6) *Self-efficacy* (an individual's belief in their own ability to achieve a specific goal in a specific setting) was added to the model (Rosenstock, Strecher, & Becker, 1988).

1.5.6. Social Cognitive Theory. The most recent addition to the HBM, self-efficacy, is based in Social Cognitive Theory (SCT), a theory of human behavior that focuses on human agency, the central mechanism of which is self-efficacy, or the belief in one's ability to organize and carry out a given task (Bandura, 1986). In SCT, competent functioning involves both confidence in one's ability to carry out the action and having the necessary skills to do so (Bandura, 1997). Determinants of adherence outcomes in SCT include the person's positive or negative self-evaluation of their own ability to carry out the treatment-related tasks; importantly, this process includes the

individual's assessment of perceived facilitators and barriers in relationship to the health behavior(s) required (Munro, et al., 2007).

1.5.7. Application of the Health Belief Model to adherence research. In the HBM, the likelihood of adherence is dependent upon the balance between perceived benefits and barriers, weighed against perceived vulnerability (which includes both perceived susceptibility and disease severity). These main constructs of the model are modified by other variables, such as past experience, skill, education, and other individual characteristics. The HBM has been used to facilitate research addressing a range of pediatric adherence issues, including penicillin prophylaxis for prevention of pneumococcal infections in sickle cell disease (Elliott, et al., 2001), pediatric emergency room follow-up care (Soliday & Hoeksel, 2000), and adolescent diabetes (Bond, Aiken, & Somerville, 1992). Additionally, the HBM provides a framework for clinical interactions focused on the perceived benefits and harms of treatment, and on the potential consequences of non-treatment (Becker, 1974). Since health motivation is a central focus of the HBM (National Cancer Institute, 2005), the theory is a good fit for addressing concerns regarding adherence in health conditions such as childhood A.L.L., in which patients or parents/caregivers are likely to be highly motivated to enact a health behavior based on high perceived vulnerability (due to perceived severity of the illness and perceived susceptibility to it), and a belief that the health behavior (adherence) will produce the desired outcome (long-term health).

Chapter 2: Review of Literature

2.1. Adherence Defined

2.1.1. Definitions from the literature. The terms "adherence" and "compliance" are often used interchangeably in the health sciences literature. The term "compliance" has been associated with both negative connotations of paternalism and inequity in the healthcare provider-patient relationship (Evangelista, 1999), and positive connotations of responsibility and self-care (Kyngas, Duffy, & Kroll, 2000). "Persistence" has also been recently added to the terminology describing adherence behaviors, and describes the patient's continuation of treatment for the prescribed duration (Cramer, et al., 2008). Alternate terms, such as "adherence" and "concordance" are often used in place of compliance (Pritchard, Butow, Stevens, & Duley, 2006), and "adherence" has more recently been accepted as the preferable term, implying "consistency and a steady propensity to stick to a prescribed regimen" (Bradley-Springer, 1998, p. 17). Review of the evolution of these terms in the literature reveals that adherence is more commonly used in recent and current literature, and in some cases is used in place of compliance. However, compliance was the more dominant term in the literature throughout the 1970's and 1980's.

2.1.1.1. *Compliance.* The classic definition of compliance comes from the biomedical literature. Sackett (1979) defined compliance as "the extent to which a person's behavior (in terms of taking medications, following diets or executing other life-style changes) coincides with the clinical prescription" (p. 1). Additional definitions of compliance include those with a paternalistic connotation, such as "following a prescribed

regimen" (Evangelista, 1999, p. 7), as well as those with an aspect of participation and mutuality, such as "the extent to which an individual chooses behaviors that coincide with a clinical prescription" (Dracup & Meleis, 1982, p. 31), and "the patient's active, intentional and responsible process of self-care, in which the patient works to maintain his or her health in close collaboration with healthcare staff" (Kyngas, et al., 2000, p. 7). Evangelista (1999) described the five defining attributes of compliance as the "ability to complete or perform what is due, flexibility, adaptability, malleability, and subordinate behaviors" (p. 7).

Similar to compliance, definitions for non-compliance vary and range from "behaviors that vary from the consensual regimen" (Dracup & Meleis, 1982, p. 31) that form "a continuum from the occasional lapse to total refusal" (Lilleyman & Lennard, 1996, p. 1220), to "a person's informed decision not to adhere to a therapeutic recommendation" (Kim & Moritz, 1982, p. 299). The essential characteristics described within these definitions can be summarized by the observation that "the complexity of non-compliance cannot be reduced to and adequately reflected in the labeling of the individual as being either compliant or non-compliant" (Kyngas, et al., 2000, p. 11).

2.1.1.2. ***Adherence.*** Dracup & Meleis (1982) define adherence as "a willingness on the part of the patient to participate with the prescribed regimen" (p. 31). Shay (2008) describes adherence as "one's ability to maintain the behaviors associated with a plan of care. This often involves taking medications, keeping appointments, or changing health behaviors" (p. 42). Non-adherence with oral medication is described as "when the failure to comply is sufficient to interfere appreciably with achieving the therapeutic goal"

(O'Hanrahan & O'Malley, 1981, p. 291), and "can range from a complete failure to take the prescribed medication to the patient's altering of either dose or duration of therapy" (Festa, Tamaroff, Chasalow, & Lanzkowsky, 1992, pp. 808-809). Given the overlapping definitions and use of surrogate terms in the context of oral chemotherapy for childhood A.L.L., the terms "adherence" and "compliance" can and have been used interchangeably to represent different attributes of this multifaceted and complex concept. Although 100% adherence (i.e., "optimal adherence") serves as a basis for comparison (Ruddy, Mayer, & Partridge, 2009), no specific threshold has been identified to date to define optimal adherence levels for 6MP in childhood A.L.L.

2.2. Significance of Adherence

Adherence to treatment has significant implications for health outcomes in children with chronic conditions, particularly in those conditions for which ongoing daily medication has been shown to be play a critical role in treatment, such as diabetes mellitus (Kyngas, 2000), cystic fibrosis (Zindani, Streetman, Streetman, & Nasr, 2006), human immunodeficiency virus (HIV) infection (Martin, et al., 2007), organ transplant (Magee, et al., 2004), and A.L.L. (Koren, Ferrazini, et al., 1990; Relling, et al., 1999). In addition to common problems with medication adherence that have been identified in the general population (Haynes, McDonald, & Garg, 2002), further relevant adherence-related issues must be taken into consideration for pediatric patients (Rapoff, 1999). In pediatrics, adherence is a complex process, which is dependent both on the parent/caregiver administering (or overseeing administration of) the medication, and on the child ingesting the medication. Successful ingestion of the medication may prove

problematic in some children due to palatability and pill-swallowing issues (Garvie, Lensing, & Rai, 2007). Additionally, successful ingestion is also dependent on behavioral factors related to the child's temperament and developmental stage, and may prove particularly challenging during in adolescence (B. A. Smith & Shuchman, 2005).

2.3. Measuring Adherence in Childhood A.L.L.

Techniques of measuring adherence to oral chemotherapy in children with A.L.L. can be classified as objective (direct) and subjective (indirect). Objective measures of adherence can be easily quantified; however, they vary in reliability, and the use of some methods in clinical practice may be limited by availability and costs. Subjective measures of adherence can also be quantified; however, they may be limited in their application due to concerns regarding accuracy and reliability of self-reported measures, while the appeal of these measures lies in their easy accessibility, low cost, and potential for practical application in the clinical setting.

2.3.1. Objective measurements of adherence. Objective measures that have been used to assess adherence in children with A.L.L. include drug assays (Lennard & Singleton, 1992), pill counts (Cramer, Mattson, Prevey, Scheyer, & Ouellette, 1989), and electronic monitoring devices (Lau, et al., 1998), as well as surrogate measures, such as white blood cell count or neutrophil count.

2.3.1.1. ***Pill counts.*** Pill counts are inexpensive and easy to implement by asking patients to regularly return pill bottles containing their unused medications to the clinic; the remaining tablets are then counted. Procedures may vary from straightforward pill counting to the surreptitious over-filling of the bottle aimed at providing more doses than

prescribed so that some tablets should always remain in the bottle at the return visit (Wright, 1993). Pill counts are subject to reliability problems, including patient interference, since unused pills can be intentionally discarded prior to clinic visits ("pill dumping"), resulting in overestimates of adherence (Cramer, et al., 1989).

2.3.1.2. ***Electronic measures of adherence.*** Electronic monitoring chips incorporated into pill bottle caps have been widely used in clinical trials to assess medication adherence (Cramer, et al., 1989; Lau, et al., 1998; Olivieri, Matsui, Hermann, & Koren, 1991). These devices record the date and time of pill bottle opening and have been shown to provide more accurate data regarding medication adherence than other non-biological monitoring methods (Urquhart, 1997). However, electronic monitoring does not provide complete assurance that the medication was ingested, since opening of the bottle does not guarantee that a pill is actually taken out or swallowed (Davies & Lilleyman, 1995). Additionally, limitations include high cost, potential device malfunction, and lack of technology to measure adherence in those receiving liquid formulations of the medications (Riekert & Drotar, 2000).

2.3.1.3. ***Drug levels.*** Because of the short half-life of 6MP, plasma and urine levels are indicative only of the previous day's dose and not of chronic exposure; usefulness of these measures in research and clinical practice is therefore limited (Davies & Lilleyman, 1995; Macdougall, et al., 1992). Red blood cell (RBC) assays for the active metabolites of 6MP, including thioguanine nucleotide (6TGN), methylated mercaptopurine (MMP), and 6-methylthioinosine monophosphate (MethylTIMP) are available and are reflective of doses taken in the previous 1 to 4 weeks (Lennard &

Singleton, 1992; Lennard, et al., 1995). However, caution is warranted in the interpretation of RBC assays in the assessment of adherence in childhood A.L.L. because of the multiple factors that may contribute to the results, such as differences in absorption, distribution, and metabolism of the agent, and the potential contribution of inadequate dosing by the clinician.

2.3.2. Subjective measurements of adherence. Subjective measurements of adherence include patient self-report or reports of other individuals familiar with the patient, such as parents/caregivers and healthcare providers.

2.3.2.1. *Clinical assessments.* Studies assessing the ability of healthcare providers to estimate adherence have shown that healthcare providers tend to overestimate adherence in their patients, and are generally not reliable predictors of adherence (Riekert, Wiener, Drotar, & Sprunk, 1999; Zeller, Taegtmeyer, Martina, Battegay, & Tschudi, 2008).

2.3.2.2. *Self-reports.* Self/parent-caregiver report can be assessed retrospectively via questionnaires or interviews by asking the patient/parent to recall how often the medication was taken (Davies, et al., 1993; MacDougall, Wilson, Cohn, Shuenyane, & McElligott, 1989; Tebbi, et al., 1986). Additionally, self-reporting methodology can be used to collect information about patient beliefs, attitudes, and experiences with their medication regimens (Bender, Milgrom, Wamboldt, & Rand, 2000). Self-report data can also be collected in real-time via medication diaries, in which each dose is recorded at the time the medication is taken (Pritchard, et al., 2006). Collection of self-report data is appealing because it is relatively easy to obtain and cost effective (Riekert & Drotar,

2000). However, reliability of self-report data is of concern, since self-report methodology depends on patients' ability to remember or record medication adherence over a period of time, and because it may be subject to over-reporting due to social desirability effects (i.e., the desire of the patient/caregiver to please the healthcare provider) (Rapoff, 1999). Despite these limitations, in studies assessing both self-reported and objective measures of adherence, consistencies between self-reports and the objective measures suggest that self-report may be useful in assessing adherence in children with cancer (Davies, et al., 1993; Tebbi, 1993; Tebbi, et al., 1986). However, self-reports of non-adherence may be more reliable than self-reports of adherence (Kennard, et al., 2004; Liptak, 1996). If reliability issues can be addressed, self-report has the potential for practical application in both research and clinical settings, since it requires minimal time and resources.

2.4. Adherence in Pediatric Oncology

2.4.1. Adherence to oral corticosteroids. Early studies of adherence in children with cancer focused on a heterogeneous group of children taking corticosteroids, because concentrations of these drugs could be easily measured in the urine or blood. These early studies were the first to identify adherence as a concern in the pediatric oncology population, and the first to suggest that differences in adherence might explain differences in outcome in children with cancer (S. D. Smith, Rosen, Trueworthy, & Lowman, 1979).

The earliest study examined adherence in 52 children with leukemia or lymphoma between 8 months and 17 years of age who were taking oral prednisone at a dose of 60

milligrams per square meter of body surface area per day. Random urinary 17-ketogenic steroid levels were measured to determine adherence to the regimen. Overall, 33% of patients were found to be non-adherent with prednisone based on urinary 17-ketogenic steroid/creatinine ratios. Among children age 11 or older, 59% were found to be non-adherent, a highly significant difference compared to adherence in the younger age group ($P < 0.0001$) (S. D. Smith, et al., 1979).

A similar approach was used in a study of adherence to oral prednisone in 31 patients younger than age 15 with A.L.L. Overall, using the same definition of adherence applied in the S. D. Smith et al. (1979) study, 42% of patients were non-adherent. Findings indicated a wide range of adherence behaviors on the continuum from complete non-adherence to those who took most prescribed doses; however, no child in this study was found to be 100% adherent (Lansky, Smith, Cairns, & Cairns, 1983). Psychological correlates of adherence in both parents and children were also measured, and adherence was found to be more closely related to the psychological traits of the parents rather than the children. Anxiety appeared to be the strongest motivator for adherence, particularly among parents of boys.

Tebbi et al. (1986) used structured interviews to assess self- and parent-reported adherence at 2, 20, and 50 weeks post-diagnosis in 46 patients with cancer ranging from 2 to 23 years of age who were taking oral corticosteroids and other oral chemotherapy agents (including 6MP, methotrexate, procarbazine and tamoxifen). Reports of adherence were grouped into three categories: (1) no doses missed; (2) occasional missed doses; and (3) frequent missed doses; patients with responses in the latter two categories

were considered non-compliers. To confirm the accuracy of self/parent-reported adherence, these data were compared to serum corticosteroid levels measured using the liquid chromatography technique in 16 patients; the bioassay corroborated self/parent-reported adherence in every case. At the 2-week time point, 81.2% of participants reported complete adherence; this decreased to 60.5% at 20 weeks and 65.0% at 50 weeks. Lower adherence was associated with patient age $\geq$ 10 years ($P < 0.05$), larger family size ($P = 0.008$), and poor understanding of medication instructions ($P = 0.04$). Lack of congruence between patient and parent regarding who is responsible for medication administration was more apparent in non-adherent than in adherent patients. Barriers to adherence identified by participants included forgetfulness, busy schedules, and non-availability of medication.

Lack of congruence between patient and parent regarding attribution of responsibility for medication administration and patient-parent lack of concordance regarding knowledge and understanding of illness, medications, and treatment was further evaluated in a group of 16 adolescent patients with cancer and their parents. Poorer adherence was found in those parent-adolescent pairs who lacked concordance regarding their understanding of medication instructions and effectiveness of the medication, and in those who lacked concordance with their parent/caregiver regarding identification of the person who was responsible for home medication administration (Tebbi, Richards, Cummings, Zevon, & Mallon, 1988).

Festa et al. (1992) evaluated adherence to prednisone in 21 adolescent and young adult patients with leukemia or lymphoma. Adherence was assessed by measuring

morning levels of serum dehydroepiandrosterone sulfate (DHEA-S), the main adrenal androgenic steroid that is suppressed by prednisone administration. DHEA-S levels were assessed at baseline and at 7 and 14 days of prednisone therapy. Eleven of the 21 patients (52%) failed to demonstrate DHEA-S suppression, indicative of non-adherence.

2.4.2. Adherence to oral 6MP. Macdougall et al. (1992) used urinary liquid chromatography to measure 6MP levels the morning after a prescribed evening dose of 6MP in 39 children with A.L.L.; 19% of these children had no trace of the drug a first-morning urine sample, suggestive of non-adherence.

Davies, Lennard & Lillyman (1993) studied 35 children with A.L.L. in first remission who had been receiving 6MP as part of their maintenance chemotherapy at a standard dose of 75 milligrams per square meter of body surface area for at least nine months. Patients underwent an initial evaluation for four weeks during which 13 patients required downward dose adjustments for neutropenia or thrombocytopenia, and the remaining 22 patients were designated as "tolerant" of the treatment and were continued on the standard dose. Adherence was assessed in the 22 tolerant patients by measuring RBC 6TGN levels and by performing a structured interview. Highest and lowest 6TGN levels were recorded for each patient and expressed as a ratio; ratios closest to 1.0 were suggestive of consistent adherence. Six of the 22 (17%) patients showed wide fluctuations in 6TGN levels (highest to lowest 6TGN ratio $\geq$1.9); five of these patients were determined to be non-adherent or had equivocal adherence per the structured interview. Overall, the results suggested that up to one in five children may fail to fully comply with oral 6MP as prescribed during A.L.L. maintenance therapy.

Lennard et al. (1995) studied intracellular 6MP metabolites (6TGN and MMP) in 327 children treated on United Kingdom Medical Research Council A.L.L. trials who had been receiving the full protocol-directed dose of 6MP (75 milligrams per square meter of body surface area per day) for a minimum of 7 days prior to the drug assay. There was a wide variation in concentration of the 6MP metabolites. MMP levels were anticipated to negatively correlate with 6TGN levels, since MMP is catalyzed by TPMT via a competing metabolic pathway; however, 32 (10%) of the children had concentrations of both metabolites in the lower quartile, an unexpected finding. The investigators concluded that the most likely explanation for this finding was that these patients had failed to adhere to their prescribed therapy with 6MP, either partially or completely.

In a larger study of 496 children with A.L.L. between 5 and 18 years of age treated on leukemia protocols in the United Kingdom, Lancaster, Lennard, & Lilleyman (1997) identified 9 patients (2%) with undetectable levels of 6TGN, indicative of complete non-adherence with 6MP. Adolescents were more likely than younger children to be completely non-adherent ($P < 0.02$), but there were no other obvious sociodemographic differences between the completely non-adherent group and the remainder of the cohort.

Lau et al. (1998) used an electronic medication event monitoring system (MEMS, Aprex Corporation, Fremont, CA) to evaluate 6MP adherence for a mean of 44 days in 24 patients (age 2-17 years) with A.L.L. who were on maintenance therapy. Patients and their parents were not advised of the function of the MEMS device. One-third (33%) of patients took less than 90% of prescribed doses and 17% took less than 80% of their

prescribed doses. Only 42% of patients took 95% or more of their prescribed doses. Eight patients were also evaluated for differences in adherence between morning and evening administration of 6MP; an evening schedule was found to improve adherence.

In a study of 48 adolescents (age 12 to 19 years) with A.L.L. receiving maintenance chemotherapy, Traore et al. (2006) measured RBC 6TGN and MMP levels over a 4-month period and grouped the results into four "clusters" based on the 6MP metabolite levels. MMP levels were anticipated to negatively correlate with 6TGN levels, since MMP is catalyzed by TPMT via a competing metabolic pathway (Lennard, et al., 1995). Patients whose 6MP was held for toxicity or illness during the study demonstrated low levels (below the third quartile) for both 6TGN and MMP (Cluster 3) as expected; levels of 6TGN and MMP for these patients plotted in one of the other clusters when their 6MP therapy was resumed. In an accompanying editorial, Gaynon (2006) concluded that non-adherence could be an additional reason to explain Cluster 3 metabolite levels for patients whose doses were not intentionally held by the prescriber.

2.5. Determinants of Adherence

The first step in determining how medication adherence can be improved is to understand why patients do or do not adhere to their medications. Therefore, identifying determinants of adherence (or non-adherence) is important, because the identified factors can be used to develop risk profiles of patients likely to be non-adherent to therapy. Interventions targeted to potentially modifiable factors (e.g., regimen complexity) or geared to vulnerable sub-groups identified based on sociodemographic factors (e.g., age) can then be developed. Additionally, determinants of adherence can be used to improve

internal validity of interventional research studies by matching participants on relevant predictors (e.g., age, socioeconomic status) prior to randomization. Determinants of adherence fall into three broad classifications: (1) Patient/family factors; (2) Disease-related factors; and (3) Regimen-related factors (Rapoff, 1999).

2.5.1. Patient/family factors. Patient and family factors that have been correlated with adherence in studies of pediatric chronic diseases include (1) sociodemographic factors; (2) knowledge/understanding of the disease process; (3) coping and adjustment; and (4) parental monitoring (Rapoff, 1999).

2.5.1.1. ***Sociodemographic factors.*** Sociodemographic factors reported to be associated with poor adherence to oral chemotherapy in childhood A.L.L. include older age, particularly adolescence (Baker, et al., 1993; Festa, et al., 1992; Tamaroff, Festa, Adesman, & Walco, 1992), male gender (Lennard, et al., 1995; Macdougall, et al., 1992; S. D. Smith, et al., 1979), larger family size (Lancaster, et al., 1997; Tebbi, et al., 1986), maternal employment outside the home (Tebbi, et al., 1986), lower levels of parental education, and lower socioeconomic status (MacDougall, et al., 1989).

2.5.1.2. ***Knowledge/understanding of disease process.*** The diagnosis of leukemia is an extremely stressful event for both children and families and involves a period of transition, during which time the family comes to terms with the seriousness of the diagnosis (Clarke-Steffen, 1993b). This results in an intense increase in informational needs, as parents (and patients if old enough) attempt to understand the implications of the diagnosis and the associated treatment regimen (Hinds, Gattuso, & Mandrell, 2006). Poor adherence to childhood cancer treatment has been linked with a lack of

understanding regarding the diagnosis and treatment plan (Spinetta, et al., 2002) and denial of the diagnosis (Tamaroff, et al., 1992). The need for information varies greatly between individuals and over time (Hummelinck & Pollock, 2006). Families may have preconceived notions that childhood leukemia is invariably fatal, a common misconception among the lay public resulting from past eras when successful treatment for childhood A.L.L. was not available. Therefore, communication of the child's prognosis to the patient/family is a first step in promoting accurate understanding of the disease and its treatment. For most children with A.L.L. diagnosed in the current era, there is an 80-90% probability of 5-year survival, after which time the likelihood of disease recurrence is extremely low (Jemal, et al., 2009). However, prognosis depends on multiple factors, including age at diagnosis, biological characteristics of the leukemia, and rapidity of response to therapy (Table 1.1). Presence of unfavorable characteristics necessitates more intensified therapy, and some patients with unfavorable characteristics may face a poorer prognosis (Pui & Evans, 2006). Children who have more information about their disease appear to be better equipped to cope with their illness, because they develop a better understanding of the importance of taking their medication, feel able to discuss their worries and concerns with their parents, and are more trusting of their families and healthcare providers (Clarke, Davies, Jenney, Glaser, & Eiser, 2005).

Most children with A.L.L. are enrolled on treatment protocols (standardized treatment plans designed by pediatric oncology clinical trials groups) or are treated in a standardized manner similar to these protocols. Phases of therapy are therefore pre-defined, and much of the anticipated treatment plan can be outlined for patients and

families beginning at the time of diagnosis, potentially enhancing their understanding of the therapeutic regimen.

2.5.1.3. ***Coping and adjustment.*** Family adaptation to the diagnosis and ongoing treatment for childhood cancer has been the focus of several studies by Clarke-Steffen (1993a; 1993b; 1997). In a model of transition developed from these studies, Clarke-Steffen (1993a) describes a "fracturing of reality" that occurs at the time a diagnosis of childhood cancer is suspected. This is followed by a period of "limbo" until the diagnosis is confirmed, and a phase of "reconstructing reality," which incorporates strategies that include changing future orientation, managing the flow of information, assigning meaning to the illness, reorganizing roles, managing the therapeutic regimen, and evaluating and shifting priorities. This reconstruction of reality eventually results in a new normal for the family, which integrates uncertainty and a different world view along with an altered daily routine (Clarke-Steffen, 1993a).

The process of reconstructing a new normal begins for most families within three months of the time that the child's disease achieves remission status (Clarke-Steffen, 1997). Three strategies employed during the "reconstructing reality" phase have particular relevance to the concept of adherence. "Changing future orientation" involves shifting focus regarding goals for the child's future, moving from a long-term vision (e.g., college, marriage) to a short-term view (e.g., the next few days or weeks). This is necessary because of uncertainty regarding the day-to-day course of the illness and the child's long-term prognosis, and allows energy to be focused on immediate concerns. Treatment protocols provide the healthcare team with a framework for explaining the

anticipated course of treatment, and also set the stage for introducing the family to the importance of finding and building a "new normal" for the child, a process that encourages the child to lead as normal a life as possible throughout their leukemia treatment, with the goal of optimizing the child's psychological well-being throughout the illness and beyond into long-term survivorship (Earle, Clarke, Eiser, & Sheppard, 2007). "Reorganizing roles" involves the negotiation among family members of provider and caretaker roles and time allocation for care of the sick child; mothers often renegotiate their work role in order to provide ongoing care for the child. Coordinating the child's care and attending medical appointments occupies a great deal of time and requires shifting of other responsibilities. "Managing the therapeutic regimen" includes the process of understanding and following the child's treatment protocol, administering medications, and managing the child's adaptation to the illness. All of these strategies involve implementation of a complex set of tasks and are most often managed by the mothers (Clarke-Steffen, 1993a). The goals of implementing these strategies are for families to "maximize the health of the child, to get through the period of treatment, and to normalize their lives" (Clarke-Steffen, 1997, p. 284).

Adjustment and coping factors that have been correlated with adherence in studies of other pediatric illnesses include higher self esteem, increased perceived autonomy and independence, internal locus of control (belief that one's actions control health outcome), higher social functioning, better disease-specific adjustment, belief in the efficacy of the treatment (perceived benefit), a sense of optimism, well developed problem-solving skills, and family support, cohesion, and organization (Rapoff, 1999). Correlates of non-

adherence include behavioral or emotional problems, poor parental coping, and parental depression and/or anxiety (Rapoff, 1999).

2.5.1.4. ***Parental monitoring.*** During adolescence, role reorganization may result in unclear delineation of responsibility; therefore, assessment of the quality of parent-teen relationships is important in assisting teens and their parents to effectively negotiate role transitions (Leonard, Garwick, & Adwan, 2005). The issue of parent-teen role transitions is particularly salient in regard to medication adherence, since parents may not clearly define who is "in charge" of medication management and may be overly optimistic regarding the adolescent's ability to manage their ongoing oral chemotherapy (Levenson, Copeland, Morrow, Pfefferbaum, & Silberberg, 1983), despite that fact that some adolescents prefer to have parents take the lead in managing their care (including oral medications) throughout A.L.L. treatment (Malbasa, Kodish, & Santacroce, 2007). In two studies of adherence to the therapeutic regimen in adolescents with diabetes mellitus, parental "nagging" was associated with improved regimen adherence (Burroughs, Pontious, & Santiago, 1993; La Greca, et al., 1995). Conversely, lack of parental monitoring, or ambiguity regarding who assumes primary responsibility for regimen adherence has been associated with non-adherence in adolescents with chronic illness (Ingersoll, Orr, Herrold, & Golden, 1986; Tebbi, et al., 1988).

2.5.2. Disease and regimen-related factors. Disease and regimen-related factors that may adversely affect adherence in young people with chronic illness include treatment-related factors (e.g., complexity of treatment), and healthcare system-related factors (e.g., relationship with the healthcare provider).

2.5.2.1. ***Treatment-related factors.*** Factors that have been shown to influence adherence in children with leukemia include complexity of the therapeutic regimen (increasing complexity associated with decreasing adherence) (Tebbi, et al., 1986), time on treatment (decreased adherence associated with longer time on treatment) (Lancaster, et al., 1997; Tebbi, et al., 1986), palatability of medications (poorer palatability of medications associated with decreased adherence), and frequency of clinic visits (more frequent visits associated with increased adherence) (S. D. Smith, et al., 1979). Notably, contemporary protocols for treatment of childhood A.L.L. are generally complex in design. In addition to the parenterally-administered medications given in the hospital and clinic, most children with A.L.L. require multiple oral medications at home (e.g., daily 6MP and weekly methotrexate, corticosteroids, and frequent administration of supportive care medications including prophylactic antibiotics and antifungal agents, antiemetics, histamine type-2 receptor agonists and oral care regimens). In other chronic pediatric illnesses, rapidity of the treatment benefit (e.g., immediate symptom relief) is positively associated with adherence, while factors negatively associated with adherence include asymptomatic disease states (absence of physiologic "cues to action"), having more health problems or being hospitalized frequently, and increased costs of care (Rapoff, 1999).

2.5.2.2. ***Healthcare system-related factors.***

2.5.2.2.1. *Relationship with healthcare providers.* Poor patient-healthcare provider relationships and poor communication regarding potential benefits and side effects of the prescribed treatment, have also been shown to adversely affect adherence

(Osterberg & Blaschke, 2005). Conversely, establishing a trusting relationship with the child's healthcare provider may positively influence adherence (Spinetta, et al., 2002). Clarke-Steffen (1997) describes barriers that some parents encounter in obtaining information regarding their child's illness. These include "complex technical language, reluctance to disclose information, or attitudes of the persons providing the information" (Clarke-Steffen, p. 282). Spinetta (2002) concluded that "insufficient and inadequate doctor/patient/family dialogue, relationship, trust, and mutual information is one of the most important causes of nonadherence" (Spinetta, et al., p. 115). Parents of children with A.L.L. have identified the importance of receiving clear, honest, and sensitive communication from healthcare providers (McGrath, 2002), and have indicated that the communication style of the healthcare professional, as well as the parent, can both positively and negatively influence the therapeutic alliance between family and the healthcare team (Taylor, 2006). In a study of parents' perceptions of caring for a child undergoing cancer treatment, the most helpful intervention identified by parents was "carefully delivered accurate information about their ill child" from healthcare professionals (James, et al., 2002). Clarke-Steffen (1997) identified the importance to families of the healthcare team's willingness "to listen without judgment and to anticipate their basic needs as well as their needs for support and information" (Clarke-Steffen, p. 286), highlighting the role of the communication process in establishing parent/family trust in the healthcare provider.

For families with limited English proficiency, language barriers may present additional challenges in attaining clear communication. Even with the use of interpreters,

concern has been expressed regarding the potential for miscommunication of key information critical to the child's care when language barriers are present (Abbe, Simon, Angiolillo, Ruccione, & Kodish, 2006).

The inclusion of patients (particularly adolescents) and their families in the decision-making process from the time of diagnosis may help to establish trust and rapport with the healthcare team and may positively influence adherence (Spinetta, et al., 2002). Additionally, providing continuity of care throughout treatment, including identification of a primary oncologic care provider, has also been acknowledged as an important component in the process of developing and maintaining trust in the healthcare team (Spinetta, et al., 2002).

2.5.2.2.2. *Care delivery.* In 1986, passage of U.S. Public Law 99-457 resulted in a legislative mandate for the family-centered care model, requiring that families (rather than the child alone), be considered the recipient of services for children with special healthcare needs. Thus, the family-centered model of care is currently considered standard practice for children with chronic illness in the United States. In this model, healthcare professionals and families work collaboratively to make healthcare decisions and plan chronic care for children with special needs (Ely, 1997; Holm, Patterson, & Gurney, 2003). An active partnership between the healthcare provider, patient, and family, known as "therapeutic alliance," is an integral component of this model (Holm, et al., 2003). In children with A.L.L. who are receiving daily oral chemotherapy during the maintenance phase of therapy, this triadic partnership may play an important role in promoting adherence to the child's treatment regimen (De Civita & Dobkin, 2004).

2.5.2.2.3. *Healthcare accessibility and costs of care.* Accessibility of healthcare may be problematic for some families of children with leukemia. Distance to the treatment center is frequently substantial, since pediatric oncology services are often provided only at regional medical centers. Required travel may present significant challenges for some families, necessitating parental time off work to accompany the child for prolonged periods, resulting not only in financial hardship, but also often requiring disruption of routines for siblings and extended family members (Taylor, 2006). Socioeconomic factors may also strongly influence a family's ability to provide care for the child with leukemia. In addition to the obvious costs of medical care, which may pose a significant burden depending on the family's medical insurance coverage, further financial obligations incurred by families of children with leukemia may be substantial and may include increased expenditures for treatment-related travel and lost parental wages. In a study of 145 parents of children with cancer in the United Kingdom (a country with universal healthcare coverage), Eiser & Upton (2007) found that 68% of families reported financial concerns related to their child's care, despite the fact that the majority of families received governmental benefits and assistance from charitable organizations.

2.5.2.2.4. *Supportive presence.* Hinds et al. (2006) identified "supportive presence" as an important component of care for children with leukemia and their families. Supportive presence involves conveying to the patient and family that they are not alone in their experience, and includes nonjudgmental listening, providing active comfort, and demonstration of sensitivity to the family's needs by facilitating

involvement of multiple healthcare team members as indicated by each family's specific concerns. Supportive presence also involves ongoing monitoring regarding the patient's and family's understanding of their leukemia treatment and correcting any "incomplete or misinterpreted information that could result in negative outcomes, such as ignoring a treatment guideline" (Hinds, et al., 2006, p. 884). The provision of supportive presence by healthcare professionals may play an important role in adherence to medications, particularly in adolescents. In a study designed to describe factors that predict adherence among adolescents with chronic illness, the most powerful predictor was support from nurses (odds ratio [OR] 7.28, 95% confidence interval [CI] 3.95-13.42); support from physicians was also a strong predictor of adherence (OR 3.42; 95% CI 1.87-6.25) (Kyngas & Rissanen, 2001).

2.6. Conclusions: Adherence in Childhood A.L.L.

2.6.1. Characteristics of adherence in childhood A.L.L. Adherence to oral chemotherapy in childhood A.L.L. is a complex, multidimensional behavior that is predicated on the parent/child understanding and correctly carrying out complex instructions from the healthcare provider regarding a variety of medications, some with associated parameters regarding time of day when the medication is to be administered and/or administration without food or dairy products, and all of which may require frequent dose adjustments in response to blood counts, infections, clinical course, or changes in weight or body surface area (Davies & Lilleyman, 1995; Landier, 2001; Pui & Evans, 1998).

Therefore, adherence involves not only a willingness to stick to the prescribed regimen over a prolonged, defined period, but also the cognitive capacity and psychomotor skills to carry out the process (including development of methods to overcome potential barriers such as forgetfulness, change in routine, or lack of ability to swallow pills). Socioeconomic and cultural issues, such as financial barriers and difficulty accessing medical care, may also affect the patient/family's ability to adhere to the prescribed regimen.

2.6.2. Unique adherence issues in childhood A.L.L. Although by definition, A.L.L. is a chronic childhood illness (in that it requires treatment over a period of 2 to 3 years), there are many characteristics of the disease that make it unique in comparison to most chronic illnesses of childhood. A review of some salient characteristics of common pediatric chronic illnesses is therefore instructive in conceptualizing the uniqueness of childhood A.L.L. in regard to adherence-related issues. Unlike most chronic diseases of childhood (e.g., HIV, type 1 diabetes mellitus [DM], cystic fibrosis [CF], asthma, and juvenile rheumatoid arthritis [JRA]), treatment for A.L.L. is delivered with curative intent. Additionally, in sharp contrast to treatment for most pediatric chronic illnesses, treatment for A.L.L. is finite and time-limited.

While symptoms guide treatment and/or alert parents or clinicians to non-adherence in most chronic childhood illnesses (e.g., frequent asthmatic exacerbations; pain, joint swelling and/or dermatologic manifestations in JRA; malabsorption and/or exacerbation of respiratory infections in CF; signs of organ rejection in transplant recipients; and poorly controlled blood glucose levels in children with DM), children

with A.L.L. have no disease-related symptoms once remission is achieved, and in fact, symptoms that occur beyond the initial induction phase (e.g., nausea, mucositis, fatigue) are treatment-related rather than disease-related.

A.L.L., like many chronic disease of childhood (e.g., HIV, CF), is life-threatening and potentially fatal; however, unlike most chronic pediatric illnesses, the onset is abrupt and the severity (i.e., life-threatening nature) of the disease is self-apparent; without immediate intervention, children will A.L.L. will not survive. However, once the initial crisis has been addressed and the child enters maintenance therapy, treatment for childhood A.L.L. is dependent on a long phase of self/parent-administered oral medication. Once the therapy is completed and deemed effective, most children with A.L.L. will be able to live a healthy life without the need for ongoing medications. Therefore, adherence to daily oral chemotherapy over the prolonged required period of treatment, during which the child is typically asymptomatic, is a fundamental expectation for the successful treatment of childhood A.L.L.

Chapter 3: Methodology

3.1. Background

3.1.1. Preliminary work. A 2-year qualitative pilot study entitled *Understanding the Barriers and Facilitators to Adherence to Oral Chemotherapy in Hispanic Youth with Acute Lymphoblastic Leukemia* was recently completed [(Landier, Hughes, et al., 2009); 5P20CA118775 (Kane); City of Hope-California State University Los Angeles Collaborative to Study Cancer Disparities; Co-PIs: Wendy Landier, MSN, CPNP, Cynthia Hughes, EdD; Senior Mentor: Smita Bhatia, MD, MPH]. The primary objective of this pilot study was to develop and validate a grounded theory-based model to explain the process of adherence and identify barriers and facilitators to oral chemotherapy in Hispanic youth with A.L.L. Semi-structured interviews were conducted with Hispanic youth with A.L.L. and their parents/caregivers, and with a referent group of non-Hispanic white youth and their parents/caregivers. Twenty-two patients were enrolled and a total of 38 semi-structures interviews (21 with parents/caregivers, 17 with patients) and four focus groups (3 with parents/caregivers, 1 with patients) were conducted. Data were analyzed using the constant comparative method.

Facilitators to adherence identified in this pilot study included the delineation of roles and responsibilities for medication-taking between parent and child, parental vigilance (parents consistently checking in with children to assure that medications were taken), and the use of reminder systems (such as notes, calendars, or alarms) to assure that medications were given on schedule. Barriers to adherence identified in this study included forgetfulness, lack of organization, disruption of normal routine, taking a

passive role in treatment, not developing a routine for taking medications, difficulty related to medication ingestion (palatability, pill-swallowing, dietary restrictions, dose schedule related to sleep patterns), confusion regarding instructions for taking medications, and lack of parental supervision of medication-taking.

"Doing Our Part (Taking Responsibility)" was identified as the core category in this grounded theory that explains the process of adherence to oral chemotherapy among patients and parents/caregivers in the pilot study. Those who acknowledged more adherent behaviors implemented effective strategies to initially manage home medication administration ("Taking Control"), and then developed ongoing strategies to maintain their adherent behaviors throughout the treatment ("Managing for the Duration"). A mediating factor explaining adherence in this pilot study was the recognition by the patient/parent that taking oral chemotherapy was essential in order to get well ("Making the Connection"). Participants who demonstrated an understanding of the association between taking oral chemotherapy and control/cure of their disease described medication-taking behaviors and patterns consistent with adherence and reported overcoming barriers, or taking medication despite barriers that could not be overcome. Participants who lacked this understanding ("Missing the Connection") reported non-adherent behaviors and consistently cited barriers as reasons for not taking prescribed medication. Focus group data provided confirmation for the theory.

Figure 3.1 on the next page visually depicts the grounded theory that was developed from the pilot study data.

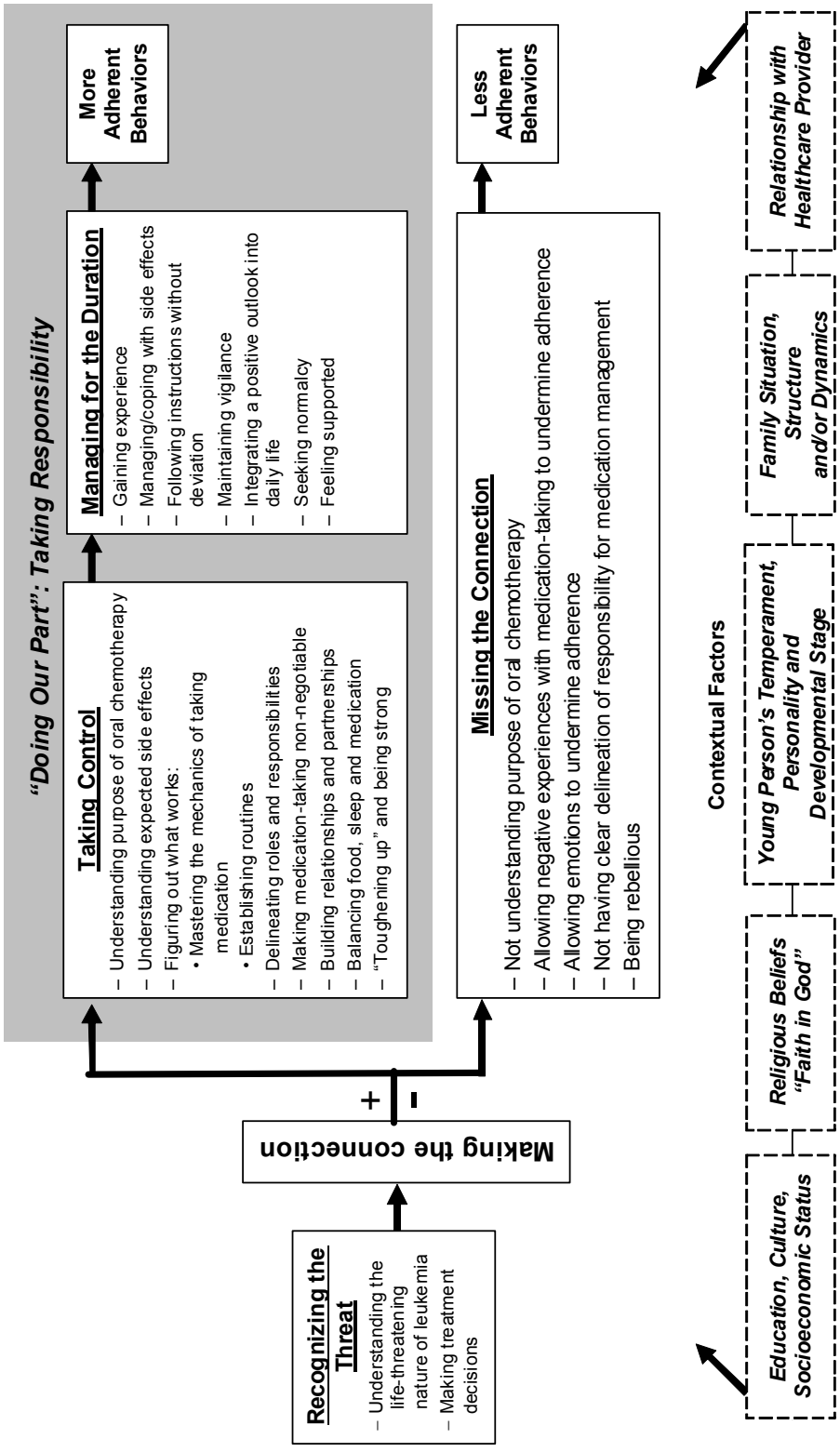


Figure 3.1. A grounded theory of the process of adherence in children with A.L.L.

[from Landier, Hughes et al. (2009)]

Findings from the pilot study are consistent with the Health Belief Model, in which adherence-related behaviors are determined by a person's perceived susceptibility to and severity of illness weighed against perceived benefits of and barriers to prescribed treatment regimens, coupled with the individual's belief in their own capability to perform the required actions needed to achieve adherence (self-efficacy/taking responsibility). Results of this pilot study have provided a rich source of information regarding the facilitators to adherence and reasons for non-adherence in youth with A.L.L. The findings of the pilot study helped to inform the selection of variables to examine, describe, and identify behavioral predictors of adherence for this study.

3.1.2. The Children's Oncology Group (COG). The Children's Oncology Group is a cooperative clinical trials group funded by the National Cancer Institute to conduct clinical trials in pediatric oncology. COG is a multidisciplinary organization that includes physicians, nurses, basic scientists, epidemiologists, statisticians, psychologists, pharmacists, and other healthcare professionals specializing in childhood cancer. COG develops and coordinates pediatric oncology clinical trials that are conducted at over 200 member institutions, which include pediatric oncology programs at most major universities and teaching hospitals in the United States and Canada, and at additional sites in Europe, Australia, and New Zealand (O'Leary, Krailo, Anderson, & Reaman, 2008).

3.1.3. Outcomes-focused A.L.L. research in the COG. Evaluations conducted by Children's Oncology Group investigators of outcomes in large cohorts of children with A.L.L. have demonstrated differences in survival by race/ethnicity. Five-year survival rates for African-American and Hispanic children with A.L.L. have been shown

to be significantly lower than for non-Hispanic whites and Asians (Bhatia, et al., 2002; Kadan-Lottick, Ness, Bhatia, & Gurney, 2003; Pollock, et al., 2000). The reason for this disparity in survival by race/ethnicity is unclear and could not be explained by prognostic factors known to be associated with adverse outcomes in pediatric A.L.L., such as age at diagnosis, initial white blood count, and cytogenetic abnormalities (Bhatia, et al., 2002).

3.1.4. COG AALL03N1. The Children's Oncology Group is currently evaluating the causes of the observed differences in survival in childhood A.L.L. by race/ethnicity in a 5-year prospective longitudinal study (COG AALL03N1: Understanding the Ethnic and Racial Differences in Survival in Children with Acute Lymphoblastic Leukemia; Study Chair, Smita Bhatia MD, MPH [1 RO1 CA096670, Principal Investigator: Smita Bhatia]). The study hypothesizes that differences in systemic exposure to 6MP during maintenance therapy are responsible for the observed racial/ethnic differences in survival, and that differences in adherence to 6MP explain the ethnic variability in systemic exposure, and hence differences in survival. To test this hypothesis, the study is measuring pharmacogenomics of TPMT and other drug metabolizing enzymes, as well as adherence to oral 6MP, in a cohort of children with A.L.L. from four ethnic and racial groups (Hispanic, non-Hispanic white, African-American, and Asian). Adherence to oral 6MP is being assessed comprehensively, by using multiple measures of adherence (serial red cell 6MP metabolites [6TGN and MethylTIMP], electronic pill monitoring, and self/parent report questionnaires). The study described herein utilized the extant data drawn from the self/parent-reported questionnaires collected for this larger Children's Oncology Group study.

3.2. Purpose and Specific Aims

The objective of this study was to identify behavioral predictors of self/parent-reported non-adherence to oral 6MP during the maintenance phase of A.L.L. therapy among pediatric patients who participated in the Children's Oncology Group clinical trail, COG AALL03N1.

3.2.1. Specific Aim 1. Describe the mean percent self/parent-reported adherence to 6MP in pediatric patients with A.L.L. receiving maintenance therapy.

a. Describe the prevalence of self/parent-reported non-adherence to 6MP during the maintenance phase of A.L.L. therapy.

b. Describe the impact of sociodemographic and disease-related factors on non-adherence to 6MP during the maintenance phase of A.L.L. therapy.

Definitions:

- Percent adherence was defined as the ratio of the difference between the number of days in the study period (i.e., 28) and the number of days 6MP was missed during the study period for non-medical reasons, to the number of days in the study period (i.e., 28), multiplied by 100.

- Non-adherence was defined as a mean level of percent adherence over the study period falling below a statistical cut-point in the data that was clinically relevant as defined in Section 4.4.2.

3.2.2. Specific Aim 2. Describe the behavioral determinants of non-adherence to 6MP during the maintenance phase of A.L.L. therapy.

3.2.3. Research Questions

1. What is the self/parent-reported mean percent adherence to 6MP and what is the prevalence of non-adherence to 6MP (at each time point and overall) in this cohort of pediatric patients receiving maintenance therapy for A.L.L.?
2. What is the impact of sociodemographic and disease-related factors on non-adherence to 6MP in this cohort?
3. What are the behavioral determinants of self/parent-reported non-adherence to oral chemotherapy in children receiving maintenance therapy for A.L.L.?
4. Which components of the Health Belief Model are the strongest predictors of self/parent-reported non-adherence to oral chemotherapy in these children?

3.2.4. Hypotheses

1. Lack of acknowledgement of the seriousness of the disease and the child's potential susceptibility to the disease will be predictive of self/parent-reported non-adherence *(HBM: Perceived Vulnerability)*
2. Lack of acknowledgement of the perceived benefits of oral 6MP chemotherapy will be predictive of self/parent-reported non-adherence *(HBM: Perceived Benefits)*
3. Lack of identification of a parent/caregiver who is responsible for home administration of oral chemotherapy will be predictive of self/parent-reported non-adherence *(HBM: Self-Efficacy/Taking Responsibility)*
4. Lack of a consistent routine for home medication administration will be predictive of self/parent-reported non-adherence *(HBM: Cues to Action)*

3.3. Significance

Poor medication adherence is known to be a substantial problem in contemporary health care (Osterberg & Blaschke, 2005), and is a potential contributor to the unexplained relapses in children with A.L.L. (Lilleyman & Lennard, 1996). Children who suffer relapse of their leukemia require intensified therapies that result in increased healthcare costs, and potentially increased morbidity and mortality for patients (Nguyen, et al., 2008). If non-adherence to oral chemotherapy is prevalent in therapeutic clinical trials for pediatric A.L.L., this could potentially result in erroneous conclusions being drawn regarding efficacy of the trials; thus, determining the prevalence of non-adherence is crucial to the integrity of such trials. Additionally, undetected non-adherence to therapy may result in erroneous clinical decisions regarding dosing of oral chemotherapy, or may result in unnecessary modifications to therapeutic regimens.

By determining the prevalence of self/parent-reported adherence to oral 6MP and identifying potentially modifiable behavioral risk factors that predict adherence during the maintenance phase of therapy for A.L.L., findings from this study provide a foundation for development of interventions to improve adherence to oral chemotherapy among children with A.L.L. Since treatment with oral antineoplastic agents is a therapeutic strategy employed in the treatment of other pediatric cancers, including non-Hodgkin lymphoma, Hodgkin lymphoma, and neuroblastoma, development of interventions to improve adherence to oral chemotherapy could potentially have important clinical applications in pediatric oncology practice beyond childhood A.L.L.

3.4. Study Design

This study consisted of analysis of the extant self/parent-reported adherence questionnaire data that was collected as part of the prospective, longitudinal COG AALL03N1 study. Eligibility criteria for enrollment onto AALL03N1 included: (1) Diagnosis of A.L.L. at age 21 or younger; (2) In first remission at time of study enrollment; (3) Treatment on or according to a protocol that included the following dosing of oral chemotherapy: (a) oral 6-Mercaptopurine at 75 mg per square meter of body surface area per day (75 mg/m^2/day) and (b) oral Methotrexate at 20 mg per square meter of body surface area per week (20 mg/m^2/week); (4) Completion of at least 24 weeks of maintenance chemotherapy and scheduled for at least 24 additional weeks of maintenance chemotherapy at the time of study enrollment; (5) Treatment at a COG-affiliated institution with ethics board approval for the study; and (6) Signed informed consent/assent.

Study participants were followed prospectively for a 6-month period during A.L.L. maintenance therapy. The patient and/or their parent/caregiver completed a demographic questionnaire at study entry and a self/parent-reported adherence questionnaire on Days 29, 57, 113, and 141 following study enrollment. A record of the 6MP dose prescribed by the healthcare provider, and details regarding the child's leukemia, health status, and treatment, were reported by the child's treating institution at the same time points.

Figure 3.2 on the next page illustrates the study design schema. Details regarding study questionnaires and data collection forms are included in Section 3.8.

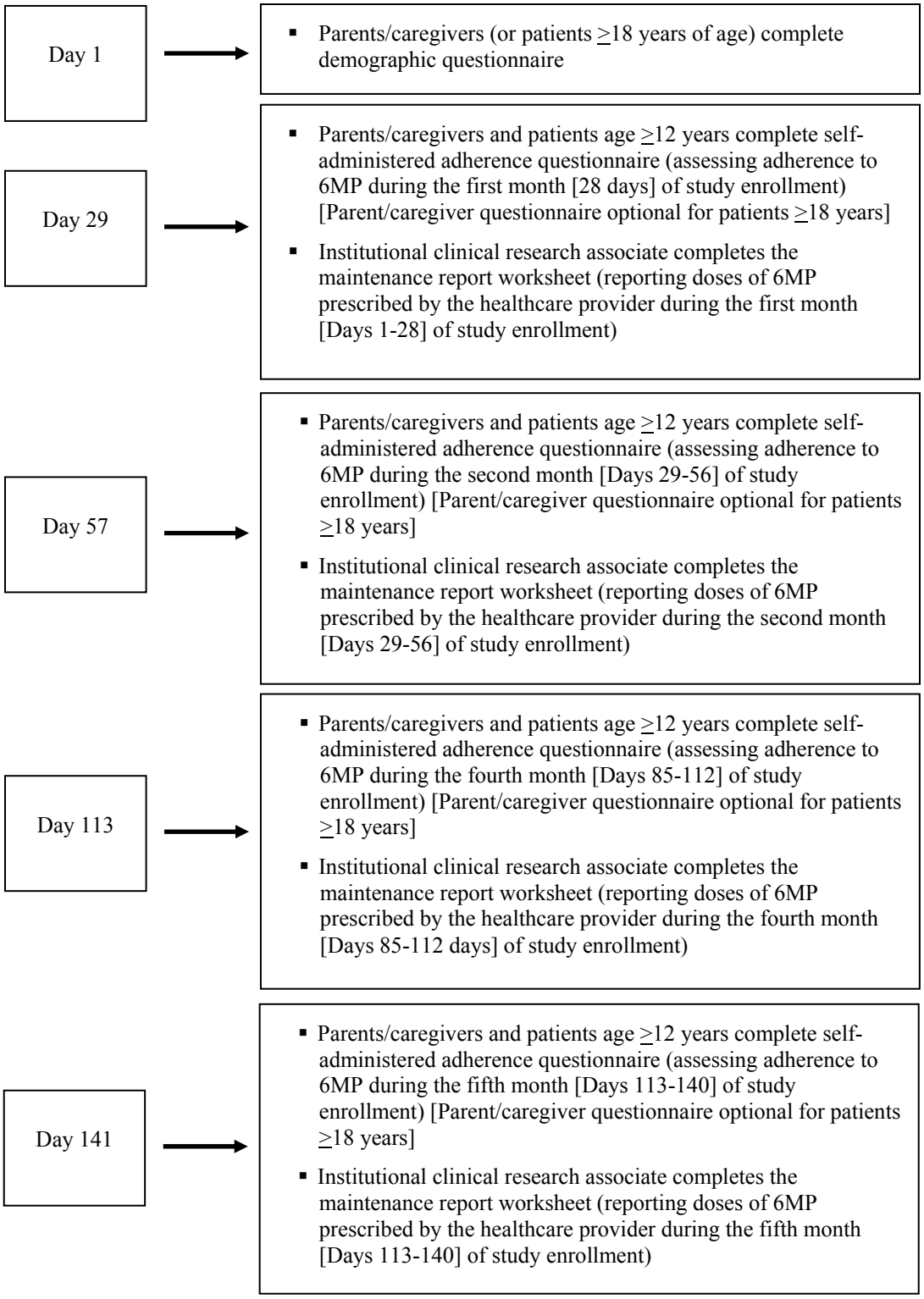


Figure 3.2. Study design schema

3.5. Sample

The sample consisted of existing data collected from 255 Hispanic and 241 non-Hispanic white children who were enrolled on the COG AALL03N1 protocol and followed at 86 Children's Oncology Group institutions in the U.S., Canada, and Australia. Permission for access to these data was obtained from Smita Bhatia, MD, MPH, the COG principal investigator for this study (Appendix A). Data collection for these patients was completed and the data set frozen for this analysis in January 2010.

3.6. Power Analysis

Power analysis was performed using G*Power 3.1.0 software (Universitat Kiel, Germany, 2008). The study sample was adequate to provide at least 80% power for a minimum detectable odds ratio (MDOR) of 1.8 if 50% of the patients had the behavioral predictor of interest present and at least 20% of the patients were non-adherent (Table 3.1)

Table 3.1. Power for behavioral predictor that is present in 50% of the sample

Power for behavioral predictor that is present in 50% of sample/absent in 50% of sample

MDOR	Proportion of non-adherent patients (Total N=496)				
	10%	15%	20%	25%	30%
1.2	0.10	0.12	0.13	0.15	0.16
1.4	0.22	0.29	0.35	0.39	0.42
1.6	0.40	0.52	0.60	0.66	0.70
1.8	0.58	0.72	0.80	0.85	0.88
2.0	0.74	0.86	0.92	0.95	0.96
2.2	0.85	0.94	0.97	0.98	0.99
2.4	0.93	0.98	0.99	0.99	0.99
3.0	0.99	0.99	0.99	0.99	0.99

MDOR = Minimum detectable odds ratio; α = 0.05, binomial distribution

3.7. Human Subjects Protection

COG AALL03N1 was approved by the City of Hope Institutional Review Board (IRB #01141) [study coordinating center], by the National Cancer Institute's Pediatric Central IRB (Rockville, MD), and by the Institutional Review Boards at all institutions contributing patients. Prior to study enrollment, informed consent was obtained from each patient or their parent/caregiver by the COG investigator at the treating institution. Assent was obtained from minor patients per institutional policy. Study-related data were coded with a unique COG study-identification number prior to submission to the coordinating center in order to protect patient identity. All data were maintained in secure locked files and password-protected databases at the study coordinating center at City of Hope.

Prior to initiating this analysis, Human Subjects Protection applications were prepared and submitted to the following three regulatory bodies for expedited review and approval: (1) The City of Hope Cancer Protocol Review and Monitoring Committee (approved January 4, 2010); (2) The City of Hope Institutional Review Board (approved January 18, 2010); and (3) The University of Hawai'i Institutional Review Board (approved February 3, 2010). Copies of all regulatory approvals are provided in Appendix B.

3.8. Study Instruments

3.8.1. Adherence questionnaire (AQ) *[patient and parent/caregiver versions]*. This 37-item instrument, modified from a questionnaire originally developed by Dr. Eric Kodish, was based on the work of Tebbi (1986) and Drotar (Riekert & Drotar, 2002).

Two versions of the AQ (Patient and Parent/Caregiver) were available in both English and Spanish. The Spanish version was translated from English by two professional medical translators employed by Interpreting Services International, a member of the American Translators Association. Parents/caregivers and patients (age 12 and older) were asked to complete the AQ at four study time points (Days 29, 57, 113, and 141 since study enrollment); parent/caregiver questionnaires were optional for patients age 18 or older at enrollment. Thus, for patients younger than age 12, there was the potential for completion of a total of 4 questionnaires (one at each time point by the parent/caregiver); for patients 12 to 17 years of age, there was the potential for completion of 8 questionnaires (2 at each time point, one by the patient and one by the parent/caregiver); and for patients 18 and older, there was the potential for completion of 4 questionnaires by the patient (one at each time point), and an optional additional 4 questionnaires by the parent/caregiver (one at each time point). For a small subset of patients who participated in the pilot phase of the study (N=21), adherence questionnaires were collected at only 2 study time points; the potential number of total questionnaires that could have been completed for these 21 patients was thus reduced by 50%. Items were dichotomous or multiple choice (n=22), short answer (n=13), and mixed dichotomous/short answer (n= 2). Completion time averaged 15 minutes.

The AQ was designed to operationalize the following behavioral predictors of adherence as defined by the Health Belief Model: (1) *Belief in health threat* (perceived vulnerability), which incorporates (1a) *Perceived severity* (of leukemia) and (1b) *Perceived susceptibility* (consequences of not taking oral chemotherapy as prescribed);

(2) *Belief in efficacy of health behavior*, which includes (2a) *Perceived benefits* (understanding of treatment; beliefs about efficacy of the prescribed treatment) and (2b) *Perceived barriers* (length of treatment, difficulties with medication administration, complexity of medication routine, medication side effects); (3) *Taking responsibility* for medication administration (by self or parent/ caregiver), which incorporates *self efficacy* (belief that parent/patient is capable of performing the skills necessary to achieve the desired outcome); and (4) *Cues to action* (medication routine, reminders). Importantly, although symptoms of disease are generally considered an important cue to action in the HBM, disease-related symptoms are notably absent in children with A.L.L. in remission. Figure 3.3 depicts the AQ items as components of the Health Belief Model, and Table 3.2 depicts the relationship of the AQ items to the Health Belief Model constructs.

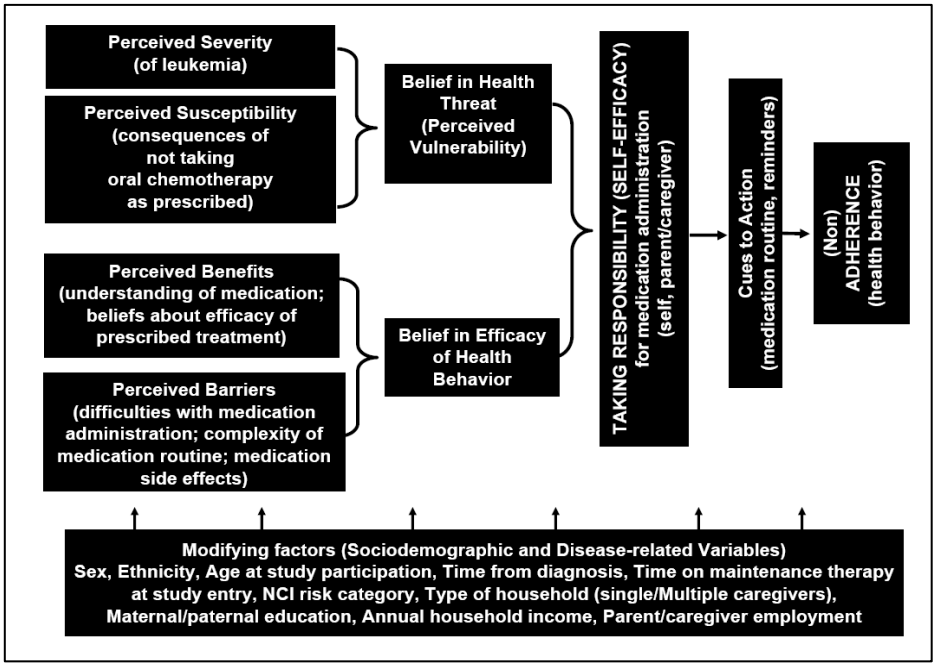


Figure 3.3. Behavioral predictors of adherence [Adapted from Stroebe (2000)]

Table 3.2. Relationship of adherence questionnaire items to Health Belief Model constructs

Health Belief Model Constructs		Item #	Item Description
Belief in health threat/ Perceived vulnerability	*Perceived severity* (of illness)	1	Has there been a change in the child's health in the past month?
	Perceived susceptibility (to illness)	35	What would happen if child stopped taking 6MP?
Belief in efficacy of health behavior	*Perceived benefits* Understanding treatment	9	How does 6MP work?
	Perceived barriers Length of treatment	3	How long has child taken 6MP?
		4	How much longer will child take 6MP?
	Complexity of medication regimen	5	Does child take same dose of 6MP daily?
		6	What 6MP dose does child take on each day?
		2/7/8	Has 6MP dose changed? Reason?
	Difficulties with medication administration/ schedule	11/12	Example of when child did not take 6MP (ever)
		15	If child did not take 6MP at least once in past month, list reason(s)
		16/17	Did child ever take different 6MP dose than prescribed? (Example)
		18/19	Did child ever decide not to take 6MP? (Example)
		20/21	Did parent/caregiver ever decide not to give 6MP? (Example)
		22/23	Reason that child might not take 6MP as prescribed (Example)
		30	Does child take 6MP with food? (Describe)
		31	Does child take 6MP with milk/dairy? (Describe)
		32	Does child take 6MP with liquid? (Describe)
		33	Does child swallow 6MP tablet whole?
		34	How is 6MP dose prepared?
	Side effects	36	If child has stopped taking 6MP, why?
		37	Anything else to tell about 6MP?
Taking responsibility/ Self efficacy	Delineation of responsibility for medication administration	10	Was child involved in the decision to take 6MP?
		25/26/27	Is 6MP administration supervised at home? (If so, by whom, how?)
Cues to Action	Medication routine/reminders	24	What is child's usual routine for taking 6MP
		28/29	Does child take 6MP at same time daily? What time?

3.8.2. Demographics questionnaire (DQ). This 13-item instrument was developed for the larger COG study. The DQ was available in English and Spanish (translated by two professional translators employed by Interpreting Services International), and was completed by the parent/caregiver (for patients age 17 or younger) or by the patient (if age 18 or older) at study entry. The following self/parent-reported data was elicited: (1) Patient date of birth; (2) Patient sex; (3) Patient race/ethnicity; (4) If patient was adopted (yes/no); (5) Mother's race/ethnicity; (6) Father's race/ethnicity; (7) Type of residence; (8) Members of household and their relationship to patient; (9) Current occupation of mother, father, other primary caretaker, and patient; (10) Mother's highest level of education; (11) Father's highest level of education; (12) Total household income in past year; and (13) Patient's current grade in school or highest grade completed. Completion time averaged 5 minutes.

3.8.3. Maintenance report worksheet (MRW). This 31-item instrument was developed for the larger COG study and submitted for each of the same four 4-week time periods that the self/parent-reported adherence data was collected on the AQ. The MRW was completed by the clinical research assistant (CRA) at the treating COG institution using medical record or clinician-reported data, and included the patient's leukemia status and treatment during the reporting period, hospitalizations if any, current height, weight and relevant laboratory results, healthcare provider report of prescribed doses of daily oral 6MP during the 4-week period, and dates and reason(s) prescriber ordered the patient to stop taking 6MP, if applicable.

Table 3.3 below provides a summary of the time points at which the questionnaire data were collected.

Table 3.3. Summary of data collection time points

Study Day	**1**	**29**	**57**	**113**	**141**
Demographic Questionnaire	X				
Patient and/or Parent/Caregiver Adherence Questionnaire		X	X	X	X
Maintenance Report Worksheet		X	X	X	X

3.9. Data Analysis Procedures

3.9.1. Variables included in the analysis

3.9.1.1. Outcome variable. "Non-Adherence," a dichotomous variable, was the dependent/outcome variable for this analysis. A patient was defined as non-adherent if his/her mean level of percent adherence over the study period fell below a statistical cut-point in the data that was clinically relevant, as defined in Section 4.4.2; otherwise he/she was considered adherent. Details regarding the process used for the dichotomization of this variable are provided in Section 3.9.4.6.

3.9.1.2. Independent variables. The primary independent variables used in this analysis were the behavioral predictors of adherence elicited from the AQ according to the major constructs of the Health Belief Model (*Belief in health threat/Perceived vulnerability [Perceived severity/ susceptibility], Belief in efficacy of the health behavior [Perceived benefits and barriers], Taking responsibility/Self efficacy* and *Cues to action)* (Figure 3.3; Table 3.2). The analysis was adjusted for sociodemographic and disease-

related variables (modifying factors) that explained some of the variance between the behavioral variables and non-adherence (Table 3.4). The predictor variables were dichotomous, categorical, or continuous as appropriate for the type of data. Predictor variables were first evaluated univariately. Those predictors found to be significant ($P<0.05$) or to approach a significance level of $P<0.20$ in the univariate analysis, and those identified a priori as clinically relevant, were explored in the multivariate models.

3.9.2. Creation of SPSS Files and Data Cleaning. Quantitative data analysis was conducted using SPSS Version 18.0 (PASW Statistics; SPSS, Inc., Chicago, IL, 2009). Each step of the data analysis process was recorded in a study log book. Initial steps in analyzing the data consisted of creating SPSS data files (separate files for adherence questionnaire, demographic, and disease/treatment-related variables) and importing the raw data into these files. Variables were coded in the SPSS format and the corresponding keys recorded in an electronic code book. This was followed by data screening and cleaning. Outliers were verified or corrected by checking the source documents; each correction was verified with the City of Hope research assistant prior to updating the database. In some cases, communication with the treating institution was required in order to obtain the information necessary for verification or correction; when required, the direct communication with the treating institutions was done through the City of Hope research assistant according to Children's Oncology Group standard procedures.

3.9.3. Analysis of sociodemographic and disease-related variables. Demographic and disease-related variables were evaluated descriptively using standard

parametric and non-parametric tests. Using existing variables, many additional variables were computed (e.g., age at diagnosis, age at study participation, and time from diagnosis were computed using the date of birth, date of diagnosis, and date of study entry variables) in order to fully characterize the cohort. In some cases, missing data were imputed (using single imputation) from existing variables (e.g., the maintenance start date was not available from the treating institution for all patients; in these cases, the "time on maintenance" variable was imputed using the date of diagnosis and the standard time to start of maintenance calculated based on the patient's treatment protocol). Descriptions of sociodemographic and disease-related variables are provided in Table 3.4 on the next page.

Table 3.4. Sociodemographic and disease-related variables

Variable	Description	Source	Values/Codes
SEX	Sex of child with A.L.L.	DQ Item #2	Male Female
ETHNICITY	Ethnicity of child with A.L.L.	DQ Item #3	1 = Non-Hispanic white 2 = Hispanic
AGE AT STUDY PARTICIPATION	Age of child at time of enrollment onto study	DQ Item #1 (DOB) and Page 1 (Today's date = Protocol Day 1)	Age in years (continuous)
AGE AT DIAGNOSIS	Age of child at time of A.L.L. diagnosis	DQ Item #1 (DOB) and DHTSW Item #4 (Date of ALL Diagnosis)	Age in years (continuous)
MATERNAL EDUCATION	Highest level of maternal education	DQ Item #10	0= Some education post high school 1≤High school
PATERNAL EDUCATION	Highest level of paternal education	DQ Item #11	0= Some education post high school 1≤High school
SINGLE PARENT HOUSEHOLD	Child with A.L.L. residing in single parent/caregiver household? (yes/no)	DQ Item #8	0 = No 1 = Yes
HOUSEHOLD SIZE	Members in household	DQ Item #8	Number of persons residing in household (continuous)
HOUSEHOLD INCOME	Annual household income	DQ Item #12	0= ≥$20,000 1= <$20,000
TIME FROM DIAGNOSIS	Time elapsed between diagnosis of A.L.L. and child's enrollment onto study	DQ Page 1 (Protocol Day#1) and DHTSW Item #4 (Date of ALL Diagnosis)	Time in years (continuous)
TIME FROM START OF MAINTENANCE	Time elapsed between initiation of A.L.L. maintenance therapy and child's enrollment onto study	DQ Page 1 (Protocol Day#1) and MRW Addendum Item #1 (Date of first day of Maintenance Course #1)	Time in months (continuous)
NCI RISK GROUP	Risk classification of A.L.L. based on NCI criteria at time of diagnosis	DHTSW Items #4 (Date of ALL Diagnosis), #6 (Initial WBC) DQ Item #1 (DOB)	0=Standard 1=High
CAREGIVER EMPLOYMENT	Caregiver employment status (works outside home)	DQ Item #9	0=At least one caregiver is at home 1=All caregivers work outside the home

Abbreviations: DQ=Demographics Questionnaire; MRW=Maintenance Report Worksheet; NCI=National Cancer Institute; DHTSW=Disease History and Therapeutic Summary Worksheet

3.9.4. Adherence categorization

3.9.4.1. Self/parent-report of 6MP administration. All self/parent-reported 6MP doses taken (Adherence Questionnaire - Item 14) and not taken (Adherence Questionnaire - Item 13) [Table 3.5] during the 28 days of each of the four study time periods were reviewed for each patient. Logic rules were implemented to account for any discrepancies in the self/parent-report values. For example, if a patient reported 2 missed doses for Item 13, but did not report the number of doses taken for Item 14, the missing value was corrected to reflect 26 doses taken. Since non-adherence was the main focus of this analysis, in cases where there was a discrepancy between the report of doses taken and not taken (e.g., if the sum of doses taken and not taken did not equal 28 doses), the report of doses not taken was retained and the report of doses taken was corrected to correspond with the report of doses not taken. If there were no responses indicating the number of doses taken or missed, but if a response to Adherence Questionnaire Item 15 ("If you/your child did not take 6MP at least once during the past 28 days, what caused you/your child to not take 6MP on that/those day(s)?") indicated a reason why 6MP had been missed during the study period (e.g., "I forgot,"), then one missed dose was recorded in order to conservatively account for the missed dose(s) described in Item 15. If an actual number of doses missed were stated in the Item 15 response (e.g., "I forgot to take it 2 times"), then that actual number was entered. Reports that did not include sufficient responses to Items 13, 14 and/or 15 to allow for determination of missed 6MP doses were marked as inevaluable for the study period.

Once all missed 6MP doses had been recorded, reviewed, and corrected using logic rules, the reasons for all missed doses were coded using the response to Item 15 ("what caused you/your child to not take 6MP?"), as follows: (1) illness (2) low blood counts/abnormal laboratory tests, (3) forgot, (4) fell asleep, (5) timing related to food/dairy products, (6) not at home/disruption in usual routine, (7) parental miscommunication, (8) did not have pills (due to pharmacy problems, appointment date change, etc.), (9) misunderstood healthcare provider instructions, (10) behavioral/active refusal, (11) vomiting, gagging, or nausea related to pill ingestion, (12) side effects, and (13) don't know/no reason given. These reasons were subsequently dichotomized to indicate doses missed for medical (responses coded 1 and 2) versus non-medical (responses coded 3-13) reasons.

3.9.4.2. Determination of percent adherence by study period. Reports of missed 6MP doses due to illness, low blood counts, or abnormal laboratory values were verified based on comparison with the healthcare provider report of held doses for each corresponding study period (Maintenance Report Worksheet – Items 24-28) [Table 3.5]. Patients with self/parent-reported missed doses due to illness/laboratory abnormalities during a study period were credited with 100% adherence during that study period unless they stated that they had also missed doses for non-medical reasons during that period (in which case, the procedure for coding missed doses for non-medical reasons was followed for those doses, as described in section 3.9.4.3). For patients who reported missed doses but did not state a reason for missing the dose, the healthcare provider report for that period was reviewed; if doses had been held by the healthcare provider for illness or

abnormal blood counts during the study period in a pattern similar to that reported per self-report, the missed doses were coded as missed due to medical reasons, and the patient credited with 100% adherence for the study period. Otherwise, the reason for the missed doses was coded as "forgot." Sources of data used in determining adherence categorization are presented in Table 3.5

Table 3.5. Sources of data for determining adherence categorization

Variable[†]	Description	Source	Coding
6MP NOT TAKEN SR [Day 29, 57, 113, 141]	In past 28 days, number of days child did not take 6MP (self-report)	Adherence Questionnaire (Patient Version) Item #13	Number of days (continuous)
6MP NOT TAKEN PCR [Day 29, 57, 113, 141]	In past 28 days, number of days child did not take 6MP (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #13	Number of days (continuous)
6MP TAKEN SR [Day 29, 57, 113, 141]	In past 28 days, number of days child took 6MP (self-report)	Adherence Questionnaire (Patient Version) Item #14	Number of days (continuous)
6MP TAKEN PCR [Day 29, 57, 113, 141]	In past 28 days, number of days child took 6MP (parent/caregiver report)	Adherence Questionnaire (Parent/Caregiver Version) Item #14	Number of days (continuous)
6MP PRESCRIBED HCPR [Day 29, 57, 113, 141]	In past 28 days, number of days child was prescribed to take 6MP, doses held, reasons for held doses (healthcare provider report)	Maintenance Report Worksheet Items #24-28	6MP held during study period? (categorical) Reason(s) 6MP held (categorical) Number of days 6MP prescribed/held (continuous)

[†]Note: Multiple iterations of each variable were created for each study time point [Day 29 = Month 1, Day 57 = Month 2, Day 113 = Month 4, or Day 141 = Month 5] as indicated by brackets. Study time point was identified on page 1 of the Patient and Parent/Caregiver Adherence Questionnaire ("Protocol Day #) and on page 1 of the Maintenance Report Worksheet (Study Month #)

Abbreviations: 6MP = 6-Mercaptopurine; SR = Self-report; PCR = Parent/Caregiver Report; HCPR = Healthcare Provider Report

3.9.4.3. Calculation of percent adherence. To calculate percent adherence, the total number of 6MP doses missed for non-medical reasons were subtracted from the number of days in the study period (i.e., 28), the remainder divided by the total number of days in the study period (i.e., 28), and the quotient multiplied by 100. For example, if a patient reported 2 missed doses for non-medical reasons during a 28-day study period, percent adherence for that study period was determined by the following calculation: [(28 – 2)/28] x 100 = 92.857.

Percent adherence was determined in the manner described above in order to allow for the proper categorization of patients who missed doses for both medical and non-medical reasons during a single 28-day study period. There were few instances in which reports of missed doses for both medical and non-medical reasons occurred in a single study period for any patient; however, when this did occur, had the denominator for the study period been decreased to account for the number of doses held for medical reasons, then the adherence categorization could have been affected. For example, if 6MP had been held for medical reasons for 14 of the 28 days of the study period, and the patient also reported missing one 6MP dose for non-medical reasons during the same study period, the calculation of percent adherence based on actual number of days 6MP was prescribed would have been: [(14 – 1)/14] x 100 = 92.857, which is equivalent to a percent adherence value representative of 2 missed doses in a full 28-day study period. Similarly, had a correction factor been used in order to obtain a 28-day denominator adjusted for the number of days that 6MP was actually prescribed (e.g., in the example above, multiplying both numerator and denominator by 2 in order to obtain a

denominator of 28 days), the adherence categorization would have been similarly affected (e.g., [(14-1) x 2]/(14x2) x 100 = 92.857). Thus, to allow for proper categorization of non-adherence based on doses missed solely for non-medical reasons, the decision was made to use the full 28-day study period as the denominator in all percent adherence calculations.

Percent adherence was determined for each respondent type (patient and/or parent/caregiver) for each study period. Descriptive statistics (mean, standard deviation) were then calculated for percent adherence by respondent type for each of the study time periods. Percent adherence calculations by number of doses missed for non-medical reasons during a 28-day study period are shown in Table 3.6.

Table 3.6. Percent adherence calculations (by number of 6MP doses missed for non-medical reasons during a 28-day study period)

6MP doses missed*	Percent adherence
0	100.000
1	96.428
2	92.857
3	89.285
4	85.714
5	82.142
6	78.571
7	75.000
8	71.428
9	67.857
10	64.285
11	60.714
12	57.142
13	53.571
14†	50.000

*6MP doses missed for non-medical reasons during the past 28 days

†No study participant reported missing more than 14 doses of 6MP for non-medical reasons during any one study period

3.9.4.4. Determining combined patient/parent-reported percent adherence. Data for patients younger than age 12 at the time of questionnaire completion were limited to parent/caregiver reports of adherence, while data for patients age 12 years or older were either a combination of patient and parent/caregiver-reports of adherence, or patient self-report exclusively. Therefore, a composite variable was created to reflect this combination of parent/caregiver and patient reports of adherence collected across the cohort for each study time point, as described in Table 3.7.

Table 3.7. Determination of combined patient/parent-reported percent adherence for each study time point (as a composite variable)

Patient Age Group[†]	Respondent Type(s)	Percent Adherence Value
Less than 12 years old	Parent/caregiver	Determined from the parent/ caregiver report for the study time point
Age 12 years and older	Patient only	Determined from the patient self-report for the study time point
	Both parent/ caregiver and patient	The sum of the percent adherence values from both the patient and parent-caregiver reports for the study time point divided by 2. If only the patient or parent-caregiver percent adherence value was reported for the study time point and the other value was missing, the single value available was used.

[†]Age at time of questionnaire completion

3.9.4.5. Determining overall mean percent adherence. Overall mean percent self/parent-reported adherence (as a continuous composite variable) was computed for each patient by adding all available percent adherence values from all time points for all

report types (i.e., patient and/or parent/caregiver) and dividing by the number of available percent adherence values for that patient. For example, to determine the overall mean percent adherence value for a patient younger than age 12 who had one parent-reported percent adherence value per study time period, the 4 parent-reported percent adherence values were added together and the sum divided by 4; whereas for a patient age 12 or older with one parent-reported and one self-reported percent adherence value for each time period, those 8 values were added together and the sum divided by 8. For patients with missing or inevaluable reports at any of the study time points (e.g., a patient with only 2 evaluable patient self-reports and 3 evaluable parent/caregiver reports for the entire study period), all available values were summed and divided by the total number of evaluable reports to determine the overall mean percent adherence (e.g., [% adherence Day29parent + % adherence Day29patient + % adherence Day 57parent + % adherence Day 113patient + % adherence Day 141parent] divided by 5). For patients with only one evaluable self- or parent/caregiver-report, that single value was used as the overall mean percent adherence.

3.9.4.6. Determining the self/parent-reported non-adherence categorization. Since no clinically meaningful levels of non-adherence for 6MP have been described in children with A.L.L. to date, the adherence/non-adherence categorization for this analysis was determined from the study data. A patient was defined as non-adherent if his/her mean level of percent adherence over the study period fell below a statistical cut-point in the data that was clinically relevant, as defined in Section 4.4.2; otherwise he/she was considered adherent. Overall mean percent adherence values for the entire cohort were

used as the basis for determination of the dichotomized self/parent-reported adherence/non-adherence categorization. This was accomplished by evaluating the frequency table, stem-and-leaf plot, and box plot for the overall mean percent adherence variable in order to determine the mean, median and range of values, to evaluate the frequency and distribution of values, and to identify the lower, middle, and upper quartiles. The demarcation between values indicative of adherence versus non-adherence, based on overall mean percent adherence, was subsequently determined after thorough review of all available statistical information considered in the context of the need for a clinically meaningful categorization schema.

3.9.5. Determining concordance of patient and parent/caregiver reports. For patients age 12 and older who had at least one patient report and one parent/caregiver report of percent adherence at the same study time point, concordance between patient and parent/caregiver reports of adherence was evaluated using the paired-samples t-test. Assuming normal distribution of the difference between the patient and parent-reported adherence values, the paired-samples t-test was used to determine if the difference between these values was significant (for non-normal distribution of the difference, the Wilcoxon Signed Rank Test would be used in place of the paired-samples t-test).

3.9.6. Evaluating the behavioral predictors of adherence

3.9.6.1. Analysis of adherence questionnaire data. The AQ was designed to elicit quantitative data regarding behavioral predictors of self/parent-reported adherence to 6MP (22 items), supplemented by open-ended questions that elicited short-answer qualitative (narrative) data (13 items); two items in the AQ contained both quantitative

and narrative components (Appendix C). The narrative data from the open-ended items were quantitized into categorical variables for use in the multivariable analysis (Teddlie & Tashakkori, 2009). Variables from the AQ collected for purposes of assessment of the behavioral determinants of non-adherence to 6MP have been previously described in Table 3.2 and illustrated in Figure 3.3. Details regarding the specific behavioral-related variables included in the analysis, their specific data sources, and variable names, are provided in Table 3.8.

Table 3.8. Behavioral variables from Health Belief Model included in univariate analysis.

Construct	Item	Variable Name	Data Source
Belief in health threat/ Perceived vulnerability *[Perceived severity, Perceived susceptibility]*	Has not experienced change in health status in past month *[Perceived severity]*	K.healthcorr. 1PT	AQ-Item 1 – first reporting period [composite Pt/Par variable][†]
	Unaware of consequences of not taking 6MP as prescribed *[Perceived susceptibility]*	K.stopRECODED .1PT	AQ-Item 35 – composite of all reporting periods [composite Pt/Par variable]
Belief in efficacy of health behavior *[Perceived Benefits]*	Unaware of purpose/ function of 6MP	K.how6MPdichot. 1cum	AQ-Item 9 - composite of all reporting periods [composite Pt/Par variable]
Belief in efficacy of health behavior *[Perceived Barriers]*	Months on maintenance [time on maintenance therapy prior to study participation]	TimeOnMaint Months	DQ – Cover Page [Protocol Day 1 date] MRW Addendum - Item 1 [Date of first day of Maintenance Course #1]
	6MP dose varies from day to day	K.same6MPcorr.1 PT	AQ-Item 5- first reporting period [composite Pt/Par variable]

Table 3.8. (Continued) Behavioral variables from Health Belief Model included in univariate analysis

Construct	Item	Variable Name	Data Source
Belief in efficacy of health behavior *[Perceived Barriers] (continued)*	6MP prescription has ever changed	K.change6MPcorr .1PT	AQ-Item 7 - first reporting period [composite Pt/Par variable]
	6MP prescription changed in past month	K.leukinfoCoded Dichot.1PT	AQ-Item 2 - first reporting period [composite Pt/Par variable]
	Child takes 6MP without food and/or milk	K.foodmilkCOM BO.1PT	AQ-Items 30, 31 - first reporting period [composite Pt/Par variable]
	Child cannot swallow 6MP tablet whole	K.swallowCORR. 1PT	AQ-Item 33 - first reporting period [composite Pt/Par variable]
Taking Responsibility/ Self efficacy *[Delineation of responsibility for medication administration]*	Child not involved in decision to take 6MP	K.child6MPdichot. 1PT	AQ-Item 10 - first reporting period [composite Pt/Par variable]
	No adult involved in monitoring 6MP administration	K.monitorCOMB ODichot.1PT	AQ-Items 25, 26, 27 - first reporting period [composite Pt/Par variable]
Cues to Action *[Medication routine/ reminders]*	No systematic approach/ routine for 6MP administration	K.howmonitor RECODEDdichot. 1PT	AQ-Item24 - first reporting period [composite Pt/Par variable]
	6MP not administered at same time daily	K.sametime.1PT	AQ-Items 28, 29 - first reporting period [composite Pt/Par variable]
	6MP administered late at night	K.timeofday Dichot.1PT	AQ-Item 29 - first reporting period [composite Pt/Par variable]

Abbreviations: AQ= Adherence Questionnaire; DQ=Demographics Questionnaire; MRW=Maintenance Report Worksheet

[†]Composite Pt/Par variables reflect parent/caregiver report for patients under age 12 and patient report for patients age 12 and older (if provided by patient)

3.9.6.2. Quantitating the qualitative data. Data conversion (transformation) is the process through which narrative qualitative data are converted into numeric data that can be analyzed statistically; this process is known as "quantitizing" (Sandelowski, 2000; Teddlie & Tashakkori, 2009). Narrative data from qualitative items were first reviewed by the investigator and condensed into thematic categories using content analysis techniques (Krippendorff, 2004). A coding list containing all identified categories for each open-ended item was developed; similar categories were collapsed and combined together until each code reflected a single theme, yielding dichotomized variables for analysis. Each narrative response was assigned a code from the coding list. Numerical values were then used to code each variable dichotomously for entry into the database (0 = Absence of the characteristic of interest; 1 = Presence of the characteristic of interest). The coding list was validated by Dr. Smita Bhatia, Chair of COG AALL03N1, who also reviewed the coding of a representative sample of narrative responses to ensure reliability. Disagreements regarding coding assigned to any of the items were discussed and resolved by the two investigators and the coding finalized.

As an example of the qualitative coding process, the narrative responses to Item #35 from the AQ (Patient Version), *"What do you think would happen if you stopped taking your mercaptopurine?"* yielded a list of codes that included the following categories: 0: "Nothing" 1: "Relapse, disease progression, sick, die" 2: "Blood counts affected" 3: "Treatment affected" 4: "Something bad" 5: "Feel better" 6: "Non-cancer related" 99: "Don't know." The narrative response, *"The leukemia may come back and out of hiding,"* was coded as "1/Relapse"; while the narrative response *"It would not be*

good for him. Lower chances of cure" was coded as "4/Something bad," and the response *"Maybe he will be easier for him to catch something if someone else is sick"* was coded as 6/Non-cancer related, while the response *"Have no clue"* was coded as "99/Don't know." Following initial coding, variables amenable to dichotomization were further transformed into their dichotomous form. For Item #35, a variable termed *"Unaware of consequences of not taking 6MP as prescribed,"* reflecting the HBM construct of *Perceived health threat/vulnerability (perceived susceptibility)*, was created by combining the categorical responses indicative of awareness of the potential consequences of not taking 6MP (i.e., responses coded 1-4) to create the "Aware" condition (coded "0"), and combining the remaining categorical responses indicative of lack of awareness of the potential consequences of not taking 6MP (i.e., responses coded 0, 5, 6, or 99) to create the "Unaware" condition (coded "1"). This newly created dichotomized "quantitated qualitative" variable was then included as a behavioral predictor in the regression portion of the analysis. The coding schema for key qualitative variables included in the analysis and samples of coding verification are provided in Appendix D.

3.9.6.3. Incorporating the quantitated qualitative data into the quantitative data analysis. The outcome variable (non-adherence) was dichotomized as previously described in Section 3.9.4.6. The sociodemographic and disease-related predictor variables were evaluated univariately as previously described in Section 3.9.3. The quantitated behavioral variables were dichotomized as described in Section 3.9.6.2 and evaluated univariately for association with the outcome variable. Those predictors found

to be significant ($P<0.05$) or to approach a significance level of $P<0.20$ in the univariate analysis and those identified a priori as clinically relevant, were explored in the multivariate logistic regression models.

3.9.6.4. Developing composite variables. Composite variables, using data from each of the four study time points, were created for items representing key constructs in the analysis in order to summarize the response to each item across the four study time points. For those patients age 12 and older for whom both Patient and Parent/Caregiver versions of the questionnaires were completed, a composite variable was created incorporating the Patient and Parent/Caregiver response. For items in which overlap between constructs was detected, similar items involving each construct were condensed into a single composite variable in order to limit the number of variables in the analysis. Since patient self-report data was available only for those 12 years of age and older, the analysis was stratified by age (after completing the initial analysis based on the composite variables) in order to determine if there were differences in predictors of adherence for older patients with self-report data (age 12 and older) versus younger patients with only parent-caregiver report data (age younger than 12 years).

3.9.6.5. Developing the multivariable models. Multivariable logistic regression models were developed to identify significant behavioral predictors of self/parent-reported adherence to 6MP. Behavioral predictors considered in the analysis were based on the HBM and included (1) *Perceived health threat/vulnerability* (awareness of disease severity and perceived susceptibility/consequences of not taking 6MP); (2) *Belief in efficacy of the health behavior,* which includes *(2a) Perceived benefits* (awareness of

purpose/function of 6MP) and (2b) *Perceived barriers,* including length of time on maintenance therapy, complexity of treatment, and difficulties with medication-taking, including pill swallowing difficulties and scheduling difficulties related to ingestion of food and milk; (3) *Taking responsibility* for medication administration (home supervision of 6MP administration by parent), which incorporates *self efficacy* (belief in one's ability to perform the required action) and, and (4) *Cues to action* (medication routine/use of reminders and timing for medication administration). Relevant sociodemographic and disease-related variables, as described previously, were controlled for in the multivariable model.

The direct ("forced entry") method of binary logistic regression was used for this analysis. In the direct method of logistic regression, all covariates are entered into the regression model in one block, and the parameter estimates are calculated for the entire block (Field, 2005). The advantage of this method is that it limits random variation in the data (Tabachnick & Fidell, 2007). One limitation of this method is that cases with missing data are deleted list-wise. However, since composite variables summarizing the four study time points were used in this analysis, there were less than 10% missing data overall for all variables with the exception of one sociodemographic predictor variable (caregiver employment), which was excluded from the analysis due to more than 10% missing data for that variable. The goodness of fit of the models was assessed by comparing the constant-only model with the full model using the log-likelihood technique (Tabachnick & Fidell, 2007). The Cox & Snell R Square and the Nagelkerke R Square (both pseudo R square statistics), were used as indicators for the amount of

variation in the outcome variable explained by the model. Collinearity diagnostics including the Condition Index, Variance Proportion, Tolerance and Variance Inflation Factor (VIF), were used to assess for multicollinearity of the variables in the final model; standardized residuals and Cook's distance were evaluated to identify outliers that could have dramatic effects on the coefficients in the model (Field, 2005; Tabachnick & Fidell, 2007). The data analysis schema is summarized in Figure 3.4 below.

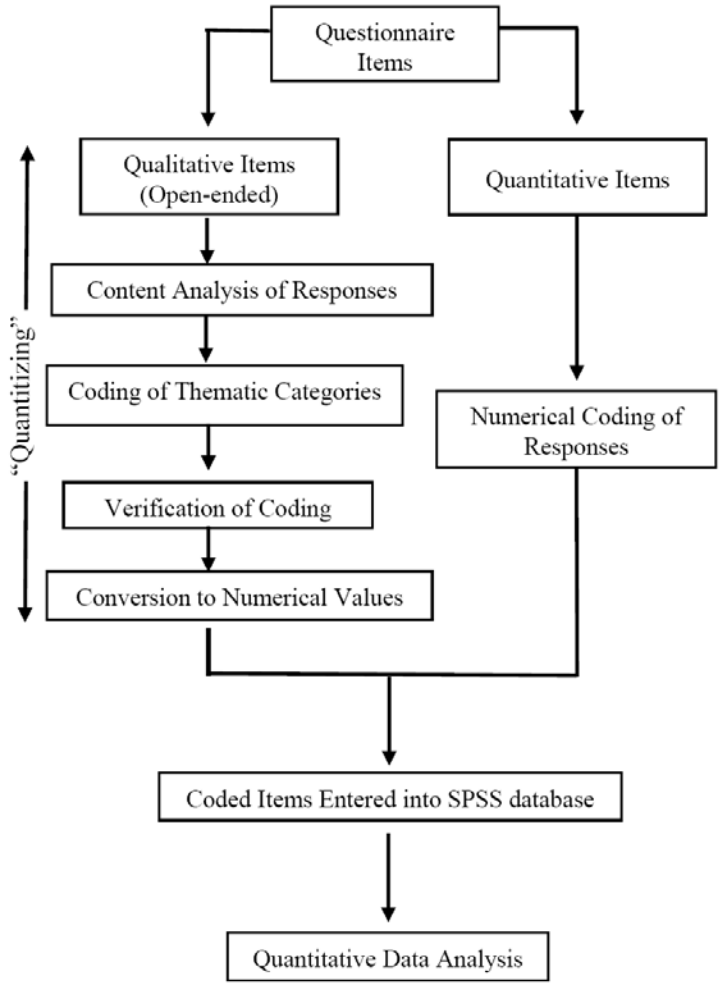


Figure 3.4. Data analysis schema

Chapter 4: Results

4.1. Participant Characteristics

A total of 496 patients from the COG AALL03N1 cohort, contributed by 86 COG institutions (Appendix E), met eligibility criteria (Section 3.4) for this analysis. Self-reported questionnaires were completely lacking for one patient, who was thus deemed inevaluable and excluded from the analysis. The sociodemographic and clinical characteristics of the remaining 495 evaluable study participants are summarized in Table 4.1. Nearly seventy percent of study participants were male; 51.3% of the study participants were Hispanics. Median age at diagnosis was 5.0 (range 1.0 – 19.0) years, median age at study participation was 6.6 (range 2.6 – 20.7) years, median time from diagnosis was 1.5 (range 0.9 – 3.0) years, and median time on maintenance therapy was 8.6 (range 2.7 – 26.5) months. The majority (58.4%) of participants had NCI standard risk disease, and 91.1% had precursor B-cell immunophenotype. Forty four percent of mothers and 59.1 percent of fathers reported an educational level of high school or less, and 24.2% of families reported an annual income of less than $20,000. Median family size was 5, with a range of 2 to 12 family members. Over three-quarters (78.0%) of the participants resided in a single family dwelling and 85.1% reported more than one adult caregiver in the home.

Table 4.1. Participant characteristics

Characteristic	N (%)
Cohort size	495 (100.0)
Sex	
Male	344 (69.5)
Female	151 (30.5)
Ethnicity	
Non-Hispanic white	241 (48.7)
Hispanic	254 (51.3)
Age at diagnosis (years)	
Mean (SD)	6.68 (± 4.65)
Median (range)	5.04 (1.01 – 19.03)
Age at study participation (years)	
Mean (SD)	8.29 (± 4.71)
Median (range)	6.58 (2.56 – 20.69)
NCI Risk Classification	
Standard risk	289 (58.4)
High risk	199 (40.2)
Missing	7 (1.4)
Immunophenotype	
Precursor B-cell	451 (91.1)
T-cell	38 (7.7)
Other	2 (0.4)
Missing	4 (0.8)
Time from diagnosis (years)	
Mean (SD)	1.61 (± 0.48)
Median (range)	1.54 (0.89 – 2.97)
Time on maintenance (months)	
Mean (SD)	10.72 (± 5.40)
Median (range)	8.62 (2.73 – 26.51)
Maternal education	
Less than high school	99 (20.0)
High school graduate	119 (24.0)
Technical training post high school	46 (9.3)
Some college	92 (18.6)
College graduate	88 (17.8)
Graduate school	39 (7.9)
Missing	12 (2.4)

Table 4.1. (Continued) Participant characteristics

Characteristic	N (%)
Paternal education	
Less than high school	119 (24.0)
High school graduate	124 (25.1)
Technical training post high school	37 (7.5)
Some college	82 (16.6)
College graduate	66 (13.3)
Graduate school	46 (9.3)
Missing	21 (4.2)
Annual household income	
Less than $20,000	120 (24.2)
$20,000 to $49,999	172 (34.7)
$50,000 to $74,999	69 (13.9)
$75,000 to $99,999	40 (8.1)
$100,000 or higher	63 (12.7)
Missing	31 (6.3)
Number of caregivers	
0 (patient cares for self)	1 (0.2)
1 (single parent household)	64 (12.9)
2	379 (76.6)
3 or more	42 (8.5)
Missing	9 (1.8)
Caregiver employment‡	
At least one caregiver is at home	242 (48.9)
All caregivers work outside home	202 (40.8)
Missing	51 (10.3)
Family size	
Mean (SD)	4.71 (± 1.41)
Median (range)	5 (2-12)
2 family members	15 (3.0)
3 family members	64 (12.9)
4 family members	160 (32.3)
5 family members	133 (26.9)
6-7 family members	91 (18.4)
8-9 family members	21 (4.2)
10 or more family members	2 (0.4)
Missing	9 (1.8)
Dwelling type	
Single family	386 (78.0)
Apartment/other	96 (19.4)
Missing	13 (2.6)

‡Variable not included in analysis due to >10% data missing

4.2. Participant characteristics relevant to self-report questionnaire

Participant characteristics relevant to Adherence Questionnaire (AQ) completion are presented in Table 4.2.

Table 4.2. Characteristics relevant to self-report questionnaire completion

Participant characteristic	N (%)
Cohort size	495 (100.0)
Patient age at study participation	
Less than 12 years	389 (78.6)
12 to 17 years	75 (15.2)
18 years or older	31 (6.3)
Person completing self-report questionnaire	
All questionnaires completed by parent/caregiver only	389 (78.6)
At least one questionnaire completed by parent/caregiver and patient	69 (13.9)
All questionnaires completed by patient only	37 (7.5)
Questionnaire language by ethnicity	
Completed all self-report questionnaires in English	
Non-Hispanic white	241 (100.0)
Hispanic	136 (53.8)
Completed at least one self-report questionnaire in Spanish	
Non-Hispanic white	0 (0.0)
Hispanic	117 (46.2)
Missing	1 (0.2)
Questionnaire completion	
All possible self-report questionnaires completed	375 (75.8)
One or more self-report questionnaires missing	120 (24.2)
Median (range) number of questionnaires completed:	
Entire cohort	4 (1-8)
Less than 12 years at study participation	4 (1-8)[†]
12 to 17 years at study participation	7 (2-8)
18 years or older at study participation	4 (2-4)
Mean (SD) number of questionnaires completed	
Entire cohort	4.06 (1.36)
Less than 12 years at study participation	3.69 (0.78)
12 to 17 years at study participation	6.15 (1.92)
18 years or older at study participation	3.68 (0.65)

[†]Range was 1-4 for all patients in this age group with the exception of 6 patients age 11.75 to 11.99 at study participation, who each submitted 2-4 Patient AQs and 3-4 Parent/Caregiver AQs, and thus had a range of 6-8 AQs

As described in Section 3.8.1, patient age determined which version(s) of the AQ (Patient and/or Parent/Caregiver) were administered. At least one Parent/Caregiver version of the AQ was submitted for all of the 389 patients younger than age 12 (100%); for 68 (90.7%) of the 75 patients between 12 and 17 years of age; and for 1 (3.2%) of the 31 patients age 18 or older at study participation. At least one Patient version of the AQ was submitted for 6 (1.5%) of the 389 patients younger than age 12; for 69 (92%) of the 75 patients between 12 and 17 years of age; and for all 31 (100%) of the patients age 18 or older at study participation.

The 6 patients younger than age 12 at participation who submitted Patient AQs were all 11.75 years of age or older at the time of study entry and thus reached the age of 12 during the 6-month study period. The 7 patients between 12 and 17 years of age for whom there were no Parent/Caregiver AQs submitted ranged in age from 12.75 to 17.87 years, with 4 of the 7 (57%) over age 17 at study entry. The 6 patients age 12 or older who did not completed any Patient AQs ranged in age from 12.02 to 15.98 years, with 4 of the 6 (66.7%) age 13 or younger at study entry. The one patient age 18 and older for whom Parent/Caregiver AQs were submitted was 19.49 years of age at study entry.

Thus, all study questionnaires were completed by a parent/caregiver for 389 (78.6%) of the 495 patients in the study (383 of whom were younger than age 12 and 6 of whom were older than age 12 at study entry); while 69 (13.9%) of the patients (6 of whom were age 11.75 to 11.99 and 63 of whom were age 12 or older at study entry) had at least one questionnaire submitted by both the patient and a parent/caregiver; and 37 (7.5%) of the patients (all of whom were age 12 or older at study entry) completed all

self-report questionnaires themselves without co-submission of any self-report questionnaires by a parent/caregiver.

Self-report questionnaires were available in English and Spanish; 100% of the 241 non-Hispanic white participants completed the questionnaires in English, while 117 (46.2%) of the 253 Hispanic participants completed at least one self-report questionnaire in Spanish.

4.2.1. Questionnaire Completion. A total of 106 patients and 458 parent/caregivers submitted at least one self-report questionnaire over the four study time points, with patients contributing 362 (18%) of the self-report questionnaires and parents/caregivers contributing 1647 (82%) of the 2009 self-report questionnaires collected for the cohort (Table 4.3). Although some questionnaires were returned without every item completed, no questionnaires were excluded because of incompleteness.

Table 4.3. Questionnaires by respondent type

Number of questionnaires completed	Person completing questionnaire				Total Questionnaires		
	Patient		Parent/Caregiver				
	Patient only	Patient/Parent Pairs: Patient	Patient/Parent Pairs: Parent	Parent only	Patient	Parent	Total
1	0	3	6	8	3	14	17
2	3	17	8	31	40	78	118
3	4	9	13	52	39	195	234
4	30	40	42	298	280	1360	1640
Total	**37**	**69**	**69**	**389**	**362**	**1647**	**2009**

106 patients completed questionnaires

458 parents/caregivers completed questionnaires

4.2.2. Self-report questionnaire response rate. Under ideal conditions, each parent/caregiver of patients age 17 and younger and each patient age 12 or older would have completed 4 questionnaires (one for each study time point), and parents/caregivers of patients age 18 and older would have had the option of completing up to 4 questionnaires. Thus, there was the potential for submission of a total of 4 parent/ caregiver questionnaires for patients under age 12; a total of 8 questionnaires (4 parent/caregiver and 4 patient) for patients between ages 12 and 17; and a total of 4 patient (and an optional 4 parent/caregiver) questionnaires for patients age 18 and older. However, not all participants were eligible to complete self- and/or parent/caregiver questionnaires at all 4 study time points due to a number of reasons. These included participation during the initial pilot portion of the study (during which self-report

questionnaires were collected at only two study time points; see Section 3.8.1); withdrawal prior to study completion (due to relapse, complications related to the illness, or patient/parent-caregiver request); or change in patient age during the study period, resulting in initiation of patient self-report questionnaire collection (at age 12), or cessation of parent/caregiver self-report questionnaire collection (at age 18).

Questionnaire response rate was therefore calculated by dividing the total number of patient or parent/-caregiver self-report questionnaires submitted per patient by the total number of patient and/or parent/caregiver self-report questionnaires that could potentially have been completed for each patient during the study period. Based on this calculation, it was determined that a total of 2204 self-report questionnaires could potentially have been collected from the entire cohort; 2009 of these questionnaires were actually collected, for a response rate of 91.15%. (Table 4.4).

Table 4.4. Potential self-report questionnaires and actual questionnaires completed

		Number of potential self-report questionnaires		Actual self-report questionnaires completed	
		Patients by number of potential questionnaires N (%)	Total potential questionnaires N	Patients by number of questionnaires completed N (%)	Total questionnaires completed N
Number of questionnaires	**1**	1 (0.2)	1	8 (1.6)	8
	2	16 (3.2)	32	36 (7.3)	72
	3	2 (0.4)	6	56 (11.3)	168
	4	407 (82.2)	1628	338 (68.3)	1352
	5	1 (0.2)	5	6 (1.2)	30
	6	6 (1.2)	36	10 (2.0)	60
	7	0 (0.0)	0	9 (1.8)	63
	8	62 (12.5)	496	32 (6.5)	256
Total		495 (100.0)	**2204**	495 (100.0)	**2009**
		Total questionnaires completed/ total potential questionnaires = 2009/2204 = 91.15%			

All of the potential self-report questionnaires were completed for 375 (75.8%) patients in the cohort and one or more questionnaires were missing from 120 (24.2%) of the patients. The mean percentage of potential questionnaires actually completed for the entire cohort over all study time points was 91.86 (+ 15.93)%, with a median 100% of potential questionnaires completed and a range for questionnaire completion of 25 to 100% (Table 4.5).

Table 4.5. Questionnaire completion rate (ratio of total questionnaires completed to total possible questionnaires)

Percent of total possible questionnaires completed	%	Number of patients by questionnaire completion rate N (%)	Questionnaire completion rate category	Percent of patients per category
	<25	0 (0.0)	<25%	0.0%
	25	2 (0.4)	25 to <50%	0.4%
	33.3	0 (0.0)		
	50	39 (7.9)	50 to <75%	9.3%
	62.5	5 (1.0)		
	66.7	2 (0.4)		
	75	61 (12.3)	75 to <100%	14.5%
	80	1 (0.2)		
	83.3	1 (0.2)		
	87.5	9 (1.8)		
	100.0	375 (75.8)	100%	75.8%
	Total	495 (100.0)	N/A	N/A
Overall questionnaire completion rate: Mean (SD) 91.86 ±15.93 Median 100 (range 25-100)				

4.3. Specific Aim 1: Findings

Describe the mean percent self/parent-reported adherence to 6MP in pediatric patients with A.L.L. receiving maintenance therapy.

4.3.1. Overall mean percent adherence. Overall mean percent self/parent-reported adherence for the entire cohort, determined according to the methodology described in Sections 3.9.4.2 through 3.9.4.5, was 98.88 ± 2.88 standard deviation (SD) and ranged from 71.4 to 100. Of the 495 patients in this study, 386 (78%) had an overall mean percent adherence of 99.1 or higher, with 351 (70.9%) having an overall mean percent adherence of 100. See Table 4.6 for a summary of the frequencies of mean percent adherence values for the entire cohort.

Table 4.6. Frequencies of overall mean percent adherence values for the cohort

Mean Percent Adherence	Frequency	Percent	Percentage grouping	Percent of cohort within grouping
<70.0	0	0.0	<70%	0.0
71	1	0.2	70 - <80%	0.4
79	1	0.2		
83	3	0.6	80 - <90%	1.6
86	1	0.2		
87	2	0.4		
89	2	0.4		
90	2	0.4	90 - <99%	20.0
91	5	1.0		
92	8	1.6		
93	6	1.2		
94	6	1.2		
95	7	1.4		
96	13	2.6		
97	16	3.2		
98	36	7.2		
99	35	7.1	99-100%	78.0
100	351	70.9		

4.3.2. Mean percent adherence by study time period. Mean percent adherence by study time period was determined by respondent type and for the entire cohort according to the methodology outlined in Sections 3.9.4.2 through 3.9.4.4. Mean self/parent-reported percent adherence by study time point for the entire cohort, using the composite patient/parent percent adherence variable, ranged from a low of 98.85% on Day 113 to a high of 99.09% at Day 141 with a mean 98.93 percent adherence reported for the four time points. Mean percent adherence by parent/caregiver report ranged from 98.93% on Day 57 to 99.37% on Day 141 with a mean for the four study time points of 99.07%, while mean percent adherence by patient self-report ranged from 97.51% on Day 113 to

98.60% on Day 57 with a mean of 97.95% reported for the four study time points. Table 4.7 summarizes the mean percent adherence for the entire cohort and by patient and parent/caregiver report for each time point. Since not all questionnaires were received from all participants at each study time point, and since not all responses were evaluable in the questionnaires received, the numbers of evaluable responses received per study time point by respondent type are indicated in Table 4.7.

Table 4.7. Mean percent adherence to 6MP by study time point and respondent type

Data source	Mean Percent Adherence by Study Time Point				
	Day 29	**Day 57**	**Day 113**	**Day 141**	**Mean of four study time points**
Entire Cohort* (Total N=495)	98.89%	98.87%	98.85%	99.09%	98.93%
Actual N& reporting per study time point	476	450	423	400	
Parent-caregiver report† (Total N=458)	99.01%	98.93%	98.98%	99.37%	99.07%
Actual N& reporting per time point	437	405	386	367	
Patient self-report‡ (N=106)	98.17%	98.60%	97.51%	97.52%	97.95%
Actual N& reporting per time point	90	92	86	82	

*Values for the Entire Cohort (Total N=495) incorporate parent/caregiver-reported percent adherence for those with no patient self-report, combined patient/parent-caregiver-reported percent adherence for patients who had a parent/caregiver co-reporting, and patient-reported percent adherence for patients with no parent/caregiver co-reports (see Section 3.9.4.4 for details)

&Actual N reflects evaluable responses received per study time point by respondent type

†Excludes 37 patients who had no parent-caregiver report of adherence

‡Excludes 389 patients who had no patient self-report of adherence

4.4. Specific Aim 1a: Findings

Describe the prevalence of self/parent-reported non-adherence to 6MP during the maintenance phase of A.L.L. therapy.

4.4.1. Non-Adherence categorization. The overall mean percent adherence values for the entire cohort (representing the sum of all evaluable percent adherence values, divided by number of evaluable percent adherence values for each patient) were used as the basis for determination of the dichotomized self/parent-reported adherence/ non-adherence categorization. Potential points of demarcation for dichotomizing adherence versus non-adherence for the cohort were examined by evaluating the minimum and maximum values, percentile ranks, and quartiles for the overall mean percent adherence variable (Table 4.8).

Table 4.8. Summary of measures for overall mean percent adherence

Measure	Overall mean percent adherence
Maximum	100.00
75^{th} percentile (third quartile)	100.00
50^{th} percentile (middle quartile)	100.00
25^{th} percentile (first quartile)	99.10
10^{th} percentile	96.42
5^{th} percentile	92.90
Minimum	71.40

The distribution of mean percent adherence values were then further evaluated by carefully examining the frequency table (Figure 4.1), box plot (Figure 4.2), and stem-and-leaf plot (Figure 4.3) of the overall mean percent adherence variable.

PercentAdhMean

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	71.40	1	.2	.2	.2
	78.58	1	.2	.2	.4
	83.03	1	.2	.2	.6
	83.33	1	.2	.2	.8
	83.58	1	.2	.2	1.0
	86.60	1	.2	.2	1.2
	87.50	2	.4	.4	1.6
	89.28	1	.2	.2	1.8
	89.30	1	.2	.2	2.0
	90.18	1	.2	.2	2.2
	90.50	1	.2	.2	2.4
	91.10	2	.4	.4	2.8
	91.67	1	.2	.2	3.0
	91.98	2	.4	.4	3.4
	92.34	1	.2	.2	3.6
	92.85	1	.2	.2	3.8
	92.88	2	.4	.4	4.2
	92.90	4	.8	.8	5.1
	93.75	4	.8	.8	5.9
	93.78	2	.4	.4	6.3
	94.03	1	.2	.2	6.5
	94.63	1	.2	.2	6.7
	94.65	4	.8	.8	7.5
	95.27	1	.2	.2	7.7
	95.53	2	.4	.4	8.1
	95.55	3	.6	.6	8.7
	95.83	1	.2	.2	8.9
	96.40	2	.4	.4	9.3
	96.43	2	.4	.4	9.7
	96.43	2	.4	.4	10.1
	96.44	1	.2	.2	10.3
	96.45	5	1.0	1.0	11.3
	96.94	1	.2	.2	11.5
	97.02	1	.2	.2	11.7
	97.30	6	1.2	1.2	12.9
	97.31	1	.2	.2	13.1
	97.33	3	.6	.6	13.7
	97.34	1	.2	.2	13.9
	97.60	3	.6	.6	14.5
	97.63	1	.2	.2	14.7
	98.20	18	3.6	3.6	18.4
	98.23	5	1.0	1.0	19.4
	98.60	1	.2	.2	19.6
	98.66	1	.2	.2	19.8
	98.80	8	1.6	1.6	21.4
	98.82	1	.2	.2	21.6
	98.97	2	.4	.4	22.0
	99.10	34	6.9	6.9	28.9
	99.28	1	.2	.2	29.1
	100.00	351	70.9	70.9	100.0
	Total	495	100.0	100.0	

Figure 4.1. Frequencies of overall mean percent adherence values for the entire cohort

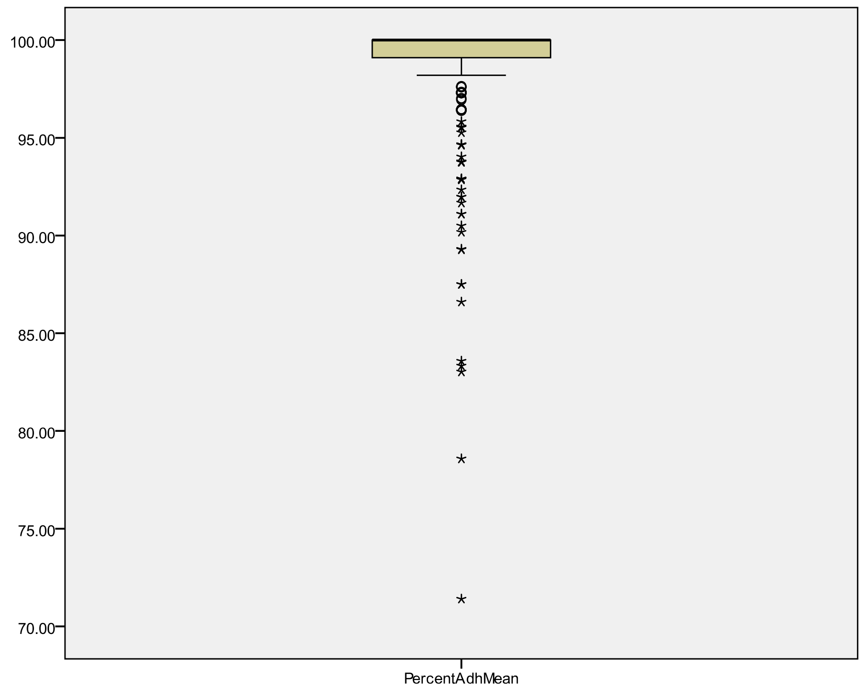


Figure 4.2. Box plot of overall mean percent adherence values for the entire cohort

```
PercentAdhMean Stem-and-Leaf Plot

 Frequency    Stem &  Leaf

    73.00 Extremes    (=<97.63)
    23.00      982 .  00002
      .00      983 .
      .00      984 .
      .00      985 .
     2.00      986 .  &
      .00      987 .
     9.00      988 .  00&
     2.00      989 .  &
      .00      990 .
    34.00      991 .  00000000
     1.00      992 .  &
      .00      993 .
      .00      994 .
      .00      995 .
      .00      996 .
      .00      997 .
      .00      998 .
      .00      999 .
   351.00     1000 .  0000000000000000000000000000000000000000000000000000000000000000000000000000000000000000

 Stem width:       .10
 Each leaf:       4 case(s)


 & denotes fractional leaves.
```

Figure 4.3. Stem-and-leaf plot of overall mean percent adherence values for the entire cohort

4.4.2. Self/parent-reported non-adherence categorization. After evaluation of the summary of measures and distribution of the overall mean percent adherence values, the first quartile was determined to be the logical point of demarcation between adherence and non-adherence for the cohort because it represented a statistical cut-point in the data that was clinically relevant, below which participants had reported missing at least 2 doses of 6MP for non-medical reasons (Figure 4.4). Patients having mean percent adherence values below the first quartile (below 99.1%) were categorized as non-adherent, while those with values at or above the first quartile (99.1% or higher) were categorized as adherent.

PercentAdhMean

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	71.40	1	.2	.2	.2
	78.58	1	.2	.2	.4
	83.03	1	.2	.2	.6
	83.33	1	.2	.2	.8
	83.58	1	.2	.2	1.0
	86.60	1	.2	.2	1.2
	87.50	2	.4	.4	1.6
	89.28	1	.2	.2	1.8
	89.30	1	.2	.2	2.0
	90.18	1	.2	.2	2.2
	90.50	1	.2	.2	2.4
	91.10	2	.4	.4	2.8
	91.67	1	.2	.2	3.0
	91.98	2	.4	.4	3.4
	92.34	1	.2	.2	3.6
	92.85	1	.2	.2	3.8
	92.88	2	.4	.4	4.2
	92.90	4	.8	.8	5.1
	93.75	4	.8	.8	5.9
	93.78	2	.4	.4	6.3
	94.03	1	.2	.2	6.5
	94.63	1	.2	.2	6.7
	94.65	4	.8	.8	7.5
	95.27	1	.2	.2	7.7
	95.53	2	.4	.4	8.1
	95.55	3	.6	.6	8.7
	95.83	1	.2	.2	8.9
	96.40	2	.4	.4	9.3
	96.43	2	.4	.4	9.7
	96.43	2	.4	.4	10.1
	96.44	1	.2	.2	10.3
	96.45	5	1.0	1.0	11.3
	96.94	1	.2	.2	11.5
	97.02	1	.2	.2	11.7
	97.30	6	1.2	1.2	12.9
	97.31	1	.2	.2	13.1
	97.33	3	.6	.6	13.7
	97.34	1	.2	.2	13.9
	97.60	3	.6	.6	14.5
	97.63	1	.2	.2	14.7
	98.20	18	3.6	3.6	18.4
	98.23	5	1.0	1.0	19.4
	98.60	1	.2	.2	19.6
	98.66	1	.2	.2	19.8
	98.80	8	1.6	1.6	21.4
	98.82	1	.2	.2	21.6
	98.97	2	.4	.4	22.0
	99.10	34	6.9	6.9	28.9
	99.28	1	.2	.2	29.1
	100.00	351	70.9	70.9	100.0
	Total	495	100.0	100.0	

ADHERENT (at or above first quartile)

NON-ADHERENT (below first quartile)

Figure 4.4. Demarcation of adherence versus non-adherence based on evaluation of the overall mean percent adherence values for the entire cohort

4.4.3. Prevalence of self/parent-reported non-adherence. The prevalence of self/parent-reported non-adherence for the entire cohort, defined as the level of mean percent adherence that falls below the first quartile for the entire study population, was determined for each patient by adding all available percent adherence values from all time points for all report types (i.e., patient and/or parent/caregiver) and dividing by the number of values for that patient. For patients with evaluable responses at all four study time points, a mean percent adherence value of 99.1 represents the equivalent of one missed 6MP dose over the 112 days of observation during the 6-month study period (i.e., 99.1% x 112 = 111), while a mean percent adherence value of less than 99.1 represents the equivalent of more than one missed 6MP dose over the observation period. Patients with overall mean percent self/parent-reported adherence values falling below the first quartile were thus categorized as non-adherent by this statistical model. Therefore, the prevalence of non-adherence based on overall mean percent self/parent-reported adherence for the cohort was 22 percent (Table 4.9).

Table 4.9. Prevalence of overall self/parent-reported non-adherence for the cohort

Mean percent adherence (over all study time points)	**Quartile**	**N**	**Percent of cohort**	**Adherence categorization**
100	Middle	351	78%	Adherent
99.1	First	35		
<99.1	Below first	109	22%	Non-adherent

4.4.4. Verification of Non-Adherence Categorization. Given the very low prevalence of self/parent-reported missed 6MP doses for the cohort, which resulted in the statistical categorization of non-adherence for patients who had more than one 6MP dose missed for non-medical reasons over the entire study period, the investigator developed a non-adherence categorization verification procedure to validate the statistical categorization. For purposes of the validation, the statistical categorization of all patients with self/parent-reported mean percent adherence of 100% were accepted by the investigator as adherent and all patients with self/parent-reported mean adherence below 98% as non-adherent. An in-depth review of all available data was then conducted by the investigator on all remaining patients deemed as having reasonable potential for incorrect categorization by the statistical model. These included patients whose values for overall mean percent adherence placed them near the boundary of the statistical adherence/non-adherence categorization (i.e., patients whose overall percent adherence fell just above or below the cut-point for the adherence/non-adherence categorization), as well as for all patients who had inevaluable responses to self and/or parent-reported number of 6MP doses missed at any time point. This resulted in an in-depth review of 36 patients classified as non-adherent based on mean percent adherence between 98.20 and 98.97, 35 patients classified as adherent based on mean percent adherence between 99.1 and 99.28, and 64 patients who had inevaluable responses to the number of 6MP doses missed on any self/parent report at any time point. All original patient questionnaires and relevant healthcare provider documentation were reviewed for these 135 patients (27% of the

cohort), resulting in an investigator categorization of adherence that confirmed and closely mirrored the statistical categorization.

Investigator review resulted in categorization of 397 (80.2%) adherent versus 98 (19.8%) non-adherent patients in the cohort, while categorization by the statistical model resulted in adherence/non-adherence categorization for the cohort of 386 (78.0%) versus 109 (22.0%) patients. There were 11 more patients categorized as non-adherent by the statistical model than by investigator review, but categorization was otherwise identical (Table 4.10). Thus, in the investigator review, there was agreement with the statistical model for all patients categorized as adherent, as well as investigator-statistical model agreement for 90% of patients categorized as non-adherent. Categorization by the statistical model was therefore deemed acceptable and slightly more conservative than by investigator review.

Table 4.10. Cross-tab of investigator adherence categorization versus statistical model categorization of adherence versus non-adherence

	Statistical Categorization			
Investigator Categorization		Adherent	Non-Adherent	Total
	Adherent	386	11	397
	Non-Adherent	0	98	98
	Total	386	109	495

4.4.5. Categorization of non-adherence by study time point. Summaries of the self-reported number of 6MP doses missed for non-medical reasons and the corresponding percent adherence by study time point are presented by respondent type in

Table 4.11 (parent/caregiver self-report) and Table 4.12 (patient self-report). Of the 2009 self-report questionnaires submitted, 1945 (96.81%) self/parent-reports of adherence were deemed evaluable and were included in the mean percent adherence calculations, including 1595/1647 (96.84%) parent/caregiver responses and 350/362 (96.69%) patient responses.

Table 4.11. Parent/caregiver self-report of number of 6MP doses missed for non-medical reasons in past 28 days and corresponding percent adherence by study time point

Parent-caregiver reports of missed 6MP doses for non-medical reasons N (%)						
		Day 29	**Day 57**	**Day 113**	**Day 141**	**Total**
6-MP doses missed during past 28 days for non-medical reasons (Percent adherence)	0 (100.0)	373 (85.4)	348 (85.9)	333 (86.3)	330 (89.9)	1384 (86.77)
	1 (96.4)	36 (8.2)	32 (7.9)	33 (8.5)	24 (6.5)	125 (7.84)
	2 (92.9)	16 (3.7)	13 (2.6)	13 (3.4)	9 (2.5)	51 (3.20)
	3 (89.3)	5 (1.1)	5 (1.2)	2 (0.5)	2 (0.3)	14 (0.88)
	4 (85.7)	4 (0.9)	1 (0.2)			5 (0.41)
	5 (82.1)	1 (0.2)	2 (0.5)		1 (0.3)	4 (0.31)
	6 (78.6)					0 (0.00)
	7 (75.0)	1 (0.2)	1 (0.2)	2 (0.5)	2 (0.5)	6 (0.38)
	8 (71.4)					0 (0.00)
	9 (67.9)					0 (0.00)
	10 (64.3)	1 (0.2)		2 (0.5)		3 (0.19)
	11 (60.7)			1 (0.2)		1 (0.06)
	12 (57.1)		1 (0.2)			1 (0.06)
	13 (53.6)		1 (0.2)			1 (0.06)
	14 (50.0)					
Total reports		437 (100.0)	405 (100.0)	386 (100.0)	367 (100.0)	1595 (100.00)[†]

[†]A total of 1647 parent questionnaires were collected over the four study time points; 52 of these had self-reported adherence values that were deemed inevaluable, thus 1595/1647 (96.84%) of parent self-reports of adherence were evaluable and are reported here

Table 4.12. Patient self-report of number of 6MP doses missed for non-medical reasons in past 28 days and corresponding percent adherence by study time point (includes patients co-reporting with parent/caregiver and patients reporting alone)

Patient self-reports of missed 6MP doses for non-medical reasons N (%)						
		Day 29	**Day 57**	**Day 113**	**Day 141**	**Total**
6-MP doses missed during past 28 days for non-medical reasons (Percent adherence)	0 (100.0)	69 (76.7)	72 (78.3)	68 (79.1)	66 (80.5)	275 (78.6)
	1 (96.4)	9 (10.0)	10 (10.9)	7 (8.1)	4 (4.9)	30 (8.6)
	2 (92.9)	4 (4.4)	5 (5.4)	4 (4.7)	6 (7.3)	19 (5.4)
	3 (89.3)	4 (4.4)	4 (4.3)	3 (3.5)	2 (2.4)	13 (3.7)
	4 (85.7)	3 (3.3)	1 (1.1)	1 (1.2)		5 (1.4)
	5 (82.1)	1 (1.1)			1 (1.2)	2 (0.6)
	6 (78.6)				1 (1.2)	1 (0.3)
	7 (75.0)			1 (1.2)		1 (0.3)
	8 (71.4)					
	9 (67.9)					
	10 (64.3)				1 (1.2)	1 (0.3)
	11 (60.7)			1 (1.2)		1 (0.3)
	12 (57.1)					
	13 (53.6)					
	14 (50.0)			1 (1.2)	1 (1.2)	2 (0.6)
Total reports		90 (100.0)	92 (100.0)	86 (100.0)	82 (100.0)	350 (100.0)[†]

[†]A total of 362 patient questionnaires were collected over the four study time points; 12 of these had self-reported adherence values that were deemed inevaluable, thus 350/362 (96.69%) of patient self-reports of adherence were evaluable and are reported here

4.4.6. Categorization of non-adherence by study time point. Following the procedure used to dichotomize adherence versus non-adherence for the entire cohort (Section 3.9.4.6), minimum and maximum values, percentile ranks, and quartiles for the percent adherence variable at each of the study time points by respondent type were examined. The first quartile (100 percent adherence) was identified as the logical point of demarcation for adherence versus non-adherence at each study time point for each respondent type. Mean percent adherence reported at each study time point was used to categorize each respondent type as adherent or non-adherent at that time point. Thus, all respondents reporting percent adherence values below 100 at any time point were categorized as non-adherent at that time point (i.e., patients reporting any missed doses for non-medical reasons at any single study time point were categorized as non-adherent at that time point).

The prevalence of self/parent-reported non-adherence for the entire cohort over the four study time points (using the composite patient/parent percent adherence variable) ranged from a high of 16.6% on Day 29 to a low of 11.8% on Day 141. The prevalence of non-adherence by parent/caregiver report ranged from a high of 14.6% on Day 29 to a low of 10.1% on Day 141. The prevalence of non-adherence by patient self-report ranged from 23.3% on Day 29 to 19.5% on Day 141. The largest proportion of respondents reported non-adherence on Day 29 (i.e., 16.6% of the entire cohort, 14.6% of parent/caregivers, and 23.3% of patients reported a missed 6MP dose for non-medical reasons on Day 29). The proportion of non-adherence reported by each respondent type declined over each of the three subsequent study time points, such that by Day 141, only

11.8% of the entire cohort, 10.1% of parent/caregivers, and 19.5% of patients reported non-adherence at the final study time point. Summaries of the prevalence of non-adherence to 6MP as a categorical variable by study time point are presented by respondent type in Table 4.13.

Table 4.13. Prevalence of self-reported non-adherence to 6MP as a categorical variable by study time point and respondent type

	Self-Report of Non-Adherence* by Study Time Point N non-adherent/Actual N reporting (%)			
Data source	**Day 29**	**Day 57**	**Day 113**	**Day 141**
Entire Cohort**	79/476 (16.6)	71/450 (15.8)	65/423 (15.4)	47/400 (11.8)
Parent-caregiver report†	64/437 (14.6)	57/405 (14.1)	53/386 (13.7)	37/367 (10.1)
Patient self-report‡	21/90 (23.3)	20/92 (21.7)	18/86 (20.9)	16/82 (19.5)

*Non-adherent (below first quartile): <100 percent adherence for the 28-day time period

**Values for the Entire Cohort (Total N=495) incorporate parent/caregiver-reported percent adherence for those with no patient self-report, combined patient/parent-caregiver-reported percent adherence for patients who had a parent/caregiver co-reporting, and patient-reported percent adherence for patients with no parent/caregiver co-reports (see Section 3.9.4.4 for details)

†Excludes 37 patients who had no parent-caregiver report of adherence

‡Excludes 389 patients who had no patient self-report of adherence

4.5. Concordance of patient and parent/caregiver reports: Findings

Of the 69 patient-parent/caregiver pairs who each submitted at least one adherence questionnaire during the study, 68 patients had at least one patient report and one parent/caregiver report of percent adherence at the same study time point.

Concordance between patient and parent/caregiver reports of adherence for these 68 pairs was evaluated using the paired-samples t-test. The difference was found to be normally distributed, and there was no significant difference between self-reported percent adherence for parents (M=98.55, SE=3.88) or patients (M=98.056, SE=3.59, $t(67)$=1.191, P=0.238, 95% confidence interval -0.334 to 1.323). The self-reported percent adherence values were significantly correlated (r=0.582, P<.0001). Of the 68 pairs, reports of percent adherence at corresponding study time points were identical in 51 pairs. Differences in reports of percent adherence in the remaining 17 pairs ranged from 1.2% to 16.7% with a mean difference of 0.49% across the cohort and 2.1% for the non-concordant pairs. Thus, the patient-parent/caregiver reports of adherence by study participants were generally concordant.

4.6. Specific Aim 1b: Findings

Describe the impact of sociodemographic and disease-related factors on non-adherence to 6MP during the maintenance phase of A.L.L. therapy.

The following sociodemographic and disease-related predictors of adherence were evaluated, because of previously published or suspected associations between these variables and adherence: patient sex, ethnicity, age at study participation, time from diagnosis, time elapsed from start of maintenance therapy to study participation, National Cancer Institute (NCI) risk classification of the leukemia [standard vs. high risk], leukemia immunophenotype (precursor B-cell vs. T-cell), number of caregivers in household, maternal education, paternal education, annual household income, residence

type (single family dwelling vs. apartment), language, and parent/caregiver employment outside the home.

In univariate logistic regression models, the sociodemographic factors found to be significantly ($P<0.05$) associated with non-adherence [defined as overall mean percent adherence below the first quartile] included Hispanic ethnicity (Odds Ratio [OR] 1.62; 95% Confidence Intervals [CI] 1.05 – 2.49; $P=0.030$), older age (in years) at study participation (OR 1.08 per year, 95% CI 1.04-1.13, $P<0.001$), and single parent household (OR 1.88, 95%CI 1.06-3.33, $P=0.031$). The only disease-related factor significantly associated with non-adherence in the univariate regression model was NCI high-risk categorization (OR 1.92, 95% CI 1.24-2.97, $P=0.003$). Results of the univariate analysis of the impact of all sociodemographic and disease-related factors on non-adherence to 6MP are presented in Table 4.14.

Table 4.14. Univariate logistic regression analysis of the impact of sociodemographic and disease-related factors on non-adherence to 6MP *(Referent groups indicated in italics)*

Factor	Categories	Non-Adherent[†] N (%)	OR	95% CI	*P*
Sex	*Female*	36 (23.8)	1.0		
	Male	73 (21.2)	0.86	0.55-1.36	0.517
Ethnicity	*Non-Hispanic White*	43 (17.8)	1.0		
	Hispanic	**66 (26.0)**	**1.62**	**1.05 – 2.49**	**0.030**[*]
Age (per year) at study entry	N/A[&]		**1.08**	**1.04-1.13**	**<0.001**[*]
Time from diagnosis (in years) at study entry	N/A[&]		0.92	0.59- 1.44	0.717
Time on maintenance (in months) at study entry	N/A[&]		1.00	0.97-1.04	0.859
NCI risk category	*Standard risk*	49 (17.0)	1.0		
	High risk	**56 (28.1)**	**1.92**	**1.24-2.97**	**0.003**[*]
Type of household	*Multiple caregivers*	87 (20.6)	1.0		
	Single parent	**21 (32.8)**	**1.88**	**1.06-3.33**	**0.031**[*]
Maternal education	*> high school*	62 (23.4)	1.0		
	≤ high school	45 (20.6)	0.85	0.55-1.32	0.469
Paternal education	*> high school*	46 (19.9)	1.0		
	≤ high school	56 (23.0)	1.20	0.77-1.87	0.407
Annual household income	*≥$20,000*	77 (22.4)	1.0		
	<$20,000	25 (20.8)	0.91	0.55-1.52	0.724
Questionnaire language	*English*	88 (23.3)	1.0		
	Spanish	21 (17.9)	0.72	0.42-1.22	0.220
Caregiver employment[‡]	*≥ one adult at home*	44 (18.2)	1.0		
	All outside home	55 (27.2)	1.68	1.07-2.64	0.023[‡]

[†]Non-adherence defined as overall mean percent adherence below the first quartile for the entire cohort
[*]P<0.05
[&]Continuous variable
[‡]Excluded due to >10% missing responses (51 missing = 10.3% of sample)

4.7. Specific Aim 2: Findings

Describe the behavioral determinants of non-adherence to 6MP during the maintenance phase of A.L.L. therapy.

4.7.1. Behavioral predictors of non-adherence. The behavioral determinants of non-adherence to 6MP examined in this analysis were components of the Health Belief Model drawn primarily from the Adherence Questionnaire and included (1) *Belief in health threat/Perceived vulnerability:* (1a) *Perceived severity* [1 item]; (1b) *Perceived susceptibility* [1 item]; (2) *Belief in efficacy of health behavior:* **(2a)** *Perceived benefits* [1 item]; (2b) *Perceived barriers* [6 items]; (3) *Taking responsibility/Self efficacy* [2 items]; and (4) *Cues to action* [3 items]. Details regarding the items, their respective data sources, and the variable names were described in Table 3.8.

4.7.2. Univariate analysis of the behavioral predictors. In univariate logistic regression models, six behavioral factors, representing five of the six major components of the Health Belief Model, were found to be significantly associated with non-adherence. Since the focus of this analysis was on non-adherence, variables were configured to reflect the lack of the HBM characteristic of interest. Thus, odds ratios reflect risk of non-adherence relevant to lack of the HBM characteristic under evaluation. The following behavioral factors were significantly associated with non-adherence in the univariate models. ***Perceived severity*****:** *No change in health status in the past month* (OR 1.88, 95%CI 1.04-3.40, P=0.038); ***Perceived susceptibility:*** *Lack of awareness of consequences of not taking 6MP as prescribed* (OR 1.73, 95%CI 1.06-2.83, P=0.027); ***Perceived benefits:*** *Lack of awareness of purpose/function of 6MP* (OR 1.81, 95%CI

1.14-2.87, P=0.011); ***Taking responsibility:*** *No monitoring of 6MP administration by parent/caregiver/adult:* (OR 2.15, 95%CI 1.02-4.52, P=0.044); ***Cues to action*****:** *6MP not administered at the same time daily* (OR 1.91, 95%CI 1.19-3.06, P=0.007), *6MP administered late at night*: (OR 2.27, 95%CI 1.07-4.80, P=0.032). There were no significant behavioral factors identified for the HBM construct ***Perceived barriers***. Results of the univariate analysis of the impact of behavioral factors on non-adherence to 6MP are presented in Table 4.15.

Table 4.15. Univariate logistic regression analysis of the impact of behavioral factors on non-adherence to 6MP *(Referent groups indicated in italics)*

Construct: Factor	Categories	Non-Adherent† N (%)	OR	95% CI	*P*
Perceived severity: No change in health status in past month	*Change in health status in past month*	15 (14.4)	1.0		
	No change in health status in past month	**93 (24.0)**	**1.88**	**1.04-3.40**	**0.038***
Perceived susceptibility: Unaware of consequences of not taking 6MP as prescribed	*Aware of consequences of not taking 6MP*	78 (19.9)	1.0		
	Unaware of consequences of not taking 6MP	**31 (30.1)**	**1.73**	**1.06-2.83**	**0.027***
Perceived benefits: Unaware of purpose/ function of 6MP	*Aware of purpose/ function of 6MP*	71 (19.2)	1.0		
	Unaware of purpose/ function of 6MP	**38 (30.2)**	**1.81**	**1.14-2.87**	**0.011***
Perceived barriers*:* Longer time on maintenance (in months)	*Time on maintenance < 9 months (at time of study entry)*	53 (21.5)	1.0		
	Time on maintenance $\geq$ 9 months	54 (23.2)	1.10	0.72-1.69	0.668

†Non-adherence defined as overall mean percent adherence below the first quartile for the entire cohort
*P < 0.05; ‡P $\geq$ 0.05 <0.20

Table 4.15. (Continued) Univariate logistic regression analysis of the impact of behavioral factors on non-adherence to 6MP ***(Referent groups indicated in italics)***

Construct: Factor	Categories	Non-Adherent† N (%)	OR	95% CI	*P*
Perceived barriers: Variation in 6MP dosing (treatment complexity)	*6MP daily dose is the same*	42 (23.6)	1.0		
	6MP dose varies from day to day	61 (20.1)	0.82	0.52-1.27	0.372
Perceived barriers: Changes in 6MP prescription ever (treatment complexity)	*6MP prescription has never changed*	25 (29.1)	1.0		
	6MP prescription has changed	81 (20.4)	0.63	0.37-1.06	0.080‡
Perceived barriers: Changes in 6MP prescription in past month (treatment complexity)	*6MP prescription did not change in past month*	91 (22.6)	1.0		
	6MP prescription changed in past month	17 (19.8)	0.84	0.47-1.50	0.561
Perceived barriers: Child cannot swallow 6MP tablet whole	*Child can swallow 6MP tablet whole*	75 (24.0)	1.0		
	Child cannot swallow 6MP tablet whole	33 (18.2)	0.71	0.45-1.12	0.139‡
Perceived barriers: Child takes 6MP without food and/or milk	*Child takes 6MP with food and/ or milk*	25 (22.7)	1.0		
	Child takes 6MP without food and/or milk	84 (21.8)	0.95	0.57-1.58	0.839
Taking responsibility: Child not involved in decision to take 6MP	*Child involved in decision to take 6MP*	15 (22.4)	1.0		
	Child not involved in decision to take 6MP	94 (22.0)	0.98	0.53-1.81	0.938
Taking responsibility: Adult does not monitor 6MP administration	*Adult monitors 6MP administration*	97 (21.0)	1.0		
	Adult does not monitor 6MP administration	**12 (36.4)**	**2.15**	**1.02-4.52**	**0.044***

†Non-adherence defined as overall mean percent adherence below the first quartile for the entire cohort
*P < 0.05; ‡P ≥ 0.05 <0.20

Table 4.15. (Continued) Univariate logistic regression analysis of the impact of behavioral factors on non-adherence to 6MP ***(Referent groups indicated in italics)***

Construct: Factor	Categories	Non-Adherent† N (%)	OR	95% CI	*P*
Cues to action: No systematic approach/routine for 6MP administration	*Has systematic approach/routine for 6MP administration*	94 (21.1)	1.0		
	No systematic approach/routine for 6MP administration	15 (30.6)	1.65	0.86-3.16	0.129‡
Cues to action: 6MP not administered at same time daily	*6MP administered at same time daily*	36 (31.0)	1.0		
	6MP not administered at same time daily	**71 (19.1)**	**1.91**	**1.19-3.06**	**0.007***
Cues to action: 6MP administered late at night (between 2300-0445)	*6MP not administered late at night*	96 (20.9)	1.0		
	6MP administered late at night	**12 (37.5)**	**2.27**	**1.07-4.80**	**0.032***

†Non-adherence defined as overall mean percent adherence below the first quartile for the entire cohort
*P < 0.05; ‡P ≥ 0.05 <0.20

4.7.3. Multivariate analysis. All behavioral factors identified as significant (P<0.05) or that approached a significance level of P<0.20 in the univariate analysis were tested in the multivariate logistic regression models. Modifying sociodemographic and disease-related factors identified as significant (P<0.05) in the univariate analysis were also tested in the multivariate analysis in order to control for these potentially modifying factors.

The nine behavioral predictors with a significance level of P<0.20 in the univariate analysis (Table 4.15) were tested initially in logistic regression models with the three significant sociodemographic factors (age at participation, ethnicity and household structure). Additional behavioral factors thought to be clinically relevant were

also tested, including the child's lack of ability to swallow the 6MP tablet whole, the interaction of age at participation and lack of ability to swallow the tablet whole, and taking 6MP without food or milk.

Behavioral factors found to be significant (P<0.05) or nearing significance in the initial models, which controlled for age, ethnicity, and household structure, included: (1) *Lack of awareness of consequences of not taking 6MP as prescribed* (OR 1.66, 95%CI 0.99-2.75, P=0.050); (2) *Lack of awareness of the purpose/function of 6MP* (OR 1.80, 95%CI 1.12-2.91, P=0.016); and (3) *No change in health status during past month* (OR 1.76, 95%CI 0.96-3.22, P=0.069). When *Lack of awareness of the purpose/function of 6MP* and *No change in health status during the past month* were added to the model simultaneously (controlling for age, ethnicity, and household structure), *Lack of awareness of the purpose/function of 6MP* remained significant (OR 1.79, 95%CI 1.11-2.89, P=0.017) and *No change in health status during the past month* retained borderline significance (OR 1.72, 95%CI 0.94-3.17, P=0.080).

Additional sociodemographic and disease-related factors believed a priori to have clinical relevance were added to and removed from the model in a series of iterations that resulted in the addition of maternal education and income to the model as important sociodemographic factors. NCI risk status, although significant in the univariate model, did not remain significant in the multivariate models and was removed. Thus, there were no significant disease-related factors in the multivariate model. The nine behavioral predictors identified as significant (P<0.05) or that approached a significance level of P<0.20 in the univariate analysis (see Table 4.15) and the two factors thought to be

clinically relevant, along with the one interaction term, were all tested in this new model that controlled for five sociodemographic factors (age at participation, ethnicity, household structure, maternal education, and income). After testing several combinations of behavioral predictors, the model with the best fit to the data was identified (Table 4.16).

Table 4.16. Final multivariate logistic model

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.066**	**.024**	**7.712**	**1**	**.005**	**1.069**	**1.020**	**1.120**
	FinalEthnicity(1)	**.812**	**.280**	**8.437**	**1**	**.004**	**2.253**	**1.302**	**3.899**
	MomEducDichotHSorLess(1)	-.454	.273	2.768	1	.096	.635	.372	1.084
	SingleParentHousehold(1)	.594	.334	3.158	1	.076	1.812	.941	3.489
	IncomeLT20K(1)	-.494	.319	2.396	1	.122	.610	.326	1.141
	K.healthcorr.1PT(1)	**.635**	**.323**	**3.878**	**1**	**.049**	**1.888**	**1.003**	**3.553**
	K.how6MPdichot.1cum(1)	**.574**	**.257**	**4.992**	**1**	**.025**	**1.775**	**1.073**	**2.937**
	Constant	-2.711	.389	48.646	1	.000	.066		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.healthcorr.1PT, K.how6MPdichot.1cum.

The final multivariate model includes two behavioral predictors representing two HBM constructs: (1) *Perceived severity: No change in health status during past month* [K.healthcorr.1PT] and (2) *Perceived benefits: Lack of awareness of the purpose/function of 6MP* [K.how6MPdichot.1cum]. Additionally, five sociodemographic factors are controlled for in the final model: (1) Age at participation (in years), (2) Ethnicity (Hispanic versus non-Hispanic white), (3) Maternal education (high school or less versus more than high school), (4) Household structure (single parent versus other), and (5) Income (less

than $20,000 per year versus $20,000 or more per year). The two behavioral predictors and two of the sociodemographic factors remained significant in the final model, as follows: (1) Older age (in years) at study participation (OR 1.07 per year, 95%CI 1.02-1.12, P=0.005); (2) Hispanic ethnicity (OR 2.25, 95%CI 1.30-3.90, P=0.004); (3) *No change in health status during past month [HBM: Perceived vulnerability (Perceived severity)]* (OR 1.89, 95%CI 1.00-3.55, P=0.049); and (4) *Lack of awareness of the purpose/function of 6MP [HBM: Belief in efficacy of the health behavior (Perceived benefits)]* (OR 1.78, 95%CI 1.07-2.94, P=0.025) [Figure 4.5].

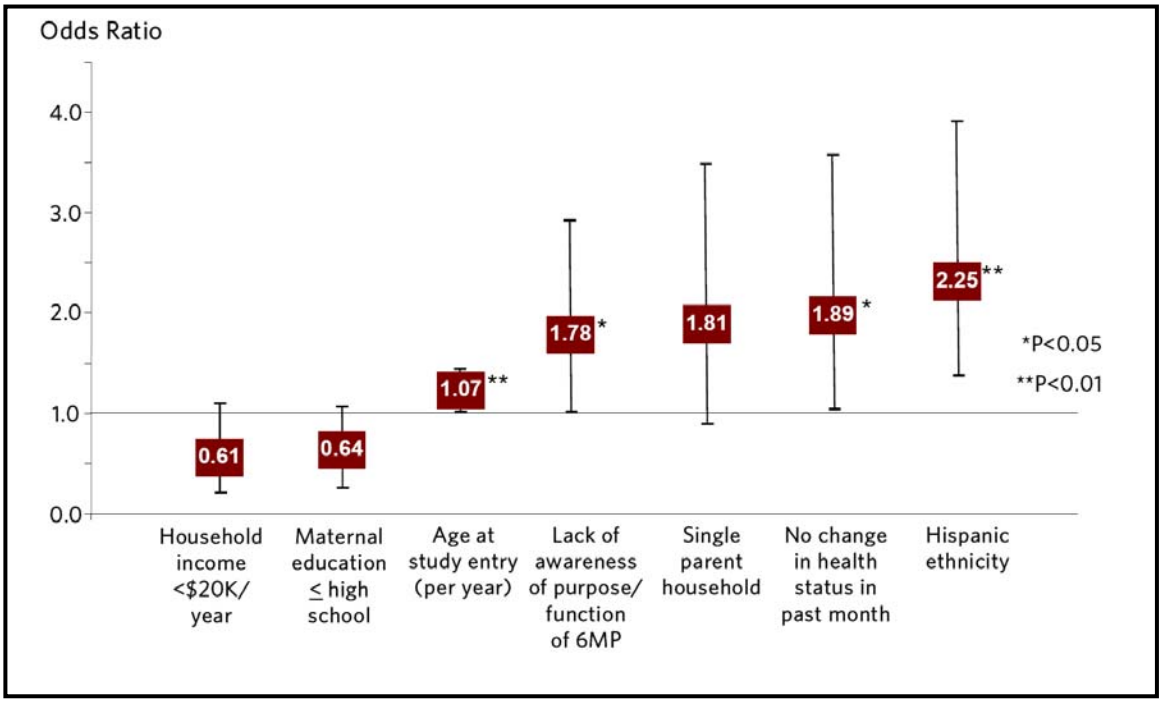


Figure 4.5. Risk factors for non-adherence

A test of the full final model with all seven predictors against a constant-only model was statistically significant (Chi-square for -2 Log likelihood [df (7), N=456] =

30.402; P=<0.001), indicating that the predictors, as a set, reliably distinguished between adherent and non-adherent participants. The model controls for 6.4% (per Cox & Snell R Square) to 9.9% (per Nagelkerke R Square) of the variation in adherence categorization, and classifies 79.2% of the cases correctly. All multivariable models tested, in the sequences described in the text, are included in Appendix F. Evaluation of collinearity diagnostics for the variables in the final model (Appendix G) confirmed that no root in the Condition Index approached 30, and no dimension had more than one Variance Proportion greater than 0.50. Tolerance values for all variables were 0.3 or greater, and Variance Inflation Factor values were all less than 3; thus there was no violation of tolerance and no evidence of multicollinearity among the variables. Additionally, there were no standardized residuals above 3.3, and the maximum value for Cook's distance was less than 1, which was indicative that there were no outliers with dramatic effects on the coefficients in the model (Menard, 1995; Tabachnick & Fidell, 2007).

4.7.4. Stratified analyses. Since age was a significant predictor of adherence in the final multivariate model, and given that the majority of patients over the age of 12 had two sets of adherence data (patient and parent/caregiver), while patients under age 12 had only one set of data (parent/caregiver), the analysis was stratified by age in order to determine if there were differences in predictors of adherence for older patients with self-report data (age 12 and older) versus younger patients with only parent-caregiver report data (age younger than 12 years). Additionally, it was thought that the inability to swallow the 6MP tablet whole (HBM construct: *Perceived barriers*) could potentially be significant in younger children, thus this variable was added to the age-stratified model.

Given that ethnicity was also significant in the final model, the analysis was also stratified by ethnicity. None of the stratified models added significantly to the study findings (Appendix H).

4.8. Findings in the context of study hypotheses

4.8.1. – Hypothesis 1. *Lack of acknowledgement of the seriousness of the disease and the child's potential susceptibility to the disease will be predictive of self/parent-reported non-adherence (HBM: Perceived Vulnerability).* Hypothesis 1 was supported by the study findings. Lack of perceived vulnerability, specifically lack of a reported change in health status over the past month *[Perceived severity]*, was a significant predictor of non-adherence in this study (OR 1.89, 95%CI 1.00-3.55, P=0.049).

4.8.2. – Hypothesis 2. *Lack of acknowledgement of the perceived benefits of oral 6MP chemotherapy will be predictive of self/parent-reported non-adherence (HBM: Perceived Benefits)*. Hypothesis 2 was also supported by the study findings. Lack of acknowledgement of the perceived benefits of oral 6MP chemotherapy, specifically lack of awareness of the purpose/function of 6MP, was found to be a significant predictor of non-adherence in this study (OR 1.78, 95%CI 1.07-2.94, P=0.025).

4.8.3. – Hypothesis 3. *Lack of identification of a parent/caregiver who is responsible for home administration of oral chemotherapy will be predictive of self/parent-reported non-adherence (HBM: Taking Responsibility).* Hypothesis 3 was partially supported by this study's findings. Lack of identification of an adult parent/caregiver responsible for home administration of oral chemotherapy was

predictive of non-adherence in the univariate analysis (OR 2.15, 95%CI 1.02-4.52, P=0.044), but failed to maintain significance in the multivariable analysis.

4.8.4. – Hypothesis 4. *Lack of a consistent routine for home medication administration will be predictive of self/parent-reported non-adherence (HBM: Cues to Action).* Hypothesis 4 was not supported by this study's findings. Lack of consistent routine for home medication administration was found to have suggestive significance (OR 1.65, 95%CI 0.86-3.16, P=0.129) in the univariate analysis but was non-significant and did not predict non-adherence in the multivariable analysis.

4.9. Summary of findings

Overall mean self/parent-reported percent adherence in this large cohort of patients with A.L.L. was 98.88 $\pm$ 2.88 SD, and ranged from 71.4 to 100. Seventy-eight percent of study participants reported an overall mean percent adherence of 99.1 or above. Non-adherence was defined as overall mean percent adherence below 99.1 (below the first quartile), and 22% of patients were categorized as non-adherent based on self/parent report. Self/parent report of 6MP doses missed for non-medical reasons per 28-day study time period over the four study time points ranged from 0 (reported by 86.8% of parents and 78.6% of patients) to 14 (reported by 0% of parents and 0.6% of patients). Only 5.4% of parent/caregiver reports and 12.8% of patient reports indicated more than one missed 6MP dose for non-medical reasons over the four study time points. There was concordance between the independent patient and parent/caregiver self-reports of adherence, with no significant difference in percent adherence reported between patient and parent/caregiver pairs at corresponding study time points (P=0.238).

In univariate analysis, sociodemographic and disease-related factors found to be significantly associated with self/parent-reported non-adherence included Hispanic ethnicity (P=0.030), older age (per year) at study entry (P<0.001), single parent household (P=0.031), and NCI high-risk categorization (P=0.003); behavioral factors found to be significantly (P<0.05) associated with self/parent-reported non-adherence included *No change in health status in the past month* (P=0.038), *Lack of awareness of the consequences of not taking 6MP as prescribed* (P=0.027), *Lack of awareness of the purpose/function of 6MP* (P=0.011), *No monitoring of 6MP administration by a parent/ caregiver/adult* (P=0.044), *6MP not administered at the same time daily* (P=0.007), and *6MP administered late at night* (P=0.032).

In multivariate analysis, while controlling for age at study participation, ethnicity, maternal education, household structure and income, two behavioral factors retained a significant association with self/parent-reported non-adherence: (1) *No change in health status in the past month (HBM construct: Perceived vulnerability)* (OR 1.89, 95%CI 1.00-3.55, P=0.049) and (2) *Lack of awareness of the purpose/function of 6MP (HBM construct: Perceived benefits)* (OR 1.78, 95%CI 1.07-2.94, P=0.025). Older age (in years) (OR 1.07, 95%CI 1.02-1.12, P=0.005) and Hispanic ethnicity (OR 2.25, 95%CI 1.30-3.90, P=0.004) were also found to be significantly associated with self/parent-reported non-adherence in the final multivariate logistic regression model.

Chapter 5: Discussion, Limitations, and Conclusion

5.1. Overview

Poor adherence to oral medication is known to be a substantial problem in contemporary health care (Osterberg & Blaschke, 2005) and may contribute to unexplained relapses in children with A.L.L. (Lilleyman & Lennard, 1996). Prior studies of adherence to oral 6MP in children with A.L.L., using varied definitions and measures of adherence, have demonstrated non-adherence rates ranging from 10 to 33% (Davies, et al., 1993; Lancaster, et al., 1997; Lau, et al., 1998; Lennard, et al., 1995; Macdougall, et al., 1992; Traore, et al., 2006). However, these studies were limited by a number of methodological issues. Adherence was measured by self/parent report for only a small number of patients, precluding an assessment of the reasons for non-adherence. This study aimed to determine the prevalence of self/parent-reported non-adherence to oral 6MP during the maintenance phase of A.L.L. therapy, and to understand the behavioral as well as sociodemographic determinants of non-adherence to 6MP.

5.2. Discussion of findings in the context of the study's research questions

5.2.1. Research question 1: *What is the self/parent-reported mean percent adherence to 6MP and what is the prevalence of non-adherence to 6MP (at each time point and overall) in this cohort of pediatric patients receiving maintenance therapy for A.L.L.?*

Findings from this study indicate that over 70% of participants were 100% adherent to prescribed 6MP by self/parent-report over the 112 days measured during a 6-month span of A.L.L. maintenance therapy. An additional 7% of participants reported

only one missed 6MP dose during this time span. Given this high level of self/parent-reported adherence, those who reported missing more than one dose of 6MP for non-medical reasons over the six-month study period fell below the first quartile for adherence in the cohort, and thus were classified as non-adherent for the purpose of identifying behavioral predictors of non-adherence.

Assessment of whether non-adherence rates reported for this cohort are comparable to those seen in other pediatric chronic disease populations is challenging, because measures of adherence and time frames for data collection differ between investigations. In a study of self-parent/caregiver-reported adherence to antiretroviral therapy among 125 pediatric patients with HIV, Van Dyke et al. (2002) reported that 31 (24.8%) of the patients had missed at least one prescribed dose of antiretroviral medications within the 3-day period prior to a clinic visit, and 6 of these patients (4.8% of the cohort) had missed all of their prescribed doses during that 3-day timeframe, for a total non-adherence rate of 29.6%. Although it is not possible to directly compare self/parent-reported adherence between these two cohorts, the data for the A.L.L. cohort in this current study were collected for 28-day periods prior to scheduled clinic visits, and thus were inclusive of 3 day pre-clinic visit periods such as those collected for the Van Dyke study. Therefore, it may be reasonable to make a limited comparison of self/parent-reported non-adherence between these groups. Self/parent-reported non-adherence rates for the A.L.L. cohort at the four time points in this study (16.6%, 15.8%, 15.4%, and 11.8%), all fell well below the 29.6% non-adherence rate at the single time point reported in the Van Dyke study. Given that there were 25 additional reporting days

collected for the A.L.L. cohort at each time point, there was considerably increased opportunity for reporting non-adherence within the A.L.L. cohort as compared to the HIV cohort. Despite this fact, the non-adherence rates in the A.L.L. cohort were lower than those reported in the HIV cohort, suggesting that the prevalence of self/parent-reported medication non-adherence may be lower in pediatric patients with A.L.L. than in those with HIV. Additional studies of pediatric HIV have also reported higher rates of self-reported non-adherence than were identified in the current study's A.L.L. cohort; for example Reddington et al. (2000) reported 17% non-adherence for one dose and 43% non-adherence over one week, and Mellins, Brackis-Cott, Dolezal, & Abrams (2004) reported 40% non-adherence rates by parent/caregiver report and 56% by patient report over one month.

Children with sickle cell disease are another pediatric population for whom ongoing oral medications are commonly prescribed. In a study of 123 children with sickle cell disease who were prescribed twice-daily oral penicillin for pneumococcal prophylaxis (Teach, Lillis, & Grossi, 1998), 40 of 123 (32.5%) children missed their most recent dose as assessed by patient/parent self-report during a structured interview, and 70 of the 123 (56.9%) had undetectable levels of penicillin activity by urine assay, an indicator that non-adherence may have been under-reported during the interview. Since the study relied on a report of non-adherence to a single prescribed dose of penicillin, and since the self/parent-reported non-adherence rate was even higher than that reported in the HIV population, this comparison also suggests that the prevalence of self/parent-

reported non-adherence in the current study's A.L.L. cohort may be lower than in patients with sickle cell disease.

The lower prevalence of self/parent-reported non-adherence among A.L.L. patients in the current study may be related to the fact that unlike treatment for most other chronic childhood illnesses, such as HIV and sickle cell disease, therapy for pediatric A.L.L. is time-limited. Although prolonged (2-3 year) treatment of A.L.L. is required, therapy does not continue indefinitely throughout the lifespan, as is currently required for most chronic illnesses diagnosed in childhood. Additionally, a diagnosis of A.L.L. in childhood is generally perceived as life-threatening, and families are typically told that cure is possible with contemporary therapy. It is therefore possible that receiving a diagnosis of a life-threatening condition with curative potential may be sufficiently motivating to sustain higher levels of adherence than are seen in other chronic pediatric diseases for which cure is not currently attainable and life-long management is required. It is also possible that differences in sociodemographic characteristics between children with A.L.L. and those with HIV or sickle cell disease may also contribute to the differences in non-adherence between these groups.

Despite the fact that the prevalence of non-adherence observed in this A.L.L. cohort appears to be lower than that reported for other pediatric chronic diseases, results from this study indicate that nearly 3 in 10 patients with A.L.L. (144/495 [29.1%]) admit by self/parent-report that they are failing to take all of their prescribed 6MP doses, potentially increasing their risk for leukemia relapse. Thus, self/parent-reports of non-adherence, which are more reliable than self-reports of adherence (Kennard, et al., 2004;

Liptak, 1996), may be useful in identifying a vulnerable subset of patients at increased risk**.**

Unlike previous studies of children with A.L.L. in which adherence was noted to drift over time (Tebbi, et al., 1986), patients in this study did not report a decline in self-reported adherence over the four study time points; in fact, self/parent-reported non-adherence was most prevalent at the first study time point, with 16.6% of the cohort reporting non-adherence at Day 29, with the prevalence of self/parent-reported non-adherence decreasing at each subsequent time point (Day 57 – 15.8%; Day 113 – 15.4%; Day 141 – 11.8%). Improvements in self/parent-reported adherence were also noted over time in a longitudinal study of self/parent-caregiver-reported adherence of pediatric HIV patients taking antiretroviral medications (Williams, et al., 2006). A structured interview was used to assess adherence during regularly scheduled clinic visits, with self-reported adherence rates improving from 77% at the first study time point to 88% after 7 or more study visits. The improvement noted in the Williams et al. study was thought to be related to discussion of adherence-related issues prompted by the structured interviews, which may have served as an unintended educational intervention. Unlike the Williams et al. study, adherence assessments for the current study were collected via a written questionnaire designed to be completed by the patient and/or parent independent of the healthcare provider. However, it is possible that the process of completing adherence-related questionnaires, and awareness on the part of the parent and/or child that adherence-related behaviors were being monitored, may have motivated some participants to practice more adherent behaviors throughout the study period.

Alternately, it is possible that non-adherence may have been under-reported via self/parent-report in this study, potentially as a result of social desirability bias (the tendency to present oneself in keeping with socially acceptable patterns of behavior so as to avoid criticism) (Marlowe & Crowne, 1961). There may have been particular reluctance on the part of study participants to report non-adherence repeatedly over multiple assessments, which may potentially explain the higher prevalence of non-adherence reported at initial time point. If this is the case, then self/parental acknowledgement of what may appear to be only an occasional missed dose of 6MP for non-medical reasons (categorized as non-adherence in this study), may serve as an important indicator of adherence problems in this population. Non-adherence in this cohort was defined at a statistical cut-point in the data that was clinically relevant, below which participants had missed at least 2 doses of 6MP for non-medical reasons. While it is certainly conceivable that one missed dose may occur as a result of an exceptional circumstance or lapse in vigilance that is plausible over the prolonged period of observation employed in this study, additional missed dose(s) may be indicative of a more systematic problem (such as poor organizational skills or lack of prioritization of oral chemotherapy administration) in need of corrective active. While it is possible that some of those reporting more than one missed 6MP dose over the study period in fact rarely missed a dose, it is also possible that reports of occasional missed doses under-represent the number of actual doses missed. Additionally, some non-adherent participants may have failed to acknowledge any missed doses, possibly as a result of poor recall, selective memory, or social desirability bias; thus, self-report measures may

fail to identify a subset of at-risk patients. Therefore, the use of multiple measures of adherence may be prudent in order to fully identify and characterize non-adherence within the population.

The relatively small number and infrequent reporting of missed 6MP doses by study participants may have important clinical implications. Clinicians should be aware that self/parent admission of even an occasional missed 6MP dose is uncommon in this population and may be indicative of a problem with adherence. Thus, clinicians should explore the reason(s) for any missed doses with the parent/patient, express concern regarding the dose(s) missed, and address any identified barriers to adherence. Additionally, adherence should be assessed at each clinic visit in order to consistently reinforce the importance of taking 6MP as prescribed, and to identify patients with ongoing adherence problems who may be in need of assistance.

5.2.2. Research question 2: *What is the impact of sociodemographic and disease-related factors on non-adherence to 6MP in this cohort?*

Sociodemographic factors identified as significantly associated with self/parent-reported non-adherence in this study included Hispanic ethnicity (P=0.004) and older age (P=0.005). The risk of non-adherence increased by 7% per year of age, and Hispanic patients were more than twice as likely as non-Hispanic whites to report non-adherence. In the univariate model, single parent household was associated with a 1.9-fold increased risk of non-adherence (P=0.031), but this retained only borderline significance (P=0.076) in the multivariate model. There were no disease-related factors associated with non-adherence in the final multivariate model.

The risk for non-adherence associated with single parent household, although of borderline significance in the multivariate model, may be suggestive of differences in role reorganization between single parent households and those with multiple adult caregivers. The process of family adaptation following a child's diagnosis of leukemia, as described by Clarke-Steffen (1993a, 1997), includes shifting of responsibilities among adult caregivers (i.e., role reorganization) in order to coordinate care and manage the therapeutic regimen, and thus this process may play an important role in adherence. It is possible that in some single parent families, there may not be other adult caregivers available to assist, and therefore the single parent may be unable to shift responsibilities to others. Additionally, when the patient is an adolescent, delineation of responsibility (i.e., parent vs. patient) for medication management is typically part of the process of role reorganization that occurs during the teen years (Leonard et al., 2005); it is therefore possible that for adolescents within a single parent family structure, there may be increased parental expectations for the teen to self-manage their own medications due to lack of availability of other adult caregivers to oversee the home aspects of the teen's treatment regimen. This may adversely affect day-to-day medication management and may explain the lower adherence rates observed in this group.

Older age, particularly adolescence, has been associated with decreased adherence to therapy in a number of studies in pediatric A.L.L. (Lancaster, et al., 1997; Macdougall, et al., 1992; S. D. Smith, et al., 1979; Tebbi, et al., 1986) and in other pediatric chronic conditions, including asthma, HIV, and renal disease (Orrell-Valente, Jarlsberg, Hill, & Cabana, 2008; Rianthavorn & Ettenger, 2005; Williams, et al., 2006). Adolescence is a

unique developmental period during which individuals acquire the cognitive ability to discern the long-term consequences of their behavior (Nevins, 2002); however, not all individuals master this task, and some may have considerable difficulty doing so, particularly when the positive consequences of their actions (e.g., cure of leukemia) do not manifest immediately, and the short-term consequences of therapy (e.g., medication side effects, limitations in social interactions) are viewed by the adolescent as undesirable. Additionally, some adolescents who may have achieved the ability to discern the future consequences of their actions may regress developmentally in response to illness-related stressors (Malbasa, et al., 2007; Nevins, 2002), and some may engage in non-adherent behaviors as a defensive coping mechanism in an attempt to preserve autonomy and normalcy (Friedman & Litt, 1987; B. A. Smith & Shuchman, 2005; Wolff, Strecker, Vester, Latta, & Ehrich, 1998).

The association between Hispanic ethnicity and non-adherence may be related to a number of confounding factors, including sociodemographic characteristics, cultural issues, and language barriers. It is possible that socioeconomic barriers in Hispanics may limit healthcare access, and linguistic and contextual barriers may preclude effective communication between patients and/or parents and their healthcare providers (Hewitt, Greenfield, & Stovall, 2006; Patino, Sanchez, Eidson, & Delamater, 2005; Sobo, 2004; Tumiel-Berhalter & Zayas, 2006). Additionally, differences in cultural and ethnic backgrounds may influence illness-related beliefs and treatment expectations and could also affect adherence (Bhatia, 2004). However, unlike studies in other pediatric chronic disease that have found an association between low income and lower levels of adherence

(Blais, Beauchesne, & Levesque, 2006; Brownbridge & Fielding, 1994; Marhefka, Tepper, Brown, & Farley, 2006; Modi, Morita, & Glauser, 2008), an increased risk for non-adherence was not seen in this study in patients from low-income families on univariate analysis (OR 0.91; P=0.724) or in the final multivariate model (OR 0.61, P=0.122). Although an association between linguistic barriers and non-adherence has also been noted in other studies (Manson, 1988), an increased risk of non-adherence was not seen in this study in patients from Spanish-speaking compared to English-speaking households on univariate analysis (OR 0.72; P=0.220). Additionally, unlike previous studies that have shown an association between lower levels of education and non-adherence in pediatric A.L.L. (MacDougall, et al., 1989; S. D. Smith, et al., 1979) and in HIV (Kalichman, Ramachandran, & Catz, 1999), the risk of non-adherence in this study was not increased related to lower educational level of the mother (OR 0.85, P=0.469) or father (OR 1.2, P=0.407).

Stratified analysis by ethnicity also failed to show an increased risk for non-adherence related to sociodemographic variables in this study. This may be related to a number of factors. It is possible that differences in adherence related to income and language barriers in other populations may have been somewhat ameliorated in this cohort, given that the patients were all being treated in specialized pediatric oncology programs within the Children's Oncology Group that are required to adhere to standards that include the provision of support from a multidisciplinary team (Corrigan, Feig, & American Academy of Pediatrics, (2004)). Thus, some of the problems commonly associated with limited income, such as transportation barriers, and problems related to

communication with healthcare providers among monolingual Spanish-speaking families, may have been overcome by provision of support services by these specialized teams. The increased prevalence of non-adherence among Hispanics seen in this study may therefore be related to factors other than language barriers and low income, such as cultural beliefs. Since the primary measures used in this study were not designed to assess cultural beliefs, it is possible that these measures failed to identify cultural differences related to health beliefs or treatment expectations among Hispanics that may have influenced adherence in this group of patients.

5.2.3. Research question 3: *What are the behavioral determinants of self/parent-reported non-adherence to oral chemotherapy in children receiving maintenance therapy for A.L.L.?*

The two behavioral factors significantly associated with non-adherence in multivariate analysis included *Lack of awareness of the purpose/function of 6MP* (P=0.025), and *Not reporting a change in health status in the past month* (P=0.049).

The association between lack of treatment-related knowledge and lower levels of adherence to prescribed regimens is consistent with other studies in pediatric A.L.L. (Tamaroff, et al., 1992; Tebbi, et al., 1986) and other chronic pediatric illnesses (Becker, 1974; Martin, et al., 2007; Nicholson, Mellins, Dolezal, Brackis-Cott, & Abrams, 2006; Veinot, et al., 2006). In this study, patients and/or their parents/caregivers who failed to identify 6MP as chemotherapy or who failed to acknowledge that 6MP was part of their leukemia treatment or had a role in the prevention of leukemia relapse, were at 1.8-fold

increased risk of non-adherence than those who acknowledged understanding the purpose/function of 6MP.

This finding has significant clinical implications, because children with A.L.L. take multiple oral medications over the course of their maintenance therapy. It is therefore possible that if the child and/or parent/caregiver do not understand the importance of 6MP, then they may make poor decisions in regard to its day-to-day administration. For example, in addition to oral chemotherapy, a number of other medications are often prescribed during A.L.L. maintenance therapy for symptom control, oral hygiene, and pneumonia prophylaxis. If a parent (or patient) were to decide not to administer some of the prescribed medications (such as if the child was nauseous, feeling overwhelmed, or having behavioral difficulties, or if the family was having difficulty paying for medications), then it would be important for the child/parent to understand that oral chemotherapy administration (i.e., daily 6MP, weekly methotrexate) should be given highest priority. This underscores the importance of the clinician frequently reviewing the purpose and function of each of the child's medications with the family, delineating the relative priority of each, and maintaining open lines of communication with the patient/parent. This establishes that the clinician is available to assist when problems regarding home medication arise, while consistently reinforcing the message regarding the importance of taking daily 6MP as prescribed.

The association between *Lack of perceived severity* of a given health condition and non-adherence has been reported in studies of patients with A.L.L. (Tamaroff, et al., 1992) and other chronic medical conditions (Bush & Iannotti, 1990; Palardy, Greening,

Ott, Holderby, & Atchison, 1998). In this current study, *Perceived severity* was assessed by whether or not the patient/parent reported a change in the child's health status during the past month. Patients who did not experience a change in their health status over the past month (resulting in a false sense of security regarding the potentially life-threatening nature of the disease if not treated appropriately) were at a 1.9-fold increased risk of non-adherence (P=0.049, 95% CI 1.00-3.55) compared to those who had experienced a change in health over the past month (which presumably increased awareness of vulnerability related to having a serious health condition).

Lack of perceived severity of a serious health condition is of particular concern in children with A.L.L. in the maintenance phase, since there are no signs or symptoms of the leukemia, which is in remission during this treatment phase. Thus, the perception of severe illness on the part of the patient/parent when the child is asymptomatic may require recall of past illness experiences (i.e., at the time of leukemia diagnosis). Patients who experience symptoms (i.e., intercurrent illnesses related to impaired immunity or complications related to treatment-related effects) may perceive themselves as more vulnerable and the disease as more severe than those who lack these symptoms. These findings may have important clinical implications, since patients/parents may need to be reminded by the clinician of the subclinical and asymptomatic nature of A.L.L. in remission, and of the important role of maintenance therapy delivered over a prolonged time period in the curative therapy for A.L.L. (Gale & Butturini, 1991).

5.2.4. Research question 4: *Which components of the Health Belief Model are the strongest predictors of self/parent-reported non-adherence to oral chemotherapy in these children?*

Perceived vulnerability and *Belief in efficacy of the health behavior* were the two major constructs from the Health Belief Model identified as the strongest predictors of self/parent-reported non-adherence to oral 6MP in this study. The risk of non-adherence in patients with low levels of perceived vulnerability, as a result of not experiencing a change in health status over the past month (and thus not perceiving the severity of their health condition), was nearly twice as high as for patients who had experienced a change in health status. This finding has important implications, given the asymptomatic nature of subclinical A.L.L. during maintenance therapy, which may decrease perceived vulnerability and increase the risk for non-adherence in this cohort. Additionally, patients who lacked awareness of the purpose and function of oral 6MP (and thus failed to acknowledge belief in the efficacy of taking this chemotherapy as prescribed) were also at nearly twice the risk for non-adherence compared to those who understood the purpose and function of 6MP.

There were also two major constructs from the Health Belief Model that were significantly associated with non-adherence in univariate analysis, but failed to retain significance in the multivariate model. *Taking Responsibility (no monitoring of 6MP administration by parent/caregiver/adult)* was associated with a 2-fold risk of non-adherence in univariate analysis (P=0.044, 95%CI 1.02-4.52), and *Cues to Action (6MP not administered at the same time daily)* was associated with a 1.9-fold increased risk

(P=0.007, 95%CI 1.19-3.06), but neither retained significance in the multivariate model. It is also possible that the constructs are not significant predictors of non-adherence, or that the measures of the constructs used in this study were not sufficiently robust.

One major construct of the Health Belief Model, *Perceived Barriers*, was not found to be significantly associated with non-adherence in univariate or multivariate analysis. This is important because barriers associated with taking oral medication, such as difficulties with medication administration, complexity of medication routine, and medication side effects, are widely thought to contribute to non-adherent behaviors (Haynes, et al., 2002; McDonald, Garg, & Haynes, 2002). However, results from the qualitative pilot study that preceded this analysis indicate that the presence of barriers alone does not explain adherence. All patients in the pilot study reported experiencing some barriers associated with taking oral chemotherapy, yet those who acknowledged the importance of oral chemotherapy in their treatment regimen reported overcoming barriers, or taking their chemotherapy despite barriers that could not be overcome; while those who failed to acknowledge the importance of oral chemotherapy cited barriers as reasons for their non-adherence. Thus, those patients who believed in the efficacy of the health behavior (taking oral chemotherapy as prescribed) did not allow barriers to negatively influence their adherence (Landier, Hughes, et al., 2009). Therefore, it is possible that barriers alone are not sufficient to explain non-adherence to oral chemotherapy in childhood A.L.L., and that the *Perceived Barriers* construct from the Health Belief Model is not useful in predicting adherence behaviors in this population.

5.3. Limitations

The results of this study must be considered in the context of its limitations. Although this is the largest reported study of self/parent-reported adherence to oral chemotherapy in children with A.L.L. conducted to date, it is possible that the sample may be biased towards more adherent participants, since those with poorer adherence may have chosen not to enroll in the study. Thus, the prevalence of non-adherence in the larger population of children with A.L.L. may be underestimated.

It is also possible that measuring adherence by self/parent-report may result in an underestimation of the true prevalence of adherence because it may fail to identify certain subgroups of non-adherent patients who may have been reluctant to admit less than optimal adherence behaviors. This limitation could be overcome by including more objective measures of adherence in the analysis and comparing those measures with self/parent report. In this particular cohort, it will be possible to compare self-report data with electronic medication monitoring and red cell 6MP metabolite levels in future studies, because these adherence measures were collected in the larger COG study over the six-month study period.

Additionally, the self-report questionnaire used for this study asked patients to recall missed doses over a period of 28 days. It is possible that not all participants may be able to accurately recall missed doses over a 28-day time period, thus non-adherence may have been under-reported as a result of poor recall. In an effort to increase the accuracy of recall, collection of self-reported adherence data in some studies has been limited to the previous 3 to 7 days (Van Dyke, et al., 2002; Williams, et al., 2006).

However, even if recall of missed 6MP doses in this study was poor after 3 or 7 days, estimation of non-adherence would be no worse than if only 3 or 7 days of data had been collected, and the collection of 28 days of data provides more opportunity for reporting of missed doses, if the patient/parent is able to recall them.

Finally, the study-related process of completing the adherence questionnaires may have in itself served as a reminder of the importance of adherence, thus unintentionally prompting improved adherence behaviors. This concern was largely addressed by the study design that called for collection of data over a six-month time span, diminishing the novelty of the study and allowing the opportunity to observe patients over a time span during which adherence behaviors, if affected by the novelty or unintended interventional effects of the study, would likely return to baseline levels at the later study time points.

Despite these limitations, this is the first study to describe the prevalence of self/parent-reported non-adherence to oral chemotherapy, and to identify behavioral predictors of non-adherence, in a large cohort of children with A.L.L.

5.4. Conclusion

In a large cohort of children with A.L.L., self/parent-report indicates that about 1 in 5 children are non-adherent to oral chemotherapy. Although the prevalence of self/parent-reported non-adherence appears to be lower for childhood A.L.L. than is reported for other pediatric chronic illnesses, such as HIV and sickle cell disease, the number of children who do not adhere to their 6MP prescriptions is substantial, and may place these children at risk for leukemia relapse.

Significant behavioral predictors of self/parent-reported non-adherence to 6MP identified in this study include *Lack of perceived illness severity* and *Lack of perceived benefits of treatment*, which represent two major constructs of the Health Belief Model: *Perceived vulnerability* and *Belief in efficacy of the health behavior*. Thus, risk of non-adherence is significantly increased for those who fail to perceive the severity of the child's illness or the benefits of treatment with oral 6MP. Vulnerable subgroups identified include older patients (with the risk of non-adherence increasing with each year of age) and those of Hispanic ethnicity.

Findings from this study are of importance to clinicians and suggest that even occasional reports of missed doses of oral chemotherapy may herald a significant problem with adherence; that patients and their parents may need ongoing reminders regarding the subclinical and asymptomatic nature of leukemia in remission; and that frequent review with families regarding the purpose, function, and proper administration of oral 6MP is imperative.

Future studies are needed to determine the reliability of self/parent-report of adherence to oral 6MP as compared with other measures of adherence, to explore reasons for identified sociodemographic differences in non-adherence (such as cultural factors and household structure), and to confirm and further refine the behavioral predictors of adherence to oral 6MP in additional cohorts of children with A.L.L. Additionally, findings from this study suggest that interventional strategies to improve adherence to oral chemotherapy in children with A.L.L. should focus on assisting patients/parents who report even occasional missed doses to understand the subclinical nature of leukemia in

remission, and the purpose, function, and importance of oral chemotherapy during the maintenance phase of therapy.

Appendices

Appendix A. Permission for Access to Data Set

City of Hope

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Chair, Division of Population Sciences

April 21, 2008

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RE: Wendy Landier, PhD student
Plans for Dissertation Research

Dear Dr. LeVasseur,

I had the pleasure of meeting with Dr. Francisco Conde and Ms. Wendy Landier on April 19th to discuss the plans for Ms. Landier's dissertation research. The following serves as a summary of our discussion and a proposed outline of the projected plan.

Ms. Landier has worked closely with me over the past 10 years and has been involved since the planning stages as a co-investigator on my R01-funded study "Understanding the Ethnic and Racial Differences in Survival in Children with Acute Lymphoblastic Leukemia" (1 R01 CA096670). Briefly, this study hypothesizes that observed ethnic and racial differences in survival in children with acute lymphoblastic leukemia are due to low systemic exposure to oral 6-mercaptopurine, primarily as a result of non-adherence to this oral antimetabolite chemotherapy during the maintenance phase of treatment. Targeted enrollment in this longitudinal Children's Oncology Group (COG) study is 720 patients (200 Caucasians, 200 Hispanics, 200 African-Americans, and 120 Asians) and data collection spans a 6-month period during each patient's maintenance phase of chemotherapy. We are measuring adherence to oral 6-mercaptopurine (6MP) by collecting: (1) serial blood samples for measurement of red cell 6MP metabolites (6TGN and 6 MethylTIMP), (2) frequency of 6MP dosing via an electronic pill monitoring system (MEMS), and (3) self-/parent-report of adherence via questionnaire. It is this third component – the questionnaire data - for which Ms. Landier has taken the lead throughout the study, and as discussed with Dr. Conde, will serve as the source of data for her dissertation research.

In the original pilot protocol, the grant application, and later in the cooperative group protocol for this study, Ms. Landier developed the background material and authored the grant/protocol sections relating to the adherence questionnaire. This stemmed primarily from Ms. Landier's interest in understanding the facilitators and barriers to non-adherence in this population, which differs from my primary interest, which is measuring adherence in these children and determining the impact of adherence on ethnic and racial differences in survival, particularly in regard to the red cell 6MP metabolite levels and MEMS data.

Ms. Landier has been involved in all aspects of study development and implementation for this project, including development of the cooperative group protocol and informed consent forms; obtaining IRB approval at City of Hope, and assisting with applications for the NCI Pediatric Central IRB and for many of the 135 participating COG institutions; development of kits for blood specimen collection; development of study-related forms, such as study eligibility forms, data collection reminders, parental and pharmacy instructions regarding use of electronic caps, and clinical report forms; and development of patient recruitment materials. She is also involved in supervision of the study's research assistants at the coordinating center and with ongoing study communication with the COG Study Development Office.

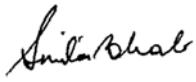
For her dissertation research, as discussed with Dr. Conde, Ms. Landier will analyze adherence questionnaire data in order to address the following Specific Aim: ***To describe predictors of adherence using the questionnaire data***. Ms. Landier will be required to develop a specific plan for analysis (including both quantitative and qualitative components), carry out that plan, and write up the results in a format suitable for publication. Of course, she will also be required to prepare the other related components of the dissertation, such as the literature review. Given the current rate of study data collection and the projected start date for Ms. Landier's analysis (Fall 2009), it is likely that the analysis will focus on the Caucasian and Hispanic cohorts from this study; however, the final determination regarding the cohort(s) to be analyzed by Ms. Landier will be made at a later date.

As discussed with Dr. Conde, ownership of the dissertation itself would be Ms. Landier's alone. However, as in any large, multi-investigator, multi-site trial such as this one, multiple members of the research team would have authorship rights in any publication resulting from the analysis. Therefore, Ms. Landier would be the first author of the primary paper evolving from the analysis, I would be the senior author, and several additional members of the research team, and potentially members of the dissertation committee including Dr. Conde, would be included in the authorship (depending on the number of authors allowed by the targeted journal). As we discussed, in order to assure that at least one paper provides authorship opportunities for the entire dissertation committee, a paper targeted to a nursing journal (with a focus relevant to nursing), should be developed from the analysis and the entire dissertation committee could then be represented in the authorship of the nursing paper. It should also be noted that since this is a Children's Oncology Group study, all publications related to the study would need to be submitted through the COG publications office rather than directly to the targeted journal, and the title of all publications would include the statement: "A Report from the Children's Oncology Group."

The plan outlined above is fully acceptable to me, and as the Principal Investigator of both the grant and the cooperative group study, I am willing to release the questionnaire data set to Ms. Landier for purposes of analysis related to her dissertation research as described above. As I indicated to Dr. Conde, I am also willing to serve as a member of Ms. Landier's dissertation committee.

Should you have any questions, or require any additional information, please do not hesitate to contact me at 626-471-7321 or sbhatia@coh.org.

Sincerely,



Smita Bhatia, MD, MPH
Professor and Chair
Division of Population Sciences
City of Hope National Medical Center
Associate Director, Population Research
City of Hope Comprehensive Cancer Center

cc: Francisco Conde, RN, PhD

Appendix B. Regulatory Approvals

CITY OF HOPE MEDICAL CENTER
CANCER PROTOCOL REVIEW & MONITORING COMMITTEE

ACTION NOTICE

TO: Wendy Landier, R.N., M.S.N., N.P.

FROM: Arlene Carroll, Cancer Protocol & Review Committee

Signature applied by Arlene Carroll on 01/04/2010 03:34:35 PM PST

DATE: January 04, 2010

PROTOCOL: 09006: Use of Existing Data to Identify Predictors of Non-Adherence to Oral Chemotherapy in Children with Acute Lymphoblastic Leukemia

The Cancer Protocol Review and Monitoring Committee (CPRMC) took the following action on the protocol referenced above:

APPROVED

The new protocol submitted 12/16/09 received expedited review and was approved and signed off 01/04/09.

If you have any questions, please contact Gwen Jorgensen at extension 63034. Thank you.

cc: IRB

CITY OF HOPE MEDICAL CENTER
NOTICE OF INSTITUTIONAL REVIEW BOARD ACTION ON A RESEARCH PROTOCOL

TO: **Wendy Landier, R.N., M.S.N., N.P.,** Principal Investigator
COH - Outcomes Research

FROM: Gwenn S.F. Oki, M.P.H., Director, Research Subjects Protection

Signature applied by Gwenn Oki on 01/19/2010 07:37:00 AM PST

DATE: **January 18, 2010**

SUBJECT: **Protocol Entitled: Use of Existing Data to Identify Predictors of Non-Adherence to Oral Chemotherapy in Children with Acute Lymphoblastic Leukemia**

ACTION: **NEW PROTOCOL**

IRB #: **09006**

As of **1/18/2010** the following action is in effect:

EXPEDITED APPROVAL FROM 1/18/2010 UNTIL 1/17/2011 WITH COMMENT(S)

COMMENT(S):

I. This retrospective protocol is approved for waiver of informed consent and waiver of HIPAA authorization.

II. This research is approved for use of retrospective data already collected as of 01/18/2010 only.

NOTE: DURING THE PERIOD COVERED BY IRB APPROVAL ANY CHANGES IN THE PROTOCOL, OR ANY UNEXPECTED PROBLEMS INVOLVING HUMAN SUBJECTS, MUST BE SUBMITTED IN WRITING TO THE IRB FOR REVIEW. NO CHANGES CAN BE INITIATED UNTIL APPROVAL HAS BEEN OBTAINED.

IRB Contact: Nancy Debretsion

UNIVERSITY OF HAWAI'I

Committee on Human Studies

MEMORANDUM

February 3, 2010

TO: Wendy Landier, RN
Principal Investigator
School of Nursing & Dental Hygiene

FROM: Nancy R. King
Interim Executive Secretary

SUBJECT: CHS #17840- "Use of Existing Data to Identify Predictors of Non-Adherence to Oral Chemotherapy in Children with Acute Lymphoblastic Leukemia"

Your project identified above was reviewed by the Chair of the Committee on Human Studies through Expedited Review procedures. The project qualifies for expedited review by CFR 46.110 and 21 CFR 56.110, Category (5) of the DHHS list of expedited review categories.

This project was approved on February 2, 2010 for one year. If in the active development of your project you intend to change the involvement of humans from plans indicated in the materials presented for review, prior approval must be received from the CHS before proceeding. If unanticipated problems arise involving the risks to subjects or others, report must be made promptly to the CHS, either to its Chairperson or to this office. This is required in order that (1) updating of protective measures for humans involved may be accomplished, and (2) prompt report to DHHS and FDA may be made by the University if required.

In accordance with the University policy, you are expected to maintain, as an essential part of your project records, all records pertaining to the involvement of humans in this project, including any summaries of information conveyed, data, complaints, correspondence, and any executed forms. These records must be retained for at least three years from the expiration/termination date of this study.

The CHS approval period for this project will expire on February 2, 2011. If your project continues beyond this date, you must submit a continuation application to the CHS at least four weeks prior to the expiration of this study.

We wish you success in this endeavor and are ready to assist you and your project personnel at any time.

Enclosed is your certification for this project.

Enclosure

1960 East-West Road, Biomedical B104, Honolulu, Hawaii 96822-2303
Telephone: (808) 956-5007, Facsimile: (808) 956-8683, Website: www.hawaii.edu/irb

Appendix C. Sources of Behavioral-Related Variables

Variable	Construct	Description	Source	Data Type
CHANGES IN HEALTH SR [Composite: Day 29, 57, 113, 141]	[General health status]	Any changes in child's health in past month? (yes/no) (patient self-report)	Adherence Questionnaire (Patient Version) Item #1	Quantitative, dichotomous
CHANGES IN HEALTH PCR [Composite: Day 29, 57, 113, 141]	[General health status]	Any changes in child's health in past month? (yes/no) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #1	Quantitative, dichotomous
EXPLAIN HEALTH CHANGE SR [Composite: Day 29, 57, 113, 141]	[General health status]	Explain any change in child's health in past month (patient self-report)	Adherence Questionnaire (Patient Version) Item #1	Qualitative (short answer)
EXPLAIN HEALTH CHANGE PCR [Composite: Day 29, 57, 113, 141]	[General health status]	Explain any change in child's health in past month (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #1	Qualitative (short answer)
CHANGES IN TREATMENT SR [Composite: Day 29, 57, 113, 141]	[General health status]	Any changes in child's treatment in past month? (yes/no) (patient self-report)	Adherence Questionnaire (Patient Version) Item #2	Quantitative, dichotomous
CHANGES IN TREATMENT PCR [Composite: Day 29, 57, 113, 141]	[General health status]	Any changes in child's treatment in past month? (yes/no) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #2	Quantitative, dichotomous
EXPLAIN TREATMENT CHANGE SR [Composite: Day 29, 57, 113, 141]	[General health status]	Explain any change in child's treatment in past month (patient self-report)	Adherence Questionnaire (Patient Version) Item #2	Qualitative (short answer)
EXPLAIN TREATMENT CHANGE PCR [Composite: Day 29, 57, 113, 141]	[General health status]	Explain any change in child's treatment in past month (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #2	Qualitative (short answer)
TIME TAKING 6MP SR [Day 29]	Perceived barriers	Length of time child has been taking 6MP in months (patient self-report)	Adherence Questionnaire (Patient Version) Item #3	Quantitative, continuous
TIME TAKING 6MP PCR [Day 29]	Perceived barriers	Length of time child has been taking 6MP in months (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #3	Quantitative, continuous
HOW MUCH LONGER 6MP SR [Day 29]	Perceived barriers	Length of time child will be taking 6MP in months (patient self-report)	Adherence Questionnaire (Patient Version) Item #4	Quantitative, continuous
HOW MUCH LONGER 6MP PCR [Day 29]	Perceived barriers	Length of time child will be taking 6MP in months (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #4	Quantitative, continuous
SAME DAILY 6MP DOSE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take same number of 6MP pills daily? (yes/no/don't know) (patient self-report)	Adherence Questionnaire (Patient Version) Item #5	Quantitative, categorical

Variable	Construct	Description	Source	Data Type
SAME DAILY 6MP DOSE PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take same number of 6MP pills daily? (yes/no/don't know) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #5	Quantitative, categorical
DAILY 6MP DOSE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Number of 6MP pills child takes by day of week (Mon, Tues, Wed, Thurs, Fri, Sat, Sun) [separate variable for each day of week] (patient self-report)	Adherence Questionnaire (Patient Version) Item #6	Quantitative, continuous
DAILY 6MP DOSE PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Number of 6MP pills child takes by day of week (Mon, Tues, Wed, Thurs, Fri, Sat, Sun) [separate variable for each day of week] (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #6	Quantitative, continuous
DAILY 6MP DOSE HCPR [Composite: Day 29, 57, 113, 141]	[Confirmation of prescribed dose by HCP]	6MP prescribed dose by day of week (Mon, Tues, Wed, Thurs, Fri, Sat, Sun) [separate variable for each day of week] (healthcare provider report)	Maintenance Report Worksheet Item #24	Quantitative, continuous
6MP DOSE EVER CHANGED SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has number of 6MP pills child takes each day ever changed? (yes/no/don't know) (patient self-report)	Adherence Questionnaire (Patient Version) Item #7	Quantitative, categorical
6MP DOSE EVER CHANGED PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has number of 6MP pills child takes each day ever changed? (yes/no/don't know) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #7	Quantitative, categorical
REASON 6MP DOSE CHANGED SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Reason child's 6MP dose changed (blood counts, infection/illness, weight/height, other) (patient self-report)	Adherence Questionnaire (Patient Version) Item #8	Quantitative, categorical
REASON 6MP DOSE CHANGED PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Reason child's 6MP dose changed (blood counts, infection/illness, weight/height, other) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #8	Quantitative, categorical
HOW 6MP WORKS SR [Composite: Day 29, 57, 113, 141]	Perceived benefits	What is your understanding of how 6MP works? (patient self-report)	Adherence Questionnaire (Patient Version) Item #9	Qualitative (short answer)
HOW 6MP WORKS PCR [Composite: Day 29, 57, 113, 141]	Perceived benefits	What is your understanding of how 6MP works? (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #9	Qualitative (short answer)

Variable	Construct	Description	Source	Data Type
INVOLVEMENT IN 6MP DECISION SR [Day 29]	Belief in efficacy of health behavior	Was child involved in decision to take 6MP? (yes/no/don't remember) (patient self-report)	Adherence Questionnaire (Patient Version) Item #10	Quantitative, categorical
INVOLVEMENT IN 6MP DECISION PCR [Day 29]	Belief in efficacy of health behavior	Was child involved in decision to take 6MP? (yes/no/don't remember) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #10	Quantitative, categorical
THINK OF EXAMPLE 6MP NOT TAKEN SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Can you think of example of time child did not take 6MP when it was prescribed? (yes/no) (patient self-report)	Adherence Questionnaire (Patient Version) Item #11	Quantitative, dichotomous
THINK OF EXAMPLE 6MP NOT TAKEN PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Can you think of example of time child did not take 6MP when it was prescribed? (yes/no) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #11	Quantitative, dichotomous
EXAMPLE 6MP NOT TAKEN SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time child did not take 6MP when it was prescribed (patient self-report)	Adherence Questionnaire (Patient Version) Item #12	Qualitative (short answer)
EXAMPLE 6MP NOT TAKEN PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time child did not take 6MP when it was prescribed (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #12	Qualitative (short answer)
REASON 6MP NOT TAKEN SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Reason child did not take 6MP for 1 or more days during past 28 days (patient self-report)	Adherence Questionnaire (Patient Version) Item #15	Qualitative (short answer)
REASON 6MP NOT TAKEN PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Reason child did not take 6MP for 1 or more days during past 28 days (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #15	Qualitative (short answer)
6MP STOPPED HCPR [Composite: Day 29, 57, 113, 141]	[General health status]	In the past 28 days, did prescriber order patient to stop taking (hold) 6MP? (yes/no) (healthcare provider report)	Maintenance Report Worksheet Item #27	Quantitative, dichotomous
REASON 6MP STOPPED HCPR [Composite: Day 29, 57, 113, 141]	[General health status]	Reason prescriber ordered patient to stop taking (hold) 6MP during this maintenance period [ANC too low; platelet count too low, elevation of liver enzymes and/or bilirubin, infection/illness, other (describe)] (healthcare provider report)	Maintenance Report Worksheet Item #28	Quantitative, categorical
HOSPITALIZATION HCPR [Composite: Day 29, 57, 113, 141]	[General health status]	Was this patient hospitalized during this maintenance period? (yes/no) (healthcare provider report)	Maintenance Report Worksheet Item #8	Quantitative, dichotomous

Variable	Construct	Description	Source	Data Type
HOSPITALIZATION REASON HCPR [Composite: Day 29, 57, 113, 141]	[General health status]	If hospitalized during past maintenance period, reason for hospitalization (healthcare provider report)	Maintenance Report Worksheet Item #10	Qualitative (short answer)
TOOK DIFFERENT 6MP DOSE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has child ever taken a dose of 6MP that was different than prescribed? (yes/no/don't remember) (patient self-report)	Adherence Questionnaire (Patient Version) Item #16	Quantitative, categorical
TOOK DIFFERENT 6MP DOSE PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has child ever taken a dose of 6MP that was different than prescribed? (yes/no/don't remember) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #16	Quantitative, categorical
EXAMPLE DIFFERENT 6MP DOSE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time child took different 6MP dose than prescribed (patient self-report)	Adherence Questionnaire (Patient Version) Item #17	Qualitative (short answer)
EXAMPLE DIFFERENT 6MP DOSE PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time child took different 6MP dose than prescribed (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #17	Qualitative (short answer)
DECIDED NOT TO TAKE 6MP SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has child ever decided not to take 6MP? (yes/no/don't remember) (patient self-report)	Adherence Questionnaire (Patient Version) Item #18	Quantitative, categorical
DECIDED NOT TO TAKE 6MP PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has child ever decided not to take 6MP? (yes/no/don't remember) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #18	Quantitative, categorical
EXAMPLE DECIDED NOT TO TAKE 6MP SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time child decided not to take 6MP (patient self-report)	Adherence Questionnaire (Patient Version) Item #19	Qualitative (short answer)
EXAMPLE DECIDED NOT TO TAKE 6MP PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time child decided not to take 6MP (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #19	Qualitative (short answer)
DECIDED NOT TO GIVE 6MP SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has parent/caregiver ever decided not to give 6MP? (yes/no/don't remember) (patient self-report)	Adherence Questionnaire (Patient Version) Item #20	Quantitative, categorical
DECIDED NOT TO GIVE 6MP PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Has parent/caregiver ever decided not to give 6MP? (yes/no/don't remember) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #20	Quantitative, categorical
EXAMPLE DECIDED NOT TO GIVE 6MP SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time parent/caregiver decided not to give child 6MP (patient self-report)	Adherence Questionnaire (Patient Version) Item #21	Qualitative (short answer)

Variable	Construct	Description	Source	Data Type
EXAMPLE DECIDED NOT TO GIVE 6MP PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Example of time parent/caregiver decided not to give child 6MP (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #21	Qualitative (short answer)
THINK OF REASON CHILD NOT TAKE 6MP SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Can you think of a reason why child might not take 6MP as prescribed? (yes/no) (patient self-report)	Adherence Questionnaire (Patient Version) Item #22	Quantitative, dichotomous
THINK OF REASON CHILD NOT TAKE 6MP PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Can you think of a reason why child might not take 6MP as prescribed? (yes/no) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #22	Quantitative, dichotomous
REASON CHILD NOT TAKE 6MP SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Reason child might not take 6MP as prescribed (patient self-report)	Adherence Questionnaire (Patient Version) Item #23	Qualitative (short answer)
REASON CHILD NOT TAKE 6MP PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Reason child might not take 6MP as prescribed (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #23	Qualitative (short answer)
6MP ROUTINE SR [Composite: Day 29, 57, 113, 141]	Cues to Action	Child's usual routine for taking 6MP (patient self-report)	Adherence Questionnaire (Patient Version) Item #24	Qualitative (short answer)
6MP ROUTINE PCR [Composite: Day 29, 57, 113, 141]	Cues to Action	Child's usual routine for taking 6MP (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #24	Qualitative (short answer)
HOME SUPERVISION 6MP SR [Composite: Day 29, 57, 113, 141]	Taking responsibility for medication administration	Does someone make sure child takes 6MP at home daily? (yes/no/don't remember) (patient self-report)	Adherence Questionnaire (Patient Version) Item #25	Quantitative, categorical
HOME SUPERVISION 6MP PCR [Composite: Day 29, 57, 113, 141]	Taking responsibility for medication administration	Does someone make sure child takes 6MP at home daily? (yes/no/don't remember) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #25	Quantitative, categorical
WHO SUPERVISES 6MP SR [Composite: Day 29, 57, 113, 141]	Taking responsibility for medication administration	Who supervises child taking 6MP daily? (child/mother/father/ stepmother/ stepfather/ grandparent/brother/ sister/ other) (patient self-report)	Adherence Questionnaire (Patient Version) Item #26	Quantitative, categorical
WHO SUPERVISES 6MP PCR [Composite: Day 29, 57, 113, 141]	Taking responsibility for medication administration	Who supervises child taking 6MP daily? (child/mother/father/ stepmother/ stepfather/ grandparent/brother/ sister/ other) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #26	Quantitative, categorical
HOW 6MP SUPERVISED SR [Composite: Day 29, 57, 113, 141]	Taking responsibility for medication administration	How does person supervising make sure child takes 6MP daily? (patient self-report)	Adherence Questionnaire (Patient Version) Item #27	Qualitative (short answer)

Variable	Construct	Description	Source	Data Type
HOW 6MP SUPERVISED PCR [Composite: Day 29, 57, 113, 141]	Taking responsibility for medication administration	How does person supervising make sure child takes 6MP daily? (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #27	Qualitative (short answer)
6MP SAME TIME SR [Composite: Day 29, 57, 113, 141]	Cues to Action	Does child take 6MP at same time every day? (yes/no/don't know) (patient self-report)	Adherence Questionnaire (Patient Version) Item #28	Quantitative, categorical
6MP SAME TIME PCR [Composite: Day 29, 57, 113, 141]	Cues to Action	Does child take 6MP at same time every day? (yes/no/don't know) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #28	Quantitative, categorical
6MP TIME SR [Composite: Day 29, 57, 113, 141]	Cues to Action	What time does child take 6MP daily? (patient self-report)	Adherence Questionnaire (Patient Version) Item #29	Quantitative, continuous
6MP TIME PCR [Composite: Day 29, 57, 113, 141]	Cues to Action	What time does child take 6MP daily? (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #29	Quantitative, continuous
6MP WITH FOOD SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take 6MP with food? (with food/without food) (patient self-report)	Adherence Questionnaire (Patient Version) Item #30	Quantitative, dichotomous
6MP WITH FOOD PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take 6MP with food? (with food/without food) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #30	Quantitative, dichotomous
6MP FOOD TYPE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child takes 6MP with food specify type (patient self-report)	Adherence Questionnaire (Patient Version) Item #30	Qualitative, short answer
6MP FOOD TYPE PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child takes 6MP with food specify type (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #30	Qualitative, short answer
6MP WITH MILK SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take 6MP with milk or dairy products? (with milk-dairy/without milk-dairy) (patient self-report)	Adherence Questionnaire (Patient Version) Item #31	Quantitative, dichotomous
6MP WITH MILK PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take 6MP with milk or dairy products? (with milk-dairy/without milk-dairy) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #31	Quantitative, dichotomous
6MP MILK TYPE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child takes 6MP with dairy product, specify type (patient self-report)	Adherence Questionnaire (Patient Version) Item #31	Qualitative, short answer
6MP MILK TYPE PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child takes 6MP with dairy product, specify type (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #31	Qualitative, short answer
6MP WITH LIQUID SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take 6MP with liquid? (with liquid/without liquid) (patient self-report)	Adherence Questionnaire (Patient Version) Item #32	Quantitative, dichotomous
6MP WITH LIQUID PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child take 6MP with liquid? (with liquid/without liquid) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #32	Quantitative, dichotomous

Variable	Construct	Description	Source	Data Type
6MP LIQUID TYPE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child takes 6MP with liquid, specify type (patient self-report)	Adherence Questionnaire (Patient Version) Item #32	Qualitative, short answer
6MP LIQUID TYPE PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child takes 6MP with liquid, specify type (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #32	Qualitative, short answer
6MP SWALLOWS WHOLE SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Does child swallow 6MP tablet whole? (yes/no) (patient self-report)	Adherence Questionnaire (Patient Version) Item #33	Quantitative, dichotomous
6MP SWALLOWS WHOLE PCR [Day 29, 57, 113, 141]	Perceived barriers	Does child swallow 6MP tablet whole? (yes/no) (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #33	Quantitative, dichotomous
6MP PREP SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	How is 6MP prepared for child? (patient self-report)	Adherence Questionnaire (Patient Version) Item #34	Qualitative, short answer
6MP PREP PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	How is 6MP prepared for child? (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #34	Qualitative, short answer
CONSEQUENCE NOT TAKING 6MP SR [Composite: Day 29, 57, 113, 141]	Belief in health threat (vulnerability)	What do you think would happen if child stopped taking 6MP? (patient self-report)	Adherence Questionnaire (Patient Version) Item #35	Qualitative, short answer
CONSEQUENCE NOT TAKING 6MP PCR [Composite: Day 29, 57, 113, 141]	Belief in health threat (vulnerability)	What do you think would happen if child stopped taking 6MP? (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #35	Qualitative, short answer
WHY 6MP STOPPED SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child was taking 6MP in past but has now stopped, why did child stop taking 6MP? (patient self-report)	Adherence Questionnaire (Patient Version) Item #36	Qualitative, short answer
WHY 6MP STOPPED PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	If child was taking 6MP in past but has now stopped, why did child stop taking 6MP? (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #36	Qualitative, short answer
ADDITIONAL INFO SR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Is there anything else you would like to tell us about taking 6MP? (patient self-report)	Adherence Questionnaire (Patient Version) Item #37	Qualitative, short answer
ADDITIONAL INFO PCR [Composite: Day 29, 57, 113, 141]	Perceived barriers	Is there anything else you would like to tell us about taking 6MP? (parent/caregiver-report)	Adherence Questionnaire (Parent/Caregiver Version) Item #37	Qualitative, short answer

Abbreviations: 6MP = 6-Mercaptopurine; SR = Self-report; PCR = Parent/Caregiver Report; HCPR = Healthcare Provider Report

Appendix D. Qualitative Coding

Codebook – Key Qualitative Variables

Has not experienced a change in health status in past month
[K.healthcorr.1PT]

		Value	Count	Percent
Valid values	0	Changes in health in past month	104	21.0%
	1	No changes in health in past month	387	78.2%
Missing Values	System		4	.8%

Unaware of disease severity/consequences of not taking 6MP as prescribed
[K.stopRECODED.1PT]

		Value	Count	Percent
Valid Values	0	Relapse/something bad/Aware of consequences of not taking 6MP as prescribed	392	79.2%
	1	Don't know/Unaware of consequences of not taking 6MP as prescribed	103	20.8%

Unaware of purpose/function of 6MP
[K.how6MPdichot.1cum]

		Value	Count	Percent
Valid Values	0	Understands how 6MP works	369	74.5%
	1	Doesn't understand how 6MP works	126	25.5%

6MP dose varies from day to day
[K.same6MPcorr.1PT]

		Value	Count	Percent
Valid Values	0	Yes, same 6MP dose daily	178	36.0%
	1	No, daily 6MP dose differs	303	61.2%
Missing Values	System		14	2.8%

6MP prescription has changed (ever)
[K.change6MPcorr.1PT]

		Value	Count	Percent
Valid Values	0	6MPdoseNeverChanged	86	17.4%
	1	6MPdoseHasChanged	397	80.2%
Missing Values	System		12	2.4%

Changes in treatment (in past month)
[K.leukinfoCodeddichot.1PT]

		Value	Count	Percent
Valid Values	0	None/no change in treatment	402	81.2%
	1	Change in treatment	86	17.4%
Missing Values	System		7	1.4%

Child takes 6MP without food or milk
[K.foodmilkCOMBO.1PT]

		Value	Count	Percent
Valid Values	0	Takes 6MP with food and/or milk	110	22.2%
	1	Takes 6MP without food or milk	385	77.8%

Child cannot swallow 6MP tablet whole
[K.swallowCORR.1PT]

		Value	Count	Percent
Valid Values	0	Yes, swallows tablet whole	313	63.2%
	1	No, does not swallow tablet whole	181	36.6%
Missing Values	System		1	.2%

Child not involved in decision to take 6MP
[K.child6MPdichot.1PT]

		Value	Count	Percent
Valid Values	0	Involved in decision to take 6MP	67	13.5%
	1	Not involved in decision to take 6MP	428	86.5%

No adult involved in monitoring 6MP administration
[K.monitorCOMBOdichot.1PT]

		Value	Count	Percent
Valid Values	0	Adult involved in monitoring	462	93.3%
	1	No monitor/child only	33	6.7%

No systematic approach/routine for 6MP administration
[K.howmonitorRECODEDdichot.1PT]

		Value	Count	Percent
Valid Values	0	Has routine/reminder system	446	90.1%
	1	No routine/reminder system	49	9.9%

6MP not administered at same time daily
[K.sametime.1PT]

		Value	Count	Percent
Valid Values	0	Yes, child takes 6MP at same time each day	372	75.2%
	1	No, child does not take 6MP at same time each day	116	23.4%
Missing Values	System		7	1.4%

6MP administered late at night
[K.timeofDaydichot.1PT]

		Value	Count	Percent
Valid Values	0	Morning/aft/Evening 0500 - 2245	459	92.7%
	1	Night 2300 - 0445	32	6.5%
Missing Values	System		4	.8%

Appendix D (continued):
Samples of Coding Verification for Patient/Parent Questionnaire Responses

EXAMPLE OF INITIAL CODING:
1a/1b. Have there been any changes in child's health in the past month? [healthcorr.1] If yes, please explain [healthinfoCODED.1]:

Code	Category	Sample responses
0	No change in health	▪ N/A (no response required if response to question 1a indicated that there was no change in child's health in past month)
1	Fever/infection **AGREE**	▪ Sinus infection ▪ cold ▪ case of shingles ▪ Cold - Cough for two week, infection on leg from moluscom ▪ He had the flue w/a fever for less than 48 hrs ▪ Not leukemia related - a chest infection requiring antibiotics. ▪ Got crup - had to go to hospital for constricted airway ▪ Had a sinus infection treated with omince for 10days ▪ Child was admited due to infection ▪ Influenza B - hospitalized twice -Gallbladder removal ▪ Has a head cold. ▪ 9 days ago vomited stomach virus, medications were held for 3 days ▪ RSV pnemonia ▪ Bronchitis/Pneumonia/Bad reaction to Vinchristine ▪ -cold and an ear infection ▪ A small cold ▪ cold & cough ▪ Was hospitalized due to an infection ▪ Cold/Congestion ▪ viral infection ▪ fighting a cold for 3 wks - nasal & chest congestion ▪ She had fever & was in-patient for 3 days 3wks ago her home meds were reduced ▪ viral infection occurrence ▪ Sick -Phnamonia + infection ▪ Slight cold-approximate duration 10 days ▪ she got tonsilitis and walking pneumonia ▪ Herpes ▪ COLD ▪ Pneumonia ▪ Has had a "cold" virus ▪ developed CMV ▪ Pngumonia, Levo-flaxin USGD as anti-biotic ▪ He had a fever, ear infection and cough ▪ She had a cold & was treated with Zithromax ▪ on day 14 he got a fever of 101.4 it lasted for 4 days (99.5-101.6) ▪ ANC ha been a little lower & she has had a slight cough. ▪ sinus infection / cold ▪ only 2 days low grad fever but ok now - no change in treatment ▪ cold 2 wks ago ▪ 8/7/07 red, swollen, painful, pus from left great toe - culture positive for staph aureus, given Augmentin x 10 days ▪ left ear infection. 2nd flu.

Item 1a/1b (continued): Have there been any changes in child's health in the past month? [healthcorr.1] If yes, please explain

Code	Category	Sample responses
2	Low counts/ abnormal labs/ (liver problems) **AGREE**	▪ Neutropenic ▪ elevated liver enzymes ▪ His blood counts lowered ▪ liver was acting up so they dropped 6mp level. ▪ 3/6 --> 3/12/06 stopped all meds due to low ANC ▪ ANC was very low but rose up again after being taken off ALL MEDS ▪ she's had liver alterations due to 6MP. She's had fevers and been in the for infections. ▪ Low ANC ▪ As she took the complete dose her blood counts dropped ▪ low counts or defenses ▪ Had his counts very low. ▪ fluctuation in blood counts
3	Non-leukemia related **AGREE**	▪ Broken arm ▪ stuffy nose (probably allergies) ▪ Broke ankle ▪ Had a bad asthma attack - ended up in emergency.
4	Feeling better/improved **AGREE**	▪ Feeling stronger. physically. ▪ I feel better ▪ reponding well to treatment feeling better ▪ The medications help him combat his sickness. ▪ Feel better ▪ He is hungrier and he has more energy ▪ doing alot better ▪ Ive noticed im more prone to Physical injouries although I feel healthier
5	Treatment side effects/ complications **AGREE (except comment)** **RESOLUTION: NOT ENOUGH INFORMATION; DO NOT CHANGE.**	▪ becomes ill after Vancristine and has problems with Dex (stomach cramping & pains in joints) ▪ He been having headaches ▪ Port removed & port inserted. Otherwise fine ▪ Allergic reaction to Pentathadyme ▪ more nausea/ vomiting ▪ doesn't seem to feel as well ▪ He eats less than before, but not much ▪ - Increased steroid doseage --> bad back pain (worse than normal) also nauseous. ▪ small rash on back of neck; tires more easily ▪ hair has fallen out ▪ weaker legs ▪ he is experiencing muscle pain in legs. ▪ She's not as hungry. She used to have a big appetite. ▪ Foot Hurts ▪ His attitude is aggressive. ▪ hospitalzed for pancreatitis ▪ alot of planter's wart's ▪ gained weight, they had to remove her gallbladder, the pancreas is inflamed. ▪ He has declined in his activity levels, doesn't eat like he does when he isn't taking the medication ▪ Started having nausea, vomiting and general discomfort. ▪ During this month he has had a nose bleed twice. ▪ he has developed hives
6	Leukemia-related	▪ Her last spinal showed a blast in the fluid
88	Not evaluable	▪ Increase due to weight gain ▪ the teeth, the ears, the head

Comment [s1]: ? infection

Comment [w2]: Not enough information to determine reason for port removal – leave as-is

EXAMPLES OF DICHOTOMIZED CODING OF KEY VARIABLES:

9. What is your understanding of how 6MP works? [how6MPdichot.1cum]:

[Dichotomized: 0=Understands how 6MP works 1=Doesn't understand how 6MP works]

Code	Category	Sample responses
0	Understands how 6MP works **AGREE**	▪ It is part of the treatment for keeping his leukemia under control and in remission ▪ Treating her Leukemia ▪ fights leukemia in some way ▪ Killing the bad cells from leukemia ▪ Attacks all cells withe the leukemia cells, and helps with combination of his treatment ▪ All I know is that it is a drug to help fight leukemia - He is to have it at night and at least an hour after he has had any food. ▪ It kills cell Luckemic and other to stop spread of Luckemic cells ▪ All I know is it affects his ANC each week. So my guess is, its a chemo medication to help eliminate cancer cells in his blood. ▪ That its a form at chemo and helps fight the leukemia. ▪ It helps fight her cancer ▪ Helps keep leukemia away. ▪ these pills help to my son against the leukemia ▪ It's medicine that helps my son fight leukemia ▪ kills cells to prevent cancer from coming back ▪ Helps to kill leukemia cells ▪ Attacking the bad cells? I believe. ▪ its a medicine to treat the deases ▪ It's oral chemo he take on a daily basis for the next 2 years, a lower dose to continue fighting the cancer ▪ Hmm. . . it kills cancer cells! It is chemotherapy! ▪ Fights cancer- not sure on details. Trust Hospitals Doctors &what they prescribe my daughter ▪ ?suppression of rapid growing cells? ▪ need a refresher: I believe it's a cancer fighting medicine ▪ Chemo drug that helps to keep him in remission. ▪ All I remember its a medtabolite it some how attacks cancer cells ▪ keeps his blood counts low to also keep the cancer cells from coming back ▪ Part of road map treating Leukemia. I don't know exact specifics ▪ It is chemotherapy & helps to prevent a recurrence of leukemia. It also effects blood counts. ▪ chemotherapy, kills cancer, slows down cell growth ▪ 6-MP IS A CHEMO THAT TREATS CANCER CELLS IN THE BLOOD. ▪ It's a sort of kimo ▪ It is part of chemotherapy regimen prescribed by the MD. ▪ a pill form of Kemo ▪ Part of chemotherapy medicine ▪ It is a type of chemo that is long-term and is to be taken daily ▪ Oral chemo taken home. ▪ Oral kemotherapy ▪ I am not sure , I think it's a low dose of oral chemo ▪ It is chemo to fight the cancer ▪ My understanding is that it is a chemo drug to help with her ALL. ▪ Has quemo therapy ▪ I'm not sure. I know it's a chemo medicine ▪ I don't remember. It is just what he needs to take. ▪ part of treatment

Comment [s3]: This would fall under the "don't know" category?

Comment [w4R3]: Agree – re-coded as "1"

Item 9 (continued): What is your understanding of how 6MP works?

Code	Category	Sample responses
0	Understands how 6MP works	▪ part of protocol ▪ Because if part of her treatment. ▪ It's a treatment for his leukemia ▪ I'm not sure how it works just understand it is a important part of her treatment. ▪ Works well ▪ very good ▪ I think it functions well, when giving the pill adequately. ▪ I believe that until now it has given good results for my son. ▪ It provides my child with more energy and strength ▪ I think it works well because he's getting over this ▪ very well, thanks to God ▪ very good ▪ I believe well because he hasn't had any symptoms. ▪ I believe it functions well. The only thing is that seeing how much my son suffers, this medication is too strong for his bodu. Or maybe he is too sensitive to it. ▪ Very well. ▪ well ▪ it functions very well for my son ▪ I think that it functions well because he has not relapsed and when they check his blood it indicates everything is well. ▪ Very well because he has not demonstrated any side effects. ▪ It works very well ▪ As for my daughter I haven't noted any changes so I understand it is helping her very good.
1	Doesn't understand how 6MP works **AGREE**	▪ I Don't now ▪ No ▪ Not sure ▪ don't know ▪ I don't know exactly ▪ I forgot ▪ Can't remember but it was explained ▪ not sure ▪ His father was the one involved with his treatments, since he's no longer with us I took over, but I'm not sure, he was the one that knew. ▪ I'm not sure. ▪ we are not exactly sure! ▪ No.I have not beentold I just give it ▪ ? ▪ I don't know how it works. ▪ Don't know never told or if I have been told I have forgotten ▪ Not to sure ▪ Don't know ▪ My husband and I have read on it but its been a while now that its just "what we do" that we cant really remember! ▪ It was explained to me but at the moment I do not remember. ▪ not sure ▪ Don't have a clue. ▪ I don't understand ▪ I don't know (but would like to) ▪ don't remember, it's been so long ▪ Works best if taken before bed/evening ▪ No milk products with the medication. ▪ It is well because it covers whatever infection

15. If child did not take 6MP at least once during the past 28 days, what caused child to not take 6MP on those days [whynotSICKCODED.1]:

[Dichotomized: 0=Missed due to medical reasons 1=Missed due to non-medical reasons]

Code	Category	Sample responses
0	Missed due to illness/ low blood counts/ abnormal laboratory tests [medical reasons] **AGREE**	▪ Illness (pneumonia) and a virus ▪ He was sick and counts were low ▪ low ANC counts ▪ Low ANC counts ▪ High Bilirabin counts ▪ too low ANC; Dr's taking him off of it. ▪ counts, he was sick ▪ LOW COUNTS ▪ She was admitted to the hospital with fever and had a bacteria. ▪ 6MP on hold due to Low ANC ▪ Low Blood Counts ▪ counts too low. ▪ case of shingles ▪ 1 day - missed dose.7 days - withdrawn due to infection. ▪ low ANC count ▪ His counts were too low so all chemo was pulled for a week then was prescribed to take it for 6 days /off the 7th ▪ He contracted a viral infection that reduced his blood counts - 6MP was cut out completely until his counts returned ▪ Was instructed by Dr. B to stop taking 6-mp because her counts dropped ▪ low blood counts, doctors orders ▪ Fever (and he also had bronchitis) ▪ Due to being admitted to the hospital ▪ because of the virus he had ▪ Counts were low. ▪ his blood counts were too low ▪ Was in the hospital and the nurse said no. ▪ because her counts were low ▪ because he was an inpatient ▪ having diarehea ▪ Her counts were low and they suspended it until her counts rose to a good number ▪ paused for counts ▪ Same as #12 Low counts ▪ Blood Count Low ▪ low counts ▪ Because the counts were low. ▪ His counts were too low so we were told to not give it to him. ▪ Was coughing a lot. ▪ he is sick ▪ counts off and being hospitalized for infection ▪ Because her blood counts were low ▪ He didn't take it because he had an infection - chicken pox ▪ fever & low counts ▪ low counts or illness- chemo held per doctor's orders ▪ She was sick, I took her to the hospital. ▪ Viral infection caused ANC to drop to 300

Comment [s5]: Belongs to missed because of non-sickness related issues"

Comment [w6R5]: Changed to code 1

Item 15 (continued): If child did not take 6MP at least once during the past 28 days, what caused child to not take 6MP on those days?

Code	Category	Sample responses
1	Missed other than illness/ low blood counts/ abnormal laboratory tests [for non-medical reasons]	▪ First two days pick medication late two other different days for got ▪ Counts low and I forgot to give it to him a couple of times, then there a week we had to do 50% ▪ We fell asleep early ▪ I went to sleep and forgot to wake up to take it. ▪ I forgot to remind her to take it. ▪ I forgot ▪ Forgot to give it before bed. ▪ Parents take twins- we sometimes think the other has given it and it is missed ▪ Same reason as #12 [WL: PER ITEM #12, DUE TO PARENTAL MISCOMMUNICATION] ▪ I was sleeping and I didn't wake up. ▪ He fell asleep early. ▪ As I said I just forgot to take it at night. ▪ Forgetfulness ▪ One night we forgot because we had to go to the hospital. ▪ We both forgot to remind her to take it and it had been 24 hrs. so we skipped it ▪ she got home late and forgot ▪ spent nite w/ friend - (unplanned) meds at home ▪ He fell asleep. He is a hard sleeper and sleeps thru my vaccuming, carring to vehicles, etc. I can't get him awake enough to swallow pills. ▪ fell asleep ▪ Forgot, took many others ▪ My son went to sleep early ▪ Forgot she take milk do late math ▪ Was away from home overnight & father forgot. ▪ forgetfullness ▪ Fell asleep early. ▪ We forgot once. The other two times she did get the correct dose for the week, but we had given a whole instead of half as was prescribed at this time and so intentionally omitted the next night to correct the dosing. ▪ not @ home ▪ Went on a trip and forgot it. ▪ I forgot. We were out of the house. ▪ Well, because I forgot and I fell asleep. ▪ Forgot ▪ Missed dose ▪ We forgot to give it to him ▪ Slept over at a friends house ▪ Forgot to wake him up for his med late ta night due to a late night snack & 2 hr before & after restriction with the med for eating. ▪ Because I forgot ▪ Simply it was a late evening comeing home from Grandmas. We forgot in the comotion of bedtime. ▪ he fell asleep ▪ CRA NOTE-CLINIC RECORDS SHOW PT MISSED ONE DOSE WHILE WITH HIS FATHER, HE FORGOT TO GIVE ▪ forgot ▪ We had gone to the emergency room and forgot to take it. Not shure it might of been 2 days. ▪ Forgot that evening ▪ He forgot to

Comment [s7]: Code "0"

Comment [w8R7]: Includes both medical and non-medical, so code 1 applies

Item 15 (continued): If child did not take 6MP at least once during the past 28 days, what caused child to not take 6MP on those days?

Code	Category	Sample responses
1	Missed other than illness/ low blood counts/ abnormal laboratory tests [for non-medical reasons]	▪ Was away for the weekend. ▪ forgot ▪ ran out ▪ She fell asleep early and I forgot to give it to her ▪ Parent forgot ▪ On the 18 of April we went to my mother in law and end up sleeping over and didn't took his meds. Yesterday 28 of april my husband and I felt asleep. ▪ fell asleep before it could be taken ▪ laziness ▪ Became late, she fell asleep. And I just totally forgot to give it to her. ▪ She ate Late that evening and fell asleep without taking her pill ▪ fall asleep ▪ fell asleep prior to taking pills. Did make up next day. ▪ he was fast asleep and I didn't want to wake him, he was very tired. ▪ i forgot ▪ when he got spinal tap [WL: PER COMMENTS MISUNDERSTOOD INSTRUCTIONS AND HELD BOTH 6MP AND MTX ON DAY OF SPINAL TAP] ▪ she forgot ▪ Vacation just forgot it ▪ he takes his pill in the evening, my husband had given him his med the night before, he was do for a refill and had no medication that night, he has placed back on sched the next evening ▪ WL: PER COMMENTS MISSED DUE TO VACATION ▪ The medicine had not arrived. ▪ refused - unable to fight her or forgot ▪ He arrived late and didn't take it ▪ Out of town

24. What is the usual routine for taking 6MP? [k.howmonitorRECODEDdichot.1PT]:

[Dichotomized: 0=Has routine 1=No routine]

Code	Category	Sample responses
0	Has routine **AGREE**	▪ He takes his 6mp in the evening as perscribed by the doctor ▪ After dinner - before bed ▪ I take Purinethol everyday in the night at 9pm ;3pills ▪ 2 hours after Dinner Right before bed ▪ He takes his medicine at 11 o'clock pm every day. ▪ Evenings 2 or more hours after last time eating any food. ▪ Each night while she takes a bath I get her meds together and get a drink and when she finishes bathing she takes her meds. before brushing her teeth. ▪ Receives his 6-mp every evening between 8 & 9pm (before bed time) ▪ He takes it before going to bed generally. ▪ She takes her 6MP pill every night between 9-10pm right before she falls asleep. (A couple of times I wok her up at 10:00 to give her pill to her) ▪ He takes the medicine every day at 9:00pm ▪ Takes before bedtime. We use pills and crush with a pill crusher. We mix with peanut butter and he takes from spoon. ▪ take it every night ▪ At bedtime ▪ at night ▪ I take my prescribed dose every night before bed. ▪ As close to bedtime as possible on an empty stomach ▪ 1-2 hrs after dinner with a glass of water. ▪ After dinner time - 1 hour later ▪ Dinner around 6:00pm, 6MP around 8:00pm ▪ We have Dinner put on the timer wait 1 hr - then take 6mp then wait an hour then we an eat - Also no milk products after 4pm. ▪ Takes his 6MP before dinner on a empty stomach. ▪ He usually eat dinner we wait 1 1/2 hours and then he takes his 6MP and after he goes to sleep ▪ After he goes to bed at night- I wake him up & give his meds when I go to bed that way its on an empty stomach (one hour before meals and 2 hrs after meals) ▪ Mom wakes him before she goes to bed. ▪ I give him the medicine in the morning or in the evening - it depends on how busy the morning is ▪ nothing to eat or drink except water 2 hours before + 1 hour after ▪ he takes pill time and on the same time every days of week. ▪ She usually takes it after dinner or before bedtime ▪ she takes it about 9pm, I put a pill in a small amount of water and put unselved pill & water in to the syringe, my daughter drinks it from it. ▪ 2/3 hours after dinner and 1 hour before his night bottle (either or) ▪ 1 tablet every night, 1 1/2 tablet sunday ▪ Every day. ▪ every day ▪ Every day of the week but on Tue &Sat 1.5 a pill ▪ 2 every day except on sunday when I just take one ▪ Every day Monday-Friday 1.5 ▪ Saturday and Sunday - 1 ▪ When his blood counts are well he takes it 3 times a week. ▪ On tuesday and Sunday 1.5 pills. And the other days 1 pill. ▪ 1 tablet a day

Comment [s9]: This speaks to a lack of routine

Comment [w10R9]: Changed to 1

Item 24 (continued): What is the usual routine for taking 6MP?

Code	Category	Sample responses
0	Has routine	▪ He take 1 pill monday thru thursday and 1 1/2 friday thru sunday ▪ look at question 6 ▪ to take 3 every day ▪ 6 Day 75 1 day 50 ▪ Take it daily 1 tablet ▪ -Last thing before bed - at least 1 hour after eating - just with water. ▪ Every evening 2-3 hours after dinner. The pill is crushed and mixed with a small amount of strawberry syrup. ▪ He checks the clock when he is done eating for the day - usually around 6:00 or 7:00p.m. He makes sure he waits at least 2 hours, then takes the pills with water. ▪ I wake him from his sleep (usually between 11pm & midnight) to give him his daily dose. ▪ every night before going to sleep ▪ 90 minutes after dinner with small amount of applesauce. ▪ Everyday between 5 & 6 at night ▪ He usually takes it between 8:30-9:30, but there has been times when I get too distracted with my homework or cleaning that I completely forgot and had to give it to him at 10:00 or later, but he takes it every night. ▪ Eats at 5:00pm and wait two hours before giving it at 7:00pm (normally) ▪ After dinner, crush the pill, mix the 6-MP w/ water and she takes it with a syringe ▪ Crushed mixed with water and given by dropper between 630 &730pm daily ▪ I give before bed time with a cup of juice. ▪ at night 2-2.5 hrs after snack in between 9-10pm ▪ meds are dispensed weekly into a pill box and he takes his meds daily from this at bedtime ▪ At night time, when I did take my medicine, I give him his medicine ▪ my daughter takes her pill every night before going to sleep and she takes it without food or milk ▪ before he goes to sleep - every day. before bed. ▪ At night before putting her to bed, I put them in a tiny plate, I put a bit of fruit, tiny pieces of bread, cake, gellatin, or something and I cut it in two, she takes it and her little hands and she puts it in each piece of food and eats it. ▪ Eat well, to take it before sleep ▪ In the afternoon before bed. ▪ Before bed - no dairy an hour prior given with rice milk - ice cream & choc syrup. ▪ Usually before bed time
1	No routine **AGREE**	▪ She swallows her medicine. ▪ Sometime his gives me a hard time, but he still takes it. ▪ yes ▪ Remembering ▪ so that he can get well quickly ▪ 1/2 of tablet ▪ ass order only ▪ Have an empty stomach. ▪ drinks plenty of water ▪ He makes sur he taks his mercaptopurine ▪ He is very small to understand his problem or sickness ▪ oral ▪ She knows that she has to do it for her health ▪ Don't know

Comment [s11]: ?

Comment [w12R11]: ½ tab 4 x/week, 1 tab 3 x/week

35. What do you think would happen if child stopped taking 6MP? [K.stopRECODED.1PT]:

[Dichotomized: 0=Aware of disease severity/consequences of not taking 6MP as prescribed; 1=Unaware of disease severity/consequences of not taking 6MP as prescribed]

Code	Category	Sample responses
0	Relapse/something bad [Aware of disease severity/consequences of not taking 6MP as prescribed] **AGREE**	▪ The leukemia may come back and out of hiding ▪ It may take her out of remission? ▪ The cancer would increase. ▪ I don't know they tell me that the cancer will come back. ▪ It could happen that ALL returns again. ▪ might have a greater risk of getting cancer cells again ▪ leukemia may return ▪ risk of relapse ▪ Relapse ▪ risk of relapse later??? not sure ▪ cancer would come back ▪ have a Relasse ▪ will have a relapse ▪ Relapse ▪ The Leukemia could return ▪ RELAPSE ? OTHER ILLNESSES? ▪ Relapse ▪ His canser can return ▪ He would get sick or I don't know what would happen. ▪ May increase chances of a relapse ▪ I don't know. I assume the purpose of 6MP is added prevention of relapse. ▪ He can get recurrence of leukemia. ▪ Bad cells Grow up ▪ my blood counts would go higher, possibly relapse ▪ Survival rate wouldn't be as high ▪ Increase the risk of her cancer returning. ▪ The chances would increase of the leukemia coming back ▪ leukemia would ocme back ▪ Maybe leukemia would come back ▪ I don't know but I think his recuperation would be slower. ▪ She might not be cured fom leukemia ▪ I would be afraid that she wouldn't be cured. ▪ sick!!! ▪ He would/could relapse and we would start treatment all over again. ▪ he might not stay well ▪ He might be at risk for a relapse, depending on how long he stopped taking this medication. But I am not sure. ▪ - Relapse. ▪ will get sick. ▪ I assume my child would relapse ▪ affect his ability to fight his leukemia ▪ He could get too sick again ▪ greater risk for return of leukemia ▪ Possible return of leukemia cells ▪ Leukemia would come back. Relapse. ▪ that the leukemia would come back. ▪ it would stop helping him fighting his A.L.L. He would not be fighting his A.L.L. as well.

Item 35 (continued): What do you think would happen if child stopped taking 6MP?

Code	Category	Sample responses
0	Relapse/something bad [Aware of disease severity/consequences of not taking 6MP as prescribed]	▪ he would get gravely ill ▪ probably my counts would shoot up and possibly if there are still cancer cells they would reproduce again. ▪ The lymphoblasts could begin regnerating. ▪ Her chemotherapy will be messed up and she could relapse. ▪ Well, I believe that I would get more sick than I already am. ▪ I woudl be concerned that he would relapse. I know he is getting other treatments. But I asume he gets this for a reason and in conjuction w/ the other medication it does the job it is supposed to do. W/out it his treatments may not be as effective. ▪ we would be afraid that leukemia will come back ▪ The leukimia would came back ▪ Leukemia - Relapse ▪ She can get sick again. ▪ possible relapse ▪ I think that is it part of his medication and if he did not take it, perhaps his Leukemia would return. ▪ My understanding is that 6-MP is an important medication in "maintaining" remission ▪ She would not be getting the treatment she needs to fight the deasese ▪ I think it is a bit difficult to respond to this question. I know that it combats the bad cells, but it also eliminates the good ones, but it is good and it is indispensable when you have cancer. ▪ it would interfer with his treatment ▪ I've never thought about it. It is just part of his treatment and he will continue to take it until the Dr. instructs us not to. ▪ I don't think anybody knows for sure, but I understand that it is an important part of treatment. ▪ not sure - I like to think he is already cured & he would be fine, but u we get the go ahead to stop he will continue to take it. ▪ I'm afraid that the treatment is incomplete that one medicine works v another but at the same time I think that he would feel better. ▪ I imagine that the treatment wouldn't work and he wouldn't get bette ▪ Treatment for ALL would be ineffective. ▪ I would be good for He's treatment. ▪ He would be behind in his treatment and not have as good of results ▪ Interrupt his treatment. ▪ maybe would decline not sure ▪ It would stop working ▪ I don't know what would happen, but I think something bad would happen. I know I have to eventually stp taking it because of treatment ▪ His Doctor would still beat me for that. nothing changed. ▪ dangerous ▪ he will not recover fast ▪ I don't want to think about that ▪ I believe her health would worsen since mercaptopurine is part of her chemotherapy. ▪ I wouldn't get better ▪ I don't want to think about this yet! ▪ her health condition may be affected and at risk. ▪ It would take longer to aliviate. ▪ I'm to scared to think of that. To us there has neverbeen the thought of making that choice. ▪ I don't know, I think that it is part of his chemotherapy and for his well-being and because I trust that he will be cured, he has to do it.

Comment [s13]: Belongs to "don't know"

Comment [w14R13]: Yes – re-coded as "1"

Comment [s15]: Belongs to "don't know"

Comment [w16R15]: Yes – re-coded as "1"

Comment [s17]: Belongs to "don't know"

Comment [w18R17]: Agree – recoded as "1"

Item 35 (continued): What do you think would happen if child stopped taking 6MP?

Code	Category	Sample responses
0	Relapse/something bad [Aware of disease severity/consequences of not taking 6MP as prescribed]	▪ would not like to know ▪ he could get worse ▪ I don't know, but it can't be good. ▪ We don't know – [name] or Doc might yell ▪ I don't know, I wouldn't want to find out ▪ It would affect him greatly. I could assume hopitalization or have a f back ▪ We would not be sticking with what we believe is a life saving protocol so we would be risking his health. We would not consider ignoring Dr.'s orders. ▪ It could delay the recuperation from the leukemia. ▪ We don't care to find out - we have no idea - I assume his blood counts would increase ▪ His condition would worsen (crossed out) get worse ▪ I don't want to find out - We will stop when the Drs. tell us it is time. ▪ Don't want to find out! ▪ possibly side effects, not sure ▪ I don't want to find out- we will stop when the doctor tells us to. ▪ it might affect his recovery ▪ Don't know and wouldn't want to find out. He will continue taking his 6MP as directed by his doctors till treatment is over. ▪ not good!
1	Nothing/Don't know [Unaware of disease severity/consequences of not taking 6MP as prescribed] AGREE	▪ nothing ▪ nothing happens ▪ I believe nothing if the doctor indicates it. ▪ nausea would reduce a little bit. ▪ he would be very happy not to take any more meds! ▪ No answer ▪ For a day I saw no difference. ▪ Don't know ▪ The truth is we don't know. ▪ We still do not know the reaction ▪ I don't know exactly what would happen because I don't know what the function of those pills is ▪ dont know ▪ not sure ▪ I don't know ▪ ? ▪ I'm not sure but I feel the doctors know what is good for my son and what is not. ▪ I don't know! ▪ not sure ▪ his counts could go up ▪ counts should go back to normal ▪ his counts will go up. ▪ blood counts would mess up ▪ It would affect his defenses. ▪ Maybe he will be easier for him to catch something if someone else is sick ▪ Nothing

Comment [s19]: "don't know"

Comment [w20R19]: Agree – recoded as "1"

Appendix E. COG Institutions Contributing Patients

Institution	Patients Contributed
All Children's Hospital	2
Allan Blair Cancer Centre	5
British Columbia's Children's Hospital	2
Brooklyn Hospital Center	3
Children's Healthcare of Atlanta, Emory University	3
Childrens Hospital & Clinics Minneapolis & St Paul	11
Children's Hospital and Regional Medical Center	4
Children's Hospital Central California	7
Childrens Hospital Los Angeles	17
Childrens Hospital Medical Center-Akron, Ohio	1
Children's Hospital of Austin	6
Children's Hospital of Michigan	1
Childrens Hospital of Philadelphia	6
Children's Hospital of Pittsburgh	17
Childrens Hospital of Western Ontario	11
Children's Hospital San Diego	3
Children's National Medical Center - D.C.	17
Children's of New Orleans/LSUMC CCOP	5
City of Hope National Medical Center	35
Columbus Children's Hospital	4
Connecticut Children's Medical Center	3
DeVos Children's Hospital	16
Driscoll Children's Hospital	7
Duke University Medical Center	2
Eastern Maine Medical Center	1
Geisinger Medical Center	6
Georgetown University Medical Center	1
Hackensack University Medical Center	10
Hurley Medical Center	1
Inova Fairfax Hospital	5
IWK Health Centre	1
Joe DiMaggio Children's Hospital at Memorial	6
Kingston General Hosp/Kingston Regional Cancer	1
Lutheran General Childrens Medical Center	2
Marshfield Clinic	1
McGill Univ Health Ctr - Montreal Children's Hosp	2
Midwest Children's Cancer Center	1
Miller Children's Hospital/Harbor-UCLA	15
Nemours Children's Clinic-Jacksonville	1
New York Medical College	5
New York University Medical Center	2
Presbyterian Hospital	2
Primary Children’s Medical Center	1

Institution	Patients Contributed
Princess Margaret Hospital for Children	17
Raymond Blank Children's Hospital	3
Rush-Presbyterian St. Luke's Medical Center	2
Sacred Heart Children's Hospital	5
Saint Barnabas Medical Center	1
South Carolina Cancer Center	2
Southern California Permanente Medical Group	4
Southwest Texas Methodist Hospital	5
St. Vincent Children's Hospital - Indiana	2
St. Vincent Hospital - Wisconsin	10
Stanford University Medical Center	5
State University of New York at Stony Brook	2
Sunrise Childrens Hospital, Sunrise Hosp & Med Ctr	21
SUNY Health Science Center at Brooklyn	1
SUNY Upstate Medical University	8
T.C. Thompson Children's Hospital	9
Tampa Children's Hospital	4
Texas Tech UHSC - Amarillo	3
The Children's Hospital - Denver, CO	29
The Children's Hospital of SW Florida Lee Memorial Health System	4
The Childrens Mercy Hospital	1
Toledo Children's Hospital	2
UCLA School of Medicine	15
UCSF School of Medicine	15
University of Alabama	2
University of California, Davis	4
University of Florida	3
University of Illinois	1
University of Minnesota Cancer Center	8
University of Mississippi Medical Center Children's Hospital	1
University of Nebraska Medical Center	1
University of New Mexico School of Medicine	7
University of Oklahoma Health Sciences Center	7
University of Texas Health Science Center at San Antonio	12
University of Vermont College of Medicine	1
UT Southwestern Medical Center	11
Vanderbilt Children's Hospital	6
Virginia Commonwealth Univ Health System-MCV	3
Wake Forest University School of Medicine	1
Warren Clinic, Inc.	2
Washington University Medical Center	1
West Virginia University HSC - Charleston	2
Yale University School of Medicine	1
TOTAL INSTITUTIONS = 86	496

Appendix F. Multivariate Models

REGRESSION WITH SIGNIFICANT SOCIODEMOGRAPHIC FACTORS FROM UNIVARIATE ANALYSIS (AGE, ETHNICITY, AND SINGLE PARENT)

START WITH AGE AND ETHNICITY:

Missing Cases = 0

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.081**	**.022**	**13.744**	**1**	**.000**	**1.084**	**1.039**	**1.132**
	FinalEthnicity(1)	**.484**	**.224**	**4.663**	**1**	**.031**	**1.622**	**1.046**	**2.517**
	Constant	-2.239	.265	71.245	1	.000	.107		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity.

1=Hispanic

ADD HOUSEHOLD STRUCTURE Missing cases = 9

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.081**	**.022**	**13.294**	**1**	**.000**	**1.084**	**1.038**	**1.132**
	FinalEthnicity(1)	**.477**	**.227**	**4.412**	**1**	**.036**	**1.611**	**1.032**	**2.513**
	SingleParentHousehold(1)	.520	.301	2.985	1	.084	1.682	.932	3.033
	Constant	-2.295	.269	72.759	1	.000	.101		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold.

1=Single parent household

ADD SIGNIFICANT BEHAVIORAL VARIABLES

Has not experienced change in health status in past month [K.healthcorr.1PT] Missing cases = 13
(PERCEIVED VULNERABILITY [SEVERITY])

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.078**	**.022**	**12.113**	**1**	**.001**	**1.081**	**1.034**	**1.129**
	FinalEthnicity(1)	**.423**	**.229**	**3.411**	**1**	**.065**	**1.526**	**.974**	**2.389**
	SingleParentHousehold(1)	.469	.306	2.352	1	.125	1.598	.878	2.911
	K.healthcorr.1PT(1)	.562	.309	3.303	1	.069	1.754	.957	3.216
	Constant	-2.686	.365	54.067	1	.000	.068		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.healthcorr.1PT.

1=No change in health in past month

Unaware of consequences of not taking 6MP as prescribed [k.stopRECODED.1PT] Missing cases = 9
(PERCEIVED VULNERABILITY [SUSCEPTIBILITY])

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.078**	**.022**	**12.397**	**1**	**.000**	**1.081**	**1.035**	**1.129**
	FinalEthnicity(1)	**.456**	**.228**	**3.994**	**1**	**.046**	**1.577**	**1.009**	**2.466**
	SingleParentHousehold(1)	.497	.302	2.704	1	.100	1.643	.909	2.971
	K.stopRECODED.1PT(1)	**.506**	**.259**	**3.828**	**1**	**.050**	**1.659**	**.999**	**2.754**
	Constant	-2.375	.274	74.887	1	.000	.093		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.stopRECODED.1PT.

1=Unaware of consequences of not taking 6MP as prescribed

Unaware of purpose/function of 6MP [k.how6MPdichot.1cum] Missing cases = 9
(PERCEIVED BENEFITS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.078**	**.022**	**12.140**	**1**	**.000**	**1.081**	**1.035**	**1.129**
	FinalEthnicity(1)	**.493**	**.229**	**4.659**	**1**	**.031**	**1.638**	**1.046**	**2.563**
	SingleParentHousehold(1)	.476	.303	2.461	1	.117	1.609	.888	2.915
	K.how6MPdichot.1cum(1)	**.590**	**.244**	**5.851**	**1**	**.016**	**1.804**	**1.118**	**2.909**
	Constant	-2.436	.279	76.395	1	.000	.087		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.how6MPdichot.1cum.

1=Unaware of purpose/function of 6MP

6MP prescription has ever changed [k.change6MPcorr.1PT]
(PERCEIVED BARRIERS) Missing cases = 20

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.085**	**.023**	**13.998**	**1**	**.000**	**1.088**	**1.041**	**1.138**
	FinalEthnicity(1)	.424	.236	3.224	1	.073	1.528	.962	2.427
	SingleParentHousehold(1)	.447	.308	2.110	1	.146	1.563	.856	2.856
	K.change6MPcorr.1PT(1)	-.405	.284	2.037	1	.154	.667	.382	1.163
	Constant	-1.970	.365	29.118	1	.000	.140		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.change6MPcorr.1PT.

1=6MP prescription has ever changed

Cannot swallow 6MP tablet whole [k.swallowCORR.1PT]
(PERCEIVED BARRIERS) Missing cases = 10

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.082**	**.025**	**10.782**	**1**	**.001**	**1.085**	**1.033**	**1.139**
	FinalEthnicity(1)	**.460**	**.227**	**4.099**	**1**	**.043**	**1.585**	**1.015**	**2.475**
	SingleParentHousehold(1)	.538	.302	3.178	1	.075	1.712	.948	3.093
	K.swallowCORR.1PT(1)	.071	.268	.070	1	.791	1.073	.635	1.813
	Constant	-2.328	.331	49.575	1	.000	.097		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.swallowCORR.1PT.

1=Does not swallow tablet whole

Interaction between Age at participation and cannot swallow 6MP tablet whole [k.swallowCORR.1PT] (PERCEIVED BARRIERS) Missing cases = 10

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.079**	**.023**	**12.103**	**1**	**.001**	**1.082**	**1.035**	**1.132**
	FinalEthnicity(1)	**.462**	**.227**	**4.120**	**1**	**.042**	**1.587**	**1.016**	**2.478**
	SingleParentHousehold(1)	.534	.301	3.141	1	.076	1.706	.945	3.078
	AgeAtParticipationYears by K.swallowCORR.1PT(1)	.004	.036	.012	1	.914	1.004	.936	1.076
	Constant	-2.290	.294	60.832	1	.000	.101		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, AgeAtParticipationYears * K.swallowCORR.1PT .

1=Does not swallow tablet whole

Longer time on Maintenance [TimeOnMaintMonths]: (Missing cases 24)
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.084**	**.022**	**14.255**	**1**	**.000**	**1.088**	**1.041**	**1.137**
	FinalEthnicity(1)	**.528**	**.231**	**5.228**	**1**	**.022**	**1.696**	**1.078**	**2.667**
	SingleParentHousehold(1)	.583	.306	3.636	1	.057	1.792	.984	3.262
	TimeOnMaintMonths	.001	.020	.003	1	.954	1.001	.962	1.042
	Constant	-2.365	.348	46.321	1	.000	.094		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, TimeOnMaintMonths.

6MP taken without food/milk[K.foodmilkCOMBO.1PT]: (Missing cases = 9)
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.081**	**.022**	**13.450**	**1**	**.000**	**1.085**	**1.039**	**1.133**
	FinalEthnicity(1)	**.475**	**.227**	**4.375**	**1**	**.036**	**1.608**	**1.030**	**2.508**
	SingleParentHousehold(1)	.517	.301	2.949	1	.086	1.677	.930	3.027
	K.foodmilkCOMBO.1PT(1)	-.129	.268	.230	1	.631	.879	.520	1.487
	Constant	-2.201	.331	44.085	1	.000	.111		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.foodmilkCOMBO.1PT.

1=Takes 6MP without food/milk

Adult not involved in monitoring of 6MP intake [k.monitorCOMBOdichot.1PT] Missing cases = 9
(SELF EFFICACY/TAKING RESPONSIBILITY)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.075**	**.025**	**8.947**	**1**	**.003**	**1.078**	**1.026**	**1.132**
	FinalEthnicity(1)	**.474**	**.227**	**4.357**	**1**	**.037**	**1.606**	**1.029**	**2.507**
	SingleParentHousehold(1)	.526	.301	3.058	1	.080	1.693	.938	3.054
	K.monitorCOMBOdichot.1PT(1)	.219	.447	.240	1	.624	1.245	.518	2.991
	Constant	-2.261	.277	66.412	1	.000	.104		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.monitorCOMBOdichot.1PT.

1=No monitor/child only

No systematic approach/routine for 6MP administration [k.howmonitorRECODEDdichot.1PT] Missing cases = 9
(CUES TO ACTION)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.079**	**.023**	**12.072**	**1**	**.001**	**1.082**	**1.035**	**1.132**
	FinalEthnicity(1)	**.470**	**.228**	**4.238**	**1**	**.040**	**1.599**	**1.023**	**2.500**
	SingleParentHousehold(1)	.516	.301	2.931	1	.087	1.675	.928	3.022
	K.howmonitorRECODEDdichot.1PT(1)	.118	.364	.104	1	.747	1.125	.551	2.295
	Constant	-2.288	.270	71.924	1	.000	.101		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.howmonitorRECODEDdichot.1PT.

1=No systematic approach for 6MP administration

Does not take 6MP at same time daily [k.sametime.1PT] Missing cases = 16
(CUES TO ACTION)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.077**	**.023**	**11.428**	**1**	**.001**	**1.080**	**1.033**	**1.130**
	FinalEthnicity(1)	**.493**	**.232**	**4.506**	**1**	**.034**	**1.637**	**1.039**	**2.581**
	SingleParentHousehold(1)	.507	.311	2.653	1	.103	1.661	.902	3.057
	K.sametime.1PT(1)	.402	.256	2.464	1	.116	1.495	.905	2.470
	Constant	-2.384	.276	74.812	1	.000	.092		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.sametime.1PT.

1=Does not take 6MP at same time daily

Takes 6MP late at night (2300 – 0445) [k.timeofday.1PT] Missing cases = 13
(CUES TO ACTION)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.075**	**.024**	**10.047**	**1**	**.002**	**1.077**	**1.029**	**1.128**
	FinalEthnicity(1)	**.516**	**.229**	**5.092**	**1**	**.024**	**1.676**	**1.070**	**2.624**
	SingleParentHousehold(1)	.548	.304	3.260	1	.071	1.730	.954	3.136
	K.timeofDaydichot.1PT(1)	.425	.437	.945	1	.331	1.530	.649	3.604
	Constant	-2.300	.272	71.233	1	.000	.100		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.timeofDaydichot.1PT.

1=Takes 6MP late at night (2300-0445)

SIGNIFICANT SOCIODEMOGRAPHIC FACTORS PLUS K.Health and K.How6MP (missing cases = 13)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.074**	**.022**	**10.997**	**1**	**.001**	**1.077**	**1.031**	**1.125**
	FinalEthnicity(1)	.442	.230	3.683	1	.055	1.556	.991	2.444
	SingleParentHousehold(1)	.422	.308	1.880	1	.170	1.526	.834	2.791
	K.healthcorr.1PT(1)	.544	.311	3.063	1	.080	1.723	.937	3.170
	K.how6MPdichot.1cum(1)	**.582**	**.245**	**5.655**	**1**	**.017**	**1.790**	**1.108**	**2.893**
	Constant	-2.813	.373	56.930	1	.000	.060		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, SingleParentHousehold, K.healthcorr.1PT, K.how6MPdichot.1cum.

LOGISTIC REGRESSION WITH PATERNAL EDUCATION

START WITH AGE AND ETHNICITY:

Missing Cases = 0

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.081**	**.022**	**13.744**	**1**	**.000**	**1.084**	**1.039**	**1.132**
	FinalEthnicity(1)	**.484**	**.224**	**4.663**	**1**	**.031**	**1.622**	**1.046**	**2.517**
	Constant	-2.239	.265	71.245	1	.000	.107		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity.

1=Hispanic

Determine what income, education, and household structure add to model:

ADD PATERNAL EDUCATION:

Paternal Education (<= high school vs more than high school). Missing cases = 21:

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.079**	**.023**	**12.053**	**1**	**.001**	**1.082**	**1.035**	**1.132**
	FinalEthnicity(1)	**.525**	**.258**	**4.119**	**1**	**.042**	**1.690**	**1.018**	**2.804**
	DadEducDichotHSorLess(1)	-.073	.257	.080	1	.778	.930	.562	1.540
	Constant	-2.219	.280	62.719	1	.000	.109		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess.

1= <=High school

ADD HOUSEHOLD STRUCTURE (using Paternal Education)

Missing cases = 21

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.077**	**.023**	**11.468**	**1**	**.001**	**1.080**	**1.033**	**1.130**
	FinalEthnicity(1)	**.507**	**.258**	**3.843**	**1**	**.050**	**1.660**	**1.000**	**2.755**
	DadEducDichotHSorLess(1)	-.084	.257	.105	1	.745	.920	.556	1.523
	SingleParentHousehold(1)	.401	.323	1.538	1	.215	1.493	.792	2.813
	Constant	-2.240	.281	63.363	1	.000	.106		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold.

1=Single parent household

ADD INCOME

Missing cases = 43

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.068**	**.025**	**7.580**	**1**	**.006**	**1.070**	**1.020**	**1.123**
	FinalEthnicity(1)	**.633**	**.278**	**5.186**	**1**	**.023**	**1.883**	**1.092**	**3.245**
	DadEducDichotHSorLess(1)	.036	.270	.018	1	.894	1.037	.611	1.759
	SingleParentHousehold(1)	.521	.349	2.224	1	.136	1.683	.849	3.337
	IncomeLT20K(1)	-.509	.319	2.547	1	.110	.601	.322	1.123
	Constant	-2.173	.290	56.121	1	.000	.114		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K.

1=Income <=$20K

ADD NCI RISK

Missing cases = 50

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	AgeAtParticipationYears	.056	.033	2.961	1	.085	1.058	.992	1.127
	FinalEthnicity(1)	**.623**	**.281**	**4.916**	**1**	**.027**	**1.864**	**1.075**	**3.233**
	DadEducDichotHSorLess(1)	.099	.274	.129	1	.719	1.104	.645	1.888
	SingleParentHousehold(1)	.540	.358	2.267	1	.132	1.716	.850	3.464
	IncomeLT20K(1)	**-.658**	**.333**	**3.910**	**1**	**.048**	**.518**	**.270**	**.994**
	NCIRISK(1)	.190	.315	.362	1	.548	1.209	.651	2.243
	Constant	-2.192	.297	54.475	1	.000	.112		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, NCIRISK.

1=NCI high risk

ADD SIGNFICANT BEHAVIORAL VARIABLES + Remove NCI risk

Has not experienced change in health status in past month [K.healthcorr.1PT] Missing cases = 50

(PERCEIVED VULNERABILITY [SEVERITY])

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.065**	**.025**	**6.858**	**1**	**.009**	**1.067**	**1.016**	**1.120**
	FinalEthnicity(1)	**.564**	**.280**	**4.054**	**1**	**.044**	**1.758**	**1.015**	**3.044**
	DadEducDichotHSorLess(1)	.054	.272	.040	1	.842	1.056	.619	1.800
	SingleParentHousehold(1)	.437	.357	1.499	1	.221	1.548	.769	3.114
	IncomeLT20K(1)	-.513	.321	2.554	1	.110	.599	.319	1.123
	K.healthcorr.1PT(1)	**.742**	**.338**	**4.821**	**1**	**.028**	**2.101**	**1.083**	**4.075**
	Constant	-2.718	.403	45.521	1	.000	.066		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.healthcorr.1PT.

1=No change in health in past month

Unaware of consequences of not taking 6MP as prescribed [k.stopRECODED.1PT] Missing cases = 43
(PERCEIVED VULNERABILITY [SUSCEPTIBILITY])

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.066**	**.025**	**7.291**	**1**	**.007**	**1.069**	**1.018**	**1.121**
	FinalEthnicity(1)	**.636**	**.279**	**5.190**	**1**	**.023**	**1.888**	**1.093**	**3.263**
	DadEducDichotHSorLess(1)	.022	.270	.007	1	.935	1.022	.602	1.737
	SingleParentHousehold(1)	.509	.350	2.116	1	.146	1.664	.838	3.304
	IncomeLT20K(1)	-.519	.319	2.638	1	.104	.595	.318	1.113
	K.stopRECODED.1PT	-.439	.281	2.439	1	.118	.645	.372	1.118
	Constant	-1.806	.370	23.865	1	.000	.164		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.stopRECODED.1PT.

1=Unaware of consequences of not taking 6MP as prescribed

Unaware of purpose/function of 6MP [k.how6MPdichot.1cum] Missing cases = 43
(PERCEIVED BENEFITS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.066**	**.025**	**7.251**	**1**	**.007**	**1.068**	**1.018**	**1.121**
	FinalEthnicity(1)	**.684**	**.282**	**5.872**	**1**	**.015**	**1.981**	**1.140**	**3.445**
	DadEducDichotHSorLess(1)	-.023	.273	.007	1	.932	.977	.572	1.669
	SingleParentHousehold(1)	.494	.350	1.987	1	.159	1.638	.825	3.255
	IncomeLT20K(1)	-.507	.320	2.505	1	.113	.602	.321	1.128
	K.how6MPdichot.1cum	-.494	.260	3.599	1	.058	.610	.366	1.016
	Constant	-1.794	.347	26.799	1	.000	.166		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.how6MPdichot.1cum.

1=Unaware of purpose/function of 6MP

Cannot swallow 6MP tablet whole [k.swallowCORR.1PT]
(PERCEIVED BARRIERS) Missing cases = 44

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.067**	**.027**	**6.100**	**1**	**.014**	**1.070**	**1.014**	**1.129**
	FinalEthnicity(1)	**.594**	**.279**	**4.524**	**1**	**.033**	**1.812**	**1.048**	**3.134**
	DadEducDichotHSorLess(1)	.068	.271	.064	1	.801	1.071	.629	1.822
	SingleParentHousehold(1)	.534	.350	2.331	1	.127	1.705	.859	3.383
	IncomeLT20K(1)	-.497	.319	2.417	1	.120	.609	.325	1.138
	K.swallowCORR.1PT(1)	.063	.274	.053	1	.818	1.065	.623	1.821
	Constant	-2.203	.351	39.343	1	.000	.110		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.swallowCORR.1PT.

1=Does not swallow tablet whole

Interaction between Age at participation and cannot swallow 6MP tablet whole [k.swallowCORR.1PT]
(PERCEIVED BARRIERS) Missing cases = 44

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.066**	**.025**	**6.824**	**1**	**.009**	**1.068**	**1.017**	**1.122**
	FinalEthnicity(1)	**.595**	**.279**	**4.538**	**1**	**.033**	**1.814**	**1.049**	**3.136**
	DadEducDichotHSorLess(1)	.069	.271	.064	1	.800	1.071	.629	1.823
	SingleParentHousehold(1)	.531	.349	2.316	1	.128	1.701	.858	3.372
	IncomeLT20K(1)	-.496	.319	2.416	1	.120	.609	.326	1.138
	AgeAtParticipationYears by K.swallowCORR.1PT(1)	.007	.036	.037	1	.848	1.007	.938	1.081
	Constant	-2.181	.313	48.565	1	.000	.113		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, AgeAtParticipationYears * K.swallowCORR.1PT .

1=Does not swallow tablet whole

6MP prescription has ever changed [K.change6MPcorr.1PT]: (Missing cases 53)
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.071**	**.025**	**7.892**	**1**	**.005**	**1.073**	**1.022**	**1.128**
	FinalEthnicity(1)	**.605**	**.284**	**4.545**	**1**	**.033**	**1.832**	**1.050**	**3.197**
	DadEducDichotHSorLess(1)	-.007	.276	.001	1	.979	.993	.577	1.707
	SingleParentHousehold(1)	.456	.360	1.599	1	.206	1.577	.778	3.196
	IncomeLT20K(1)	-.570	.330	2.978	1	.084	.566	.296	1.080
	K.change6MPcorr.1PT(1)	-.453	.303	2.234	1	.135	.636	.351	1.151
	Constant	-1.784	.403	19.626	1	.000	.168		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.change6MPcorr.1PT.

1=6MP prescription has ever changed

Longer time on Maintenance [TimeOnMaintMonths]: (Missing cases 58)
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.071**	**.025**	**8.249**	**1**	**.004**	**1.074**	**1.023**	**1.127**
	FinalEthnicity(1)	**.718**	**.282**	**6.456**	**1**	**.011**	**2.049**	**1.178**	**3.565**
	DadEducDichotHSorLess(1)	.022	.272	.007	1	.934	1.023	.601	1.742
	SingleParentHousehold(1)	.601	.353	2.896	1	.089	1.824	.913	3.645
	IncomeLT20K(1)	-.559	.325	2.960	1	.085	.572	.302	1.081
	TimeOnMaintMonths	.011	.021	.285	1	.593	1.011	.970	1.054
	Constant	-2.354	.372	40.033	1	.000	.095		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, TimeOnMaintMonths.

6MP taken without food/milk[K.foodmilkCOMBO.1PT]: (Missing cases = 43)
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.069**	**.025**	**7.842**	**1**	**.005**	**1.072**	**1.021**	**1.125**
	FinalEthnicity(1)	**.635**	**.279**	**5.197**	**1**	**.023**	**1.887**	**1.093**	**3.258**
	DadEducDichotHSorLess(1)	.048	.271	.031	1	.860	1.049	.617	1.783
	SingleParentHousehold(1)	.516	.350	2.172	1	.141	1.675	.844	3.328
	IncomeLT20K(1)	-.526	.321	2.693	1	.101	.591	.315	1.108
	K.foodmilkCOMBO.1PT(1)	-.221	.280	.624	1	.430	.802	.464	1.387
	Constant	-2.018	.347	33.769	1	.000	.133		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.foodmilkCOMBO.1PT.

1=Takes 6MP without food/milk

Adult not involved in monitoring of 6MP intake [k.monitorCOMBOdichot.1PT] Missing cases = 43
(SELF EFFICACY/TAKING RESPONSIBILITY)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.057**	**.028**	**4.254**	**1**	**.039**	**1.058**	**1.003**	**1.117**
	FinalEthnicity(1)	**.627**	**.278**	**5.078**	**1**	**.024**	**1.872**	**1.085**	**3.229**
	DadEducDichotHSorLess(1)	.035	.270	.017	1	.897	1.035	.610	1.758
	SingleParentHousehold(1)	.542	.350	2.403	1	.121	1.720	.866	3.415
	IncomeLT20K(1)	-.509	.319	2.542	1	.111	.601	.322	1.124
	K.monitorCOMBOdichot.1PT(1)	.450	.510	.776	1	.378	1.568	.577	4.261
	Constant	-2.110	.298	50.019	1	.000	.121		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.monitorCOMBOdichot.1PT.

1=No monitor/child only

No systematic approach/routine for 6MP administration [k.howmonitorRECODEDdichot.1PT] Missing cases = 43 (CUES TO ACTION)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.066**	**.025**	**6.998**	**1**	**.008**	**1.069**	**1.017**	**1.123**
	FinalEthnicity(1)	**.630**	**.278**	**5.123**	**1**	**.024**	**1.877**	**1.088**	**3.238**
	DadEducDichotHSorLess(1)	.035	.270	.017	1	.896	1.036	.611	1.758
	SingleParentHousehold(1)	.516	.350	2.172	1	.141	1.675	.844	3.325
	IncomeLT20K(1)	-.512	.319	2.573	1	.109	.599	.320	1.120
	K.howmonitorRECODEDdichot.1PT(1)	.093	.415	.051	1	.822	1.098	.487	2.476
	Constant	-2.168	.291	55.561	1	.000	.114		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.howmonitorRECODEDdichot.1PT.

1=No systematic approach for 6MP administration

Does not take 6MP at same time daily [k.sametime.1PT] Missing cases = 49
(CUES TO ACTION)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.061**	**.025**	**5.776**	**1**	**.016**	**1.063**	**1.011**	**1.117**
	FinalEthnicity(1)	**.569**	**.283**	**4.041**	**1**	**.044**	**1.766**	**1.014**	**3.074**
	DadEducDichotHSorLess(1)	.081	.272	.088	1	.767	1.084	.637	1.846
	SingleParentHousehold(1)	.576	.356	2.620	1	.106	1.778	.886	3.569
	IncomeLT20K(1)	-.474	.321	2.179	1	.140	.622	.332	1.168
	K.sametime.1PT(1)	.496	.271	3.362	1	.067	1.642	.966	2.791
	Constant	-2.244	.296	57.641	1	.000	.106		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.sametime.1PT.

1=Does not take 6MP at same time daily

Takes 6MP late at night (2300 – 0445) [k.timeofday.1PT] Missing cases = 47
(CUES TO ACTION)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.067**	**.026**	**6.742**	**1**	**.009**	**1.069**	**1.017**	**1.124**
	FinalEthnicity(1)	**.679**	**.281**	**5.846**	**1**	**.016**	**1.971**	**1.137**	**3.417**
	DadEducDichotHSorLess(1)	.046	.273	.029	1	.865	1.047	.613	1.789
	SingleParentHousehold(1)	.526	.351	2.245	1	.134	1.692	.850	3.366
	IncomeLT20K(1)	-.517	.320	2.610	1	.106	.596	.318	1.116
	K.timeofDaydichot.1PT(1)	.178	.504	.125	1	.724	1.195	.445	3.210
	Constant	-2.207	.293	56.734	1	.000	.110		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.timeofDaydichot.1PT.

1=Takes 6MP late at night (2300-0445)

FULL MODEL WITH PATERNAL EDUCATION AND K.Health and K.How6MP (missing cases = 47)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.063**	**.025**	**6.548**	**1**	**.011**	**1.065**	**1.015**	**1.119**
	FinalEthnicity(1)	**.615**	**.284**	**4.676**	**1**	**.031**	**1.850**	**1.059**	**3.231**
	DadEducDichotHSorLess(1)	.000	.275	.000	1	1.000	1.000	.583	1.715
	SingleParentHousehold(1)	.408	.358	1.296	1	.255	1.503	.745	3.032
	IncomeLT20K(1)	-.512	.322	2.524	1	.112	.599	.318	1.127
	K.healthcorr.1PT(1)	**.735**	**.340**	**4.681**	**1**	**.030**	**2.085**	**1.072**	**4.057**
	K.how6MPdichot.1cum(1)	.481	.262	3.377	1	.066	1.618	.969	2.702
	Constant	-2.827	.411	47.395	1	.000	.059		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.healthcorr.1PT, K.how6MPdichot.1cum.

LOGISTIC REGRESSION USING MATERNAL EDUCATION

START WITH AGE AND ETHNICITY:

Missing Cases = 0

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.081**	**.022**	**13.744**	**1**	**.000**	**1.084**	**1.039**	**1.132**
	FinalEthnicity(1)	**.484**	**.224**	**4.663**	**1**	**.031**	**1.622**	**1.046**	**2.517**
	Constant	-2.239	.265	71.245	1	.000	.107		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity.

1=Hispanic

Determine what income, education, and household structure add to model:

ADD EDUCATION:

Maternal Education (<= high school vs more than high school). Missing cases = 12:

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.083**	**.022**	**14.176**	**1**	**.000**	**1.087**	**1.041**	**1.135**
	FinalEthnicity(1)	**.706**	**.254**	**7.718**	**1**	**.005**	**2.025**	**1.231**	**3.332**
	MomEducDichotHSorLess(1)	-.483	.254	3.621	1	.057	.617	.375	1.015
	Constant	-2.152	.270	63.315	1	.000	.116		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess.

1= <=High school

Remove Maternal Education, add **Paternal Education** (<= high school vs more than high school. Missing cases = 21

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.079**	**.023**	**12.053**	**1**	**.001**	**1.082**	**1.035**	**1.132**
	FinalEthnicity(1)	**.525**	**.258**	**4.119**	**1**	**.042**	**1.690**	**1.018**	**2.804**
	DadEducDichotHSorLess(1)	-.073	.257	.080	1	.778	.930	.562	1.540
	Constant	-2.219	.280	62.719	1	.000	.109		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, DadEducDichotHSorLess.

1= <=High school

ADD HOUSEHOLD STRUCTURE (remove paternal education, add Maternal Education)

Missing cases = 14

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.081**	**.022**	**13.190**	**1**	**.000**	**1.084**	**1.038**	**1.132**
	FinalEthnicity(1)	**.679**	**.256**	**7.027**	**1**	**.008**	**1.972**	**1.194**	**3.258**
	MomEducDichotHSorLess(1)	**-.502**	**.256**	**3.849**	**1**	**.050**	**.605**	**.367**	**1.000**
	SingleParentHousehold(1)	.565	.304	3.460	1	.063	1.759	.970	3.189
	Constant	-2.187	.272	64.559	1	.000	.112		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold.

1=Single parent household

ADD INCOME

Missing cases = 35

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.072**	**.024**	**9.293**	**1**	**.002**	**1.075**	**1.026**	**1.126**
	FinalEthnicity(1)	**.806**	**.273**	**8.723**	**1**	**.003**	**2.239**	**1.311**	**3.822**
	MomEducDichotHSorLess(1)	-.403	.268	2.263	1	.133	.669	.396	1.130
	SingleParentHousehold(1)	**.669**	**.327**	**4.179**	**1**	**.041**	**1.953**	**1.028**	**3.710**
	IncomeLT20K(1)	-.476	.315	2.284	1	.131	.621	.335	1.152
	Constant	-2.120	.280	57.326	1	.000	.120		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K.

1=Income <=$20K

ADD NCI RISK

Missing cases = 42

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.067**	**.032**	**4.385**	**1**	**.036**	**1.069**	**1.004**	**1.138**
	FinalEthnicity(1)	**.810**	**.276**	**8.634**	**1**	**.003**	**2.248**	**1.310**	**3.858**
	MomEducDichotHSorLess(1)	-.378	.272	1.937	1	.164	.685	.402	1.167
	SingleParentHousehold(1)	**.704**	**.335**	**4.417**	**1**	**.036**	**2.022**	**1.049**	**3.901**
	IncomeLT20K(1)	-.617	.328	3.547	1	.060	.539	.284	1.025
	NCIRISK(1)	.107	.315	.116	1	.734	1.113	.601	2.062
	Constant	-2.141	.287	55.624	1	.000	.118		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, NCIRISK.

1=NCI high risk

ADD SIGNFICANT BEHAVIORAL VARIABLES

+ Remove NCI risk

Has not experienced change in health status in past month [K.healthcorr.1PT] Missing cases = 39

(PERCEIVED VULNERABILITY [SEVERITY])

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.069**	**.024**	**8.418**	**1**	**.004**	**1.072**	**1.023**	**1.123**
	FinalEthnicity(1)	**.748**	**.275**	**7.401**	**1**	**.007**	**2.112**	**1.232**	**3.619**
	MomEducDichotHSorLess(1)	-.398	.269	2.178	1	.140	.672	.396	1.139
	SingleParentHousehold(1)	.634	.333	3.627	1	.057	1.885	.982	3.620
	IncomeLT20K(1)	-.483	.317	2.319	1	.128	.617	.331	1.149
	K.healthcorr.1PT(1)	**.640**	**.321**	**3.975**	**1**	**.046**	**1.896**	**1.011**	**3.554**
	Constant	-2.574	.379	45.996	1	.000	.076		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.healthcorr.1PT.

1=No change in health in past month

Unaware of consequences of not taking 6MP as prescribed [k.stopRECODED.1PT] Missing cases = 35

(PERCEIVED VULNERABILITY [SUSCEPTIBILITY)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.071**	**.024**	**8.942**	**1**	**.003**	**1.074**	**1.025**	**1.125**
	FinalEthnicity(1)	**.811**	**.274**	**8.773**	**1**	**.003**	**2.250**	**1.316**	**3.849**
	MomEducDichotHSorLess(1)	-.418	.268	2.431	1	.119	.658	.389	1.114
	SingleParentHousehold(1)	**.644**	**.329**	**3.839**	**1**	**.050**	**1.904**	**1.000**	**3.627**
	IncomeLT20K(1)	-.484	.316	2.348	1	.125	.616	.332	1.145
	K.stopRECODED.1PT(1)	.476	.277	2.956	1	.086	1.610	.936	2.769
	Constant	-2.200	.287	58.908	1	.000	.111		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.stopRECODED.1PT.

1=Unaware of consequences of not taking 6MP as prescribed

Unaware of purpose/function of 6MP [k.how6MPdichot.1cum] Missing cases = 35
(PERCEIVED BENEFITS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.070**	**.024**	**8.583**	**1**	**.003**	**1.072**	**1.023**	**1.123**
	FinalEthnicity(1)	**.870**	**.278**	**9.807**	**1**	**.002**	**2.387**	**1.385**	**4.115**
	MomEducDichotHSorLess(1)	-.463	.272	2.908	1	.088	.629	.369	1.072
	SingleParentHousehold(1)	.630	.329	3.677	1	.055	1.878	.986	3.576
	IncomeLT20K(1)	-.486	.317	2.353	1	.125	.615	.330	1.145
	K.how6MPdichot.1cum(1)	**.581**	**.256**	**5.150**	**1**	**.023**	**1.787**	**1.082**	**2.950**
	Constant	-2.260	.290	60.729	1	.000	.104		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.how6MPdichot.1cum.

1=Unaware of purpose/function of 6MP

6MP prescription has ever changed [k.change6MPcorr.1PT Missing cases = 45
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.075**	**.024**	**9.573**	**1**	**.002**	**1.078**	**1.028**	**1.131**
	FinalEthnicity(1)	**.749**	**.278**	**7.252**	**1**	**.007**	**2.116**	**1.226**	**3.650**
	MomEducDichotHSorLess(1)	-.383	.272	1.982	1	.159	.682	.400	1.162
	SingleParentHousehold(1)	.616	.336	3.356	1	.067	1.852	.958	3.581
	IncomeLT20K(1)	-.565	.327	2.988	1	.084	.568	.299	1.079
	K.change6MPcorr.1PT(1)	-.510	.300	2.894	1	.089	.600	.334	1.081
	Constant	-1.689	.388	18.918	1	.000	.185		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.change6MPcorr.1PT.

1=6MPprescription has ever changed

Cannot swallow 6MP tablet whole [k.swallowCORR.1PT]
(PERCEIVED BARRIERS) Missing cases = 36
Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.073**	**.026**	**7.631**	**1**	**.006**	**1.076**	**1.021**	**1.133**
	FinalEthnicity(1)	**.775**	**.274**	**7.990**	**1**	**.005**	**2.172**	**1.268**	**3.718**
	MomEducDichotHSorLess(1)	-.380	.268	2.007	1	.157	.684	.404	1.157
	SingleParentHousehold(1)	**.682**	**.328**	**4.329**	**1**	**.037**	**1.977**	**1.040**	**3.757**
	IncomeLT20K(1)	-.464	.316	2.160	1	.142	.629	.339	1.167
	K.swallowCORR.1PT(1)	.073	.272	.072	1	.789	1.076	.631	1.834
	Constant	-2.158	.343	39.696	1	.000	.116		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.swallowCORR.1PT.

1=Does not swallow tablet whole

Interaction between Age at participation and cannot swallow 6MP tablet whole [k.swallowCORR.1PT]
(PERCEIVED BARRIERS) Missing cases = 36
Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.071**	**.024**	**8.574**	**1**	**.003**	**1.074**	**1.024**	**1.126**
	FinalEthnicity(1)	**.777**	**.274**	**8.036**	**1**	**.005**	**2.175**	**1.271**	**3.722**
	MomEducDichotHSorLess(1)	-.380	.268	2.008	1	.156	.684	.404	1.157
	SingleParentHousehold(1)	**.680**	**.327**	**4.314**	**1**	**.038**	**1.974**	**1.039**	**3.749**
	IncomeLT20K(1)	-.464	.316	2.166	1	.141	.629	.339	1.167
	AgeAtParticipationYears by K.swallowCORR.1PT(1)	.008	.036	.048	1	.826	1.008	.939	1.082
	Constant	-2.131	.304	49.290	1	.000	.119		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, AgeAtParticipationYears * K.swallowCORR.1PT .

1=Does not swallow tablet whole

Longer time on Maintenance [TimeOnMaintMonths]: (Missing cases 50)
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.076**	**.024**	**10.004**	**1**	**.002**	**1.079**	**1.029**	**1.131**
	FinalEthnicity(1)	**.878**	**.277**	**10.024**	**1**	**.002**	**2.407**	**1.397**	**4.146**
	MomEducDichotHSorLess(1)	-.410	.270	2.299	1	.129	.664	.391	1.127
	SingleParentHousehold(1)	**.745**	**.332**	**5.027**	**1**	**.025**	**2.106**	**1.098**	**4.037**
	IncomeLT20K(1)	-.524	.322	2.649	1	.104	.592	.315	1.113
	TimeOnMaintMonths	.009	.021	.172	1	.678	1.009	.968	1.051
	Constant	-2.271	.363	39.102	1	.000	.103		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, TimeOnMaintMonths.

6MP taken without food/milk[K.foodmilkCOMBO.1PT]: (Missing cases = 35)
(PERCEIVED BARRIERS)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.073**	**.024**	**9.455**	**1**	**.002**	**1.076**	**1.027**	**1.127**
	FinalEthnicity(1)	**.810**	**.273**	**8.808**	**1**	**.003**	**2.249**	**1.317**	**3.840**
	MomEducDichotHSorLess(1)	-.407	.268	2.311	1	.128	.665	.394	1.125
	SingleParentHousehold(1)	**.669**	**.328**	**4.177**	**1**	**.041**	**1.953**	**1.028**	**3.712**
	IncomeLT20K(1)	-.484	.316	2.350	1	.125	.616	.332	1.145
	K.foodmilkCOMBO.1PT(1)	-.133	.278	.230	1	.632	.875	.507	1.510
	Constant	-2.023	.343	34.689	1	.000	.132		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.foodmilkCOMBO.1PT.

1=Takes 6MP without food/milk

Adult not involved in monitoring of 6MP intake [k.monitorCOMBOdichot.1PT] Missing cases = 35
(SELF EFFICACY/TAKING RESPONSIBILITY)

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	**AgeAtParticipationYears**	**.064**	**.027**	**5.809**	**1**	**.016**	**1.066**	**1.012**	**1.123**
	FinalEthnicity(1)	**.808**	**.273**	**8.756**	**1**	**.003**	**2.244**	**1.314**	**3.832**
	MomEducDichotHSorLess(1)	-.417	.269	2.400	1	.121	.659	.389	1.117
	SingleParentHousehold(1)	**.688**	**.328**	**4.395**	**1**	**.036**	**1.991**	**1.046**	**3.789**
	IncomeLT20K(1)	-.479	.315	2.305	1	.129	.620	.334	1.149
	K.monitorCOMBOdichot.1PT(1)	.346	.509	.462	1	.497	1.414	.521	3.837
	Constant	-2.070	.289	51.378	1	.000	.126		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.monitorCOMBOdichot.1PT.

1=No monitor/child only

Appendix G. Final Multivariate Model and Collinearity Diagnostics

Logistic Regression

Case Processing Summary

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	456	92.1
	Missing Cases	39	7.9
	Total	495	100.0
Unselected Cases		0	.0
Total		495	100.0

a. If weight is in effect, see classification table for the total number of cases.

Dependent Variable Encoding

Original Value	Internal Value
Adherent	0
Non-Adherent	1

Block 0: Beginning Block

Classification Table[a,b]

Observed			Predicted		
			AdhJuly9Below99.1		
			Adherent	Non-Adherent	Percentage Correct
Step 0	AdhJuly9Below99.1	Adherent	356	0	100.0
		Non-Adherent	100	0	.0
	Overall Percentage				78.1

a. Constant is included in the model.

b. The cut value is .500

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 0	Constant	-1.270	.113	125.872	1	.000	.281

Variables not in the Equation

			Score	df	Sig.
Step 0	Variables	AgeAtParticipationYears	9.952	1	.002
		FinalEthnicity(1)	4.355	1	.037
		MomEducDichotHSorLess(1)	.274	1	.601
		SingleParentHousehold(1)	3.495	1	.062
		IncomeLT20K(1)	.140	1	.709
		K.how6MPdichot.1cum(1)	5.237	1	.022
		K.healthcorr.1PT(1)	4.705	1	.030
	Overall Statistics		30.377	7	.000

Block 1: Method = Enter

Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	30.402	7	.000
	Block	30.402	7	.000
	Model	30.402	7	.000

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	449.327[a]	.064	.099

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Classification Table[a]

Observed			Predicted		
			AdhJuly9Below99.1		
			Adherent	Non-Adherent	Percentage Correct
Step 1	AdhJuly9Below99.1	Adherent	355	1	99.7
		Non-Adherent	94	6	6.0
	Overall Percentage				79.2

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	AgeAtParticipationYears	.066	.024	7.712	1	.005	1.069	1.020	1.120
	FinalEthnicity(1)	.812	.280	8.437	1	.004	2.253	1.302	3.899
	MomEducDichotHSorLess(1)	-.454	.273	2.768	1	.096	.635	.372	1.084
	SingleParentHousehold(1)	.594	.334	3.158	1	.076	1.812	.941	3.489
	IncomeLT20K(1)	-.494	.319	2.396	1	.122	.610	.326	1.141
	K.how6MPdichot.1cum(1)	.574	.257	4.992	1	.025	1.775	1.073	2.937
	K.healthcorr.1PT(1)	.635	.323	3.878	1	.049	1.888	1.003	3.553
	Constant	-2.711	.389	48.646	1	.000	.066		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.how6MPdichot.1cum, K.healthcorr.1PT.

COLLINEARITY DIAGNOSTICS

Collinearity Diagnostics[a]

Model	Dimension	Eigenvalue	Condition Index	Variance Proportions							
				(Constant)	AgeAtParticipationYears	FinalEthnicity	MomEducDichotHSorLess	SingleParentHousehold	IncomeLT20K	K.healthcorr.1PT	K.how6MPdichot.1cum
1	1	4.843	1.000	.00	.01	.00	.01	.01	.01	.01	.01
	2	1.010	2.190	.00	.00	.00	.01	.28	.14	.20	.01
	3	.768	2.511	.00	.00	.00	.06	.40	.00	.45	.00
	4	.581	2.887	.00	.05	.00	.09	.18	.29	.30	.02
	5	.387	3.538	.00	.00	.00	.60	.09	.43	.01	.06
	6	.253	4.378	.00	.48	.00	.02	.04	.04	.00	.44
	7	.122	6.303	.08	.36	.23	.16	.00	.04	.01	.39
	8	.036	11.605	.91	.10	.77	.05	.00	.06	.02	.06

a. Dependent Variable: AdhBelow99.1

No root in the Condition Index approached 30, no dimension had more than one Variance Proportion greater than 0.50

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Tolerance	VIF
1	(Constant)	.053	.079		.677	.499	-.102	.209		
	AgeAtParticipationYears	.012	.004	.133	2.890	.004	.004	.020	.990	1.010
	FinalEthnicity	.133	.045	.161	2.954	.003	.045	.222	.699	1.430
	MomEducDichotHSorLess	-.074	.044	-.089	-1.693	.091	-.160	.012	.754	1.326
	SingleParentHousehold	.106	.059	.087	1.801	.072	-.010	.221	.897	1.115
	IncomeLT20K	-.080	.051	-.084	-1.573	.116	-.181	.020	.723	1.384
	K.healthcorr.1PT	-.090	.046	-.090	-1.964	.050	-.181	.000	.984	1.016
	K.how6MPdichot.1cum	-.096	.044	-.101	-2.198	.028	-.182	-.010	.985	1.016

a. Dependent Variable: AdhJuly9Below99.1

Tolerance values for all variables were $\geq$0.3, and Variance Inflation Factor (VIF) values were all <3, indicating no violation of tolerance and no

Residuals Statistics[a]

	Minimum	Maximum	Mean	Std. Deviation	N
Predicted Value	-.05	.59	.22	.107	456
Std. Predicted Value	-2.481	3.432	.000	1.000	456
Standard Error of Predicted Value	.033	.085	.052	.012	456
Adjusted Predicted Value	-.08	.57	.22	.107	456
Residual	-.515	1.046	.000	.400	456
Std. Residual	-1.276	2.594	.000	.992	456
Stud. Residual	-1.300	2.634	.000	1.002	456
Deleted Residual	-.534	1.079	.000	.408	456
Stud. Deleted Residual	-1.301	2.652	.002	1.004	456
Mahal. Distance	2.081	19.438	6.985	3.641	456
Cook's Distance	.000	.027	.002	.004	456
Centered Leverage Value	.005	.043	.015	.008	456

a. Dependent Variable: AdhJuly9Below99.1

There were no standardized residuals above 3.3, and the maximum value for Cook's distance was <1, which was indicative of no outliers with dramatic effects on the coefficients in the model..

Appendix H. Stratified Multivariate Models

FULL MODEL STRATIFIED BY AGE <12, >=12

Variables in the Equation

AgeLT12atParticipation			B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
									Lower	Upper
Age 12 or older at participation	Step 1[a]	AgeAtParticipationYears	.068	.110	.389	1	.533	1.071	.864	1.328
		FinalEthnicity(1)	1.935	.645	8.995	1	.003	6.927	1.955	24.541
		MomEducDichotHSorLess(1)	-1.113	.667	2.787	1	.095	.329	.089	1.214
		SingleParentHousehold(1)	1.008	.687	2.154	1	.142	2.741	.713	10.538
		IncomeLT20K(1)	-1.585	.747	4.501	1	.034	.205	.047	.886
		K.how6MPdichot.1cum(1)	.576	.548	1.103	1	.294	1.779	.607	5.211
		K.healthcorr.1PT(1)	.541	.694	.607	1	.436	1.717	.441	6.691
		Constant	-2.944	1.857	2.514	1	.113	.053		
Younger that age 12 at participation	Step 1[a]	AgeAtParticipationYears	.122	.058	4.487	1	.034	1.130	1.009	1.265
		FinalEthnicity(1)	.541	.318	2.885	1	.089	1.718	.920	3.206
		MomEducDichotHSorLess(1)	-.272	.307	.788	1	.375	.762	.417	1.389
		SingleParentHousehold(1)	.469	.399	1.380	1	.240	1.598	.731	3.492
		IncomeLT20K(1)	-.140	.357	.154	1	.694	.869	.432	1.749
		K.how6MPdichot.1cum(1)	.671	.298	5.080	1	.024	1.956	1.091	3.506
		K.healthcorr.1PT(1)	.638	.373	2.923	1	.087	1.892	.911	3.931
		Constant	-3.064	.548	31.211	1	.000	.047		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.how6MPdichot.1cum, K.healthcorr.1PT.

FULL MODEL STRATIFIED BY AGE <12, >=12 with K.swallowCORR.1PT added

Variables in the Equation

AgeLT12atParticipation			B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
									Lower	Upper
Age 12 or older at participation	Step 1[a]	AgeAtParticipationYears	.076	.113	.450	1	.503	1.079	.864	1.346
		FinalEthnicity(1)	1.843	.651	8.014	1	.005	6.316	1.763	22.629
		MomEducDichotHSorLess(1)	-1.044	.671	2.421	1	.120	.352	.095	1.311
		SingleParentHousehold(1)	1.022	.684	2.231	1	.135	2.778	.727	10.619
		IncomeLT20K(1)	-1.548	.749	4.275	1	.039	.213	.049	.923
		K.healthcorr.1PT(1)	.512	.693	.546	1	.460	1.668	.429	6.483
		K.how6MPdichot.1cum(1)	.614	.559	1.205	1	.272	1.848	.617	5.528
		K.swallowCORR.1PT(1)	.184	1.001	.034	1	.854	1.202	.169	8.547
		Constant	-3.077	1.942	2.511	1	.113	.046		
Younger that age 12 at participation	Step 1[a]	AgeAtParticipationYears	.124	.062	4.007	1	.045	1.131	1.003	1.277
		FinalEthnicity(1)	.540	.319	2.875	1	.090	1.717	.919	3.206
		MomEducDichotHSorLess(1)	-.272	.307	.786	1	.375	.762	.418	1.390
		SingleParentHousehold(1)	.472	.402	1.379	1	.240	1.603	.729	3.523
		IncomeLT20K(1)	-.140	.357	.153	1	.695	.870	.432	1.750
		K.healthcorr.1PT(1)	.637	.373	2.919	1	.088	1.892	.911	3.930
		K.how6MPdichot.1cum(1)	.668	.301	4.910	1	.027	1.950	1.080	3.520
		K.swallowCORR.1PT(1)	.020	.297	.004	1	.947	1.020	.570	1.826
		Constant	-3.081	.607	25.773	1	.000	.046		

a. Variable(s) entered on step 1: AgeAtParticipationYears, FinalEthnicity, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.healthcorr.1PT, K.how6MPdichot.1cum, K.swallowCORR.1PT.

FULL MODEL STRATIFIED BY ETHNICITY

Variables in the Equation

FinalEthnicity			B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
									Lower	Upper
White	Step 1[a]	AgeAtParticipationYears	.059	.038	2.484	1	.115	1.061	.986	1.143
		MomEducDichotHSorLess(1)	.122	.420	.085	1	.771	1.130	.496	2.571
		SingleParentHousehold(1)	.665	.548	1.472	1	.225	1.945	.664	5.696
		IncomeLT20K(1)	.281	.691	.165	1	.685	1.324	.342	5.132
		K.healthcorr.1PT(1)	.608	.455	1.791	1	.181	1.838	.754	4.480
		K.how6MPdichot.1cum(1)	.336	.383	.769	1	.380	1.399	.661	2.964
		Constant	-2.729	.552	24.466	1	.000	.065		
Hispanic	Step 1[a]	AgeAtParticipationYears	.078	.032	5.833	1	.016	1.081	1.015	1.151
		MomEducDichotHSorLess(1)	-.833	.343	5.916	1	.015	.435	.222	.851
		SingleParentHousehold(1)	.517	.437	1.403	1	.236	1.678	.713	3.949
		IncomeLT20K(1)	-.649	.360	3.243	1	.072	.522	.258	1.059
		K.healthcorr.1PT(1)	.634	.469	1.832	1	.176	1.886	.753	4.724
		K.how6MPdichot.1cum(1)	.900	.364	6.120	1	.013	2.460	1.206	5.019
		Constant	-1.785	.542	10.847	1	.001	.168		

a. Variable(s) entered on step 1: AgeAtParticipationYears, MomEducDichotHSorLess, SingleParentHousehold, IncomeLT20K, K.healthcorr.1PT, K.how6MPdichot.1cum.

References

Abbe, M., Simon, C., Angiolillo, A., Ruccione, K., & Kodish, E. D. (2006). A survey of language barriers from the perspective of pediatric oncologists, interpreters, and parents. *Pediatric Blood and Cancer, 47*(6), 819-824.

Abraham, C., Clift, S., & Grabowski, P. (1999). Cognitive predictors of adherence to malaria prophylaxis regimens on return from a malarious region: a prospective study. *Social Science & Medicine, 48*(11), 1641-1654.

Ajzen, I., & Fishbein, M. (1980). *Understanding attitudes and predicting social behavior*. Englewood Cliffs, NJ: Prentice-Hall.

Baker, L. H., Jones, J., Stovall, A., Zeltzer, L. K., Heiney, S. P., Sensenbrenner, L., ...Zook, D. (1993). American Cancer Society Workshop on Adolescents and Young Adults with Cancer. Workgroup #3: Psychosocial and emotional issues and specialized support groups and compliance issues. *Cancer, 71*(7), 2419-2422.

Bandura, A. (1986). *Social foundations of thought and action: A social cognitive theory*. Englewood Cliffs, New Jersey: Prentice-Hall.

Bandura, A. (1997). *Self-efficacy: The exercise of control*. New York: Freeman.

Becker, M. (1974). The Health Belief Model and personal health behavior. In M. Becker (Ed.), *Health education monographs* (pp. 324-473). San Francisco: Society for Public Health Education.

Bender, B. G., Milgrom, H., Wamboldt, F. S., & Rand, C. (2000). Measurement of treatment nonadherence in children with asthma. In D. Drotar (Ed.), *Promoting adherence to medical treatment in chronic childhood illness: concepts, methods,*

and interventions (pp. 153-171). Mahwah, New Jersey: Lawrence Erlbaum Associates.

Bhatia, S. (2004). Influence of race and socioeconomic status on outcome of children treated for childhood acute lymphoblastic leukemia. *Current Opinion in Pediatrics, 16*(1), 9-14.

Bhatia, S., Sather, H. N., Heerema, N. A., Trigg, M. E., Gaynon, P. S., & Robison, L. L. (2002). Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. *Blood, 100*(6), 1957-1964.

Blais, L., Beauchesne, M. F., & Levesque, S. (2006). Socioeconomic status and medication prescription patterns in pediatric asthma in Canada. *Journal of Adolescent Health, 38*(5), 607 e609-616. doi: S1054-139X(05)00102-3 [pii]10.1016/j.jadohealth.2005.02.010.

Bond, G. G., Aiken, L. S., & Somerville, S. C. (1992). The health belief model and adolescents with insulin-dependent diabetes mellitus. *Health Psychology, 11*(3), 190-198.

Borowitz, M. J., Devidas, M., Hunger, S. P., Bowman, W. P., Carroll, A. J., Carroll, W. L., …Camitta, B. M. (2008). Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. *Blood, 111*(12), 5477-5485.

Bradley-Springer, L. (1998). Prevention: the original adherence issue. *Journal of the Association of Nurses in AIDS Care, 9*(3), 17-18.

Brownbridge, G., & Fielding, D. M. (1994). Psychosocial adjustment and adherence to dialysis treatment regimes. *Pediatric Nephrology, 8*(6), 744-749.

Burroughs, T. E., Pontious, S. L., & Santiago, J. V. (1993). The relationship among six psychosocial domains, age, health care adherence, and metabolic control in adolescents with IDDM. *The Diabetes Educator, 19*(5), 396-402.

Burton, N. K., Barnett, M. J., Aherne, G. W., Evans, J., Douglas, I., & Lister, T. A. (1986). The effect of food on the oral administration of 6-mercaptopurine. *Cancer Chemotherapy & Pharmacology, 18*(1), 90-91.

Bush, P. J., & Iannotti, R. J. (1990). A Children's Health Belief Model. *Medical Care, 28*(1), 69-86.

Clarke-Steffen, L. (1993a). A model of the family transition to living with childhood cancer. *Cancer Practice, 1*(4), 285-292.

Clarke-Steffen, L. (1993b). Waiting and not knowing: the diagnosis of cancer in a child. *Journal of Pediatric Oncology Nursing, 10*(4), 146-153.

Clarke-Steffen, L. (1997). Reconstructing reality: family strategies for managing childhood cancer. *Journal of Pediatric Nursing, 12*(5), 278-287.

Clarke, S. A., Davies, H., Jenney, M., Glaser, A., & Eiser, C. (2005). Parental communication and children's behaviour following diagnosis of childhood leukaemia. *Psychooncology, 14*(4), 274-281.

Claxton, A. J., Cramer, J., & Pierce, C. (2001). A systematic review of the associations between dose regimens and medication compliance. *Clinical Therapeutics, 23*(8), 1296-1310.

Cook, C. L., & Perri, M., 3rd. (2004). Single-item vs multiple-item measures of stage of change in compliance with prescribed medications. *Psychological Reports, 94*(1), 115-124.

Corrigan, J. J., Feig, S. A., & American Academy of, P. (2004). Guidelines for pediatric cancer centers. *Pediatrics, 113*(6), 1833-1835.

Cramer, J. A., Mattson, R. H., Prevey, M. L., Scheyer, R. D., & Ouellette, V. L. (1989). How often is medication taken as prescribed? A novel assessment technique. *JAMA: Journal of the American Medical Association, 261*(22), 3273-3277.

Cramer, J. A., Roy, A., Burrell, A., Fairchild, C. J., Fuldeore, M. J., Ollendorf, D. A., Wong, P.K. (2008). Medication compliance and persistence: terminology and definitions. *Value Health, 11*(1), 44-47.

Davies, H. A., Lennard, L., & Lilleyman, J. S. (1993). Variable mercaptopurine metabolism in children with leukaemia: a problem of non-compliance? *BMJ: British Medical Journal, 306*(6887), 1239-1240.

Davies, H. A., & Lilleyman, J. S. (1995). Compliance with oral chemotherapy in childhood lymphoblastic leukaemia. *Cancer Treatment Reviews, 21*(2), 93-103.

De Civita, M., & Dobkin, P. L. (2004). Pediatric adherence as a multidimensional and dynamic construct, involving a triadic partnership. *Journal of Pediatric Psychology, 29*(3), 157-169.

de Lemos, M. L., Hamata, L., Jennings, S., & Leduc, T. (2007). Interaction between mercaptopurine and milk. *Journal of Oncology Pharmacy Practice, 13*(4), 237-240.

Dervieux, T., Blanco, J. G., Krynetski, E. Y., Vanin, E. F., Roussel, M. F., & Relling, M. V. (2001). Differing contribution of thiopurine methyltransferase to mercaptopurine versus thioguanine effects in human leukemic cells. *Cancer Research, 61*(15), 5810-5816.

Dervieux, T., Brenner, T. L., Hon, Y. Y., Zhou, Y., Hancock, M. L., Sandlund, J. T., …Evans, W. E. (2002). De novo purine synthesis inhibition and antileukemic effects of mercaptopurine alone or in combination with methotrexate in vivo. *Blood, 100*(4), 1240-1247.

Dibenedetto, S. P., Guardabasso, V., Ragusa, R., Di Cataldo, A., Miraglia, V., D'Amico, S., Eppolito, A. M. (1994). 6-Mercaptopurine cumulative dose: a critical factor of maintenance therapy in average risk childhood acute lymphoblastic leukemia. *Pediatric Hematology/Oncology, 11*(3), 251-258.

Dracup, K. A., & Meleis, A. I. (1982). Compliance: an interactionist approach. *Nursing Research, 31*(1), 31-36.

Earle, E. A., Clarke, S. A., Eiser, C., & Sheppard, L. (2007). 'Building a new normality': mothers' experiences of caring for a child with acute lymphoblastic leukaemia. *Child: Care, Health and Development, 33*(2), 155-160.

Eiser, C., & Upton, P. (2007). Costs of caring for a child with cancer: a questionnaire survey. *Child: Care, Health and Development, 33*(4), 455-459.

Elliott, V., Morgan, S., Day, S., Mollerup, L. S., & Wang, W. (2001). Parental health beliefs and compliance with prophylactic penicillin administration in children

with sickle cell disease. *Journal of Pediatric Hematology/Oncology, 23*(2), 112-116.

Ely, E. A. (1997). Collaborative practice with children and parents. Enhancing preparation for and management of cancer treatment. *Cancer Practice, 5*(6), 387-390.

Evangelista, L. S. (1999). Compliance: a concept analysis. *Nursing Forum, 34*(1), 5-11.

Evans, W. E., & Relling, M. V. (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. *Science, 286*(5439), 487-491.

Festa, R. S., Tamaroff, M. H., Chasalow, F., & Lanzkowsky, P. (1992). Therapeutic adherence to oral medication regimens by adolescents with cancer. I. Laboratory assessment. *Journal of Pediatrics, 120*(5), 807-811.

Field, A. (2005). *Discovering statistics using SPSS* (2nd ed.). Thousand Oaks, CA: Sage Publications, Inc.

Friedman, I. M., & Litt, I. F. (1987). Adolescents' compliance with therapeutic regimens. Psychological and social aspects and intervention. *Journal of Adolescent Health Care, 8*(1), 52-67.

Gale, R. P., & Butturini, A. (1991). Maintenance chemotherapy and cure of childhood acute lymphoblastic leukaemia. *Lancet, 338*(8778), 1315-1318.

Garvie, P. A., Lensing, S., & Rai, S. N. (2007). Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics, 119*(4), e893-899. doi: 10.1542/peds.2006-1488.

Gaynon, P. S. (2006). Treatment adherence and 6-mercaptopurine metabolites. *Pediatric Blood and Cancer, 46*(2), 120-121.

Hale, J. P., & Lilleyman, J. S. (1991). Importance of 6-mercaptopurine dose in lymphoblastic leukaemia. *Archives of Disease in Childhood, 66*(4), 462-466.

Harned, T. M., & Gaynon, P. (2008). Relapsed acute lymphoblastic leukemia: current status and future opportunities. *Current Oncology Reports, 10*(6), 453-458.

Haynes, R. B., McDonald, H. P., & Garg, A. X. (2002). Helping patients follow prescribed treatment: clinical applications. *JAMA: Journal of the American Medical Association, 288*(22), 2880-2883.

Hewitt, M., Greenfield, S., & Stovall, E. (Eds.). (2006). *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, D.C.: National Academies Press.

Hinds, P. S., Gattuso, J. S., & Mandrell, B. N. (2006). Nursing care. In C. H. Pui (Ed.), *Childhood leukemias* (2nd ed., pp. 882-893). New York: Cambridge University Press.

Hochbaum, G. (1958). *Public participation in medical screening programs: A socio-psychological study*. Washington, DC: Public Health Service, United States Government Printing Office.

Holm, K. E., Patterson, J. M., & Gurney, J. G. (2003). Parental involvement and family-centered care in the diagnostic and treatment phases of childhood cancer: results from a qualitative study. *Journal of Pediatric Oncology Nursing, 20*(6), 301-313.

Horner, M. J., Ries, L. A. G., Krapcho, M., Neyman, N., Aminou, R., Howlader, N., …Edwards, B. K. (Eds.). (2009). *SEER Cancer Statistics Review, 1975-2006,*

based on November 2008 SEER data submission. Bethesda, MD: National Cancer Institute.

Hummelinck, A., & Pollock, K. (2006). Parents' information needs about the treatment of their chronically ill child: a qualitative study. *Patient Education and Counseling, 62*(2), 228-234.

Ingersoll, G. M., Orr, D. P., Herrold, A. J., & Golden, M. P. (1986). Cognitive maturity and self-management among adolescents with insulin-dependent diabetes mellitus. *Journal of Pediatrics, 108*(4), 620-623.

James, K., Keegan-Wells, D., Hinds, P. S., Kelly, K. P., Bond, D., Hall, B., …Speckhart, B. (2002). The care of my child with cancer: parents' perceptions of caregiving demands. *Journal of Pediatric Oncology Nursing, 19*(6), 218-228.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., & Thun, M. J. (2009). Cancer statistics, 2009. *CA: A Cancer Journal for Clinicians, 59*(4), 225-249.

Kadan-Lottick, N. S., Ness, K. K., Bhatia, S., & Gurney, J. G. (2003). Survival variability by race and ethnicity in childhood acute lymphoblastic leukemia. *JAMA: Journal of the American Medical Association, 290*(15), 2008-2014.

Kalichman, S. C., Ramachandran, B., & Catz, S. (1999). Adherence to combination antiretroviral therapies in HIV patients of low health literacy. *Journal of General Internal Medicine, 14*(5), 267-273.

Kennard, B. D., Stewart, S. M., Olvera, R., Bawdon, R. E., O'hAilin, A., Lewis, C. P., Winick, N. (2004). Nonadherence in adolescent oncology patients: Preliminary

data on psychological risk factors and relationships to outcome. *Journal of Clinical Psychology in Medical Settings, 11*, 30-39.

Kim, M. J., & Moritz, D. A. (1982). *Classification of nursing diagnoses: proceedings of the third and fourth national conferences*. New York: McGraw-Hill Co.

Koren, G., Ferrazini, G., Sulh, H., Langevin, A. M., Kapelushnik, J., Klein, J., ...Greenberg, M. (1990). Systemic exposure to mercaptopurine as a prognostic factor in acute lymphocytic leukemia in children. *New England Journal of Medicine, 323*(1), 17-21.

Koren, G., Langevin, A. M., Olivieri, N., Giesbrecht, E., Zipursky, A., & Greenberg, M. (1990). Diurnal variation in the pharmacokinetics and myelotoxicity of mercaptopurine in children with acute lymphocytic leukemia. *American Journal of Disease in Childhood, 144*(10), 1135-1137.

Krippendorff, K. (2004). *Content analysis: An introduction to its methodology* (2nd ed.). Thousand Oaks, CA: Sage Publications, Inc.

Kyngas, H. (2000). Compliance of adolescents with diabetes. *Journal of Pediatric Nursing, 15*(4), 260-267.

Kyngas, H., Duffy, M. E., & Kroll, T. (2000). Conceptual analysis of compliance. *Journal of Clinical Nursing, 9*(1), 5-12.

Kyngas, H., & Rissanen, M. (2001). Support as a crucial predictor of good compliance of adolescents with a chronic disease. *Journal of Clinical Nursing, 10*(6), 767-774.

La Greca, A. M., Auslander, W. F., Greco, P., Spetter, D., Fisher, E. B., Jr., & Santiago, J. V. (1995). I get by with a little help from my family and friends: adolescents' support for diabetes care. *Journal of Pediatric Psychology, 20*(4), 449-476.

Lancaster, D., Lennard, L., & Lilleyman, J. S. (1997). Profile of non-compliance in lymphoblastic leukaemia. *Archives of Disease in Childhood, 76*(4), 365-366.

Landier, W. (2001). Childhood acute lymphoblastic leukemia: current perspectives. *Oncology Nursing Forum, 28*(5), 823-833; quiz 834-825.

Landier, W., Hughes, C., Calvillo, E., Anderson, N., Briseno-Toomey, D., Dominguez, L., …Bhatia, S. (2009). *Understanding the barriers and facilitators to adherence to oral chemotherapy in a multiethnic cohort of youth with acute lymphoblastic leukemia.* Paper presented at the American Association for Cancer Research Conference: The Science of Health Disparities in Racial/Ethnic Minorities and the Medically Underserved, Carefree, AZ.

Landier, W., Toomey, D., Hughes, C., Calvillo, E., Anderson, N., Dominguez, L., …Bhatia, S. (2009). *A bitter pill to swallow: The challenges of oral medication administration in children with A.L.L.* Paper presented at the Association of Pediatric Hematology/Oncology Nurses 33rd Annual Conference and Exhibit, Orlando, FL.

Landier, W., & Wallace, J. D. (2003). Childhood leukemias. In K. Wilson, W. Landier & J. D. Wallace (Eds.), *Foundations of pediatric hematology/oncology nursing: A comprehensive orientation and review course [CD-ROM]*. Glenview, IL: Association of Pediatric Hematology/Oncology Nurses.

Lansky, S. B., Smith, S. D., Cairns, N. U., & Cairns, G. F., Jr. (1983). Psychological correlates of compliance. *American Journal of Pediatric Hematology/Oncology, 5*(1), 87-92.

Lau, R. C., Matsui, D., Greenberg, M., & Koren, G. (1998). Electronic measurement of compliance with mercaptopurine in pediatric patients with acute lymphoblastic leukemia. *Medical and Pediatric Oncology, 30*(2), 85-90.

Lennard, L., & Singleton, H. J. (1992). High-performance liquid chromatographic assay of the methyl and nucleotide metabolites of 6-mercaptopurine: quantitation of red blood cell 6-thioguanine nucleotide, 6-thioinosinic acid and 6-methylmercaptopurine metabolites in a single sample. *Journal of Chromatography, 583*(1), 83-90.

Lennard, L., Welch, J., & Lilleyman, J. S. (1995). Intracellular metabolites of mercaptopurine in children with lymphoblastic leukaemia: a possible indicator of non-compliance? *British Journal of Cancer, 72*(4), 1004-1006.

Leonard, B. J., Garwick, A., & Adwan, J. Z. (2005). Adolescents' perceptions of parental roles and involvement in diabetes management. *Journal of Pediatric Nursing, 20*(6), 405-414.

Levenson, P. M., Copeland, D. R., Morrow, J. R., Pfefferbaum, B., & Silberberg, Y. (1983). Disparities in disease-related perceptions of adolescent cancer patients and their parents. *Journal of Pediatric Psychology, 8*(1), 33-45.

Lilleyman, J. S., & Lennard, L. (1994). Mercaptopurine metabolism and risk of relapse in childhood lymphoblastic leukaemia. *Lancet, 343*(8907), 1188-1190.

Lilleyman, J. S., & Lennard, L. (1996). Non-compliance with oral chemotherapy in childhood leukaemia. *BMJ: British Medical Journal, 313*(7067), 1219-1220.

Liptak, G. S. (1996). Enhancing patient compliance in pediatrics. *Pediatrics in Review, 17*(4), 128-134.

Macdougall, L. G., McElligott, S. E., Ross, E., Greeff, M. C., & Poole, J. E. (1992). Pattern of 6-mercaptopurine urinary excretion in children with acute lymphoblastic leukemia: urinary assays as a measure of drug compliance. *Therapeutic Drug Monitoring, 14*(5), 371-375.

MacDougall, L. G., Wilson, T. D., Cohn, R., Shuenyane, E. N., & McElligott, S. E. (1989). Compliance with chemotherapy in childhood leukaemia in Africa. *South African Medical Journal, 75*(10), 481-484.

Magee, J. C., Bucuvalas, J. C., Farmer, D. G., Harmon, W. E., Hulbert-Shearon, T. E., & Mendeloff, E. N. (2004). Pediatric transplantation. *American Journal of Transplantation, 4 Suppl 9*, 54-71.

Malbasa, T., Kodish, E., & Santacroce, S. J. (2007). Adolescent adherence to oral therapy for leukemia: a focus group study. *Journal of Pediatric Oncology Nursing, 24*(3), 139-151.

Manson, A. (1988). Language concordance as a determinant of patient compliance and emergency room use in patients with asthma. *Medical Care, 26*(12), 1119-1128.

Marhefka, S. L., Tepper, V. J., Brown, J. L., & Farley, J. J. (2006). Caregiver psychosocial characteristics and children's adherence to antiretroviral therapy. *AIDS: Patient Care and STDS, 20*(6), 429-437.

Marlowe, D., & Crowne, D. P. (1961). Social desirability and response to perceived situational demands. *Journal of Consulting and Clinical Psychology, 25*, 109-115.

Marshall, S. J., & Biddle, S. J. (2001). The transtheoretical model of behavior change: a meta-analysis of applications to physical activity and exercise. *Annals of Behavioral Medicine, 23*(4), 229-246.

Martin, S., Elliott-DeSorbo, D. K., Wolters, P. L., Toledo-Tamula, M. A., Roby, G., Zeichner, S., Wood, L. V. (2007). Patient, caregiver and regimen characteristics associated with adherence to highly active antiretroviral therapy among HIV-infected children and adolescents. *Pediatric Infectious Disease Journal, 26*(1), 61-67.

McDonald, H. P., Garg, A. X., & Haynes, R. B. (2002). Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA: Journal of the American Medical Association, 288*(22), 2868-2879.

McGrath, P. (2002). Beginning treatment for childhood acute lymphoblastic leukemia: insights from the parents' perspective. *Oncology Nursing Forum, 29*(6), 988-996.

Mellins, C. A., Brackis-Cott, E., Dolezal, C., & Abrams, E. J. (2004). The role of psychosocial and family factors in adherence to antiretroviral treatment in human immunodeficiency virus-infected children. *Pediatric Infect Disease Journal, 23*(11), 1035-1041.

Menard, S. (1995). *Applied logistic regression analysis*. Thousand Oaks, CA: Sage.

Modi, A. C., Morita, D. A., & Glauser, T. A. (2008). One-month adherence in children with new-onset epilepsy: white-coat compliance does not occur. *Pediatrics, 121*(4), e961-966. doi: peds.2007-1690 [pii]10.1542/peds.2007-1690.

Munro, S., Lewin, S., Swart, T., & Volmink, J. (2007). A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? *BMC Public Health, 7*, 104.

National Cancer Institute. (2005). *Theory at a glance: A guide for health promotion practice* (2nd ed.). Bethesda, MD: National Cancer Institute.

Nevins, T. E. (2002). Non-compliance and its management in teenagers. *Pediatric Transplantataion, 6*(6), 475-479.

Nguyen, K., Devidas, M., Cheng, S. C., La, M., Raetz, E. A., Carroll, W. L., ...Loh, M. L. (2008). Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia, 22*(12), 2142-2150.

Nicholson, O., Mellins, C., Dolezal, C., Brackis-Cott, E., & Abrams, E. J. (2006). HIV treatment-related knowledge and self-efficacy among caregivers of HIV-infected children. *Patient Education and Counseling, 61*(3), 405-410.

O'Hanrahan, M., & O'Malley, K. (1981). Compliance with drug treatment. *British Medical Journal (Clinical Research Edition), 283*(6286), 298-300.

O'Leary, M., Krailo, M., Anderson, J. R., & Reaman, G. H. (2008). Progress in childhood cancer: 50 years of research collaboration, a report from the Children's Oncology Group. *Seminars in Oncology, 35*(5), 484-493.

Olivieri, N. F., Matsui, D., Hermann, C., & Koren, G. (1991). Compliance assessed by the Medication Event Monitoring System. *Archives of Disease in Childhood, 66*(12), 1399-1402.

Orrell-Valente, J. K., Jarlsberg, L. G., Hill, L. G., & Cabana, M. D. (2008). At what age do children start taking daily asthma medicines on their own? *Pediatrics, 122*(6), e1186-1192. doi: 122/6/e1186 [pii]10.1542/peds.2008-0292.

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine, 353*(5), 487-497.

Palardy, N., Greening, L., Ott, J., Holderby, A., & Atchison, J. (1998). Adolescents' health attitudes and adherence to treatment for insulin-dependent diabetes mellitus. *Journal of Developmental and Behavioral Pediatrics, 19*(1), 31-37.

Partridge, A. H., Avorn, J., Wang, P. S., & Winer, E. P. (2002). Adherence to therapy with oral antineoplastic agents. *Journal of the National Cancer Institute, 94*(9), 652-661.

Patino, A. M., Sanchez, J., Eidson, M., & Delamater, A. M. (2005). Health beliefs and regimen adherence in minority adolescents with type 1 diabetes. *Journal of Pediatric Psychology, 30*(6), 503-512.

Pollock, B. H., DeBaun, M. R., Camitta, B. M., Shuster, J. J., Ravindranath, Y., Pullen, D. J., ...Murphy, S. B. (2000). Racial differences in the survival of childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group Study. *Journal of Clinical Oncology, 18*(4), 813-823.

Pritchard, M. T., Butow, P. N., Stevens, M. M., & Duley, J. A. (2006). Understanding medication adherence in pediatric acute lymphoblastic leukemia: a review. *Journal of Pediatric Hematology/Oncology, 28*(12), 816-823.

Prochaska, J. O., & DiClemente, C. C. (1983). Stages and processes of self-change of smoking: toward an integrative model of change. *Journal of Consulting and Clinical Psychology, 51*(3), 390-395.

Prochaska, J. O., Velicer, W. F., DiClemente, C. C., & Fava, J. (1988). Measuring processes of change: applications to the cessation of smoking. *Journal of Consulting and Clinical Psychology, 56*(4), 520-528.

Pui, C. H. (2006a). Acute lymphoblastic leukemia. In C. H. Pui (Ed.), *Childhood leukemias* (2nd ed., pp. 439-472). New York: Cambridge University Press.

Pui, C. H. (Ed.). (2006b). *Childhood leukemias* (2nd ed.). New York: Cambridge University Press.

Pui, C. H., & Evans, W. E. (1998). Acute lymphoblastic leukemia. *New England Journal of Medicine, 339*(9), 605-615.

Pui, C. H., & Evans, W. E. (2006). Treatment of acute lymphoblastic leukemia. *New England Journal of Medicine, 354*(2), 166-178.

Rapoff, M. A. (1999). *Adherence to pediatric medical regimens*. New York: Kluwer Academic/Plenum Publishers.

Reddington, C., Cohen, J., Baldillo, A., Toye, M., Smith, D., Kneut, C., …Hsu, H. W. (2000). Adherence to medication regimens among children with human

immunodeficiency virus infection. *Pediatric Infectious Disease Journal, 19*(12), 1148-1153.

Relling, M. V., Hancock, M. L., Boyett, J. M., Pui, C. H., & Evans, W. E. (1999). Prognostic importance of 6-mercaptopurine dose intensity in acute lymphoblastic leukemia. *Blood, 93*(9), 2817-2823.

Rianthavorn, P., & Ettenger, R. B. (2005). Medication non-adherence in the adolescent renal transplant recipient: a clinician's viewpoint. *Pediatric Transplantation, 9*(3), 398-407.

Riccardi, R., Balis, F. M., Ferrara, P., Lasorella, A., Poplack, D. G., & Mastrangelo, R. (1986). Influence of food intake on bioavailability of oral 6-mercaptopurine in children with acute lymphoblastic leukemia. *Pediatric Hematology/Oncology, 3*(4), 319-324.

Riekert, K. A., & Drotar, D. (2000). Adherence to medical treatment in pediatric chronic illness: Critical issues and answered questions. In D. Drotar (Ed.), *Promoting adherence to medical treatment in chronic childhood illness: concepts, methods, and interventions* (pp. 3-32). Mahwah, New Jersey: Lawrence Erlbaum Associates.

Riekert, K. A., & Drotar, D. (2002). The beliefs about medication scale: Development, reliability, and validity. *Journal of Clinical Psychology in Medical Settings, 9*(2), 177-184.

Riekert, K. A., Wiener, L., Drotar, D., & Sprunk, K. (1999). *Medication use among adolescents with HIV.* Paper presented at the 7th Florida conference of Child Health Psychology, Gainseville, FL.

Rivard, G. E., Infante-Rivard, C., Hoyoux, C., & Champagne, J. (1985). Maintenance chemotherapy for childhood acute lymphoblastic leukaemia: better in the evening. *Lancet, 2*(8467), 1264-1266.

Rivard, G. E., Lin, K. T., Leclerc, J. M., & David, M. (1989). Milk could decrease the bioavailability of 6-mercaptopurine. *American Journal of Pediatric Hematology/ Oncology, 11*(4), 402-406.

Rogers, R. W. (1975). A protection motivation theory of fear appeals and attitude change. *Journal of Psychology, 91*(1), 93-114.

Rosenstock, I. M., Strecher, V. J., & Becker, M. H. (1988). Social learning theory and the Health Belief Model. *Health Education Quarterly, 15*(2), 175-183.

Ruddy, K., Mayer, E., & Partridge, A. (2009). Patient adherence and persistence with oral anticancer treatment. *CA: A Cancer Journal for Clinicians, 59*(1), 56-66.

Sackett, D. L. (1979). Introduction. In D. L. Sackett & R. B. Haynes (Eds.), *Compliance with therapeutic regimens* (pp. 1-6). Baltimore: The Johns Hopkins University Press.

Sandelowski, M. (2000). Combining qualitative and quantitative sampling, data collection, and analysis techniques in mixed-method studies. *Research in Nursing and Health, 23*(3), 246-255.

Schmidt, L. E., & Dalhoff, K. (2002). Food-drug interactions. *Drugs, 62*(10), 1481-1502.

Schmiegelow, K., Glomstein, A., Kristinsson, J., Salmi, T., Schroder, H., & Bjork, O. (1997). Impact of morning versus evening schedule for oral methotrexate and 6-mercaptopurine on relapse risk for children with acute lymphoblastic leukemia. Nordic Society for Pediatric Hematology and Oncology (NOPHO). *Journal of Pediatric Hematology/Oncology, 19*(2), 102-109.

Shay, L. E. (2008). A concept analysis: adherence and weight loss. *Nursing Forum, 43*(1), 42-52.

Simone, J. V. (2006). History of the treatment of childhood ALL: a paradigm for cancer cure. *Best Practice & Research Clinical Haematology, 19*(2), 353-359.

Skinner, B. F. (1953). *Science and human behavior*. New York, NY: Macmillan.

Smith, B. A., & Shuchman, M. (2005). Problem of nonadherence in chronically ill adolescents: strategies for assessment and intervention. *Current Opinion in Pediatrics, 17*(5), 613-618.

Smith, S. D., Rosen, D., Trueworthy, R. C., & Lowman, J. T. (1979). A reliable method for evaluating drug compliance in children with cancer. *Cancer, 43*(1), 169-173.

Sobo, E. J. (2004). Good communication in pediatric cancer care: a culturally-informed research agenda. *Journal of Pediatric Oncology Nursing, 21*(3), 150-154.

Sofianou-Katsoulis, A., Khakoo, G., & Kaczmarski, R. (2006). Reduction in bioavailability of 6-mercaptopurine on simultaneous administration with cow's milk. *Pediatric Hematology/Oncology, 23*(6), 485-487.

Soliday, E., & Hoeksel, R. (2000). Health beliefs and pediatric emergency department after-care adherence. *Annals of Behavioral Medicine, 22*(4), 299-306.

Spector, L. G., Ross, J. A., Robison, L. L., & Bhatia, S. (2006). Epidemiology and etiology. In C. H. Pui (Ed.), *Childhood leukemias* (2nd ed., pp. 48-66). New York: Cambridge University Press.

Spinetta, J. J., Masera, G., Eden, T., Oppenheim, D., Martins, A. G., van Dongen-Melman, J., ...Jankovic, M. (2002). Refusal, non-compliance, and abandonment of treatment in children and adolescents with cancer: a report of the SIOP Working Committee on Phychosocial Issues in Pediatric Oncology. *Medical and Pediatric Oncology, 38*(2), 114-117.

Stroebe, W. (2000). *Social psychology and health* (2nd ed.). Buckingham, UK: Open University Press.

Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics* (5th ed.). San Francisco: Pearson Allyn and Bacon.

Tamaroff, M. H., Festa, R. S., Adesman, A. R., & Walco, G. A. (1992). Therapeutic adherence to oral medication regimens by adolescents with cancer. II. Clinical and psychologic correlates. *Journal of Pediatrics, 120*(5), 812-817.

Taylor, B. (2006). Giving children and parents a voice--the parents' perspective. *Paediatric Nursing, 18*(9), 20-23.

Teach, S. J., Lillis, K. A., & Grossi, M. (1998). Compliance with penicillin prophylaxis in patients with sickle cell disease. *Archives of Pediatric and Adolescent Medicine, 152*(3), 274-278.

Tebbi, C. K. (1993). Treatment compliance in childhood and adolescence. *Cancer, 71*(10 Suppl), 3441-3449.

Tebbi, C. K., Cummings, K. M., Zevon, M. A., Smith, L., Richards, M., & Mallon, J. (1986). Compliance of pediatric and adolescent cancer patients. *Cancer, 58*(5), 1179-1184.

Tebbi, C. K., Richards, M. E., Cummings, K. M., Zevon, M. A., & Mallon, J. C. (1988). The role of parent-adolescent concordance in compliance with cancer chemotherapy. *Adolescence, 23*(91), 599-611.

Teddlie, C. B., & Tashakkori, A. (2009). *Foundations of mixed methods research: Integrating quantitative and qualitative approaches in the social and behavioral sciences*. Thousand Oaks, CA: Sage Publications, Inc.

Traore, F., O'Riordan, M. A., Myers, C., Groth, K., Hoff, A., Angiolillo, A., (2006). How low is too low? Use of cluster analysis to define low levels of mercaptopurine metabolites. *Pediatric Blood and Cancer, 46*(2), 187-192.

Tumiel-Berhalter, L., & Zayas, L. E. (2006). Lay experiences and concerns with asthma in an urban Hispanic community. *Journal of the National Medical Association, 98*(6), 875-880.

Urquhart, J. (1997). The electronic medication event monitor. Lessons for pharmacotherapy. *Clinical Pharmacokinetics, 32*(5), 345-356.

Van Dyke, R. B., Lee, S., Johnson, G. M., Wiznia, A., Mohan, K., Stanley, K., …Nachman, S. (2002). Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics, 109*(4), e61. doi: 10.1542/peds.109.4.e61.

Veinot, T. C., Flicker, S. E., Skinner, H. A., McClelland, A., Saulnier, P., Read, S. E., Goldberg, E. (2006). "Supposed to make you better but it doesn't really": HIV-positive youths' perceptions of HIV treatment. *Journal of Adolescent Health, 38*(3), 261-267.

Williams, P. L., Storm, D., Montepiedra, G., Nichols, S., Kammerer, B., Sirois, P. A., …Malee, K. (2006). Predictors of adherence to antiretroviral medications in children and adolescents with HIV infection. *Pediatrics, 118*(6), e1745-1757. doi: peds.2006-0493 [pii]10.1542/peds.2006-0493.

Wolff, G., Strecker, K., Vester, U., Latta, K., & Ehrich, J. H. (1998). Non-compliance following renal transplantation in children and adolescents. *Pediatric Nephrology, 12*(9), 703-708.

Wright, E. C. (1993). Non-compliance--or how many aunts has Matilda? *Lancet, 342*(8876), 909-913.

Zeller, A., Taegtmeyer, A., Martina, B., Battegay, E., & Tschudi, P. (2008). Physicians' ability to predict patients' adherence to antihypertensive medication in primary care. *Hypertension Research, 31*(9), 1765-1771.

Zindani, G. N., Streetman, D. D., Streetman, D. S., & Nasr, S. Z. (2006). Adherence to treatment in children and adolescent patients with cystic fibrosis. *Journal of Adolescent Health, 38*(1), 13-17.