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Smart Interventions for Effective Medication Adherence

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SMART INTERVENTIONS FOR EFFECTIVE MEDICATION ADHERENCE

BY

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ACCEPTANCE

This dissertation was prepared under the direction of the *NEETU SINGH's* Dissertation Committee. It has been approved and accepted by all members of that committee, and it has been accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Business Administration in the J. Mack Robinson College of Business of Georgia State University.

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I would like to dedicate my dissertation to my grandfather who had always encouraged me to pursue Ph.D. While submitting this dissertation I feel like fulfilling his dream when he is not here. I know I have his blessings.

ABSTRACT

SMART INTERVENTIONS FOR EFFECTIVE MEDICATION ADHERENCE

BY

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In this research we present a model for medication adherence from information systems and technologies (IS/IT) perspective. Information technology applications for healthcare have the potential to improve cost-effectiveness, quality and accessibility of healthcare. To date, measurement of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice. IS/IT perspective helps in leveraging the technology advancements to develop a health IT system for effectively measuring medication adherence and administering interventions.

Majority of medication adherence studies have focused on average medication adherence. Average medication adherence is the ratio of the number of doses consumed and the number of

doses prescribed. It does not matter in which order or pattern patients consume the dose. Patients with enormously diverse dosing behavior can achieve the same average levels of medication adherence. The same outcomes with different levels of adherence raise the possibility that patterns of adherence affect the effectiveness of medication adherence. We propose that medication adherence research should utilize effective medication adherence (EMA), derived by including both the pattern and average medication adherence for a patient.

Using design science research (DSR) approach we have developed a model as an artifact for smart interventions. We have leveraged behavior change techniques (BCTs) based on the behavior change theories to design smart intervention. Because of the need for real time requirements for the system, we are also focusing on hierarchical control system theory and reference model architecture (RMA). The benefit of using this design is to enable an intervention to be administered dynamically on a need basis. A key distinction from existing systems is that the developed model leverages probabilistic measure instead of static schedule. We have evaluated and validated the model using formal proofs and by domain experts.

The research adds to the IS knowledge base by providing the theory based smart interventions leveraging BCTs and RMA for improving the medication adherence. It introduces EMA as a measurement of medication adherence to healthcare systems. Smart interventions based on EMA will further lead to reducing the healthcare cost by improving prescription outcomes.

Keywords: Effective medication adherence, smart intervention, context-aware reminder, performance evaluation, health IT artifact, information systems and technologies

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Chapter 1. Introduction

Information technology (IT) applications for healthcare have the potential to improve cost-effectiveness, quality and accessibility of healthcare (Chiasson and Davidson 2004). The potential benefits of IT in healthcare can be realized by addressing the social issues (Braa et al. 2007; Kaplan 2001; Miscione 2007) related to healthcare. According to the World Health Organization (WHO 2003), medication nonadherence poses a serious social challenge and needs to be addressed to improve the healthcare quality and minimize the healthcare cost. In healthcare literature various interventions have been designed to improve medication adherence (Choi et al. 2008; Maulucci and Somerville 2011; McDonald et al. 2002; Schreier et al. 2013). The measurement of patient medication adherence and use of interventions to improve adherence are rare in routine clinical practice (Ho et al. 2009). A theoretical approach to study medication adherence improvement is largely missing in literature (Ruppar 2010). The research in this field needs advances, including improved design of feasible long-term interventions, objective adherence measures, and sufficient study power to detect improvements in patient-important clinical outcomes (Nieuwlaat et al. 2014). In this research we present a model based on health behavior change theories to study medication adherence from information systems and technologies (IS/IT) perspective. IS/IT perspective helps in leveraging the technology advancements to develop a health IT system for effectively measuring medication adherence and administering interventions.

Medication adherence is "the extent to which a patient act by the prescribed interval, and a dose of a dosing regimen." (Cramer et al. 2008). Adherence to prescribed medication regimens is critical to the quality of patient outcomes such as symptoms and other aspects of well-being, functioning, health status, general health perceptions, quality of life, health-related quality of life,

reports and ratings of healthcare. Nonadherence in patients leads to a substantial worsening of disease, death, and increased healthcare costs. In general, 80% medication adherence is considered satisfactory for chronic conditions; however, a higher level (95%) may be needed for acute conditions (Haynes et al. 2008; Osterberg and Blaschke 2005; WHO 2003).

Approximately 3.2 billion annual prescriptions are dispensed in the United States alone, and about 50% of these prescriptions are not consumed as prescribed (Osterberg and Blaschke 2005; Sicre 2007). Figure 1 shows for every 100 prescriptions that physicians write, only 50% - 70% reach pharmacy, 48% - 66% get filled, 25% - 30% taken properly and 15% - 20% refilled as prescribed (NACDS 2010).

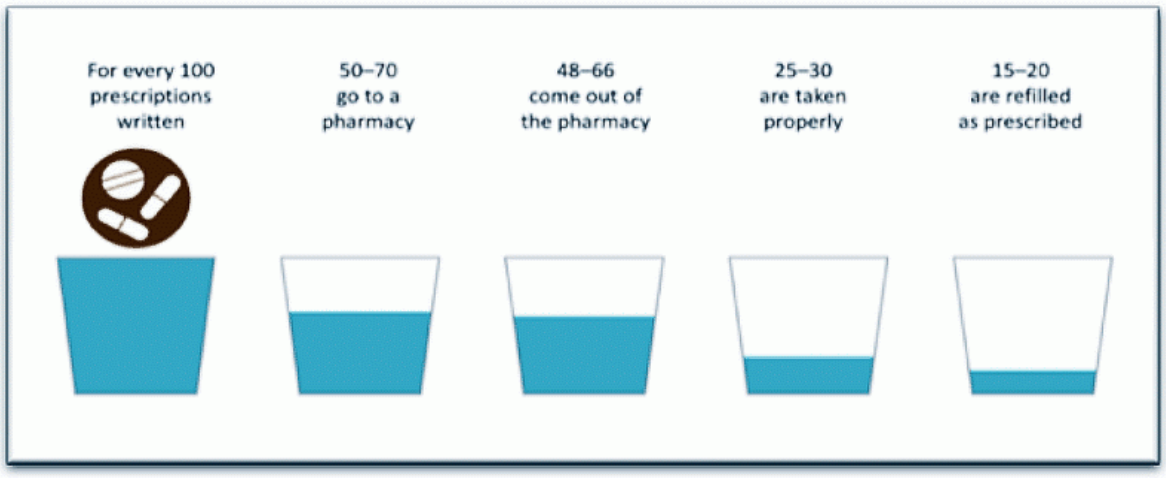


Figure 1. Gap between a written prescription and actual medication use (NACDS 2010)

A retrospective analysis of insurance claims confirms the earlier findings that poor medication adherence is a common problem across most chronic conditions (Thier et al. 2008). Nonadherence is not only prevalent but also has dramatic effects on individual and population-level health. Approximately 125,000 deaths per year in the United States are associated with nonadherence to medication (McCarthy 1998). Although the consequences of suboptimal adherence to medications are quite variable, poor adherence clearly poses a threat to the health of the U.S. population (Peterson et al. 2003; WHO 2003) that must be addressed to reduce the gap

between potential and actual healthcare quality. Extensive health benefits would result from improving medication adherence to existing treatments than developing any new medical treatments (Sabate 2007).

An economic burden of $100 to $300 billion per year came from medication nonadherence (NEHI 2009). Substantial evidence suggests that benefits attributable to improved self-management of chronic diseases could result in a cost-to-savings ratio of approximately 1:10 (Sabate 2007). As represented in Figure 2, nonadherence accounts for 10% to 25% of hospital and nursing home admissions. Recent research has found that medication nonadherence results in:

- 5.4 times increased risk of hospitalization, re-hospitalization, or premature death for patients with high blood pressure (Gwadry-Sridhar et al. 2009),
- 2.5 times increased risk of hospitalization for patients with diabetes (Lau and Nau 2004), and
- More than 40 percent of nursing home admissions (Lau and Nau 2004).

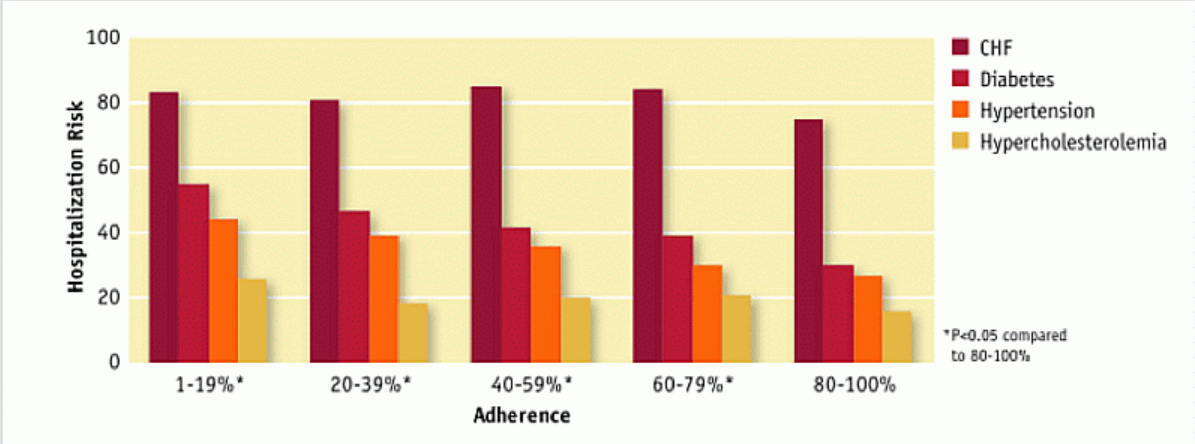


Figure 2. Impact of medication adherence on hospitalization risk (Sokol et al. 2005)

Rates of adherence, which is reported as the percentage of the prescribed doses of the medication taken by the patient over a specified period, have not changed much in the last five

decades. The extent of nonadherence varies widely, and in different studies, it has been recorded as low as 10% and as high as 92% (Osterberg and Blaschke 2005; Sokol et al. 2005).

Approximately half of nonadherence is intentional, while the remaining are unintentional because patients are either unaware that they are not taking medications as prescribed, or the regimen is just too complex. Adherence rates are typically higher among patients with acute conditions, as compared against those with chronic conditions. Studies reveal that patients with chronic illnesses take only approximately 50% of medications prescribed for those conditions. Adults aged 18–64 were almost twice as likely as adults aged 65 and over to have skipped doses, forget to take medicine, to have taken less medicine, and to have delayed filling a prescription to save money (Cohen and Villarroel 2015).

Nonadherence is a multidimensional problem influenced by several factors including patient views and beliefs, illness characteristics, social contexts, access and healthcare service issues. The problem is likely to grow as the population ages and as patients take more medications to treat chronic conditions. The potential burden of medication nonadherence outcomes on healthcare delivery makes it a significant public health concern as evident from the World Health Organization and the Institute of Medicine goals to improve medication adherence (Sokol et al. 2005; WHO 2003).

The recognition of the importance of medication adherence has been increasing over the last decade. To improve health outcomes, healthcare practitioners should engage with patients and educate them on the importance of proper medication use (Braithwaite et al. 2013). For the healthcare service providers, helping patients take medication as prescribed would help in avoiding risks of relapses, antibiotic resistance, and preventable hospitalizations.

An intervention is the means of interfering with the outcome or course especially of a condition or process (as to prevent harm or improve functioning). In medicine, an intervention is usually undertaken to help treat or cure a condition. Medication nonadherence is a growing concern to clinicians, healthcare systems, and other stakeholders because of mounting evidence that it is prevalent and associated with adverse outcomes and higher costs of care (Ho et al. 2009).

Section 1.1 Research Problem

Medication adherence is critical to the quality of patient outcomes, but high adherence is difficult to achieve. Former United States Surgeon General C. Everett Koop once said, "Drugs do not work in patients who do not take them" (Osterberg and Blaschke 2005). This simplistic yet accurate statement summarizes the dilemma faced by healthcare providers and patients in the quest for optimum healthcare. Healthcare providers (as part of a healthcare team within the health system) are an integral component of the five interacting dimensions of medication adherence identified by the World Health Organization (2003), which include social and economic dimension, healthcare system dimension, condition-related dimension, therapy-related dimension, and patient-related dimension. The multidimensional problem of nonadherence has a complex environment. Identifying strategies for improving medication adherence is a collaborative effort of all stakeholders.

This research examines the issue of nonadherence by focusing on (1) measurement of patient's medication adherence and (2) use of mobile technologies to improve adherence among patients who self-administer prescribed medications in routine clinical practice. The premise for the focus is that concordance between the patient and provider initiates the dosing regimen. The dosing regimen is observable over a period of medication/therapy persistence. The current healthcare technologies provide sufficient tools that are leveraged without modifications to

observe the actual dosing of medicines by the patient. The need, therefore, is to leverage information systems in designing a system that can help the providers in measuring the adherence within the persistence period and provide the ability to administer intervention. The ability to measure and improve medication adherence could lead to overall improvement in the patient's health outcome.

Average medication adherence (AMA) is the predominantly used measure of medication adherence. AMA considers an average dosing rate and is observable after medication persistence. In the current system, the patient taking the medication self-reports to the provider towards the end of medication persistence at the time of prescription refill or if there is a concern from a patient with the prescribed treatment. The best the provider or patient can do is to schedule reminders to take medications on time (simple intervention). This research recognizes medication persistence as a window that is monitored to (1) detect when intervention is needed and (2) identify what intervention to administer.

In the envisioned system, the rate of adherence is a probability estimate based on the medication behavior (pattern of medication adherence) of the patient and is termed Effective Medication Adherence (EMA). EMA identifies when and what intervention is administered. In envisioned system, intervention is not provided if the patient exhibits medication adherence. As interventions are not scheduled for administration at concordance but dynamically generated (when), and type is determined (what) based on the EMA, we deem such interventions as 'context-aware' or 'smart' interventions.

Section 1.2 Research Questions

The goals of this research are to (1) analyze the patterns of adherence with prescribed self-administered medications and its impact on effectiveness of medication adherence, (2) develop a

model for intervention (smart intervention) to improve effectiveness of medication adherence and reduce healthcare costs, and (3) provide a theoretical base to articulate, formalize, and fully understand the model. The research questions we will address in this study are:

RQ1: *How patterns of medication adherence impact effective medication adherence (EMA)?*

RQ2: *How smart interventions improve effective medication adherence (EMA)?*

RQ3: *How smart interventions reduce healthcare cost?*

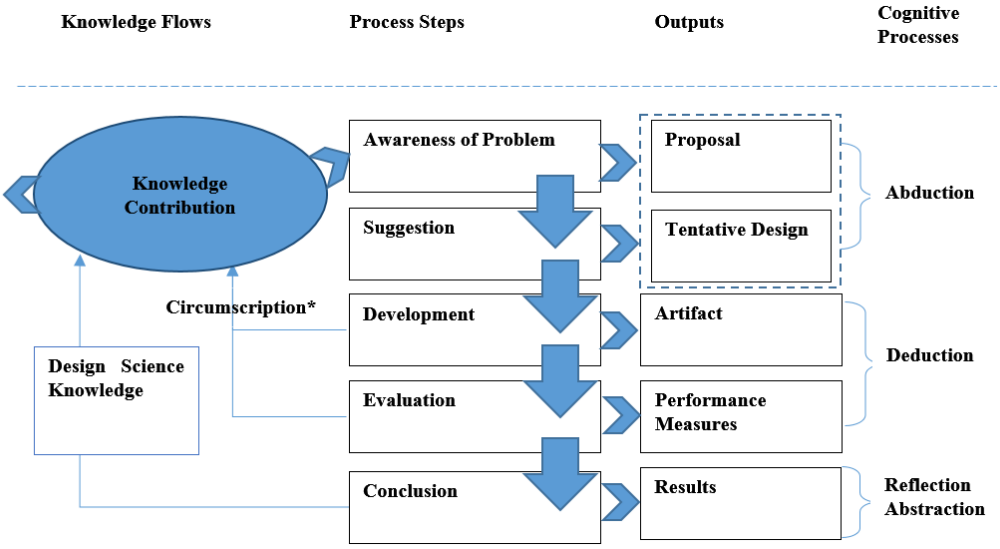
Section 1.3 Research Approach

The significant prospect in this research is the development of health information technology system for smart intervention to address the problem of nonadherence among patients prescribed self-administered medications for chronic disease. The central exercise for this research is to develop a model as an artifact for smart intervention based on effective medication adherence so as to improve simple interventions. A model is developed as an artifact to enable the representation, analysis, understanding, development and subsequent refinement of smart interventions. The implementation of artifact is done on wireless based smart medication management system (Varshney 2011) or smartphones.

The Design Science Research (DSR) Process is a natural fit for developments that are improvements over an existing model (Vaishnavi et al. 2007). Awareness of common problem motivates the DSR process. Design science research initiates with a significant prospect, challenging problem, or creativity/conjecture for some innovativeness in the application environment (Hevner 2007; Hevner et al. 2004; Iivari 2007; Vaishnavi and Kuechler 2015). The effective solution of the problem is provided by developing a better interface (Vaishnavi et al. 2007). The focus of design science research is to understand the phenomenon, some or all of

which may be created artificially instead of naturally occurring, thereby leading to artifact design and evaluation.

The DSR process model developed and revised by Vaishnavi and Kuechler (2015) is shown in Figure 3. It also shows cognitive processes used in the DSR process.



* Circumscription is the discovery of constraint knowledge about theories gained through detection and analysis of contradictions when things do not work according to theory (McCarthy 1980).

Figure 3. Design science research process model (DSR cycle) & cognitive processes

In the DSR process, all design begins with an awareness of the problem. In this step, the researcher defines the problem to be solved via the research process. Suggestions for solutions to the problem are drawn from the existing knowledge and theory bases for the problem area (Peirce 1931) or developed using an appropriate research methodology. The cognitive process of assimilation of knowledge is abductive at this step. Next, in the development step, the researcher implements an artifact according to the suggested solution. The implementation is evaluated according to the functional specification stated implicitly or explicitly in the suggestion step. The researcher may iteratively perform the suggestion, development, and evaluation steps during the research. The circumscription (the basis of the iteration) represents the addition of knowledge

from the development and evaluation steps of the process to the initial awareness of the problem, so that the problem can be re-examined. The cognitive process of assimilation of knowledge is deductive at this stage. The conclusion indicates the reflective stage where the research is concluded with the formulation of propositions relating to the problem domain. The steps of DSR process steps and output are described in Table 1 and Table 2.

Steps	Description
Awareness of Problem Step	An awareness of an interesting research problem may come from multiple sources including new developments in industry or a reference discipline. The output of this phase is a proposal, formal or informal, for a new research effort.
Suggestion Step	New functionality is envisioned based on a novel configuration of either existing or new and existing elements.
Development Step	The tentative design is further developed and implemented in this phase. The techniques for implementation will, of course, vary depending on the artifact to be created. The novelty is primarily in the design, not the construction of the artifact.
Evaluation Step	Once constructed, the artifact is evaluated according to implicit expectations or explicit criteria (Awareness of Problem phase). Deviations from expectations, both quantitative and qualitative, are explained, and Propositions are made. The deviations from the theoretical performance are iteratively refined by including new observations into the suggestion.
Conclusion Step	Not only are the results of the effort consolidated at this phase, but the knowledge gained in the effort is frequently categorized as either repeatable or anomalous. Future research areas are identified, and knowledge contribution (Gregor and Hevner 2013) is noted.

Table 1. Design science research process steps (Vaishnavi and Kuechler 2015)

Output	Description
Constructs	The conceptual vocabulary of a domain
Models	Sets of Propositions or statements expressing relationships between constructs
Frameworks	Real or conceptual guides to serve as support or guide
Architectures	High level structures of systems
Design Principles	Core principles and concepts to guide design
Methods	Sets of steps used to perform tasks; how-to knowledge
Instantiations	Situated Implementations in certain environments that do or do not operationalize constructs, models, methods, and other abstract artifacts; in the latter case, such knowledge remains tacit.
Design Theories	A prescriptive set of statements on how to do something to achieve a certain objective. A theory usually includes other abstract artifacts such as constructs, models, frameworks, architectures, design principles, and methods.

Table 2. Design science research output (Vaishnavi and Kuechler 2015)

In this research, the model for smart intervention is developed using the guidelines of Vaishnavi and Kuechler (2015) and evaluated for effectiveness using the formal proofs and evaluation by domain experts (Healthcare providers and Health IT experts) (Cleven et al. 2009; Gregor and Hevner 2013; Parsons and Wand 2008). The DSR process steps and the corresponding outputs of each step are listed in Table 3 to outline the specific outputs from this research.

DSR Process Steps	DSR Outputs	Specific Outputs
Awareness of Problem	Proposal	Medication Adherence (MA) Improvement
Suggestion	Tentative Design	Smart Intervention
Development	Artifact	Model
Evaluation	Performance Measures	Effective Medication Adherence (EMA)
Conclusion	Results	Propositions

Table 3. Specific research output at DSR process steps

A literature review is conducted to understand the current state of the research on the topic of medication adherence and the various interventions that presently exist. Specifically, environment and the factors that affect the medication adherence are studied. Any theoretical basis for medication nonadherence is analyzed for gaining a better understanding of the problem conceptually and the limitations therein. The guiding question for the awareness of problem step is - *If interventions to medication nonadherence can improve medication adherence, why such interventions are not effective?*

The understanding gained from the awareness of problem leads to the formulation of suggestions that could address the effectiveness of the interventions in improving medication adherence. The guiding question for suggestion step of the DSR process is – *How can the effectiveness of interventions be improved?*

When a suggestion for improving the effectiveness of the intervention is identified, a model is developed. As existing interventions are designs, a model (sets of propositions or statements

expressing relationships between constructs) is an appropriate artifact to improve the design as it provides the lowest possible level of operative environment for the constructs. The guiding question for development step of the DSR process is - *How closely does the new model represent the original model/design of the available interventions?*

The model from development step of DSR process is evaluated to examine the effectiveness of the improvements as envisioned in the suggestion step and according to the criteria for effective intervention identified in the awareness of problem step of DSR process. Propositions are developed about the behavior of the model. If the model does not behave as expected, revisions to the suggestion are made from the additional information gained in the development and evaluation steps and the directions suggested by deviations from expected performance. The development and evaluation steps are then repeated. The guiding question for evaluation step of the DSR process is – *What are the limiting conditions for the effectiveness of interventions utilizing new model?*

The final step in research following the DSR process is the conclusion. In addition to the practical implication of this research, the theory, and knowledge gained from model development and evaluation can become a part of design science knowledge base thereby bridging some of the literature gaps that currently exist from DSR perspective. The guiding question for conclusion step of the DSR process is – *Do the smart interventions improve effectiveness of medication adherence?*

Section 1.4 Research Contributions

This research aims to contribute model for theory based smart interventions that could improve effective medication adherence in a group of patients who are prescribed self-administered medication for chronic condition, thereby reducing the healthcare costs.

The significance of proposed research is three fold. First, it is significant to the healthcare system as the intervention will help in understanding the patterns of adherence and improves the effective medication adherence. As better health outcome is achieved, the financial burden of nonadherence will decrease. Second, it will provide an artifact which can be further evaluated using the field study. It will add value to the design science research community by providing a health IT domain specific artifact and by improving domain-specific information systems and processes. Third, it addresses the need of theoretical interventions for improving medication adherence.

What is already known about the topic?

- Medication nonadherence is a widely acknowledged and pervasive healthcare issue.
- Medication adherence holds particular significance for individuals diagnosed with chronic conditions.
- Various interventions have been designed to improve medication adherence, but few theories describe specifically the processes involved.
- Despite five decades of research, current interventions do not consistently enhance medication adherence.
- Current interventions focus on improving average medication adherence. The interventions are not generated dynamically.
- Some of the existing medication adherence applications report the nonadherence to healthcare providers, but they do not facilitate the advice/scheduling from healthcare providers.
- Existing technologies monitor and report nonadherence toward the end of medication persistence.

What this research adds?

- The scope of this dissertation research is to describe the IS/IT processes involved in developing the health IT artifact as an intervention to improve effective medication adherence.
- We address the area of medication adherence using health behavior change theory and reference model architecture theory. We discuss the application of health behavior change theory as the basis for an intervention to improve effective medication adherence.
- We evaluate that patterns of adherence and average medication adherence are important predictors of medication adherence improvement.
- Using design science research approach, we have developed model for effective medication adherence (MEMA), a health IT artifact as a system to administer smart intervention to improve effective medication adherence. Model for effective medication adherence include interactive presence of following components:
    1. Wireless medication box (WMB) which provides the dispensing and consumption information.
    2. Dynamically generated context-aware reminders using the three way interaction between wireless medication box (WMB), medication management application (MMA) and medication management server (MMS).
    3. Analysis of medication behavior that will be helpful in understanding the impact of nonadherence on treatment outcome.

Section 1.5 Research Limitations

The limitation of this dissertation lies in the fact that the health IT artifact is not generalizable to general healthcare area for medication adherence improvement. It is useful for chronic

conditions and unintentional nonadherence. More specifically, a model for effective medication adherence applies to unintentional nonadherence, and the intervention improves the effective medication adherence, i.e., the transition from Quadrant IV to Quadrant I of Figure 4. In this research, we are not focusing on unwilling patients. Figure 4 shows the intentional and unintentional nonadherence criteria.

The current design has the limitation that patient should be willing to take medication as this intervention is for prescribed self-administered medications. Regarding artifact evaluation, it can be further extended by conducting a field study where the modeled artifact can be made accessible to patients and healthcare provider to use. It will help in empirical validation of the artifact in future research.

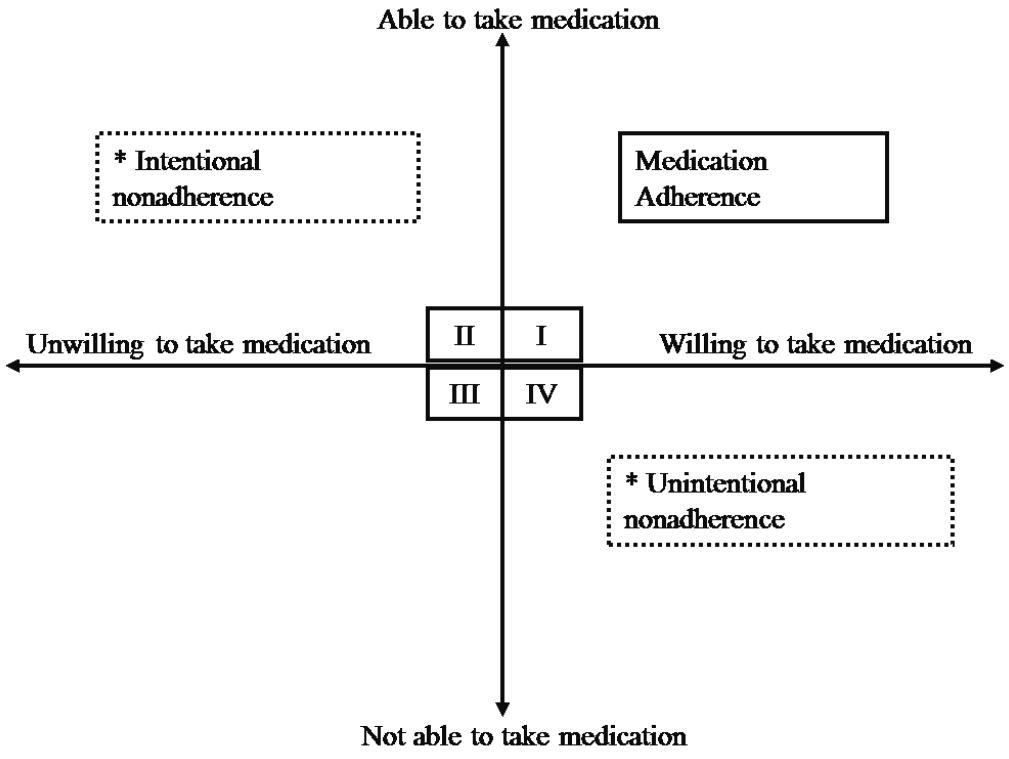


Figure 4. Intentional and unintentional nonadherence
(Ho et al. 2009; Lehane and McCarthy 2007)

Chapter 2. Awareness of Problem

The effectiveness of treatment depends on both the efficacy of a medication and patient adherence to the therapeutic regimen. Patients, healthcare providers, and healthcare systems, all have a role in improving medication adherence. A single method cannot improve medication adherence. Instead, a combination of various adherence techniques should be implemented to improve patient's adherence to the prescribed treatment.

Section 2.1 Role of Patient

Medication adherence is the extent to which patients follows the prescribed medication regimens (Cramer et al. 2008). Adherence is the preferred term because compliance suggests passivity on the part of the patient and a lack of a therapeutic alliance between patient and provider (Osterberg and Blaschke 2005; Steiner and Earnest 2000).

The manner in which a patient adheres to a prescribed medication regimen influences the health outcomes, healthcare utilization, and healthcare costs (Chewning and Sleath 1996; Delgado 2000). Multiple interrelated psychosocial factors affect medication adherence. These factors are: psychological factors (DiIorio et al. 2009), self-efficacy (DiIorio et al. 2009; Duong et al. 2001), social support (Duong et al. 2001; Fongwa et al. 2008), and socioeconomic issues (Fongwa et al. 2008; George et al. 2006).

Self-efficacy is a primary factor affecting whether or not a person will change a behavior and can affect the ability to adhere to complex medication regimens. A recent study reported that higher self-efficacy in taking medication was associated with higher medication adherence (Colbert et al. 2013).

Accurate medication adherence and the self-efficacy are important for chronic disease patients. Self-reports are the most commonly used tool for measuring adherence. Empowerment

of an individual to self-determine benefits and risks of action or behavior are crucial to change adherence to medication, and the willingness and ability to do it. For chronic patients, the cognitive and psychological burdens of treatment can often impede the medical outcome. The patient may not comprehend information about treatment if the amount of information becomes overwhelming. The patient may become unwilling to ask for help, and can undermine the importance of medication for the treatment.

Nonadherence to medications can be intentional or unintentional. Intentional nonadherence is an active process whereby the patient chooses to deviate from the treatment regimen. There may be a rational decision process in which the individual weighs the risk and benefits of treatment against any adverse effects. Unintentional nonadherence is a passive process in which the patient may be careless or forgetful about adhering to the treatment regimen (Ho et al. 2009; Lehane and McCarthy 2007). Unintentional adherence is also referred to by Vrijens et al. (2008) as the execution of the prescribed regimen, or how well patients adhere to the dosing regimen. There are six general patterns of execution:

(1) Close to perfect adherence;

(2) Take nearly all doses with some timing irregularity;

(3) Miss an occasional single day's dose, and some timing inconsistencies;

(4) Take drug holidays 3 to 4 times per year;

(5) Take drug holidays monthly or more often and have frequent omissions; and

(6) Take few or no doses.

Most deviations in medication taking are due to omissions of doses or delays in taking doses. Also, it is common for patients to improve their medication-taking behavior shortly before and

after an appointment with a healthcare provider called “white coat adherence” (Osterberg and Blaschke 2005).

Estimates of unintentional nonadherence vary considerably and range from 20% to over 50% (Ho et al. 2009; Lehane and McCarthy 2007). Forgetting to take medication (62%) was the most commonly reported behavior followed by running out of medications (37%) and being careless at times about taking the medication (23%) (Gadkari and McHorney 2012). Timely intervention can influence nonadherence of prescribed self-administered medications. The reasons for poor medication adherence are often multifactorial, and encompasses a wide range of behaviors. The consequence is an underuse or overuse of prescribed medications.

Section 2.2 Role of Prescribers

Healthcare providers play a unique and important role in assisting patients to carry out healthy behaviors (Atreja et al. 2005) and a patient’s beliefs about the benefits and risks of medicines influence whether or not they take prescribed medication (Wroth and Pathman 2006). The patient relationship with the healthcare provider influences the acquisition of knowledge and the belief of the importance of adherence (Phatak and Thomas 2006; Pratt et al. 2001). Collaborative care involving a working relationship between physicians and pharmacists has been shown to improve patient care and reduce medication errors (Kuo et al. 2004). Collaborative care is beneficial in addressing the psychosocial factors that can affect medication adherence.

Another factor is patient and provider concordance - the extent to which patients and their providers agree on whether, when, and how patient takes medication. Hence, adherence requires the patient to ***believe*** there is a benefit to the prescribed medicine and ***agree*** with instructions on how to take it. Importantly, there cannot be barriers, such as cost, which will prevent medication access. The prescriber’s role is to gain trust from the patient, understand the patient’s belief

system, find a way to treat within this belief system, interactively obtain agreement from the patient on when and how to take prescribed medication, and discuss cost issues to ensure that patient adheres to the prescription. Building trust and developing skills for successful provider and patient communications demand time, effort, knowledge, and practice.

In addition to prescribers, the office staff has a role in boosting patient adherence to medication. Wroth and Pathman (2006) evaluated correlates of medication adherence in a rural setting and found that when patients felt welcomed and comfortable by the staff, they were more likely to fill their prescriptions.

Section 2.3 Role of Interventions

Intervention is a treatment, procedure or program of healthcare that has the potential to change the course of a healthcare condition. Interventions are classified as informational or behavioral. In general, interventions for improving medication adherence include reminders, family support, educational interventions and motivational support from healthcare providers among others (Friedman et al. 1996; McDonald et al. 2002). Health IT interventions implement some of these (Moore and Benbasat 1991).

There have been major advances in design, implementation, and evaluations of systems for medication adherence. With increasing deployment of mobile and wireless technologies, including sensors, RFID, personal area networks, wireless LANs, and cellular networks, some of these interventions can be implemented on smartphone and smart medication systems (McCall et al. 2010; Varshney 2009). More specifically, enhancing standard care with reminders, disease monitoring and management, and education through applications on a smartphone can help improve health outcomes. These care processes have implications for both patients and providers

(Krishna et al. 2009). Also, a wireless-based smart medication system (SMMS) can support (Varshney 2011; Varshney 2013)

(a) Communication with patients,

(b) Monitoring of medication consumption,

(c) Context-sensitive reminders to patients, and

(d) Multiple interventions for medication adherence.

Some of the systems use wearable devices and sensors for medication adherence (Choi et al. 2008; Choi et al. 2013; DiCarlo et al. 2012; Holmes et al. 2014). Lundell et al. (2007) captured medication adherence by counting medication taking events that occurred within 90 minutes before and 90 minutes after the scheduled time. Electronic pill box has been developed and used for continuous monitoring of medication adherence (Hayes et al. 2006). In another study, an automated medication adherence tool is developed for imparting medication taking directions to patients (Maulucci and Somerville 2011).

However, existing technologies for monitoring and improving drug adherence are either costly or too complicated for general patients to use. The current methods of improving medication adherence for chronic health problems are labor-intensive, and not predictably effective (Ingersoll and Cohen 2008; Lundell et al. 2007; Maulucci and Somerville 2011; McCall et al. 2010; Moore et al. 2011; Schreier et al. 2013; Tang et al. 2011). These methods of intervention do not realize the full benefits of treatment.

Several interventions have been tried to improve the average medication adherence (Choi et al. 2008; Hayes et al. 2006; Ingersoll and Cohen 2008; Lundell et al. 2007; Maulucci and Somerville 2011; McCall et al. 2010; McDonald et al. 2002; Moore et al. 2011). Some interventions are implemented on smartphone (Krishna et al. 2009; Varshney 2009) and

medication systems (Choi et al. 2013; DiCarlo et al. 2012; Hayes et al. 2006; Holmes et al. 2014; McCall et al. 2010; Moore et al. 2011; Schreier et al. 2013; Tang et al. 2011; Varshney 2011). Most systems rely on simple alarms and do not address other determinants of health-related behavior (Hayes et al. 2006; Schreier et al. 2013)**.** Although quite diverse, these systems support communications with the patient, medication monitoring, and interventions to improve the average medication adherence.

Haynes (1976) randomly allocated, through the minimization method, 38 patients who were both hypertensive and nonadherent (less than 80% of prescribed pills) at the end of a six-month trial to an intensive adherence intervention or control. The intervention included care provided at the work site, special pill containers, counseling, reminders, self-monitoring of adherence and blood pressure, support groups, feedback and reinforcement for adequate adherence and blood pressure-lowering, all administered with bi-weekly contacts by a lay program coordinator who was supported by study funds. At six months' follow-up, there was a significantly higher adherence in the intervention group.

Most patients do not follow self-administered medical treatments as prescribed and interventions to help them follow treatments are marginally effective at best, especially for long-term medical regimens. Strategies that appear to have some effect for long-term regimens involve combinations of counseling, reminders, self-monitoring, feedback, family therapy, psychological therapy, manual telephone follow-up, and supportive care. For short-term treatments, simpler means, including counseling, written information about the importance of taking all doses, and personal phone calls can achieve high adherence.

Coomes et al. (2012) has developed a conceptual framework for using short message service (SMS) based intervention to improve healthcare quality and clinical outcomes for people living

with HIV (PLWH). They have posited that SMS-based intervention which are more personalized as well as consider mutually reinforcing behaviors and factors offer a unique opportunity to enhance treatment and prevention for PLWH (Coomes et al. 2012). Rosen et al. (2015) conducted a qualitative study to adapt and develop an mHealth app for HIV patients to improve medication adherence. The results of this study indicate that a balance of provided and requested information is important to maintain interest and support adherence (Rosen et al. 2015). These two studies provide an insight that while developing intervention, user interface and reaction to visual content of app is essential to adaptation and design of intervention.

Other studies have similarly concluded that behavioral interventions like reminders are important in improving the medication adherence. The method of administration of reminders as intervention mechanism to enforce adherence is also an important factor in influencing the patients (Rosen et al. 2015).

Chapter 3. Suggestion

Section 3.1 Evaluating adherence

Concordance is the agreement between the provider and the patient; patient/provider concordance is the extent to which patients and their providers agree on whether, when, and how to take medication (Zulman et al. 2010). The providers uniformly underestimate the problem of nonadherence. If it is not suspected, it cannot be corrected. Measuring adherence can lead to better patient compliance. **Adherence** is the extent to which a patient's behavior (regarding taking medication, following a diet, modifying habits, or attending clinics) coincides with medical or health advice (Cramer et al. 2008). **Persistence** is the duration of time from initiation to discontinuation of therapy. Continuing to take any amount of the medication is consistent with the definition of persistence (Cramer et al. 2008).

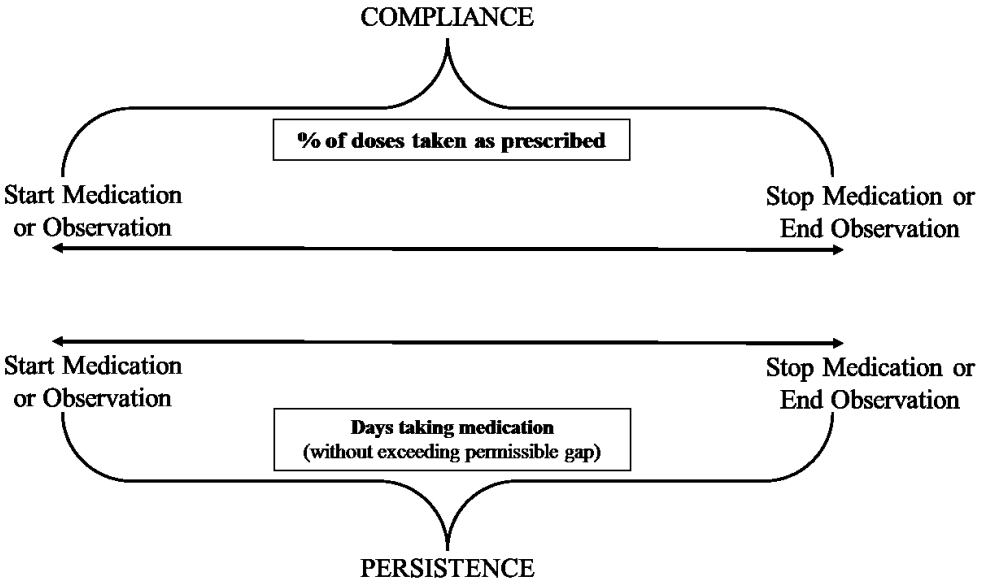


Figure 5: Adherence versus persistence (Cramer et al. 2008)

Adherence, as represented in Figure 5 is a measure of the percentage of doses taken as prescribed over the number of day medication is taken without exceeding the permissible gaps. For example, if a person is prescribed an antibiotic with a dosage of one tablet three times a day for a week, but only takes two tablets a day for four days, adherence is 38% (8/21).

We value adherence because studies have established that being compliant delivers the most effective therapeutic benefits of the prescribed medication. The stated method of measuring adherence gives us an average rate of taking medications and thus could model the therapeutic benefits arising from consuming average doses. The drawback here is it does not predict or tell us the effectiveness of such adherence on the derived therapeutic benefits. In an ideal world, everybody is assumed compliant, and the adherence is 100% and so would the effectiveness of adherence with 100% therapeutic benefits derived. In practical scenarios, the average dose may not be an effective dose.

In pharmacology, an effective dose (ED) is the dose or amount of drug that produces a therapeutic response or desired effect in some fraction of the subjects taking it. Drugs are seldom administered in a single dose to produce the desired effect. Drugs are frequently administered in successive doses to bring about lasting and effectual results. Thus, to avoid the toxic concentrations of a drug as well as to maintain its therapeutically effective concentration within the plasma, one must properly contrive a multiple dosing regimen.

Multiple Dosing Regimen We consider multiple dosing regimen with the context of adherence within a persistence to assess the effectiveness of each dose in producing the desired therapeutic output.

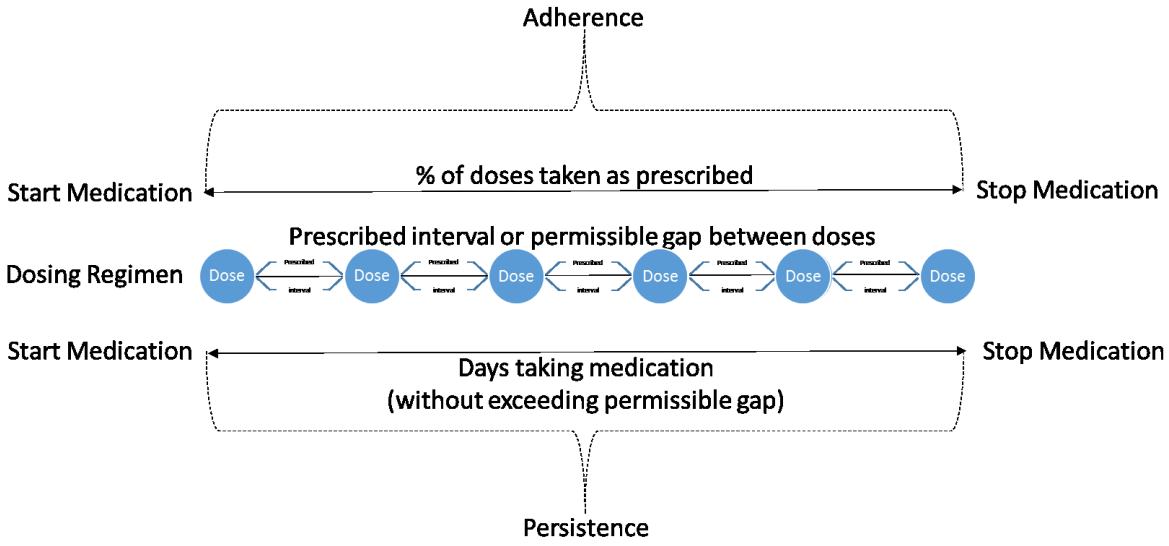
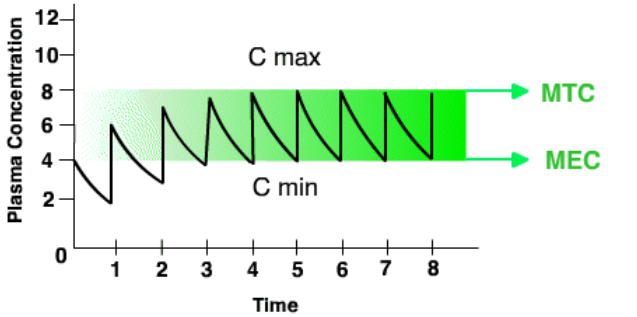


Figure 6. Repetitive dosing with adherence versus persistence

In Figure 6, we represent a drug administered on a multiple dosing regimen; each successive dosage(s) administers before the preceding doses eliminate. Accumulation of the drug routinely occurs within the body yielding a higher plasma drug concentration. The accumulation phenomenon, however, does not cause the plasma concentration to rise indefinitely. Figure 7 shows the plasma concentration plateaus where the same maximum (C_{max}) and minimum (C_{min}) concentrations are repeatedly reproduced (Lins et al. 2003). In designing a dosing regimen then, one's objectives would be to keep the drug concentration above the minimum effective concentration (MEC) and below the minimum toxic concentration (MTC).



Plot of plasma concentration versus time showing accumulation after multiple administration of drugs

Figure 7. Plasma concentration plateaus overdosing intervals (Lins et al. 2003)

3.1.1 Dose Persistence

One cannot overstate the importance of determining the therapeutic range of a drug. The range between the minimum effective dose (MED) and the maximum tolerated dose (MTD) defines the therapeutic range. The MED is the lowest dose level of a pharmaceutical product that provides a clinically significant response in average efficacy, which is also statistically significantly superior to the response provided by the placebo (Jen-pei 2010). Similarly, the MTD is the highest possible but still tolerable dose level on a pre-specified clinical limiting toxicity (Jen-pei 2010). In general, these limits refer to the average patient population. For instances in which there is a large discrepancy between the MED and MTD, it is stated that the drug has a large therapeutic window. Conversely, if the range is relatively small, or if the MTD is less than the MED, then the pharmaceutical product will have little to no practical value (Jen-pei 2010).

Figure 8 shows the persistence of the medicine over a dosing interval in the dosing regimen. Over a period, the effects of the medicine wear off. Dosing regimen specifies the interval to be duration from intake when the concentration of the drug falls below the therapeutic range.

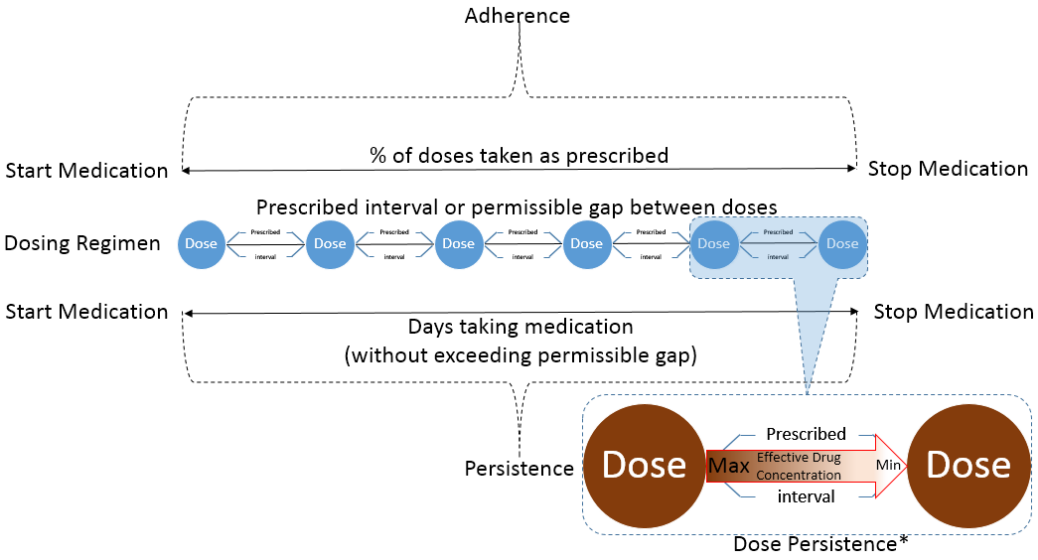


Figure 8. Dose persistence within the medication /therapy persistence

3.1.2 Nonadherence

Medication adherence helps in maintaining the effective level of drug in the body. The effects of the medication wear off due to consumption of the drug in the body. After a period, the clinical effects of the medicine become ineffective and need replenishment, i.e., taking the next dose of the medicine. This implies that three types of dosing event (DE) is captured for medication adherence:

- Consuming the medicine before the recommended interval i.e. before the time,
- Consuming the medicine after the recommended interval i.e. after the time, and
- Consuming the medicine at the recommended interval i.e. on time.

Consuming the medicine before the recommended interval leads to exceeding the minimum tolerated dose (MTD). If the minimum time (T_{MIN}) between two doses is not medically safe, then it will lead to undesirable dose event (UDE). On the other hand, consuming the medicine after the recommended interval exposes patient to below the minimum effective dose (MED) interval.

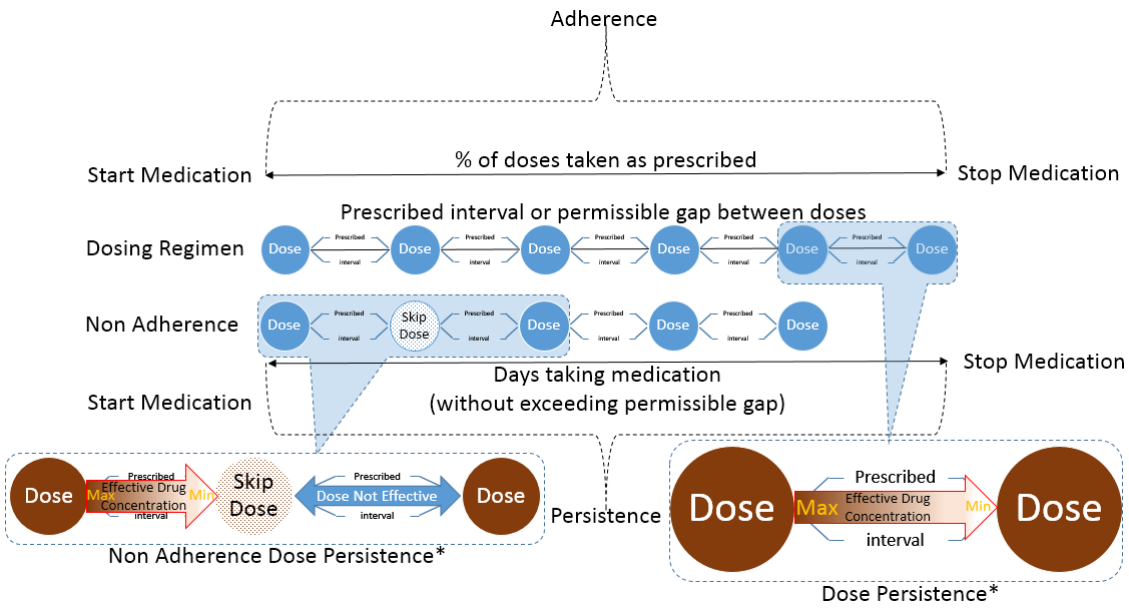


Figure 9. Nonadherence dose persistence within the medication /therapy persistence

If the maximum time (T_{MAX}) between two doses is not medically effective, then it will lead to dose not effective (DNE). Figure 9 shows that consuming the medicine at the recommended interval is the Prescribed Effective Dose (PED) event and is ideal. If any of the three events do not register for the prescribed interval, it will imply a skipped or a missed dose.

3.1.3 Patterns of Adherence

A pattern can be generated from such consumption events indicating the deviation or conformation to the prescribed dosing regimen and becomes the pattern of medication adherence. The pattern of medication adherence generates from the events associated with the intake of medication by the patient. Undesirable dose event (UDE) results in a higher concentration of medicine than the prescribed and thus deemed unsafe level in the body temporarily (from the time of consumption until the next scheduled time) and may require immediate intervention by the healthcare provider/physician.

For the purpose of this research, UDE is reported to the healthcare provider and intervention is not provided. This research focuses upon dose not effective (DNE) because our emphasis is on the effectiveness of the adherence. Analyzing the patterns of medication adherence along with the average medication adherence results in a new variable termed effective medication adherence (EMA). EMA tracks the actual adherence to the prescribed regimen of medicine intake and the deviations therein considering the periods of the ineffectiveness of the medication dose. Figure 10 shows the different patterns of adherence to a medication therapy/persistence.

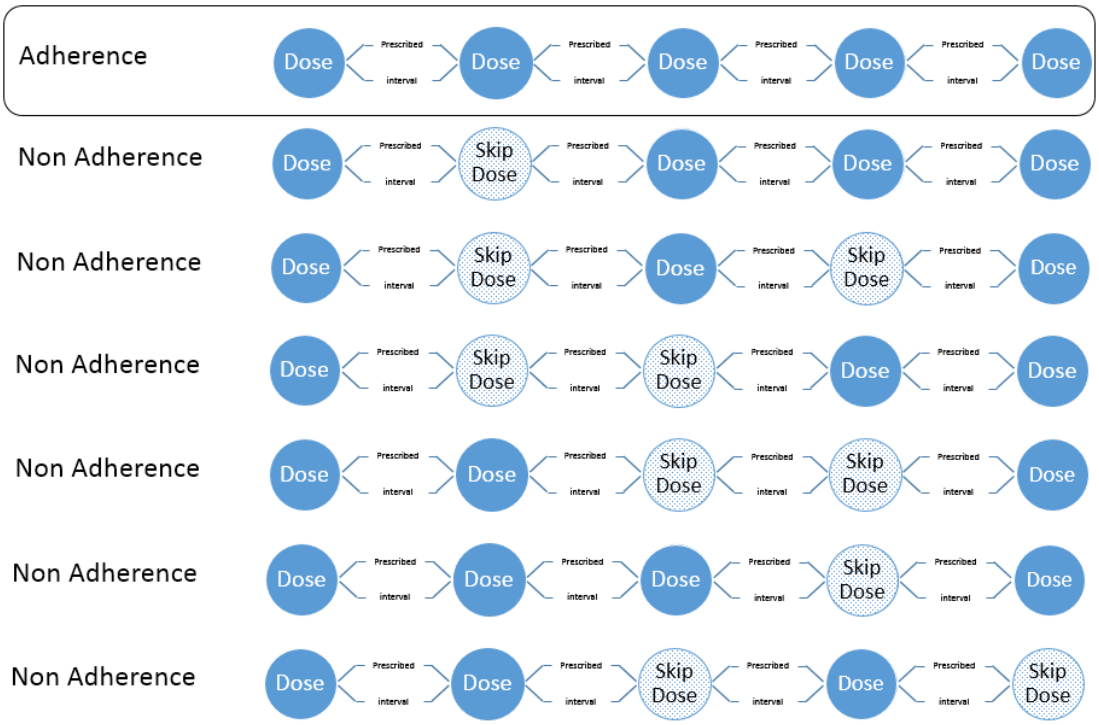


Figure 10. A simple pattern of adherence within the medication /therapy persistence

Figure 11 shows the pattern of the dose persistence/dose not effective based on a skipped dose. The sequence in which the dose not effective intervals occur has a bearing on the persistence outcome. A dose not effective interval occurring earlier in medication persistence may have an effect quite different than the dose not effective interval towards the end of the medication persistence. The effectiveness of adherence would be different in both cases on the therapeutic outcome and thus different EMA values. Figure 12 shows the patterns can vary if we consider the possibility that the patient can take multiple doses or can take the dose any time before or after the prescribed interval between the doses, or totally skip the dose. The patterns of adherence affect the therapeutic effectiveness of the prescription.

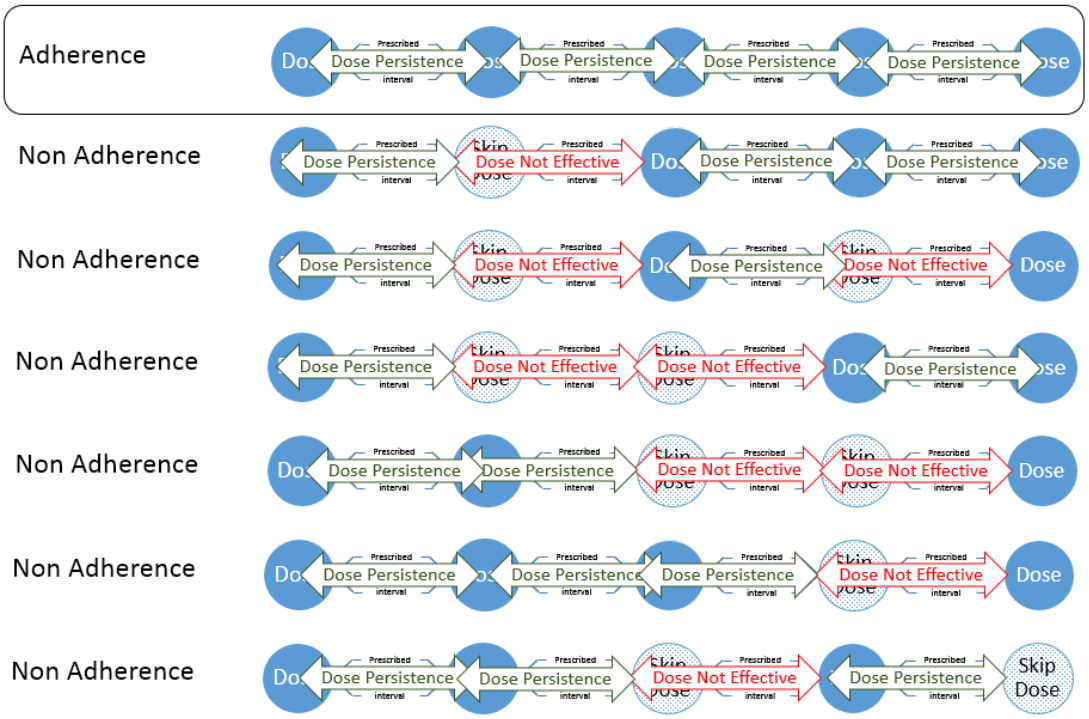


Figure 11. Effect of patterns of adherence due to skip dose on dose persistence

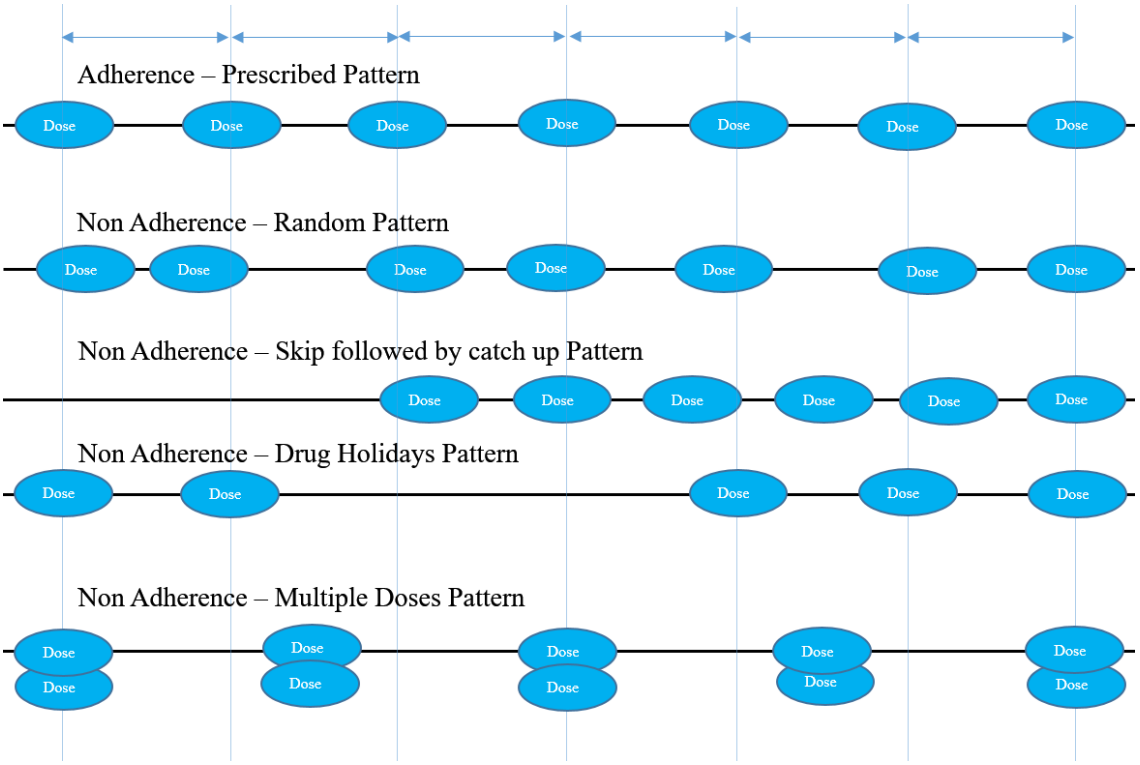


Figure 12. Various patterns of adherence due to skip dose

Section 3.2 Theoretical Background

Medication adherence is a very complex multi-faceted challenge. As an enabler, Information Technology has a major role to play. There is a need to study medication adherence interventions, and theoretical models will be needed to help such study. In this research, we present a model to study medication adherence from IS/IT perspective, more specifically health IT enabled interventions.

3.2.1 Factors

There are several factors that can affect the medication behavior of the patient, some within the control and some outside the control of the patient. The effort to identify the reasons leads to five interacting dimensions of the medication behavior. Figure 13 shows the details of following five interacting dimensions of medication behavior – (1) Social and Economic Dimension, (2) Healthcare System Dimension, (3) Condition-Related Dimension, (4) Therapy-Related Dimension, and (5) Patient-Related Dimension (WHO 2003). In Appendix A3.1, different factors affecting medication adherence in each interacting dimension are reported (Meducation 2006).

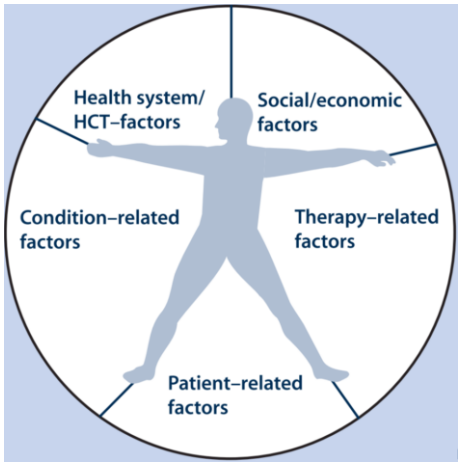


Figure 13. The five interacting dimensions of medication behavior (WHO 2003)

As behavior contributes to the cause of much current mortality and morbidity (Michie and Johnston 2012), interventions to change medication behavior are essential in prevention. Behavior change interventions are usually complex, comprising many interacting components (Craig et al. 2008).

3.2.2 Efficacy

Theories summarize the state of cumulative knowledge. They specify key constructs and relationships and the underlying scientific explanations of the processes of change and link behavior change to constructs in a systematic way. They describe how, when and why change occurs. They allow investigators to understand why and how interventions succeed or fail. Rigorous testing of theoretical principles forms a basis for future interventions. Thus, theories are fundamental in designing behavior change interventions.

Investigation of theory to support the problem domain is a central exercise in design science research. Key frameworks for designing and evaluating behavior change interventions (Collins et al. 2011; Craig et al. 2008) emphasize the importance of using theory to inform intervention design as well as specifying interventions using component behavior change techniques(BCTs). Behavior may refer to simple, specific actions, for example, swallowing a pill; about health, it is used to refer to a more complex sequence of actions. Behavior change techniques (BCTs) are observable and replicable components of behavior change interventions. They are the smallest component compatible with retaining the proposed mechanisms of change, and can be used alone or in combination with other BCTs (Easthall et al. 2013; Michie and Johnston 2012). Precise specification of BCTs may also enhance the intervention.

Dombrowski et al. (2012) found using a BCT coding scheme that instruction, self-monitoring, and practice were effective techniques. Taylor et al. (2012) also found that the extent to which

interventions were explicitly based on theory predicted their effectiveness; a finding consistent with a similar analysis of collaborative interventions (Webb et al. 2010).

The existing electronic reminder systems have been available for decades, yet there is very small improvement in the medication adherence behavior. Most of these systems rely on simple alarms and do not consider another determinant of health-related behavior. Besides the technology enablement, it is important to consider the personal traits of the patient entrusted with the prescribed self-administered medication regimen.

For both scientific and practical reasons, it is essential that behavior change interventions develop a sound scientific basis. In practice, the science will inform the technology (i.e. the techniques and methods) required to deliver effective, replicable interventions with guidance on their delivery to ensure use of effective interventions. A science of behavior change needs both good theory and reliable technology.

In this research, we develop a model to improve medication adherence from information systems and health IT perspective. Health IT enabled intervention is based on the notion of collaborative care as it leverages the patient-provider relationship and can help those who are willing to be helped. When a prescribed medication is self-administered, the choice rests with the patients and their motivation to take the medicine. An intervention is a mechanism to try and modify the behavior of the patient, in the best interests of the patient, when the concordance between patient and the provider breaks.

This research examines the problem with the lens of health behavior change theories to predict “when” and “what” intervention is required to improve the medication adherence behavior of patients, thereby making the interventions “smart interventions.” Appendix A3.2 discusses different health behavior change theories as adapted from Revere and Dunbar (2001)

For the purpose of this research, we are interested in a theory that can support a health IT artifact for affecting a behavior change. The simplest of BCTs that finds prevalence in system design are reminders, a component of both Health Belief Model and Stages-of-Change Model. We also identify effective medication adherence 'EMA' as a 'Goal' for the patient. Stages-of-Change Model and Theory of Planned Behavior and Theory of Reasoned Action support setting goals and steering of the patient towards the goal. As the theories listed in Appendix A3.2 support BCTs, we utilize the BCTs to leverage in the theory based model for effective medication adherence. We focus on when and what reminder (Cues to action/maintenance) to administer to the patient as smart intervention for improving medication adherence.

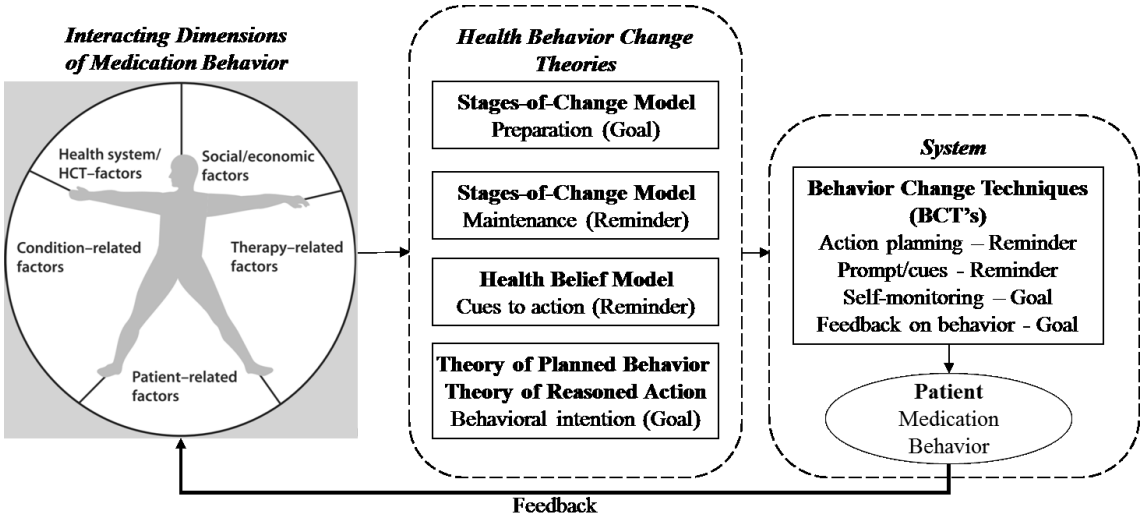


Figure 14. Generalized model based on the BCTs affecting medication behavior

Figure 14 shows a generalized theoretical model supporting the health IT system. The most prevalent Behavior Change Techniques leveraged in the development of the health IT system model are Action planning, Prompt/cues, Self-monitoring, and Feedback on behavior. These four techniques are based on the health behavior change theories of Stages-of-Change Model, Health Belief Model and Theory of Planned Behavior/Theory of Reasoned Action and specifically are focused on behavior changes tied to Goals and Reminders (Morrissey et al. 2015).

Action Planning: Prompt, detailed planning of performance of the behavior (must include at least one of context, frequency, duration, and intensity); context may be environmental or internal. An example is setting a reminder to take medication at a specific time every day

Prompt/cues: Introduce or define environmental or social stimulus for the purpose of prompting or cueing the behavior; the prompt or cue would normally occur at the time or place of performance. A reminder alarm ringing to prompt the user to take medication is a prompt/cue BCT.

Self-monitoring: Establish a method for the person to monitor and record their behavior(s) as part of a behavior change strategy. A dialog box that allows users to record whether they took or skipped their medication is a self-monitoring BCT.

Feedback on behavior: Monitor and provide informative or evaluative feedback on the performance of the behavior. An example is a log or graph that displays the user's adherence levels.

As shown in the generalized model based on the BCTs affecting Medication Behavior, we see that patient's medication behavior is a dynamic state that keeps changing, from the interventions provided by the system, and continuously feeds to the knowledge base of interacting dimensions of medication behavior. These medication behaviors are examined using the health behavior change theories. Such examinations can lead to an expansion of the existing theories or to postulate new theories for explaining a new or changed behavior encountered, and subsequently to identify new BCTs.

3.2.3 Realization

A key requirement for the envisioned model/health IT system is the ability to be real-time and dynamic i.e. administer the intervention when needed. The design of such model, or system

requires a feedback mechanism and ability to exert control as close to the source as possible. We examine the design from the theoretical perspective of control theories that provide a basis for real time control systems (Albus and Barbera 2005; Albus and Rippey 1994; Carver and Scheier 1982). Control theory is an interdisciplinary branch of engineering and mathematics that deals with the behavior of dynamic systems with inputs, and how feedback modified their behavior. The objective of control theory is to control a system, so its output follows the desired control signal, called the reference, which may be a fixed or changing value. A controller monitors the output and compares it with the reference. The difference between actual and desired output, called the error signal, is applied as feedback to the input of the system, to bring the actual output closer to the reference. Mapping this to the problem of medication adherence, we model the control system to have the ability to capture the dosing event. The controller compares the dose event to the reference prescribed dose event. If the dose is not effective or the dose is undesirable, a feedback is generated. The feedback is the probable value of effective medication adherence at next prescribed dosing event. The probable value depends on the past pattern of medication behavior of the individual. Based on the value of feedback generated, it can be decided to administer intervention.

To develop a system that can adapt to the medication behavior exhibited in real-time also leads us to examine the cognitive foundations for system design. A cognitive architecture is the organizational structure of functional processes and knowledge representations that enable the modeling of cognitive phenomena. The fundamental cognitive system is composed of a behavior generation engine driven by a model updated by a perceptual system and governed by a value system as shown in Appendix A3.3a.

Controllability and observability are main issues in the analysis of a system before deciding the best control strategy to be applied. Controllability is related to the possibility of forcing the system into a particular state by using an appropriate control signal. Observability is measuring the state of a system. There are several control techniques as represented in Appendix A3.3b which are applicable to model and strategy chosen.

Hierarchical Control System is close to our problem domain based on the multidimensional nature of the problem that involves one or more than one feedback influencing the goal or behavior. In a hierarchical control system, intelligent control can be built as units of the control system without having to change the design explicitly.

We leverage the existing hierarchical control system Reference Model Architecture (RMA) theory for Real time Control Systems for its extensible nature (Albus 1993; Albus and Rippey 1994). At its core, the RMA can be mapped directly to the controlled process or real world, avoiding the need for a mathematical abstraction, and in which time-constrained reactive planning is implemented. RMA is cognitive theory based architecture designed to enable any level of intelligent behavior.

RMA consists of a multi-layered multi-resolution hierarchy of computational agents each containing elements of sensory processing (SP), world modeling (WM), value judgment (VJ), behavior generation (BG), and a knowledge database (KD). At the lower levels, these agents generate goal-seeking reactive behavior. At higher levels, they enable decision making, planning, and deliberative behavior. RCS functional modules may add, subtract, multiply, differentiate, integrate, compute correlation functions, recognize patterns, generate names or addresses of symbolic representations, or perform planning functions at a hierarchy of levels. In its most complete theoretical form, the RCS reference model architecture provides a framework for

integrating concepts from artificial intelligence, machine vision, robotics, computer science, control theory, operations research, game theory, signal processing, filtering, and communications theory.

For the purpose of developing a system for smart intervention, we are considering a single node that is assigned the task to decide if there is a need for intervention, and when and what type of reminder to administer. A single RMA node can be used to model this requirement. Figure 15 shows a node of RMA (Albus 1993; Albus and Rippey 1994). Each node has ability for:

- Behavior generation (BG) - BG modules contain job assignment, planning, and control algorithms.
- Sensory perception (SP) - SP modules process data from sensors. It contains filtering, masking, differencing, correlation, matching, and recursive estimation algorithms, as well as feature detection and pattern recognition algorithms.
- Value judgment (VJ) - VJ modules contain algorithms for computing cost, risk, and benefit, for evaluating states and situations, for estimating the reliability of state estimations, and for assigning cost-benefit values to objects and events. VJ modules may compute statistics on information about the world based on the correlation and variance between observations and predictions.
- World Model (WM) - The WM modules models the state space of the problem domain. They contain information storage and retrieval mechanisms, as well as algorithms for transforming information from one coordinate system to another. WM modules use dynamic models to generate expectations and predict the results of current and future actions. WM modules may contain recursive estimation algorithms and processes that compute lists of attributes from

images, graphics engines that generate images from symbolic lists, and recognition and detection algorithms that perform pattern matching operations necessary to verify the identification of features, surfaces, objects, and groups. The WM module maintains a knowledge database (KD), acts as a question answering system and uses information on from the KD to predict or simulate the future.

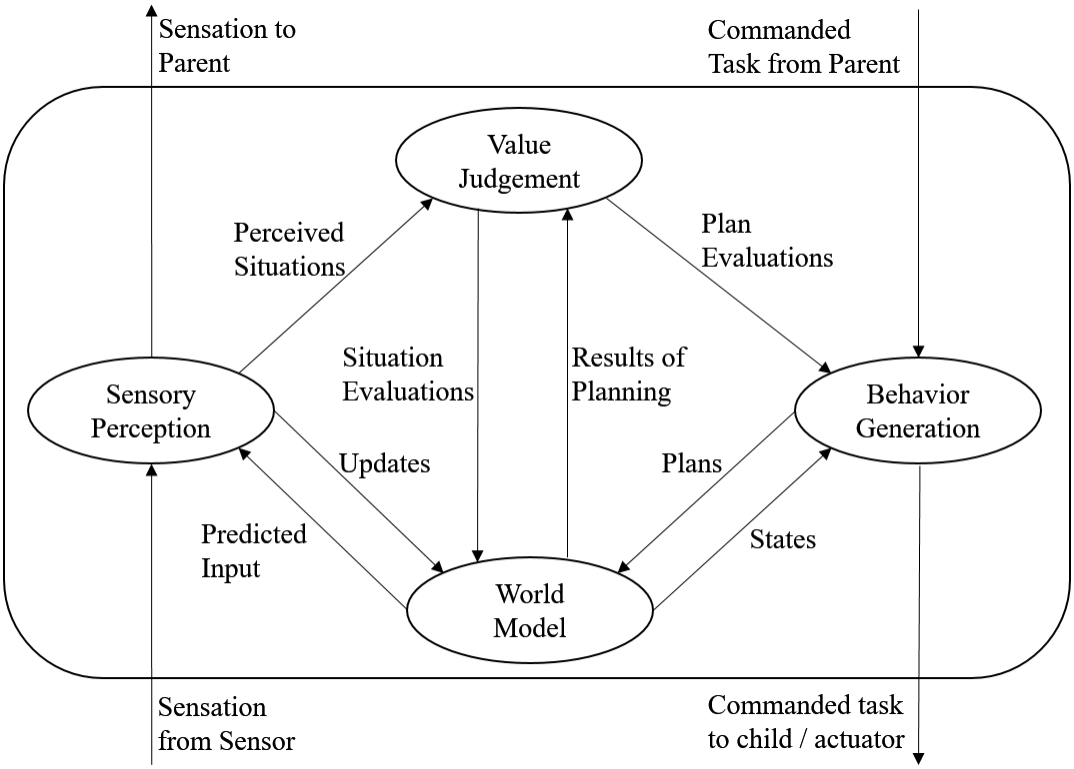


Figure 15. Node of reference model architecture (Albus 1993; Albus and Rippey 1994)

The operation of the Node of RMA is a set of steps defined by a planning period or an execution clock cycle:

While the planning period is open

{

BG planner hypothesizes a tentative plan;

WM predicts the probable result of the tentative plan;

VJ evaluates the probable result value;

BG planner checks to see if the probable result value is greater than the previous probable result value of the plan already in the current best plan buffer,

{

if it is,

then the tentative plan replaces the current plan in the current best plan buffer;

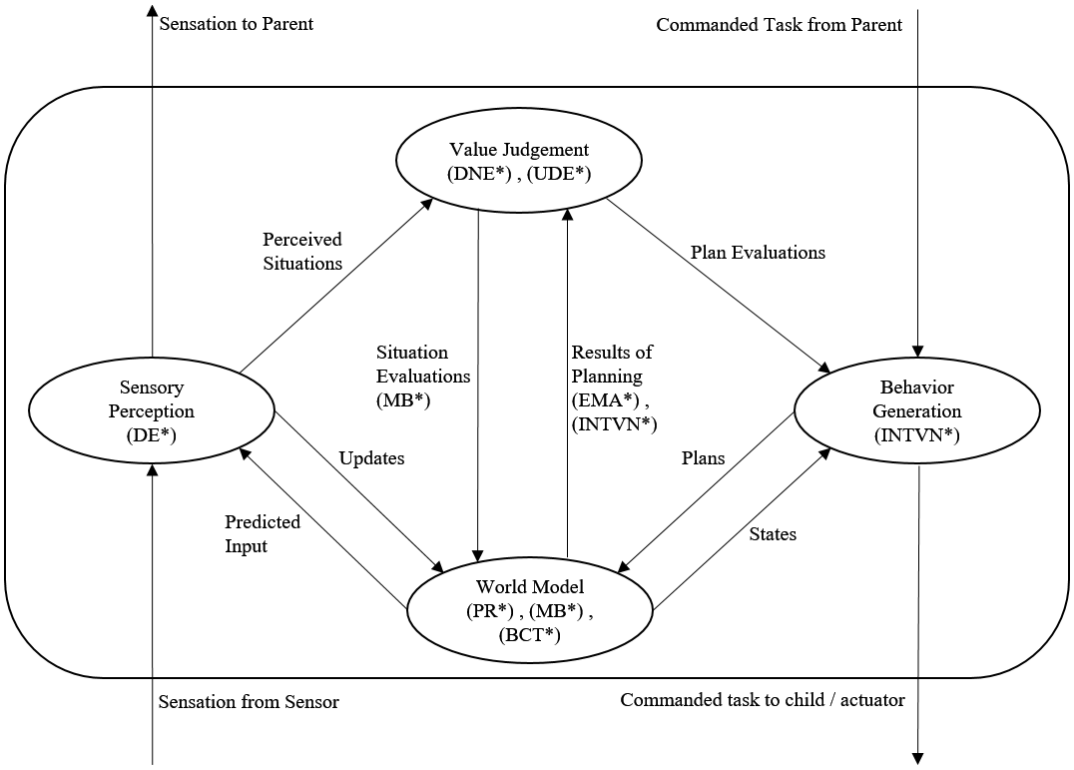
else continue;

}

};

At the top, the highest level task is defined by the highest level (i.e., mission) goal. At each successive level in the hierarchy, commanded tasks from above are decomposed into subtasks and sent to subordinates below. Finally, at the bottom, subcommand outputs are sent to actuators to generate forces and movements. Also at the bottom, sensors transform energy into signals that provide sensory input.

Figure 16 shows the dosing event (DE) being evaluated by a node in RMA model to plan and decide upon intervention based on prescribed dosing regimen (PR), dose not effective (DNE) and undesirable dose event (UDE). The sensory perception (SP) module registers an actual dose event (DE) from the patient. The value judgment (VJ) module evaluates the time of the dosing event by comparing it with the prescribed dosing regimen (PR) and identifying the dose not effective (DNE) or undesirable dose event (UDE). It then evaluates the value of effective medication adherence (EMA) for the next prescribed dose event based on a plan from the world model (WM). The value judgement (VJ) module compares the predicted the value of EMA to the prescribed value of EMA and takes decision to administer intervention (INTVN) based on applicable BCT from world model.



DE* - Dose Event, DNE* - Dose Not Effective, UDE* - Undesirable Dose Event, EMA* - Effective Medication Adherence, INTVN* - Intervention, MB* - Medication Behavior, PR* - Prescribed Dosing Regimen, BCT* - Behavior Control Techniques

Figure 16. MEMA implementation of RMA node for smart intervention

The current set of envisioned functionality is to provide a reminder (BCT) to the patients. The world model is enriched by knowledge module and inputs from other sensors, and the capability exists for enhancements in future. The usefulness of the node based on RMA model would be more suited is an enriched use case scenario.

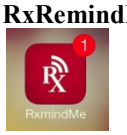
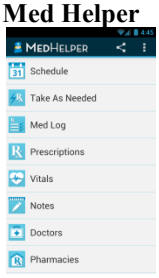
Section 3.3 Enabling Technologies

The current technologies are promising in the terms of advancements they bring. The sensor technologies for clinical use are advancing rapidly, shrinking in size and becoming personal and prevalent. The rising cost of healthcare is forcing people to make a conscious choice to stay fit and healthy. The healthcare providers are enabled with collaborative technologies and are

becoming more capable of delivering personalized clinical treatments that are self-managed by the patients. The shift towards self-management is to reduce costs. The mechanisms to monitor the drug usage in the patients has progressed. Smart medication dispenser that can dispense doses as necessary (Wireless Medication Box) are available for use.

Unfortunately, the same is not true with the application that supports medication adherence. We examine some of the applications that allow monitoring of the drug use and find at this time, only simple applications that measure average medication adherence are available and provide scheduled reminders. There is an opportunity for much more sophisticated and personalized mobile applications. Table 4 discusses current top six mobile applications used on Android/IOS platforms for medication adherence. Analysis of these applications shows that all these medication adherence applications use reminder and does not focus on goal behavior change technique.

As we can see from Table 4, most of the existing medication adherence applications seem to be reminder applications that rely on the schedule generated in advance based on the prescribed dosing regimen. The dynamic scheduling (where a reminder is scheduled if there is a need) of intervention is missing in the existing applications. In the view of this limitation of existing apps, we proposed the model for effective medication adherence. The uniqueness of model for effective medication adherence is that it does not create a schedule for intervention. It uses dynamic scheduling.

Application Name	Compatibility & Cost	Features	Limitations
Medisafe Meds & Pill Reminder 	**Android/IOS Free**	• Synchronizes information to a "family pillbox". • Allows helping family members with their pills. • Shares information with caretakers who can be notified if the patient has not checked into the app. • Provides a list of medications that are "due today" and check them off as you go. • Sync reminders with android wear a smart watch. Shake your wrist to mark that you took the medication.	• May fail to consider lifestyle factors. • Users generally enter their own information. This can be barrier among those already unlikely to follow a schedule. • No context-aware reminders. • Med-Friend feature does not work some times correctly.
MyMedSchedule 	**Android/IOS Free**	• Allows creating and saving easy-to-understand medication schedules. • Shows the times of consumption of medications or supplements, how much to take, and the purpose. • Can set up text and email reminders. • Provides information to specialists about the medications you are taking and you can access • Provider data input capable	• Does not track missed and taken doses • No persistent reminders • No context-aware reminders
MyMeds 	**Android/IOS** **Free**	• Tracks the missed doses and export that data to health providers for review. • When the patient properly uses the app, this feature can provide information to help healthcare providers assess medication adherence.	• No persistent reminders • No context-aware reminders • Not capable of provider data input
RxRemindMe 	**IOS** **Free**	• Tracks missed doses and export that data to health providers for review. • When the patient properly uses the app, this feature can provide information to help healthcare providers assess medication adherence.	• No persistent reminders • No context-aware reminders • Cloud data storage is not available • Not capable of provider data input
Med Helper 	**Android** **Free**	• Keeps track of prescriptions - Alarms reminds when medication needs to be taken when doctor's appointments are scheduled and when medicines are running low or are about to expire. • Also tracks vital signs and PRN / take-as-needed medication. • Can log and export or print detailed reports for doctor, nurse or caregiver.	• Does not track missed and taken doses • No persistent reminders • No context-aware reminders

Dosecast 	**Android/IOS** **Free**	• Reliable notifications: Nags you until you take the medicine • Flexible scheduling: helps you take doses on a daily/weekly/monthly schedule, every X day/weeks, only on certain days of the week, or even after a pre-set number of hours or days since the last dose. • Customizable dose amounts and instructions • Postpone-able reminders • Smart silencing • Private and secure: Medicine information is encrypted	• Does not keep track of daylight savings time changes. • No context-aware reminders • Not reliable tracking of actual dose consumption as not connected to a smart pill-box

Table 4. Current mobile applications for medication adherence

3.3.1 Medication Event Monitoring System (MEMS)

Electronic Monitoring (EM) units vary in design from standard pill containers with a microprocessor chip embedded in the cap to medication boxes with compartments for individual doses to metered-dose inhaler canisters that release puffs of medication. Most of the EM devices monitor medication dosing using special containers that store dosing information on a microprocessor inside the unit until the data downloads into the specialized software. Patients are shown how to use the devices and instructed not to open the unit except when medication is needed for dosing.

On return to the clinic, the unit is inserted into a communicator apparatus that reads the electronic information and transmits it to the computer. Medication event monitoring systems are progressively advancing to include wireless communication facilitating the transmission of the information in real time. Real-time observability at source i.e. when the patient takes the medication is a key requirement for the design of health IT system based on Effective Medication Adherence.

3.3.2 Smart Medication Management System (SMMS)

Smart medication management is performed by systems that can detect, process, and use context-awareness in creating suitable actions including reminders to patients (Varshney 2013). Such systems can compensate for the deficit of cognitive abilities of the elderly. Wearable, portable or environmental technologies capture the vital signs, health parameters, and system generates current context of the patient (Varshney 2011). The healthcare providers collaborate with one another and decision making system, which then interacts with medication management system for generating context-aware reminders/alerts for higher adherence.

The system also provides context-sensitive information to assist the cognitive process involved in interacting with the system, obtaining and ingesting the medication(s). For example, the patient may need help in remembering what medications to take, what dose, when and how. In cases of missed or delayed doses, the system processes on its own or in some cases with the help of a healthcare provider. The resulting actions could be to either vary the timing and quantity of left-over doses or skip the dose in the worst case if variations are not possible due to medical safety.

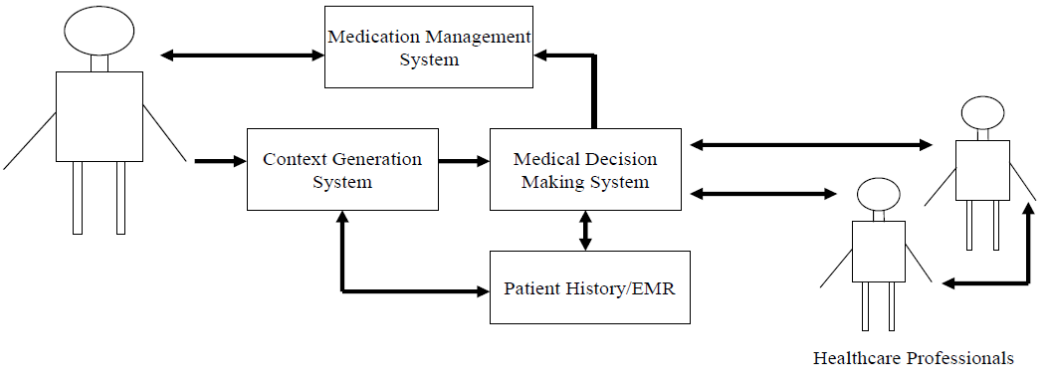


Figure 17. Smart medication management system model (Varshney 2013)

Section 3.4 Effective Adherence

The effectiveness of adherence (therapeutic) reduces if there are 'Dose not Effective' periods in the Pattern of adherence, and in some cases could lead to an appearance of ineffectiveness in the therapeutic value of the medicine. Effective Medication Adherence (EMA) is a probability measure for assessing the effect of the pattern of adherence due to 'Dose Not Effective' periods in the prescribed dosing regimen on the effectiveness of adherence.

If the adherence is 100% of the time to the prescribed interval of taking the doses, EMA will be 100%. Any pattern arising from nonadherence should lower the EMA below the 100%. An analytical model is developed to study the effect of the patterns of adherence on EMA. This research study allows us to validate the operation of this metric under a set of specified assumptions.

Section 3.5 Smart Intervention

The objective is to improve the adherence of medication; we intend to use 'EMA' as a construct in our model for deciding 'when', and 'what' intervention is desirable for nonadherence. The design of the intervention based on EMA should allow for predicting when it is most likely that intervention will be needed. The decision is made on the fly, in contrast to the conventional interventions which work at scheduled intervals. We term intervention based on EMA as Smart Intervention for the same reason that it will administer if and when there is a need for intervention. 'What' intervention will be needed is based on an assessment of factor by which the 'EMA' will get adversely affected if the patient does not take prescribed medicine at the suggest time. This research proposes that medication adherence research should utilize EMA, which includes both the pattern and average medication adherence for a patient and therefore, can lead to the identification of more effective interventions. Healthcare providers can use the

insights from EMA and related medical data to establish customized or revised prescription regimen for different groups of patients based on the patterns of medicine intake and clinical response to medication. It can also facilitate the design of smart interventions that get personalized to the patient's behavior over a period.

In this research, an improvement to existing intervention is envisioned that is termed "Smart Intervention" to distinguish it from existing intervention. Here, smart intervention mean that intervention will be necessary and provided to the patient only if the patient did not consume the prescribed self-administered medication dose at the prescribed duration. This smart intervention will be affected in the form context-aware reminders to the patient as opposed to simple and persistent reminders that existing intervention provides.

The context-awareness of smart intervention arises from the awareness and consideration of DNE events. The decision to administer intervention is then based not only on the prescribed interval between the doses but also the presence of the DNE events and the pattern in which patient generates the events. Such interventions are provided only when there is a need and are more dynamic in nature.

The possibility that patient will follow the intervention is greater when the intervention is discreet, the patient is not being overwhelmed and is cognizant of the justification for intervention based on patient's anomaly in adherence.

Table 5 shows the functional difference between intervention and smart intervention.

Intervention	Smart Intervention
Based on AMA	Based on EMA
Simple and Persistent Reminder	Context-Aware Reminder

Table 5. Intervention vs smart intervention

This research develops a smart intervention based on BCTs that have underlying theory base of Health Behavior Change and upon the Reference Model Architecture for real time systems. The system is designed to act at the source of the problem i.e. when the person takes (or skips dose at a prescribed time) and generates the probabilistic estimate of the effective medication adherence to suggest the next intervention. The impact of the smart intervention on effective medication adherence, healthcare cost and the patient outcome could be profound as the problem is detected early and action is taken instead of towards the end of medication persistence.

Chapter 4. Development

The development of the conceptual artifact (smart intervention) is the primary contribution of this research. This section includes a concise description of the artifact at the appropriate level of abstraction (Gregor and Hevner 2013). It describes a general approach for monitoring of effective medication adherence. Also, the input parameters used in the analytical model for evaluation of the artifact is described in this section. Discussion of parameters along with the artifact will provide insight into the relationship between the components of the artifact and the new measurement metric for medication adherence, i.e., effective medication adherence (EMA).

Section 4.1 Constructs

We started with developing a simplified Model for Medication Adherence based on the literature review and the current clinical environment. The dosing regimen begins with concordance between the provider who is treating and a patient being treated. In a self-administered dosing regimen, the patient bears the responsibility to take the medication in compliance or adherence with the provided advice. If the provider feels the need to monitor the effectiveness of the medication and the symptoms, they may collect the feedback from the patient. If all goes well, the therapeutic benefits of the medication are realized towards the end of the prescription.

The study indicates there are number of factors that affect the adherence of the patient to the prescribed dosing regimen and thus affect the realization of the therapeutic benefits of the medicine(s). Adherence is extent to which a patient's behavior (regarding taking medication, following a diet, modifying habits, or attending clinics) coincides with medical or health advice during the period of medication persistence i.e. the time from initiation to discontinuation of therapy. Almost invariably, the provider comes to know the outcome of the prescribed

medication after the treatment period is over and if the patient provides feedback to the provider. If the patient does not self-report, then opportunity to provide timely interventions to improve patient's condition are rare. At the time of prescribing medications to the patient, it is assumed that patient will self-report the symptoms if the condition persists beyond a reasonable duration of taking the medications.

In cases where the patient self-reports that symptoms persists, the effectiveness of the medication is assessed by discussing with the patient whether they took all the medications on the prescribed intervals and estimating the average effectiveness of the doses. Subsequent treatment plans may lead to increasing dose persistence for few more days. Figure 18 represents the simplified Model for Medication Adherence:

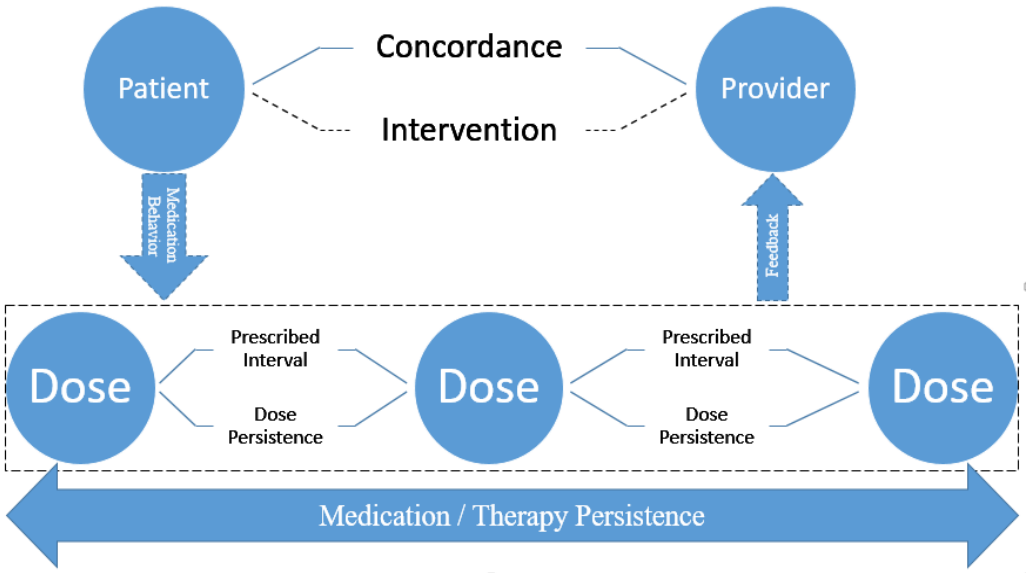


Figure 18. Simplified model of medication adherence

Section 4.2 Requirements

Our requirement is to administer smart intervention i.e. envision a model that provides an ability to choose 'when' and 'what' intervention is needed. We outline the formal requirements

of the model for effective medication adherence. The realization of this model is a health IT artifact.

The decision to administer intervention depends on the medication behavior of the patient. The medication behavior is event based i.e. if the patient takes the medicines at the prescribed intervals over the duration of the prescription. The dosing events can be mapped against a timeline for prescribed medication persistence and should ultimately develop a pattern of dosing events i.e. the medication behavior. An intervention is a mechanism to control the normal medication behavior of patient if he/she does not conform to the prescribed dosing regimen. The decision for when an intervention is needed can then be a straightforward rule: if the patient did not take the medication at prescribed times, administer the intervention. The simplified model of medication adherence can easily be extended to implement this rule if it can capture dosing events and the prescribed dosing intervals against a timeline beginning the start of the medication and ending end of the medication. We call interventions that are administered based on a schedule of prescribed doses as Scheduled Intervention.

An alarm for a reminder is a good example of scheduled intervention. An alarm can have a schedule and can remind of the repeating tasks at specified intervals. When coupled with an event capturing system that can register if a task has been performed, alarm for reminder is skipped if the task is performed before the next scheduled time. If the task needs to happen exactly at the specified interval i.e. exactly at the scheduled time, we have a situation when the alarm for the reminder and the task will occur at the same time. The alarm for reminder cannot be made to wait for the event unless we decide to schedule the alarm a few moments after the time of the task. There is theoretical limit to performing tasks when tasks are interdependent. At a time, only one task of the interdependent tasks can be performed. The usefulness of alarm for a

reminder is to prompt before the task has to be performed, so as to focus the attention of performer. In this situation when we want to have reminder before the task, the alarm is scheduled for few moments before the time of the task. The drawback of this is that it does not make use of the event capturing system and is repetitive, occurring every time before the scheduled task.

Extending this analogy to deciding when to administer intervention, we arrive at following decisive situations: Intervention scheduled before the dosing event, intervention scheduled at the same time of dosing event, and intervention scheduled after the dosing event. Interventions scheduled before the dosing event always occurs (persistent). Intervention scheduled at or after the dosing event is skipped if the dosing event has happened.

Scheduled Intervention is a prescriptive behavior again, and is determined right at the time of prescription. It has little ability to adapt to the medication behavior of the patient because the behavior does not exibit at the time of prescription.

Section 4.3 Model

We develop the model for effective medication adherence, henceforth also mentioned as MEMA, based on effective medication adherence of the patient. In this model, we do not create a schedule of administering the interventions but decide the next administration of the intervention dynamically. We create a schedule of prescribed dosing events at the time of prescription and also register actual dosing event of the patient during prescription. Value for effective medication adherence (EMA) generates at each dosing event of the patient and the prescribed dosing event. Based on the value of EMA, an appropriate type of intervention is chosen and scheduled either before or at the next dosing event for the patient. It may also happen that intervention is not deemed necessary for the next prescribed dosing event if the patient is 100% following the

prescribed dosing regimen. The type of intervention denotes the priority we associate to the next scheduled intervention in maintaining the EMA above a specified threshold (depending on the type of care and therapy). Figure 19 shows the priority of the intervention predefined in current model as 'Normal', 'Warning', and 'High' based on an allocated probability estimate of EMA for the next prescribed dosing event.

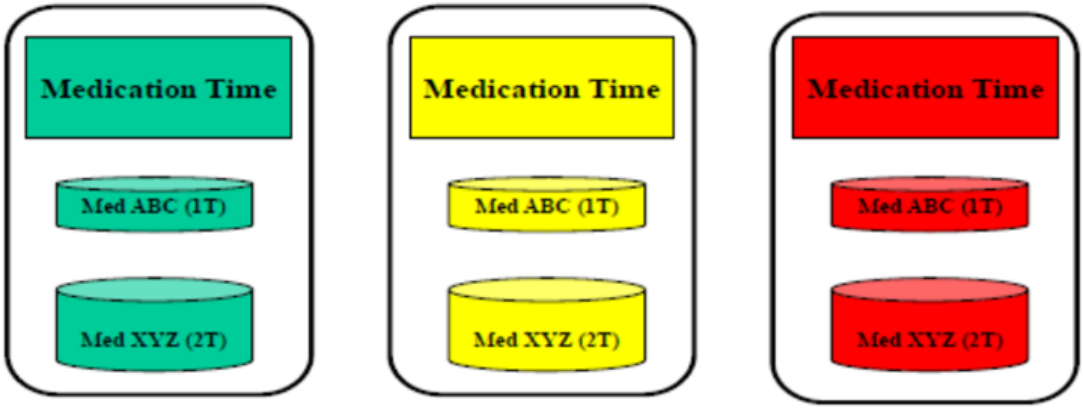


Figure 19. Predefined type (priority) of intervention (reminder) (Varshney 2013)

Deciding the 'Type of intervention' requires extensive study of therapy regimens, medication behaviors, and medical conditions. Developing classification specific to prescriptions can become an active research topic.

MEMA model is more adapted to the medication behavior of the patient as it keeps up with the actual dosing events and also provides the ability to decide what intervention is needed. Figure 20 shows the model for effective medication adherence (MEMA).

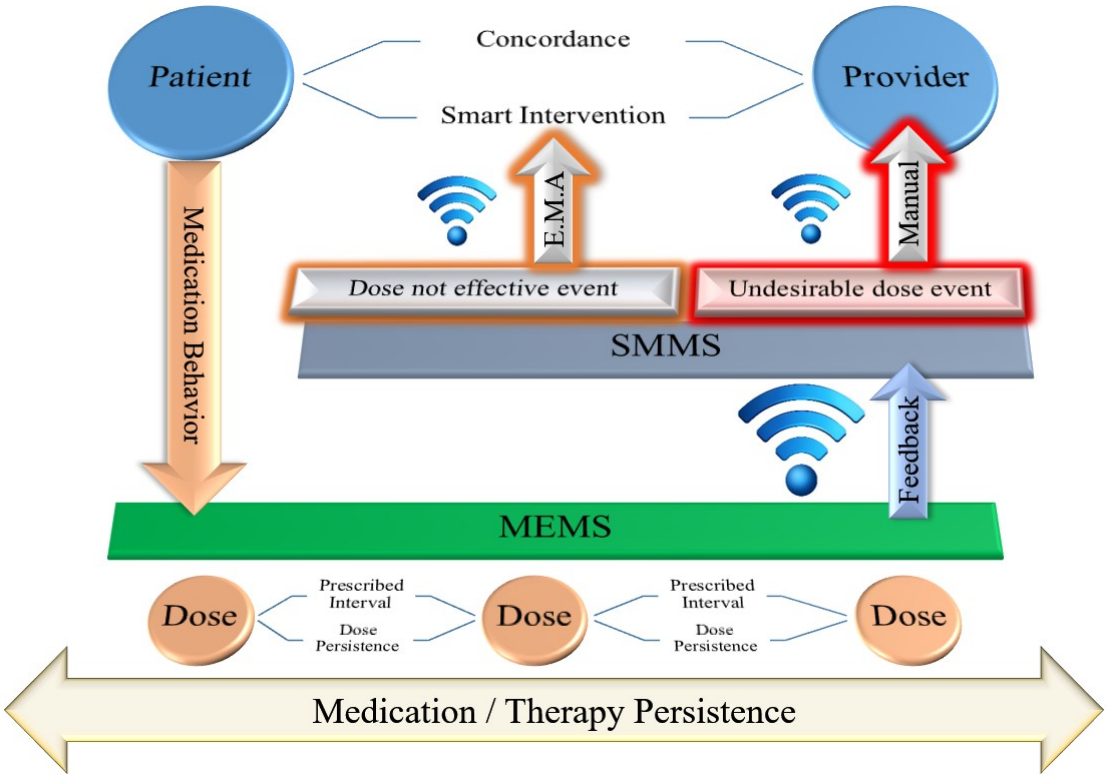


Figure 20. Detailed design of model for effective medication adherence (MEMA)

Figure 20 shows the model for effective medication adherence (MEMA). This model is for use by the healthcare provider and complements the prescriber's role in improving the medication adherence. The relationship between the healthcare provider and patient is the basis for operationalization of this model. The patient can opt in for smart interventions for a prescription drug. Upon consent, the medication behavior of the patient is monitored using Medication Event Monitoring System (MEMS) and at every dose event, the information is relayed to the Smart Medication Management System (SMMS).

The MEMA implementation of RMA node for smart intervention as depicted in Figure 16 is a component based on smart medication management system. It can record the dosing event, and decide if the dosing event is a prescribed dose event, undesirable dose event or dose not effective event. Based on the outcome, the system can either decide to calculate the effective medication

adherence value (using dose not effective), or notify the healthcare provider (undesirable dose event), or calculate EMA and decide to do nothing (prescribed dose event). If the predicted value of EMA is deemed to fall below a certain value specified for the therapy persistence, the system will schedule an intervention for the next dosing interval. The frequency and type of intervention for the next prescribed dosing event is decided based on the value of EMA and pattern of medication adherence exhibited by the patient in the past.

The MEMA model is implemented as having a systems interface and a user interface. The systems interface is for the administrator while there are two types of user interface for provider and the patient. The user interface can be affected via web based, smartphone or desktop application. The ability to connect over wireless/internet is requirement for the system to operate.

Section 4.4 Design

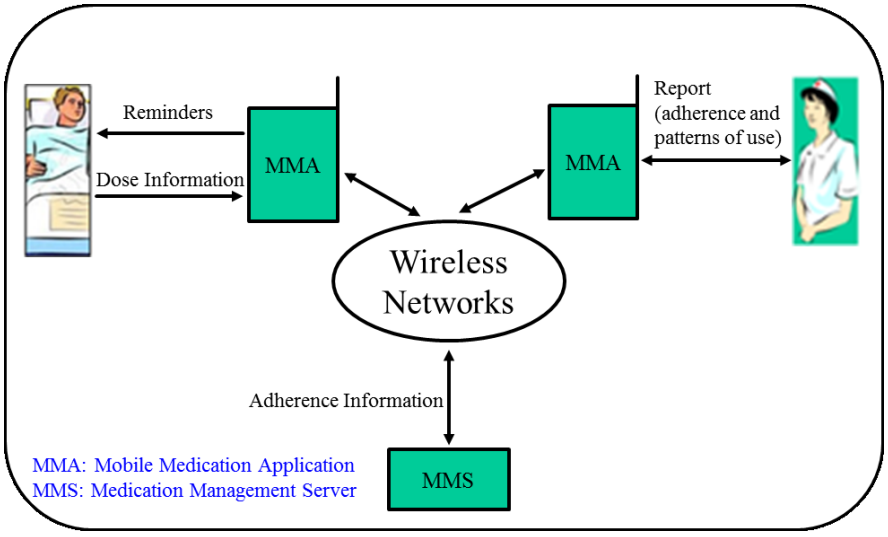


Figure 21. Model of medication adherence

Figure 21 shows a simplified model of medication adherence. We enhance the existing model to include the wireless medication box (WMB), and the application logic of medication management server (MMS) is enhanced based on the Resource Model Architecture to include the state of the system (world view).

In the model for effective medication adherence shown in Figure 22, both the patient and healthcare provider interact with the medication adherence application, which interacts with medication management server through a variety of wireless networks. The mobile application interacts with the healthcare provider and the patient. The mobile application also interacts with the medication management server to keep track of prescriptions provided by the healthcare providers' office as well as the consumption of medication by the patient. The IT supports these interactions and tracking as part of implementing the intervention for medication adherence.

More specifically, medication management server keeps track of adherence, side effects, and dosing changes which are available through mobile applications based on the reminders provided to the patient and patient's response to reminders. Also, medication management server keeps track of dose consumption and information available through wireless technologies which provide the prescribed doses to the patient. Finally, based on the interactions with mobile applications, patients, and healthcare providers, medication management server will generate the context-aware reminder for the patient. This process continues until the desired rate of effective medication adherence is achieved. We expect that many more applications on Smartphone and other smart systems using wireless technologies will become available for improving medication adherence.

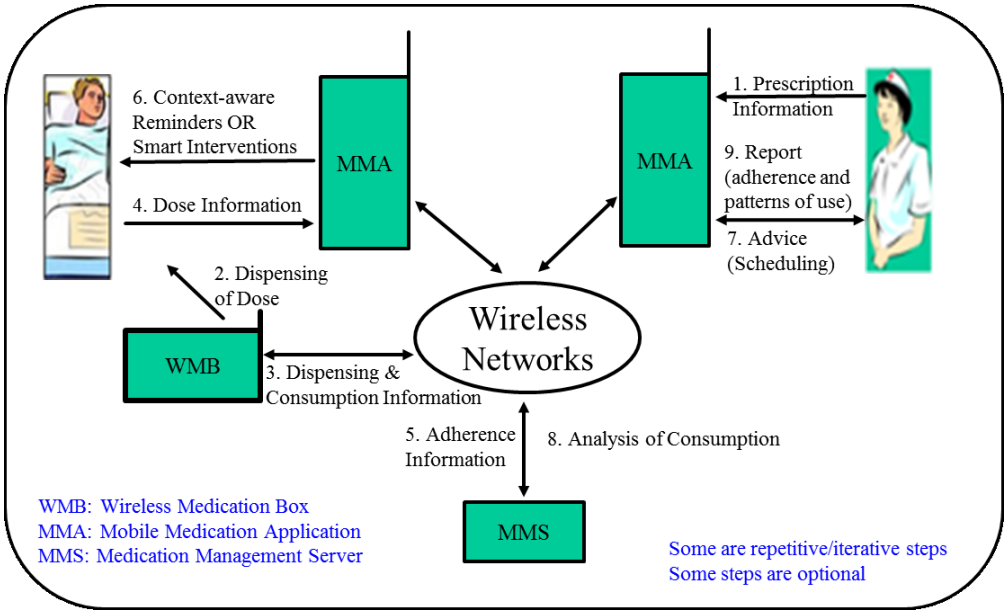


Figure 22. Model for effective medication adherence (MEMA)

The high level view showing variables used in the analytical model mapped to MEMA is represented in Figure 23. Healthcare provider enters the prescription information (λ, N_{PRES}) using mobile application, which is eventually saved in the medication management server (MMS) and shared with patient through the mobile application. Patient opens the wireless medication box to consume the prescribed dose. Dose information ($N_{TAKEN)}$ and the dispensing and consumption information (N_{TAKEN}, λ). is reported to the MMS. Using the adherence information MMS performs the analysis of consumption and calculates the EMA and UDE for different scenarios (nor reminders, simple and persistent reminders, and context-aware reminders). Based on the analysis of consumption, smart interventions (CAR, N_P, $N_{R,}$ $P_{D\text{-}R}$, $P_{ND\text{-}R}$) are generated and provide to the patient to maintain the medication adherence as prescribed by the healthcare provider. If patient misses a dose (N_{MISSED}) it is reported to the healthcare provider and healthcare provider provides the advice/scheduling based on the current EMA. On the other hand, if patient consume more than desirable doses (UDE) during the prescribed interval it is

reported to the healthcare provider too. However, no intervention is provided in the case of undesirable dose event (UDE). Smart interventions for UDEs will developed in future study.

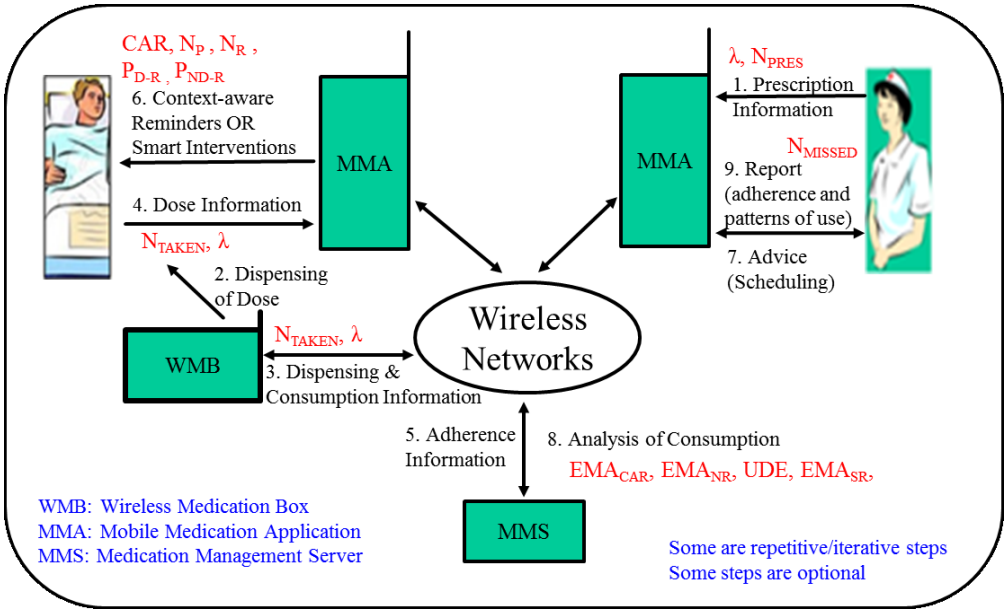


Figure 23. Variables in model for effective medication adherence (MEMA)

Section 4.5 Verification

The operation of MEMA is verified using the steps:

1. Design a mobile application for medication adherence (MMA)
2. Utilize a smart medication dispenser that can dispense doses as necessary (WMB)
3. Design a Server (MMS) that
    - Can communicate with patient and healthcare providers (via mobile application) as needed and also with medication dispenser
    - Can receive necessary dose consumption information from smart dispenser and/or the patient and can process medication consumption context of the patient
    - Can generate simple and persistent, and context-aware reminders (decide when to send reminders and how often)
    - Can analyze the consumption history and communicate with healthcare provider

4. Provide multi-network wireless access to various components (device, server) to support patient mobility
5. Check if various components (mobile medication application, mobile management server and wireless medication box) can interact with each other and with patient and healthcare provider
6. Check if medication management server receives informational contents
7. Check if context generates correctly
8. Check the timing of reminders and context-aware reminders
9. Check the number of doses, reminders and consumption history for any inconsistencies

Figure 24a shows the operation of MEMA. Figure 24b represents the algorithm to determine when and how to generate reminders to patients.

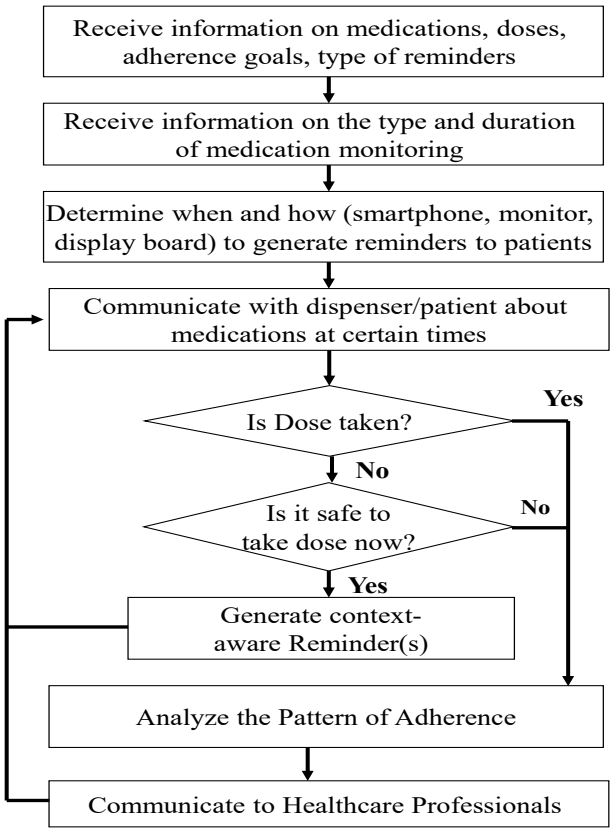


Figure 24a. The operation of the MEMA

```
Obtain dosing information
If time>=due-dose-time
    If Intervention = simple reminder
        If (time-limit-reminder = Not-expired)
            Display a reminder on patient's preferred device
            Obtain patient-dose-input
            If status-dose = taken
                Update med-consumption-history (attempts, dose status, timing, quantity)
                Else if (message-to-HP = allowed) Inform HP
            Else If intervention = persistent reminder
                While (status-dose =not-taken) and (time-limit-reminder = Not-expired)
If (number-of reminder-current-dose <Limit-persistence)
    Display a reminder on patient's preferred device
    Obtain patient-dose-input
    If status-dose = taken
        Update med-consumption-history (attempts, dose status, timing, quantity)
        Else If (message-to-HP = allowed) Inform HP
Else If intervention = context-aware reminder
    Process medication-consumption-history
If (Status-due-dose= Already-taken)
    No reminder
Else
    While (status-due-dose =not-taken) and (time-limit-reminder = Not-expired)
If (number-of reminder-current-dose <Limit-persistence)
    Display a reminder on patient's preferred device
    Obtain patient-dose-input
    If status-dose = taken
        Update med-consumption-history (attempts, dose status, timing, quantity)
    Else If (message-to-HP = allowed) Inform HP
    Record the actions (attempts, dose status and times)
    Update medication consumption history
```

Figure 24b. The algorithm to determine reminder generation

Table 6 lists the role of the model in various cases of nonadherence. The model currently supports reminders as an intervention and can be extended to include educational interventions for patients to address other reasons for nonadherence.

	Primary Reason for Nonadherence	Suitable Intervention	Model's Role in the Intervention
Case 1	Busy lifestyle	Reminders	Currently Supported
Case 2	Cognitive Decline	Reminders	Currently Supported
Case 3	Side Effects	Educational	Can be expanded
Case 4	Complexity of Regimen	Reminders/Educational	Can be expanded
Case 5	Length of chronic condition	Family Support	Can be expanded
Case 6	Cost of medications	Financial Intervention	Difficult to expand
Case 7	Lack of knowledge	Educational Intervention	Can be expanded
Case 8	Lack of trust / perceived need	Behavioral Interventions	Difficult to expand

Table 6. Nonadherence cases and the model's role in the intervention

Chapter 5. Evaluation of Process

Design science research (DSR) includes the building/design of an artifact as well as the evaluation of its use and performance (Pries-Heje et al. 2007; Vaishnavi et al. 2007). The model is evaluated using formal proofs and expert interviews (Cleven et al. 2009; Gregor and Hevner 2013; Parsons and Wand 2008). Evaluation with formal proofs such as analytical model represents an adequate evaluation method for DSR models (March and Storey 2008). The ex-ante perspective, i.e., artificial evaluation methods will help us to control the potential confounding variables more carefully and to prove or disprove the design propositions, design theories, and the utility of the developed artifact (Pries-Heje et al. 2008). Evaluations of an artifact based on formal proofs facilitate the assessment of a solution's suitability for a certain problem by implementing the solution generically.

The artifact is further evaluated (empirically) to demonstrate its worth with evidence addressing criteria such as validity, utility, quality, and efficacy (Gregor and Hevner 2013). Domain experts (healthcare providers and health IT experts) have compared the smart intervention with the existing interventions to evaluate the model. We have focused explicitly on the experts' reasoning about their preferences after comparing the simple and the smart interventions, and on relating that to the proposed health IT artifact. This evaluation provides the insights for interventions preferred by experts.

Section 5.1 Analytical Model

Analytical modeling is relevant, suitable, and useful for this work. Analytical models have been used as formal proofs for a long time to derive performance of systems in Computer Science, Decision Science, Operations Research, and Engineering (Saaty and Vargas 2012). These models provide several important insights into the design and operation of artifacts and

can be used to improve the design and operation of the artifact in an iterative fashion. In some sense, they provide intermediate and immediate results, which can help improving the design of artifacts, without waiting for subsequent empirical/multi-method studies. Many times, analytical models will help to validate the design by providing results that conform to expected performance of the artifact. We believe that analytical models could be used effectively in the design science area for both preliminary and intermediate evaluation of artifacts, followed by a more empirical evaluation.

We should be aware of numerous limitations and challenges in analytical models. The development of models may take time especially when the artifact's design and operation are still evolving. Many times, it is not clear what variables and metrics to include and what parameters to utilize and where to get those values from. The choice of model type is another challenge as a decision on whether to use deterministic (closed-form) or stochastic (random-events) approach can affect the suitability and usefulness of the model. The underlying assumptions in the model along with difficulty in validation, especially with error propagation inherent in some models, could reduce the usability of analytical models. The complexity of models in deriving accurate results is another challenge.

We evaluate the performance of smart interventions by MEMA by using the analytical model as shown in Figure 25. The approach we take in our research is to develop a simple model for the results that can help verify the basic design and operation of the model and more complex models that can provide a deeper understanding and more accurate results. In the design of computing and communications systems, such models have been used for a long time due to their ability to express complex relationships among many variables or behavior of interests. We expect that the comprehensive model, although complex, will be useful in predicting artifact’s

performance. One of the challenges has been the level of complexity in developing models and subsequent computations.

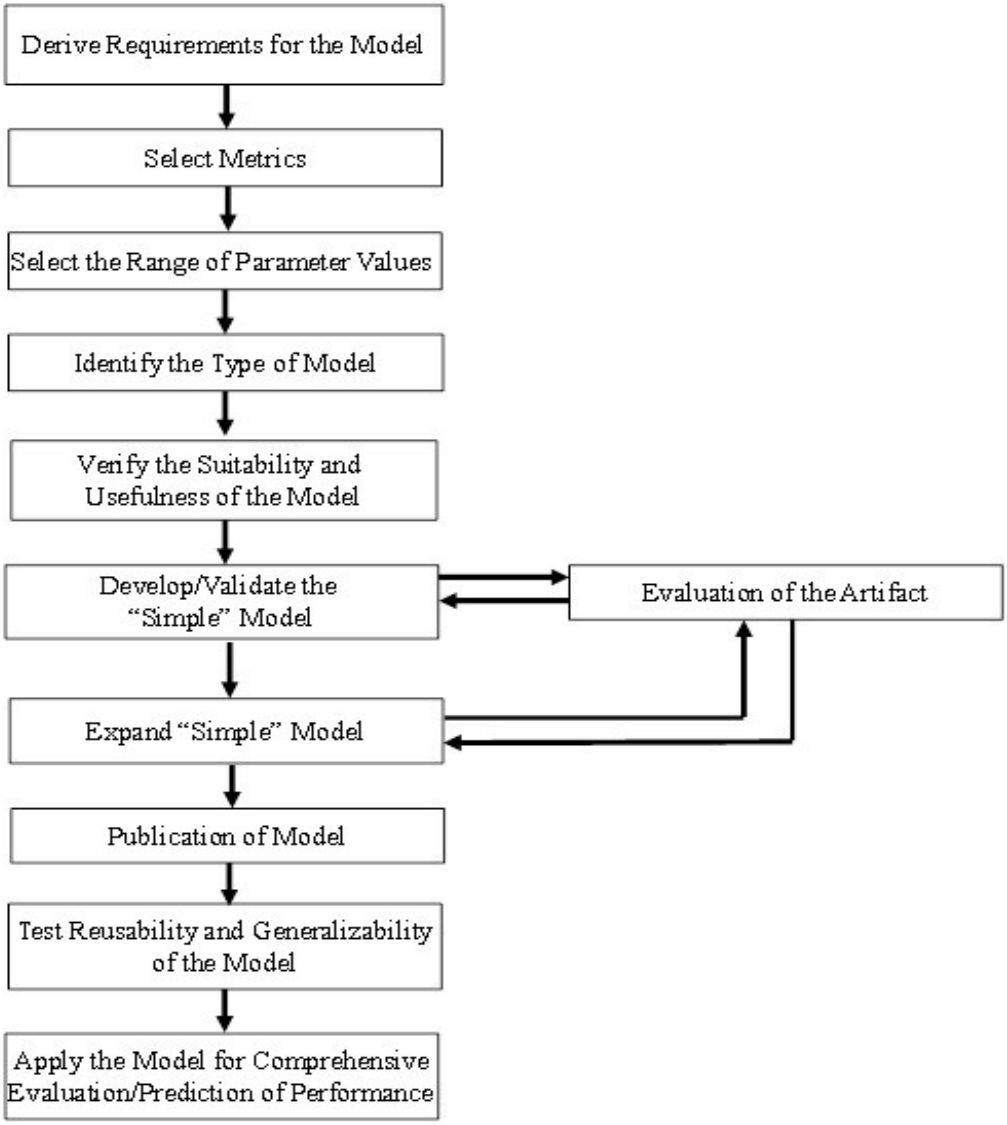


Figure 25. The use of analytical model in artifact evaluation

To address this, a model of reasonable complexity has been introduced to provide accurate results. Therefore, for evaluation of interventions for medication adherence, mathematical models are both suitable and desirable. More specifically, we measure the impact of various designed solutions and effect of multiple interventions on the rate of achievable medication

adherence. The model is developed using relationships among several independent (input) variables and dependent (output) variables discussed in Table 7.

To study patterns of adherence and effective medication adherence (EMA), we considered two distributions a) Uniform distribution, and 2) Poisson distribution. The goal is to analyze the pattern of adherence for a patient by utilizing the events when the patient takes the doses. We derive the probabilities of not being medically effective and not being safe. Patients with enormously diverse dosing behavior (random, skip followed by catch up, drug holidays, and multiple doses) can achieve the same average levels of medication adherence. Also, some patients with lower average adherence achieve more or less same outcomes as patients with higher average adherence (Sokol et al. 2005). The similar outcomes with different levels of adherence raise the possibility that patterns of adherence have something to do with the effectiveness of medication adherence. If the minimum time (T_{MIN}) between two doses is not medically safe, then it will lead to UDE. On the other hand, if the maximum time (T_{MAX}) between two doses is not medically effective then it will lead to dose not effective (DNE). This study focuses on studying the patterns of adherence along with average medication adherence (AMA), as effective medication adherence (EMA).

We started with Uniform distribution to study adherence. However, after comparing the results of both Uniform and Poisson distributions to study adherence, we observed that the differences are not huge. On the other hand, we felt that Poisson represents more variance and also there is evidence that medication consumption by people is closer to Poisson (Knafl et al. 2004). So, we decided to use Poisson distribution for the evaluation of MEMA using analytical model. The uniqueness of analytical model is that it can estimate EMA for many possible

scenarios. The scenarios are including and excluding the interventions for computing EMA. These different scenarios affect the ability to take medications.

5.1.1 Assumptions

A model is needed because data is not available on exact times patients have consumed various doses. Such data will become available in future. So for now, we make use of the analytical model to study/compare different interventions and their effectiveness. The model will evaluate effective medication adherence (EMA) as opposed to average medication adherence (AMA) in different scenarios and interventions. Several assumptions were made to keep the analytical model reasonably accurate. The analytical model assumes the following:

Assumption 1: The patients are in independent living and thus manage their medications.

Assumption 2: The dose concentration in the human body declines with time and reaches below a threshold at the certain maximum interdose-time. A medication dose taken beyond maximum interdose-time has reduced/negligible medical effectiveness.

Assumption 3: Taking more doses over time or too many doses at the same time does not improve medication adherence or health outcomes.

Assumption 4: The patients are willing to take medicine, but are not able to due to scheduling difficulties, forgetfulness, or cognitive challenges.

Assumption 5: The interventions used in the form of simple and persistent reminders, and context-aware reminders.

Assumption 6: The interventions cannot be used for unwilling patients at present.

5.1.2 Design

The basic input parameters of the model are dosing rate (λ), probability of taking dose due to reminder ($P_{D\text{-}R}$), probability of not taking dose due to reminder ($P_{ND\text{-}R}$), number of persistent

reminders (N_P), number of reminders in a day (N_R), overdose time (t), time at which I^{th} dose is taken (T_I), time at which $I+1^{th}$ dose is taken (T_{I+1}), minimum time between any two doses to remain medically safe (T_{MIN}), maximum allowed time between any two doses to remain medically effective (T_{MAX}). The output parameters are effective medication adherence (EMA) with and without interventions, healthcare cost (HC_{COST}), and side effects (UDE). Table 7 represents the summary of all the parameters used for developing the analytical model.

Notation	Meaning
N_{PRES}	Number of prescribed doses over given time
N_{TAKEN}	Number of doses taken by the patient
N_{MISSED}	Number of doses missed by the patient
λ	Ideal rate of dose consumption event (dose/hour)
T	Observed time
T_I	Time at which I^{th} dose is taken
T_{I+1}	Time at which $I+1^{th}$ dose is taken
T_{MAX}	Maximum allowed time between two doses to remain medically effective
T_{MIN}	Minimum time between two doses to remain medically safe
AMA	Average Medication Adherence
AMA_{NEW-SR}	Average Medication Adherence due to simple and persistent reminder
$AMA_{NEW-CAR}$	Average Medication Adherence due to context-aware reminder
N_P	Number of reminders per missing dose event
N_R	Number of reminders in a day (one per dose)
Q	Number of reminders that came during the last T_{MAX}
M	Multiple medications with multiple doses prescribed in a day
P_{D-R}	Probability of taking dose due to reminder
P_{ND-R}	Probability of not taking dose due to reminder
NR	No reminder
SR	Simple and persistent reminder
CAR	Context-aware reminder
DNE	Dose not effective
UDE	Undesirable dose event
EMA	Effective Medication Adherence
EMA_{NR}	Effective Medication Adherence for no interventions
EMA_{SR}	Effective Medication Adherence for simple and persistent reminder
EMA_{CAR}	Effective Medication Adherence for context-aware reminder
UDE_{BASE}	Probability that the gap between doses is less than T_{MIN}
UDE_{SR}	UDE in case simple and persistence reminders
UDE_{TOTAL}	Probability that the gap between doses is less than T_{MIN}
HC_{COSTNA}	Healthcare cost in case of nonadherent
HC_{COSTSR}	Healthcare cost in case of simple and persistent reminder
$HC_{COSTCAR}$	Healthcare cost in case of context-aware reminder
$HC_{COST-PAST}$	Disease related healthcare cost (Medical cost + drug cost)
$INTVN_{COST-SR}$	Cost of interventions for simple and persistent reminder
$INTVN_{COST-CAR}$	Cost of interventions for context-aware reminder

Table 7. Analytical model parameters/variables

We present known relationships among variables and derive new relationships. These will help us in evaluating output variables such as Effective Medication Adherence (EMA), Healthcare cost (HC_{COST}), and Undesirable dose event (UDE) under different scenarios and interventions. Different scenarios and interventions are considered to analyze the difference between the outcome of smart interventions/context-aware reminder (CAR), simple interventions/simple and persistent reminder (SR) and no interventions/no reminder (NR).

5.1.2.1 *Measuring effective medication adherence – Single medication, multiple doses daily*

The average medication adherence during an observed period of prescribed self-administered medication can be given by

$$\mathbf{AMA} = (\mathbf{N_{TAKEN}}/\mathbf{N_{PRES}}) \quad \textbf{(1)}$$

N_{PRES} is the number of prescribed doses over the given time and is given as $N_{TAKEN}+N_{MISSED}$. N_{TAKEN} and N_{MISSED} are the number of doses taken and the number of doses missed by the patient, respectively. The adherence level can have any value between 0 to 100%, both included. In rare cases, adherence level exceeds 100% if the patient took more doses than prescribed.

The time variations between doses are also important in evaluating the medical effectiveness of doses. The probability that the gap between doses has exceeded the maximum interdose-time is found using ideal dosing rate (λ) and T_{MAX} for a particular event k. Hence, the probability that I+1th dose not effective (DNE) is expressed as

$$\mathbf{DNE} = \mathbf{Prob}\big((\mathbf{T_{I+1}} - \mathbf{T_I}) > \mathbf{T_{MAX}}\big) = (\boldsymbol{\lambda t})^{\mathbf{k}} \times \frac{\mathbf{e}^{-\boldsymbol{\lambda t}}}{\mathbf{k!}} \textbf{ for } \mathbf{k = 0 \text{ and } t = T_{MAX}} \quad \textbf{(2)}$$

T_{MAX} is the maximum allowed time between any two doses to remain medically effective; λ is the ideal rate of dose consumption event, and t is the observed time.

Undesirable Dose Event (UDE) is the likelihood of events when the patient takes doses that are too close to each other, possibly resulting in toxicity and side effects, which in turn can

reduce the motivation for taking medications in future. UDE_{BASE} is the probability that the gap between doses is less than the minimum interdose-time.

$$\mathbf{UDE_{BASE}} = \mathbf{Prob}((\mathbf{T_{I+1}} - \mathbf{T_I}) < \mathbf{T_{MIN}}) = (\boldsymbol{\lambda t})^{\mathbf{K}} \times \frac{\mathbf{e^{-\lambda t}}}{\mathbf{k!}} \textbf{ for } \mathbf{k = 2} \textbf{ and } \mathbf{t = T_{MIN}} \quad \textbf{(3)}$$

T_{MIN} is the minimum interdose-time to remain medically safe, and λ is the ideal dosing rate (dose/hour).

Effective Medication Adherence (EMA) depends on both the average medication adherence and the pattern of adherence. Out of the two patterns identified in equations 2 and 3, when doses are far apart, the effectiveness of the doses is reduced. Taking doses too closely may not improve the effectiveness due to the potential for side effects or overdose, which may reduce medication adherence over time. Therefore, we model EMA to include pattern only when doses are far apart. Thus, Effective Medication Adherence can be given as

$$\boldsymbol{EMA = AMA \times (1 - DNE) = AMA \times (1 - e^{-\lambda T_{MAX}})} \quad \textbf{(4)}$$

Since we model EMA to be between 0 and 100%, and as in some cases, AMA can exceed 100% where patients are trying to catch up or taking more doses than prescribed. For these cases, the EMA is normalized as

$$\boldsymbol{Min\left(AMA \times \left(1 - e^{-\lambda T_{MAX}}\right), 1\right)}.$$

Analyzing equations 2, 3 and 4 we can see that EMA is a better predictor for measuring the medication adherence as compared to AMA. As someone can take all doses in a short period with much worse health outcomes.

Scenarios

In this section, we consider three different scenarios for the reminders. Figure 26 shows the considered scenarios (a) without any intervention, (b) with simple and persistent reminders and

(c) with context-aware reminders. We discuss each of these along with corresponding equations for EMA, UDE, and HC_{COST}.

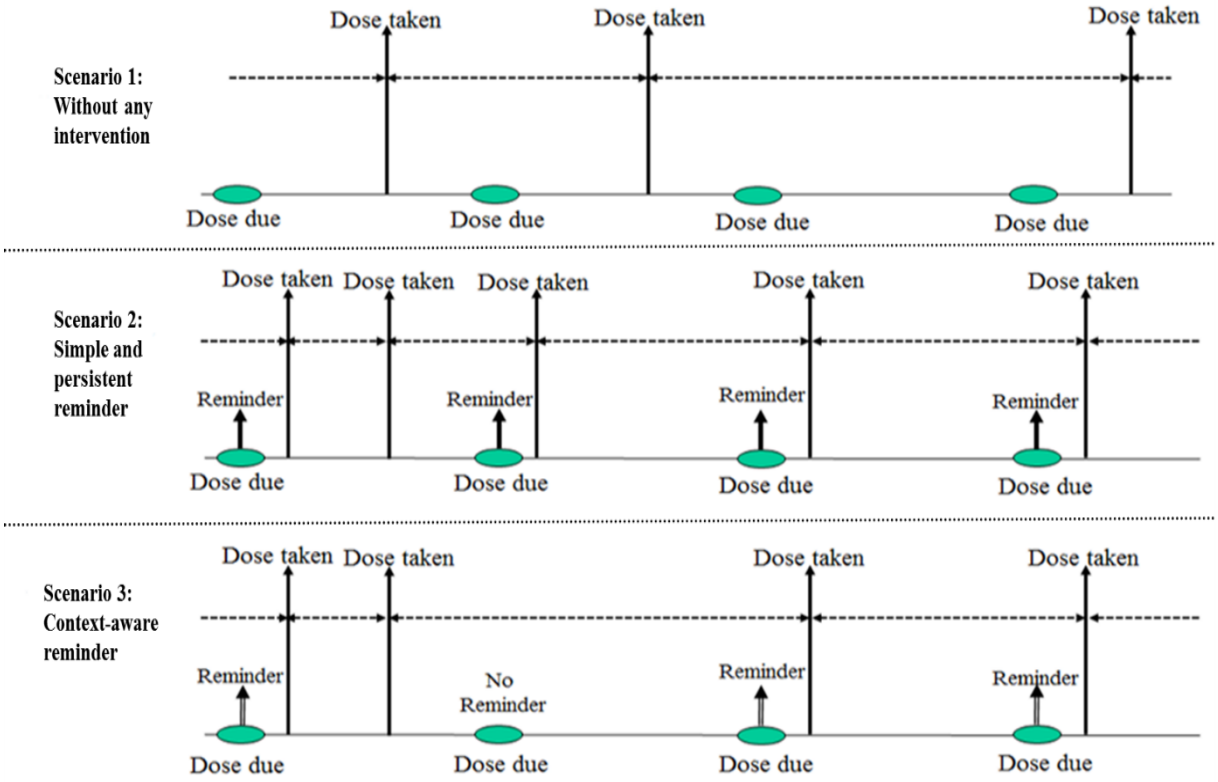


Figure 26. Different scenarios without intervention and with interventions

Scenario 1: Without any Intervention – NR

In this scenario, we compute the EMA keeping in consideration that no intervention/reminder is sent to the patient, and the patient takes doses by his/her choice and convenience. It shows that the patient did not follow the prescribed self-administered medication. Varshney and Singh (2013) have represented that memoryless distributions such as exponential distribution are suitable for medication consumption. Such behavior is observed in practice (Knafl et al. 2004). The EMA for no interventions is computed as

$$\boldsymbol{EMA_{NR} = AMA \times (1 - (\lambda t)^{k} \times \frac{e^{-\lambda t}}{k!} \text{ for } t = T_{MAX})} \quad \textbf{(5)}$$

$$\boldsymbol{Or\ EMA_{NR} = AMA \times (1 - e^{-\lambda T_{MAX}})}$$

λ is given as $\left(AMA \times \frac{N_R}{24}\right)$.

Since the patient is not following the prescribed self-administered medication in this scenario, it might lead to Undesirable Dose Event (UDE). UDE is as follows:

$$\boldsymbol{UDE_{BASE} = Prob((T_{I+1} - T_I) < T_{MIN}) = \frac{1}{2} \times (\lambda T_{MIN})^2 \times e^{-\lambda T_{MIN}}} \quad \textbf{(6)}$$

We will analyze and compare EMA_{NR} in the results section**.**

Scenario 2: With Simple and Persistent Reminders – SR

In this scenario, simple and persistent reminders are provided to the patient at the due time of the doses. Here, persistence refers to the repetitiveness of reminder. In this case, the average adherence and pattern of adherence both may be changed. We will have to study both.

In this case, the patient is following a combination of two patterns: random and deterministic. So the patient may take doses as before using Poisson distribution and may also take doses based on reminders. This results in several combinations of patterns for adherence. However, we are interested in finding out the probability that the gap between doses has exceeded the maximum interdose-time (T_{MAX}) and probability that the gap between doses is less than the minimum interdose-time (T_{MIN}).

The probability that the gap between doses has exceeded the maximum interdose-time is approximated (for simplification) as follows. At any time, the probability will be a product of two probabilities: the probability that the patient did not take any dose in last T_{MAX} time and probability that the patient did not take any dose "after all the reminders that came during the last T_{MAX}".

$$\boldsymbol{Prob\left((T_{I+1} - T_I) > T_{MAX}\right) = (P_{ND\text{-}R})^Q \times [e^{-\lambda T_{MAX}}]} \quad \textbf{(7)}$$

Q is the number of reminders that came during the last T_{MAX} and is given as $\frac{T_{MAX}}{\frac{24}{N_R}}$. $P_{ND\text{-}R}$ is the probability that the patient does not take the dose based on the reminder and is computed as 1 - $P_{D\text{-}R,}$ where $P_{D\text{-}R}$ is the probability of consuming dose due to reminder. N_R is the number of reminders in one day (or a number of doses in a day). The simple and persistent reminders are not based on if the patient has taken the dose recently on his/her own. So average medication adherence (AMA) in case of simple and persistent reminders can be given as

$$\mathbf{AMA_{NEW\text{-}SR} = Min[(AMA + (1 - P_{ND\text{-}R}) \times \lambda \times T_{MAX}), 1]} \quad \textbf{(8)}$$

Moreover, the effective medication adherence for simple and persistent reminders can be computed as follows

$$\mathbf{EMA_{SR} = AMA_{NEW\text{-}SR}\left(1 - \left(Prob\left((T_{I+1} - T_I) > T_{MAX}\right)\right)\right)}$$

Using the value of $\mathrm{Prob}\left((T_{I+1} - T_I) > T_{MAX}\right)$ from equation 7, EMA_{SR} is represented as

$$\mathbf{EMA_{SR} = AMA_{NEW\text{-}SR}\left(1 - \left((P_{ND\text{-}R})^{Q} \times \left[e^{-\lambda T_{MAX}}\right]\right)\right)} \quad \textbf{(9)}$$

On the other hand, the probability that the gap between doses is less than the minimum interdose-time would need to include two factors. One is the probability that someone took two doses in last T_{MIN} time, and the other is that someone took one dose in last T_{MIN} time on his or her own and took another dose due to the reminder. However, we will have to multiply 2nd factor by the probability that a reminder even came during T_{MIN} time and can be given as $\frac{T_{MIN}}{\frac{24}{N_R}}$.

If T_{MIN} is too small, then no reminder may come during T_{MIN}. Hence, the probability of two doses taken in less than T_{MIN} time is the sum of the probability of patient taking two doses when no reminder came and the probability that patient consumes a dose along with a dose due to the reminder.

The above possibility can raise adherence level and also improve the pattern in some cases. On the other hand, it may result in undesirable dose event (UDE). The UDE can occur when the patient has already taken the medicine at scheduled time and also consumes medicine when the reminder arrives for the same dose. UDE_{TOTAL} or the probability that the gap between doses is less than the minimum interdose-time is

$$\boldsymbol{UDE_{TOTAL} = Prob\left((T_{I+1} - T_I) < T_{MIN}\right)}$$

$$= \left[1 - \left(\frac{\boldsymbol{T_{MIN}}}{\frac{\boldsymbol{24}}{\boldsymbol{N_R}}}\right)\right] \times \left[(\boldsymbol{\lambda t})^{\mathbf{k}} \times \frac{\boldsymbol{e^{-\lambda t}}}{\boldsymbol{k!}} \; \boldsymbol{for\ k = 2, t = T_{MIN}}\right] + \frac{\boldsymbol{T_{MIN}}}{\frac{\boldsymbol{24}}{\boldsymbol{N_R}}} \times \boldsymbol{P_{D\text{-}R}}$$

$$\times \left[(\boldsymbol{\lambda t})^{\mathbf{k}} \times \frac{\boldsymbol{e^{-\lambda t}}}{\boldsymbol{k!}} \; \boldsymbol{for\ k = 1, t = T_{MIN}}\right]$$

$$= [\mathbf{1 - \lambda T_{MIN}}] \times \left[(\mathbf{\lambda T_{MIN}})^{\mathbf{2}} \times \frac{\boldsymbol{e^{-\lambda T_{MIN}}}}{\mathbf{2!}}\right] + \mathbf{\lambda T_{MIN}} \times \boldsymbol{P_{D\text{-}R}} \times \left[(\mathbf{\lambda T_{MIN}}) \times \boldsymbol{e^{-\lambda T_{MIN}}}\right] \qquad \textbf{(10)}$$

The intervention is capable of changing the gap between doses due to simple and persistent reminders. This may lead to higher UDE. In this possibility, both the pattern and adherence level go up unless patient's probability of taking doses is zero along with zero AMA. The new adherence can be more than 100% if the patient follows reminders and has access to more doses than just the daily doses. It can also increase UDE, but will improve interdose-time.

$$\boldsymbol{UDE_{SR} = UDE_{TOTAL} - UDE_{BASE}} \qquad \textbf{(11)}$$

Scenario 3: With Context-Aware Reminders - CAR

In this scenario, the patient is sent context-aware reminders based on the consumption of doses and the due time of dose. More specifically, context-aware reminders keep track of doses. The context-aware reminders do not generate a dosing rate of their own as the reminders generates only when the dose (that was due) is missed. So the patient will not run out of doses due to the context-aware reminders.

$$\boldsymbol{Prob}\big((\boldsymbol{T_{I+1}} - \boldsymbol{T_I}) > \boldsymbol{T_{MAX}}\big) = \left[(\boldsymbol{P_{ND\text{-}R}})^{\frac{\frac{T_{MAX}}{24}}{N_R}}\right]^{N_P} \times \left[(\boldsymbol{\lambda t})^{\mathbf{k}} \times \frac{e^{-\lambda t}}{k!} \; \boldsymbol{for\ k = 0, t = T_{MAX}}\right] \textbf{(12)}$$

N_R is the number of reminders and N_P is the number of reminders per missing dose event (persistence or continuity of the reminders). The optimal value of N_P can be decided based on patient's preferences and abilities, the amount of overhead in generating a reminder among other factors.

The AMA level will also go up as the patient is taking some doses after context-aware reminders. The new value of average medication adherence is

$$\boldsymbol{AMA_{NEW\text{-}CAR}} = \boldsymbol{Min}\Big[\Big(\boldsymbol{AMA} + (\mathbf{1} - \boldsymbol{P_{ND-R}}) + (\boldsymbol{P_{ND-R}})(\mathbf{1} - \boldsymbol{P_{ND-R}}) + (\boldsymbol{P_{ND-R}})^2(\mathbf{1} - \boldsymbol{P_{ND-R}}) + \cdots (\boldsymbol{P_{ND-R}})^{N_P - 1}(\mathbf{1} - \boldsymbol{P_{ND-R}})\Big), \mathbf{1}\Big]$$

$$\boldsymbol{AMA_{NEW\text{-}CAR}} = \boldsymbol{Min}[(\boldsymbol{AMA} + (\mathbf{1} - \boldsymbol{P_{ND-R}})^{N_P})), \mathbf{1}] \quad \textbf{(13)}$$

$$\boldsymbol{EMA_{CAR}} = \boldsymbol{AMA_{NEW\text{-}CAR}}\left(\mathbf{1} - \left[(\boldsymbol{P_{ND-R}})^{\frac{\frac{T_{MAX}}{24}}{N_R}}\right]^{N_P} \times \left[(\boldsymbol{\lambda t})^{\mathbf{k}} \times \frac{\boldsymbol{e^{-\lambda t}}}{\mathbf{k!}} \; \boldsymbol{for\ k = 0, t = T_{MAX}}\right]\right)$$

$$= \boldsymbol{AMA_{NEW\text{-}CAR}}\big(\mathbf{1} - (\boldsymbol{P_{ND-R}})^{\boldsymbol{\lambda T_{MAX}}}\big]^{N_P} \times [\,\boldsymbol{e^{-\lambda T_{MAX}}}]) \quad \textbf{(14)}$$

If the patient already took two doses very close to each other, there will be no context-aware reminders. In that sense, a context-aware reminder will not increase the probability of undesirable dose event (UDE). Therefore, the undesirable dose event probability (UDE_{BASE}) can still be given as

$$\mathbf{UDE_{BASE}} = \mathbf{Prob}\big((\mathbf{T_{I+1}} - \mathbf{T_I}) < \mathbf{T_{MIN}}\big) = (\boldsymbol{\lambda T_{MIN}})^2 \times \frac{\mathbf{e^{-\lambda T_{MIN}}}}{\mathbf{2!}} \quad \textbf{(15)}$$

5.1.2.2 *Healthcare cost and interventions*

Medication nonadherence increases the healthcare cost by $100-300 billion per year (NEHI 2009). To see how smart interventions minimizes the healthcare cost we have derived following relationships for all three different scenarios a) without any intervention, b) simple and persistent reminder, and c) context-aware reminder.

In the case of nonadherent patients who does not receive any intervention and consume doses as per their choice/convenience, their healthcare cost comprises of medical cost and drug cost, i.e., the all-disease cost. So, healthcare cost for nonadherent patients is calculated as follows:

$$\mathbf{HC_{COST_{NA}}} = (\mathbf{HC_{COST\text{-}PAST}}) \times (\mathbf{1.05})^{\mathbf{N}} \quad \textbf{(16a)}$$

where N represents the Nth year from the year of data.

If the patient receives simple and persistent reminders to comply with the prescribed dosing regimen, then in addition to the all-disease cost they have to pay for the intervention cost. As well as there will be some additional cost due to undesirable dose events. Therefore, we derive the healthcare cost in case of simple and persistent reminders as

$$\mathbf{HC_{COST_{SR}}} = (\mathbf{HC_{COST\text{-}PAST}}) \times (\mathbf{1.05})^{\mathbf{N}} \times (\mathbf{1} + \mathbf{UDE_{SR}}) + \mathbf{INTVN_{COST\text{-}SR}} \quad \textbf{(16b)}$$

In the case of context-aware reminder, there will be all-disease cost and the cost for the context-aware reminder. However, there will not be any additional cost for undesirable dose event. Because context-aware reminder does not lead to additional UDE as represented in equation 15. Therefore, we drive the healthcare cost due to context-aware reminder as

$$\mathbf{HC_{COST_{CAR}}} = (\mathbf{HC_{COST\text{-}PAST}}) \times (\mathbf{1.05})^{\mathbf{N}} + \mathbf{INTVN_{COST\text{-}CAR}} \quad \textbf{(16c)}$$

Therefore, from equation 16b and 16c we can see that the healthcare cost due to simple and persistent reminders includes the additional cost for UDE as compared to healthcare costs due to the context-aware reminder. Also, the intervention cost ($INTVN_{COST}$) varies for context-aware reminders as compared to the simple and persistent reminder.

Equations 1 through 15 represents the analytical model for prescribed self-administered medication of single medication in a day. The following section represents the analytical model for prescribed self-administered medication of multiple medications in a day. These multiple medications are independent of each other.

5.1.2.3 *Measuring effective medication adherence – Multiple medications, multiple doses daily*

Scenario 1: Simple and Persistent Reminders - SR

Let us assume,

- k_m is the event
- N_{Rm} is Number of prescribed doses in a day for m^{th} medicine
- λ_m is the average arrival rate for m^{th} medicine
    - where, $\lambda_m = \frac{N_{Rm}}{24}$
- $T_{(MAX)m}$ is time (t_m) observed for m^{th} medicine
- $P_{(D\text{-}R)m}$ is the Probability of taking dose due to reminder for m^{th} medicine
- $P_{(ND\text{-}R)m}$ is the Probability of not taking dose due to reminder for m^{th} medicine

$$\boldsymbol{P_{(ND\text{-}R)m} = 1 - P_{(D\text{-}R)m}} \quad \textbf{(17)}$$

- Q_m is the number of reminders came in during last $T_{(MAX)m}$ for m^{th} medicine

$$\boldsymbol{Q_m = \frac{T_{(MAX)m}}{\frac{24}{N_{Rm}}}} \quad \textbf{(18)}$$

- Probability of number of doses in the last $T_{(MAX)m}$ for m^{th} medicine, i.e., Prob(N_{Rm}) is

$$\mathbf{Prob(N_{Rm}) = (P_{(ND\text{-}R)m})^{Q_m}} \quad \textbf{(19)}$$

- Mean $\boldsymbol{\mu_m = \lambda_m \times t_m}$ **(20)**
- Probability of number of doses after the last reminder, i.e., Prob(k_m) is

$$\boldsymbol{Prob(k_m) = \frac{\left[\mu_m^{k_m} \times e^{-\mu_m}\right]}{k_m!}} \quad \textbf{(21)}$$

Multiplying equation 19 and 21 we get the probability that the gap between doses exceeded the maximum interdose-time, i.e., the dose is not effective (DNE). Therefore,

$$DNE_m = Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) > T_{(MAX)m}\right] = \left(\mathrm{P_{(ND\text{-}R)m}}\right)^{\mathrm{Q_m}} \times Prob(k_m)$$

$$\boldsymbol{DNE_m = Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) > T_{(MAX)m}\right] = \left(\mathbf{P_{(ND\text{-}R)m}}\right)^{\mathbf{Q_m}} \times \frac{\left[\mu_m^{k_m} \times e^{-\mu_m}\right]}{k_m!}} \quad \textbf{(22)}$$

We Know, $AMA_m = N_{m(Taken)}/N_{m(Pres)}$

$$\boldsymbol{AMA_{(new\text{-}SR)m} = MIN[\left(AMA_m + P_{(ND\text{-}R)m} \times Q_n\right), 1]} \quad \textbf{(23)}$$

$$EMA_{(SR)m} = AMA_{(new\text{-}SR)m} - [AMA_{(new\text{-}SR)m} \times Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) > T_{(MAX)m}\right]]$$

Alternatively, $\boldsymbol{EMA_{(SR)m} = AMA_{(new\text{-}SR)m} - [AMA_{(new\text{-}SR)m} \times DNE_m]}$ **(24)**

Suppose a patient has to consume 3 medicines in a day, i.e., M=3

Dosing regimen for 1st medicine (m_1) is

$$N_{Rm1} = 2;\ \lambda_{\mathrm{m1}} = \frac{N_{Rm1}}{24} = 0.083;$$

$$Interdose\ time = 12hrs; Smallest\ T_{MAX} = 12; Largest\ T_{MAX} = N_{Rm1} \times Interdose\ time$$

Dosing regimen for 2nd medicine (m_2) is

$$N_{Rm2} = 3;\ \lambda_{\mathrm{m2}} = \frac{N_{Rm2}}{24} = 0.125$$

$$Interdose\ time = 6hrs; Smallest\ T_{MAX} = 6\ ; Largest\ T_{MAX} = N_{Rm2} \times Interdose\ time$$

Dosing regimen for 3rd medicine (m_3) is

$$N_{Rm3} = 4;\ \lambda_{\mathrm{m3}} = \frac{N_{Rm3}}{24} = 0.167$$

$$Interdose\ time = 5hrs; Smallest\ T_{MAX} = 5\ ; Largest\ T_{MAX} = N_{Rm3} \times Interdose\ time$$

Overall EMA_M due to all three medicines will be a weighted average of EMA_{m1}, EMA_{m2} and EMA_{m3}. Where weights are determined based on primary and secondary medicines. We consider following three scenarios.

Scenario 1: All 3 medicines are primary.

$$\boldsymbol{EMA_{(SR)M} = \frac{1}{3} \times EMA_{(SR)m1} + \frac{1}{3} \times EMA_{(SR)m2} + \frac{1}{3} \times EMA_{(SR)m3}} \quad \textbf{(25)}$$

Scenario 2: Medicine 1st is primary, and 2nd and 3rd are secondary.

$$\boldsymbol{EMA_{(SR)M} = \frac{1}{2} \times EMA_{(SR)m1} + \frac{1}{4} \times EMA_{(SR)m2} + \frac{1}{4} \times EMA_{(SR)m3}} \quad \textbf{(26)}$$

Scenario 3: Medicine 1st and 2nd are primary, and 3rd is secondary.

$$\boldsymbol{EMA_{(SR)M} = \frac{2}{5} \times EMA_{(SR)m1} + \frac{2}{5} \times EMA_{(SR)m2} + \frac{1}{5} \times EMA_{(SR)m3}} \quad \textbf{(27)}$$

Therefore, $\boldsymbol{EMA_{(SR)M} = \sum_{i=1}^{M} A_i \, EMA_{(SR)mi}}$ **(28)**

Undesirable dose event in case of Simple and Persistent Reminders

Undesirable dose event (UDE)

$$UDE_{BASE(m)} = Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) < T_{(MIN)m}\right]$$

Or, $\boldsymbol{UDE_{BASE(m)} = (\lambda_m \times t_m)^{k_m} \times \frac{e^{-\lambda_m t_m}}{k!} \; for \; k_m = 2 \; and \; t_m = T_{(MIN)m}}$ **(29)**

$$UDE_m = Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) < T_{(MIN)m}\right]$$

$$\boldsymbol{UDE_m = \frac{1}{2}\left(\lambda_m \times T_{(MIN)m}\right)^2 \times e^{-\lambda_m T_{(MIN)m}}} \quad \textbf{(30)}$$

$$UDE_{(TOTAL)m} = Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) < T_{(MIN)m}\right]$$

$$UDE_{(TOTAL)m} = \left[1 - \frac{T_{(MIN)m}}{\frac{24}{N_{Rm}}}\right] \times \left[(\lambda_m \times t_m)^{km} \times \frac{e^{-\lambda_m t_m}}{k!} \; for \; k_m = 2 \; and \; t_m = T_{(MIN)m}\right]$$

$$+ \left[\frac{T_{(MIN)m}}{\frac{24}{N_{Rm}}} \times P_{(D\text{-}R)m}\right]$$

$$\times \left[(\lambda_m \times t_m)^{k_m} \times \frac{e^{-\lambda_m t_m}}{k!} \; for \; k_m = 1 \; and \; t_m = T_{(MIN)m}\right]$$

Therefore,

$$UDE_{(TOTAL)m} = \left[1 - \lambda_m T_{(MIN)m}\right] \times \left[\left(\lambda_m \times T_{(MIN)m}\right)^2 \times \frac{e^{-\lambda_m T_{(MIN)m}}}{2!}\right]$$

$$+ \left[\lambda_m T_{(MIN)m} \times P_{(D\text{-}R)m}\right] \times \left[\left(\lambda_m \times T_{(MIN)m}\right) \times e^{-\lambda_m T_{(MIN)m}}\right]$$

$$\boldsymbol{UDE_{(Total)m} = \sum_{i=1}^{M} UDE_{mi}} \quad \textbf{(31)}$$

$$\boldsymbol{UDE_{(SR)m} = UDE_{(TOTAL)m} - UDE_{(BASE)m}} \quad \textbf{(32)}$$

Scenario 2: Context-aware reminder - CAR

Let us assume,

- N_{Rm} is Number of prescribed doses in a day for m^{th} medicine at T_M intervals, where M is the number of medicines in a day
- N_{Pm} is the number of reminders per missing dose for m^{th} medicine
- k_m is the event for m^{th} medicine (k_m=0)
- λ_m is the average arrival rate for m^{th} medicine
    - where, $\lambda_m = \frac{N_{Rm}}{24}$
- $T_{(MAX)m}$ is time (t_m) observed for m^{th} medicine
- $P_{(D\text{-}R)m}$ is the Probability of taking dose due to reminder for m^{th} medicine

- $P_{(ND\text{-}R)m}$ is the Probability of not taking dose due to reminder for m^{th} medicine

$$P_{(ND\text{-}R)m} = 1 - P_{(D\text{-}R)m}$$

- Q_m is the number of reminders came in during last $T_{(MAX)m}$ for m^{th} medicine

$$\boldsymbol{Q_m = N_{Pm} \times \frac{T_{(MAX)m}}{\frac{24}{N_{Rm}}}} \quad \textbf{(33)}$$

- Probability of number of doses in the last $T_{(MAX)m}$ for m^{th} medicine, i.e., Prob(N_{Rm}) is

$$\mathbf{Prob(N_{Rm}) = (P_{(ND\text{-}R)m})^{Q_m}} \quad \textbf{(34)}$$

- Mean $\boldsymbol{\mu_m = \lambda_m \times t_m}$ **(35)**

- Probability of number of doses after the last reminder, i.e., Prob(k_m) is

$$\boldsymbol{Prob(k_m) = \frac{\left[\mu_m^{k_m} \times e^{-\mu m}\right]}{k_m!}} \quad \textbf{(36)}$$

Multiplying equation 34 and 36 we get the probability that the gap between doses exceeded the maximum interdose-time, i.e., the dose is not effective (DNE).

$$DNE_m = Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) > T_{(MAX)m}\right] = [(P_{(ND\text{-}R)m})^{Q_m} \times Prob(k_m)]$$

$$\boldsymbol{DNE_m = Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) > T_{(MAX)m}\right] = [(P_{(ND\text{-}R)m})^{Q_m} \times \frac{\left[\mu_m^{k_m} \times e^{-\mu m}\right]}{k_m!}]} \quad \textbf{(37)}$$

We Know, $AMA_m = N_{m(Taken)}/N_{m(Pres)}$

$$\boldsymbol{AMA_{(new\text{-}CAR)m} = MIN[\left(AMA_m + P_{(ND\text{-}R)m} \times Q_m\right), 1]} \quad \textbf{(38)}$$

$$EMA_{(CAR)m} = AMA_{(new\text{-}CAR)m} - [AMA_{(new\text{-}CAR)m} \times Prob\left[\left(T_{(I+1)m} - T_{(I)m}\right) > T_{(MAX)m}\right]]$$

Or, $\boldsymbol{EMA_{(CAR)m} = AMA_{(new\text{-}CAR)m} - [AMA_{(new\text{-}CAR)m} \times DNE_m]}$ **(39)**

Suppose a patient has to consume 3 medicines in a day, i.e., M=3 and N_{Pm}=2

Dosing regimen for 1^{st} medicine (m_1) is

$$N_{Rm1} = 2;\ \lambda_{m1} = \frac{N_{Rm1}}{24} = 0.083;$$

$$Interdose\ time = 12hrs; Smallest\ T_{MAX} = 12; Largest\ T_{MAX} = N_{Rm1} \times Interdose\ time$$

Dosing regimen for 2nd medicine (m_2) is

$$N_{Rm2} = 3;\ \lambda_{m2} = \frac{N_{Rm2}}{24} = 0.125$$

$$Interdose\ time = 6hrs; Smallest\ T_{MAX} = 6\ ; Largest\ T_{MAX} = N_{Rm2} \times Interdose\ time$$

Dosing regimen for 3rd medicine (m_3) is

$$N_{Rm3} = 4;\ \lambda_{m3} = \frac{N_{Rm3}}{24} = 0.167$$

$$Interdose\ time = 5hrs; Smallest\ T_{MAX} = 5\ ; Largest\ T_{MAX} = N_{Rm3} \times Interdose\ time$$

Overall $EMA_{(CAR)M}$ due to all three medicines will be a weighted average of $EMA_{(CAR)m1}$, $EMA_{(CAR)m2}$, and $EMA_{(CAR)m3}$. Where weights are determined based on primary and secondary medicines. We consider following three scenarios.

Scenario 1: All 3 medicines are primary.

$$\boldsymbol{EMA_{(CAR)M} = \frac{1}{3} \times EMA_{(CAR)m1} + \frac{1}{3} \times EMA_{(CAR)m2} + \frac{1}{3} \times EMA_{(CAR)m3}} \quad \textbf{(40)}$$

Scenario 2: Medicine 1st is primary, and 2nd and 3rd are secondary**.**

$$\boldsymbol{EMA_{(CAR)M} = \frac{1}{2} \times EMA_{(CAR)m1} + \frac{1}{4} \times EMA_{(CAR)m2} + \frac{1}{4} \times EMA_{(CAR)m3}} \quad \textbf{(41)}$$

Scenario 3: Medicine 1st and 2nd are primary, and 3rd is secondary.

$$\boldsymbol{EMA_{(CAR)M} = \frac{2}{5} \times EMA_{(CAR)m1} + \frac{2}{5} \times EMA_{(CAR)m2} + \frac{1}{5} \times EMA_{(CAR)m3}} \quad \textbf{(42)}$$

Therefore, $\boldsymbol{EMA_{(CAR)M} = \sum_{i=1}^{M} A_i\, EMA_{(CAR)mi}}$ **(43)**

5.1.3 Model Validation

Analytical models are the representations of mechanisms that govern natural phenomena that are not fully recognized, controlled or understood (Tedeschi 2006). They have become

indispensable tools via decision support systems for policy makers and researchers (Tedeschi 2006). The main reason for modeling problems is it permits serious analysis and consideration of a problem, which has important financial, organizational and practical implications (Guerrero 2010). However, certain techniques must be used to evaluate mathematical models for objectives, scope and assumptions, appropriateness or validation, and limitations. Essentially, the model should be appropriate for its intended purpose under the given conditions.

For evaluation of smart interventions for effective medication adherence, our mathematical model is used to estimate dose-event (dose not effective, undesirable dose event), effective medication adherence (a single and multiple medications with multiple dosing regimen), and healthcare cost benefits of smart interventions. The model considers patients are living independently, their adherence behavior (0-100% medication adherence covering no-adherence, semi-adherence, and satisfactory adherence), and the type of illness (several chronic conditions), and prescribed self-administered medications. The model allows the study of

- Multiple chronic diseases including Diabetes, Hypertension (high blood pressure/BP), Hypercholesterolemia, and Chronic Heart Failure (CHF)
- Independently living patients i.e. patients who are not living in a healthcare provider assisted environment
- Healthcare cost including medical and drug cost
- Simple and persistent reminders and context-aware reminders

The model is appropriate (Tedeschi 2006) for studying adherence in chronic illnesses, where use of multiple medications extend over a period. The model can approximate the intervention and their cost. Therefore, the model is a valid and sound model and does what it is supposed to do

(Tedeschi 2006). Further, the three steps of model validation (Hamilton 1991): verification of the model, sensitivity analysis, and evaluation of the model, are performed below.

The verification involved step by step checking of the model and debugging where one or more changes in inputs could lead to unacceptable output (Hamilton 1991; Tedeschi 2006). Further, the model was calibrated using values from other studies (Gibson et al. 2010; Roebuck et al. 2011; Sokol et al. 2005). The model builds upon prior models, and other studies also support the results obtained from this model. The model is validated by testing for many known cases to verify its functioning. Further, the causal relationships of medication adherence with medical cost, drug cost, and the intervention cost for multiple chronic conditions were utilized (Sokol et al. 2005). All relationships in the model are verified, and known relationships were utilized for deriving additional relationships.

The sensitivity analysis was performed to test the behavior of every equation in the model (Hamilton 1991). There are several ways to perform sensitivity analysis for mathematical models (Christopher Frey and Patil 2002). We focused on the nominal range sensitivity, which works well for models where there are no significant interactions among input values and the ranges of plausible values can be defined (using one's judgment or from the literature). For our model, we broadly defined the ranges of all input values, obtained from other studies and expanded even further to cover more extreme cases. The analysis included combining several input values and measuring outputs for these combinations of inputs. The results section of this document presents the outcome of this analysis. It also helps in answering "what-if" questions such as "what if the patient does not consume the dose within the prescribed interval" or "what if patient consumed the dose one hour before or after the dose is due" or "what if an intervention stopped working".

The evaluation of model was done to test the adequacy (or robustness) of the model based on precision and accuracy of results (Hamilton 1991; Tedeschi 2006). The model is precise as it produces values that are close to one another in multiple iterations. The accuracy of model is on (a) known relationships and (b) calibration of results for decision making. To measure accuracy further, we tested our model on input data and results from (Gibson et al. 2010; Roebuck et al. 2011; Sokol et al. 2005). We further evaluated our model by computing the savings due to improved adherence under the all-disease cost of medications (Sokol et al. 2005). These values are in close agreement, so our results on effective medication adherence, undesirable dose event, and healthcare cost are validated using published data, while other results on smart interventions are extrapolated based on known relationships and available data from multiple studies.

Several assumptions (see section 5.1.1) were made to keep the analytical model tractable and reasonably accurate. In future work, these assumptions may be relaxed.

The model can estimate the savings due to the improved effective medication adherence, the cost of various interventions, and the overall budget for various interventions. For a given improvement, knowing when an intervention is cost effective for a given condition can help an insurance company and/or employer in allocating healthcare resources. The analytical model, implemented in Excel (Guerrero 2010) and included in Appendix (A2), can be used to derive effective medication adherence for different dosing events, estimate savings due to improved medication adherence, and evaluate effective medication adherence for multiple medications.

5.1.4 Limitations

The model is primarily designed to address medication adherence in independent living, and will need extensions before its use in other more controlled environments such as assisted living

and hospitals. The model is designed to provide results with reasonable complexity, and in some cases, more refined results may be obtained by developing more complex models.

Section 5.2 Empirical

To see the validity of the proposed conceptual artifact domain experts (healthcare providers and health IT experts) have evaluated the artifact by comparing the health IT artifact with existing simple interventions. The evaluation of conceptual artifact is based on research design adapted from Parsons and Wand (Parsons and Wand 2008). The artifact evaluation protocol is available in Appendix (A1). After discussing the dissertation research with IRB, the application was submitted as non-human subject research to IRB for approval. Appendix (A1) includes the outcome letter of approval.

We have focused explicitly on the experts' reasoning about their preferences between the existing and our smart interventions, and on relating that reasoning to the proposed health IT artifact. The evaluation will provide the insights for interventions preferred by experts.

5.2.1 Participants and Task

Domain experts consisted of six healthcare provider and six health IT experts. More specifically, healthcare providers are the physicians with extensive experience in advising and monitoring patients with chronic conditions prescribed self-administered medications. The three categories of health IT experts includes (1) two researchers in information systems with research and/or practical experience in medication adherence research, (2) two researchers in information systems with research and/or practical experience in health IT research, and (3) two health IT experts with extensive experience in healthcare system modeling and development. Health IT experts from information systems were chosen because of their familiarity with the medication adherence and health IT research and expected to be sufficiently motivated to provide thoughtful

responses. Also, modeling experts were chosen because they were expected to have relevant practical experience with the reasoning that takes place when developing a health IT system.

Participants were asked to follow the instructions in Appendix A1 to compare Artifact1 and Artifact2 in Table 1 of the appendix (A1). The objectives for comparison were to:

1. Focus participant's attention on the differences in Artifact1 and Artifact2,
2. Ask participants to formulate questions that could be asked to clarify the reasons why the differences arose,
3. Observe which of the two artifact is considered more useful and realistic by the participants based on their domain experience,
4. Observe which of the two artifacts is considered more reliable by the domain experts,
5. Focus on participants reasoning for which artifact leads to overdose or over medication.

Participants were not informed about the rules used to develop Artifact2.

5.2.2 Analysis of Simple vs. Smart Intervention

As discussed in the development section, following are the major differences between Artifact1 (Simple Intervention) and Artifact2 (Smart Intervention):

1. Wireless Medication Box is used as an additional support for dose dispensing, and dispensing and consumption information of dose in Artifact2 as compared to Artifact1
2. Analysis of consumption is done by Medication Management Server component of Artifact2.
3. Medication Management Server in Artifact2 helps in providing context-aware reminders leading to smart interventions.
4. Advice/scheduling support is available by a healthcare provider.

Participant (Healthcare provider-HCP; Health IT Experts – HITE)	What differences can be identified between the two models?	What questions could be asked to clarify the reasons for these differences?	Which of the two might be more useful or realistic based on your general knowledge of the domain?	Which one of these is more reliable or less likely to fail?	Which one of these will lead to overdose/over medication?
HCP 1	• 2nd is smarter, assuming the patient takes/swallows the pill. • 2nd is less annoying – user friendly. • 1st is More mechanical, repetitive.	• Tell me more details of WMB: Is it portable? • Does is it have an alarm to get attention? • What happens if one misses the dose?	• 2nd will be more useful if above features added.	• Second will be more reliable as long as the patient is honestly taking pills.	• First – as it keeps sending reminders even when the patient has taken medicines.
HCP 2	• Model 2 has an additional component (WMB) which allow intelligence to be incorporated in the design leading to contextual awareness of "what" happened versus "when" it happened.	Related to WMB • Is it pill/liquid based meds • Sensors in WMB sensitive to time alone or can patient open it anytime.	• Model 2 has additional layers of information. However, it limits the type of patients who can benefit; namely: taking solid pills, having a specific frequency (chronic medicines).	• Reliability will depend on the healthcare "end" on how compatible it is on their side. • On the patient side model 2, is better than 1 as it gives information and reminders from the nurse.	• Overdosing is possible with Table/model 1.
HCP 3	• The second model involves the addition of a wireless medication box and active scheduling with the healthcare provider.	• The additional steps could perhaps help dispense the appropriate dose and schedule of medications and avoid inappropriate dosing of medications.	• The second model is probably more useful.	• The second model is probably less likely to fail, but no system is perfect.	• First model.
HCP 4	• Wireless medication box in model 2 is present,	• Precise dose dispensing is important. • Dose schedule could	• Model 2	• Model 2	• Model 1

	• Context-aware reminders and analysis of consumption between MMS and wireless network. • Advice scheduling between MMA and healthcare provider.	be altered depending upon the response of medication. • In the case of sub dosing or overdosing, analysis of consumption and context-aware reminders will be of immense help.			
HCP 5	• Model 2 adds a wireless medication-dispensing device and • Provides for analysis and sharing of dispensing and consumption information with the healthcare provider.	• Don't you think that for the independent-minded and the health-conscious people, the fact that there would be too much involvement and reminders with pill taking with model 2-may be off-putting?	• Model 2	• Model 2	• Both are unlikely to lead to overmedication.
HCP 6	• In addition to going through compliance and patterns of use Artifact 2, has advice on scheduling & WMB; dispensing and consumption information. *patient symptom improvement could be added	• Will it increase adherence/compliance and better outcome of treatment?	• useful Artifact 2 • Realistic Artifact 1 because of less time consumption.	• Artifact 2 is more reliable, & less likely to fail	• Artifact 1 will lead to overdose because no feedback on scheduling.
HITE 1	• MMS needs to be "Smart", i.e., needs to have more processing capability to be able to do the	• How do you decide that useful input has been done? • What is the difference between the MMS of	• If the system can be designed to be foolproof or close to foolproof, then Model 2, (utilizing	• Model 1: If the adherence is monitored by the doctor/nurse/caregiver. • Model 2: If technology	• Model 2: If technology is not designed/implemented properly. • Model 1: If patient/caregiv

	context-aware analysis. • Artifact2 is heavily reliant on good input data, i.e., should not become a case of garbage data in garbage data out.	Model 1 & Model 2?	technology) would be more useful.	can be made reliable enough (WMB/MMS)	er are not careful.
HITE 2	• WMB - wireless medication box has been introduced for dispensing the dose. • Dispensing and consumption information have been stored for further analysis. • A context-aware reminder has been added. • Healthcare provider can provide dose scheduling advice through MMA.	• How wouldddd these additional steps contribute towards the speedy recovery of the patient? • How the information being stored would help in preventive care?	• diagram 2	• diagram 2	• diagram 1
HITE 3	• Advice scheduling • WMB, plus connections • Context-aware reminders • Analysis of consumption • "Simple" vs. "Smart."	• What is the connection between contextual reminders and the patient? • Is the MMA still necessary with the WMB?	• Model 1 seems more practical • Model 2 has potential to be more effective but may cost more to implement	• More likely Model 2	• More likely Model 1
HITE 4	• Smart Intervention is contexted. • Smart intervention analyzes the consumption information and provides updated dispensing info.	• What does context-awareness mean? What factors are considered? • Why there is a separate entity (WMB) for the feedback	• Both are applicable solutions, based on my experience with IT solutions.	• Second model (Smart)	• Simple intervention Model 1.

		provision? (Separate from MMA).			
HITE 5	• Model 1 provides interaction between the patient and the provider based on simple information exchange, • while under model 2, the intervention is enhanced by using more contextual and personalized information based on dose assumption information	• Functionality • Usability • The degree of clinical decision support	• The success of IT implementation or adoption depends on many factors. By assuming, that other factors of the two models are same, and the patient really has the capability to interact correctly with the system, generally model 2 will be useful. • A smarter solution more helps the process of medical intervention.	• The simpler solution model 1 would be more reliable. • Model 2 integrates more information together and supports a higher level of clinical decision support, but it is more fragile	• Model 1 may lead to overdose as there is no reminder based on personalized dose and consumption analysis.
HITE 6	• The second one uses context-aware reminders. • The second one includes the wireless medication box, which can trace patients' medication-taking behavior more objective than self-report. • The mobile application also provides scheduling advice in the second model.	• How to guarantee the medication-taking information is accurate and reliable? • Which kind of reminder would be more effective in changing patients' behavior? • Normal reminder or context-aware reminder?	• The second one will be more useful.	• I think more simple means more stable. Thus, I think the first one is less likely to fail.	• I think both of them should have a fairly low possibility of overdose, but the second one may have a higher possibility of taking medication not at the prescribed time.

Table 8a. Participants feedback on comparison of artifact1 and artifact2

After analyzing the response of the participants recorded in Table 8a, all of the 12 participants have identified these differences in the two artifacts. However, the clarification questions for the differences varies among participants. Table 8b categorizes the different types of questions, corresponding participants and identifying the question as functional or technical (Artifact2). Functional or technical identification will be helpful in analyzing and improving the artifact further for future research.

Clarification question category	Participant	Functional versus Technical
Category1: Details of WMB such as portability, sensitivity, types of medicines supported, will it increase adherence, confirmation of medication consumption	HCP1, HCP2, HCP5, HCP6, HITE2, HITE6	Functional
Category2: Use of two separate entities WMB and MMA	HCP3, HITE2, HITE3, HITE4	Functional
Category3: Too much involvement and reminders might be cumbersome for the patient.	HCP5	Technical
Category4: Connection between context-aware reminder and patient, and analysis of consumption and context-aware reminder?	HCP4, HITE4, HITE6	Functional
Category5: Difference between MMS of Artifact1 and Artifact2	HITE1, HITE5, HITE6	Technical

Table 8b. Categorizing clarification questions

While developing the artifact we came across same types of questions and the developed artifact answers all these questions. For example, all the details of WMB are considered while using it as one of the components. WMB and MMA both are required because WMB is used by patient and provides dosing consumption information to MMS. On the other hand, MMA provides an interface between the patient, healthcare provider, and MMS. Similarly questions in Category 4 and Category 5 addressed in the development section above. The concern of participant HCP5 about the artifact being cumbersome for the patient is important concern. However, the system is not as cumbersome as it seems to be. Patient, as well as healthcare provider, will interact with the MMA. MMA is a simple app to provide three-way interaction

between patient, healthcare provider and MMS. All the complexity is in MMS for making intelligent decisions and generating smart interventions and providing the smart intervention in the form of an informed message to the patient. This further reduces the complexity at the patient's point of contact. Since MEMA comprises of functional and technical components and the clarification questions falls in both categories. It inclines the development process with the solution to real world problem scenario.

Table 8c summarizes how 12 participants categorize Artifact1 and Artifact2 based on which model is useful, realistic, reliable or less likely to fail and lead to overdose/over medication.

Model	Artifact1	Artifact2
Useful	HITE4	HCP1, HCP2, HCP3, HCP4, HCP5, HCP6, HITE1, HITE2, HITE3, HITE4, HITE5, HITE6
Realistic	HCP6, HITE3, HITE4	HCP1, HCP2, HCP3, HCP4, HCP5, HITE1, HITE2, HITE4, HITE5
Reliable or less likely to fail	HITE5, HITE6	HCP1, HCP2(patient side), HCP3, HCP4, HCP5, HCP6, HITE1, HITE2, HITE3, HITE4
Lead to overdose/over medication	HCP1, HCP2, HCP3, HCP4, HCP6, HITE1, HITE2, HITE3, HITE4, HITE5	HITE1, HITE6

Table 8c. Categorizing artifact1 and artifact2

As we can see from Table 8c, all the 12 participants identified Artifact2 (smart intervention) useful as compared to Artifact1. However, participant HITE4 says "Both are applicable solutions, based on my experience with IT solutions." Moreover, for the same reason, HITE4 identifies Artifact1 and Artifact2 to be realistic too. Also, participant HITE3 and HCP6 categorizes Artifact1 (simple intervention) to be realistic. Participant HCP6 says "realistic Artifact 1 because of less time consumption." All participants except HITE5 and HITE6 categorizes model3 to be reliable or less likely to fail. However, participant HCP2 says "Reliability will depend on the healthcare "end" on how compatible it is on their side. On the

patient side model, 2 is better than 1 as it gives information and reminders from nurse". It shows that participant is observing the involvement of healthcare provider and compatibility with technology for the reliability of the system.

The decision for the reliability of a model by participant HITE1 bases on the argument "Model 1: If the adherence is monitored by the doctor/nurse/caregiver. Model 2: If technology can be made reliable enough (WMB/MMS)". Since we have discussed in development section that in Artifact1 adherence is monitored by the healthcare provider at the end of the prescribed dosing regimen not during the prescribed dosing regimen, so we have categorized the response of HITE1 as Artifact2 to be reliable keeping in mind that technology (WMB/MMS) is reliable.

However, as no system is perfect so we would like to identify the limitation of our system here that if the wireless network is not working then WMB and MMS will not be able to interact, and the technology will not be reliable at that point of time. All the participants except HITE1 and HITE6 have identified Artifact1 leading to overdose/over medication. Participant HITE1 says "Model 2: If technology is not designed/implemented properly. Model 1: If patient/caregiver are not careful." It relates to the same concern HITE1 has with the reliability of the system.

So we can see that the integration of technology plays a crucial role in the effectiveness of the smart intervention. On the other hand, participant HITE6, mentions that "I think both of them should have a fairly low possibility of overdose, but the second one may have a higher possibility of taking medication, not at the prescribed time." However, this reasoning does not align with the difference participant HITE6 mentioned between Artifact1 and Artifact2 in Table 8a "The second one uses context-aware reminders. The second one includes the wireless medication box, which can trace patients' medication-taking behavior more objective than self-

report. The mobile application also provides scheduling advice in the second model." On the other hand, participant HCP5 mentions that "both unlikely to lead to overmedication."

The evaluation of smart intervention (Artifact2) with simple intervention (Artifact1) by domain experts is insightful in identifying that smart intervention seems to be a better intervention for improving the effectiveness of medication adherence. It is further verified by the analysis presented in Table 8a, 8b, and 8c as well as from the analysis description. However, as mentioned above smart intervention can be made more robust after addressing some of the concerns of healthcare providers and health IT experts related to the techniques and reliability of the system.

Section 5.3 Results

Using the analytical model, we derived several results for the impact of patterns of medication of adherence on effective medication adherence; compared effective medication adherence without any intervention, with simple and persistent reminders, and context-aware reminders for single medication multiple doses as well as multiple medications multiple doses. Also, we compared undesirable dose event for different scenarios. Last but not the least we have derived and compared the healthcare cost savings due to context-aware reminders, and healthcare cost saving due to simple and persistent reminders with healthcare cost when the patient was nonadherent.

5.3.1 Patterns of Adherence

To show the impact of the pattern, we take an example of three patients with different average levels and patterns of medication adherence. Table 9 shows the results, where the patient 3 can achieve satisfactory effective adherence by having a highly desirable pattern.

	Patient 1	Patient 2	Patient 3
Doses consumed	100%	90%	80%
Pattern	Lot of variations (20% probability of exceeding maximum interdose-time)	Some variations (10% probability of exceeding maximum interdose-time)	(0% probability of exceeding maximum interdose-time)
Average medication adherence	100%	90%	80%
Effective medication adherence	80%	80%	80%
Comment	Variations resulted in lower effective adherence	Variations reduced effective adherence	The best pattern leads to satisfactory adherence

Table 9. Different adherence and patterns

The patterns of adherence are studied based on Uniform and Poisson probability distributions. The results of both the distributions are used to confirm the effectiveness of medication over a particular interval of time. For example, a patient is prescribed 3 doses in a day for 30 days. However, the patient takes less than prescribed doses for 5 days and for rest of the 25 days he tries to catch-up before doctor's appointment. Alternatively, the patient takes less than prescribed doses for 10 days and again uses catch-up for 20 days. Here, the average rate of adherence is important, and the different patterns of adherence could make a difference. While calculating effective adherence we focused on the average probability of ideal timing and catch-up timing.

We considered both Uniform and Poisson distribution to study adherence. As shown in Figure 27, the differences are not huge, but we felt that Poisson will represent more variance and also there is evidence that medication consumption by people is closer to Poisson (Knafl et al. 2004). So for rest of the results, we used Poisson distribution.

Next, we study three different patterns of adherence. The average value was 100% as the patients consumed all doses using different patterns. In Random, every dose followed a random timing. One of the catch-up patterns involved a patient going easy on doses in the first 5 days (2

doses as opposed to 3/day) and then did catch up for the next 25 days, while the other catch-up pattern involved the same for 10 days of easy going and then catch up on 20 days. The effective medication adherence is present in all three patterns with Random showing the worst Effective Medication Adherence as compared to other catch up patterns. This is shown in the Figure 28. More flexible dose regimen (by using higher maximum interdose-time) leads to better Effective Medication Adherence.

Next, we derive the probabilities of multi-dosing by the patients within the minimum interdose-time. The probability of 2 doses was higher than 3 or 4 doses as expected in Figure 29.

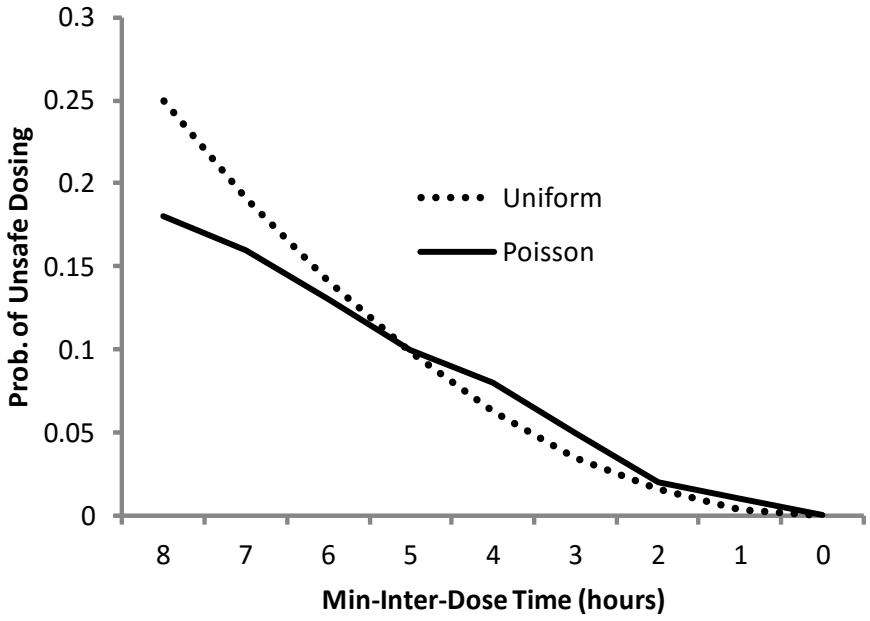


Figure 27. Distributions for studying patterns of adherence

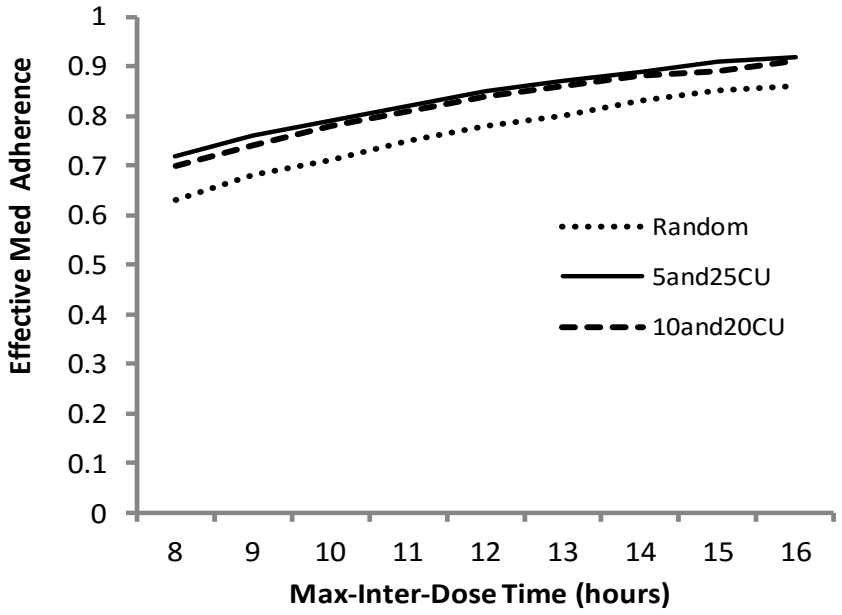


Figure 28. The impact of maximum interdose-time on effective adherence

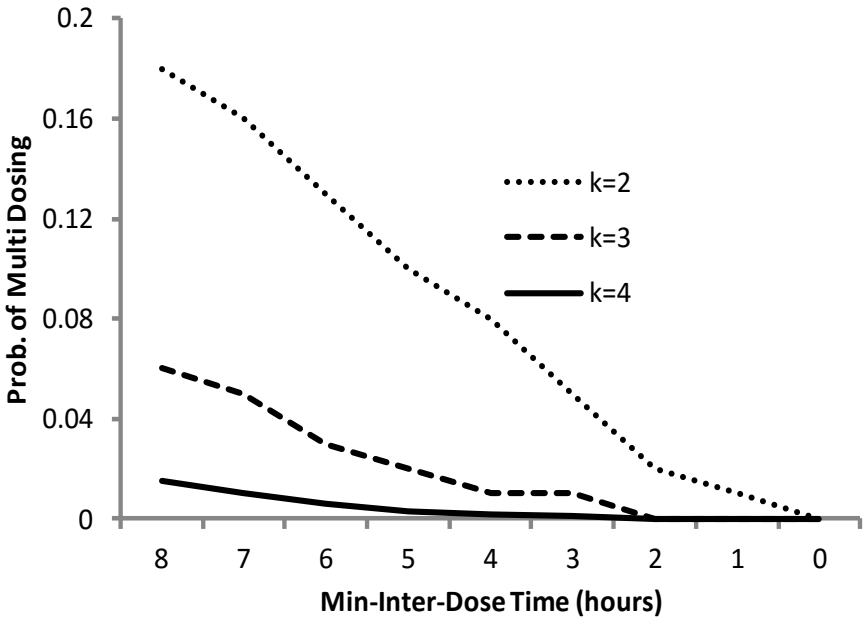


Figure 29. The probability of multi-dosing

Next, we study three different levels of average adherence and their resulting Effective Medication Adherence as shown in Figure 30. As before, the effective medication adherence is higher as the maximum interdose-time increased.

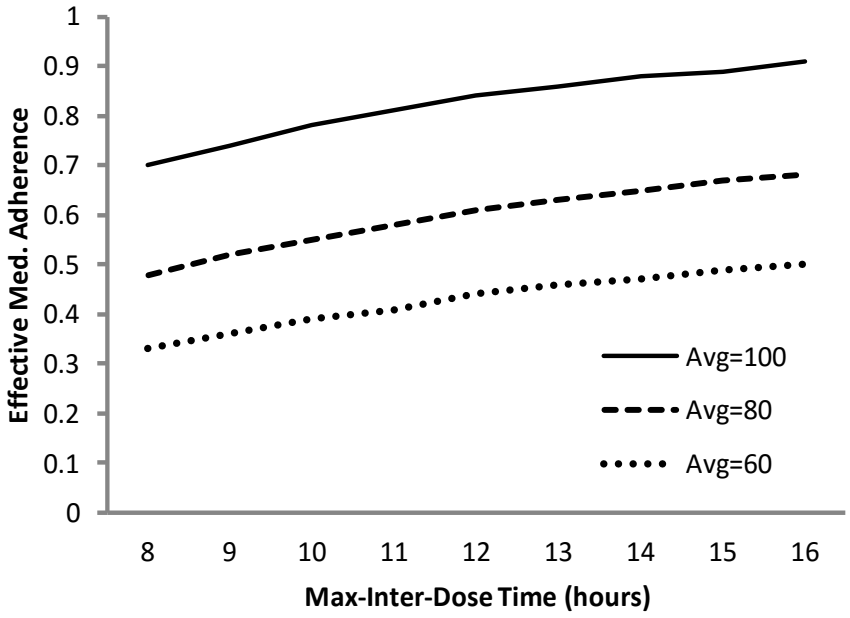


Figure 30. Effective adherence for different average values

5.3.2 Effective Medication Adherence for Single Medication

To validate the model, each of the equations for EMA is evaluated for a range of parameter values and the computed results are compared and analyzed to study the varied patterns of EMA. The patterns are compared and analyzed for different levels of medication adherence and probabilities of dose consumption due to reminders ($P_{D\text{-}R}$). The levels of the number of reminders per missing dose (N_P) are also varied to analyze the patterns of adherence in case of context-aware reminders (CAR). The results shown in the Figures 31, 32 and 33 are graphs plotted between T_{MAX} in hours (Horizontal axis) versus EMA (Vertical Axis); and the plane represents the comparison between different scenarios as mentioned in the respective graphs.

Figures 31 and 32 show the comparison of no reminders (NR), simple and persistent reminders (SR) and context-aware reminders (CAR) for average medication adherence (AMA) of 100% and 80% respectively. From the graphs of Figures 31 and 32, we can see that the patterns of adherence are best in the case of CAR when the probability of taking dose due to the reminder ($P_{D\text{-}R}$) is higher (85%-100%).

Figure 31a shows EMA of a person when he/she is 100% adherent to medication for NR, SR, and CAR (with 1, 2, 3 and 4 persistent reminders). Also, the person follows the reminders only 20% of the times. In the case of NR, the EMA_{NR} is in the range of 63%-86%. On the other hand, for SRs, EMA_{SR} ranges from 64%-87%. In case of CARs, EMA_{CAR} ranges from 70%-91% (N_P=1); 76%-94% (N_P=2); 81%-96% (N_P=3); 85%-98% (N_P=4).

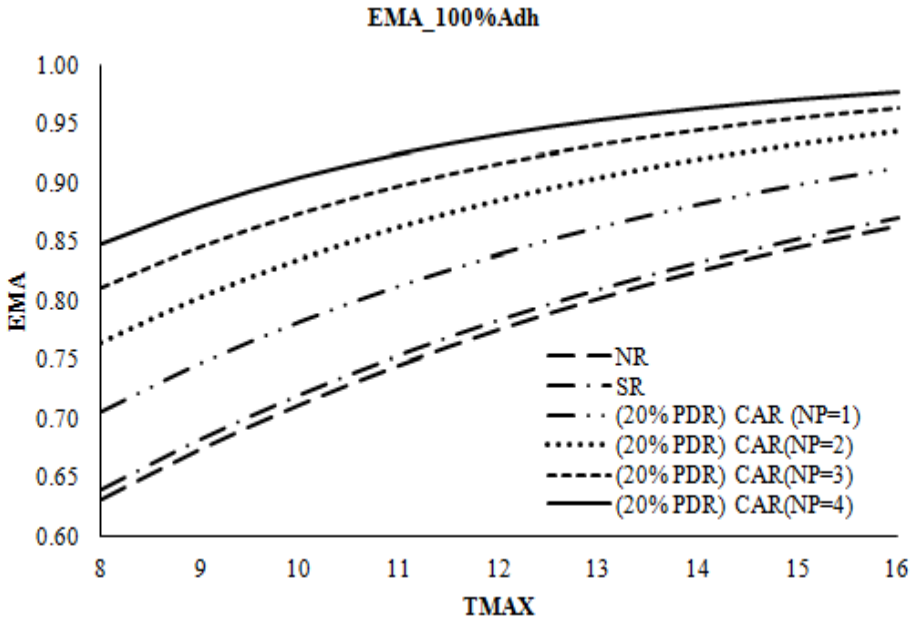


Figure 31a

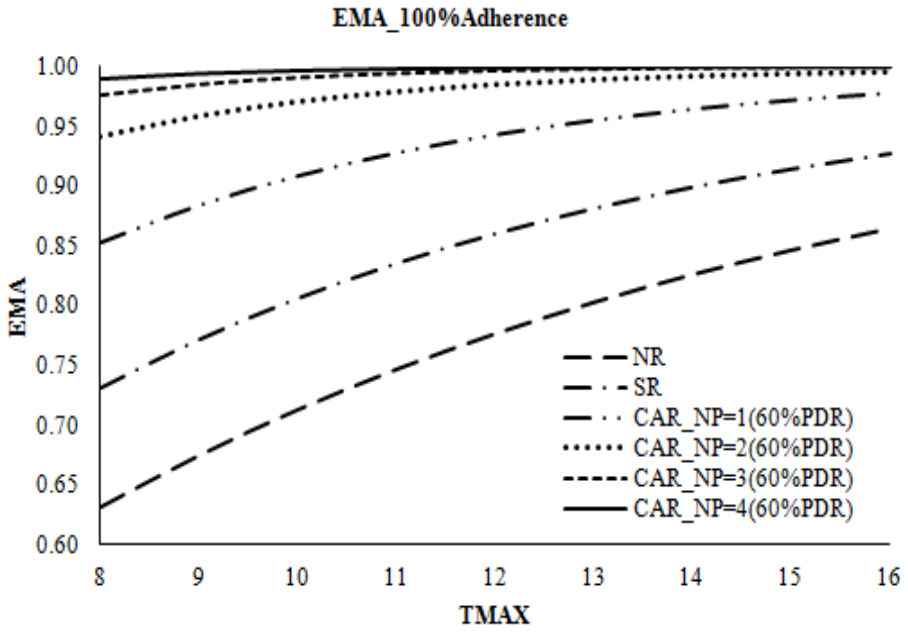


Figure 31b

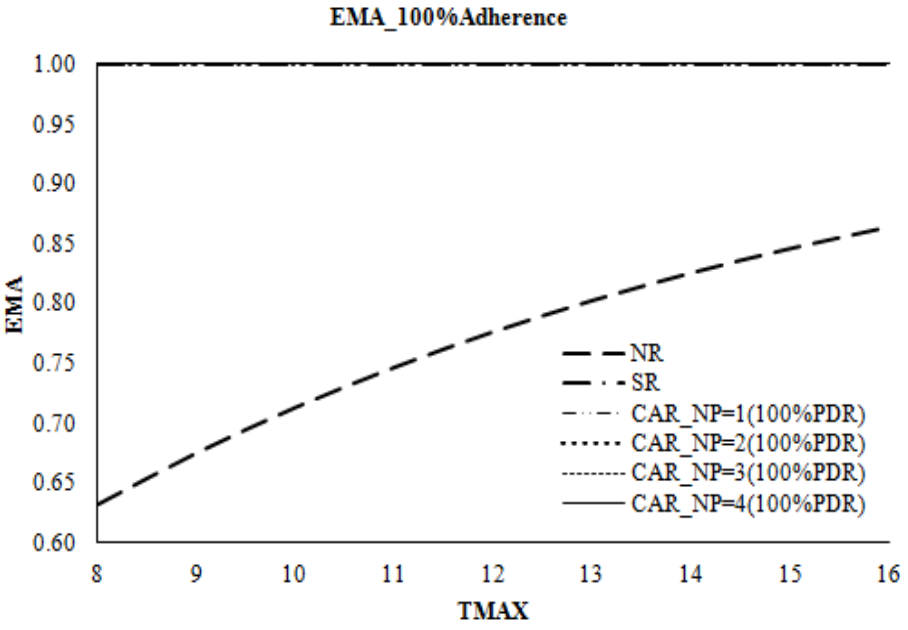


Figure 31c

Figure 31. Comparing EMA for NR, SR and CAR (AMA=100%)

From Figure 31a, we can conclude that increase in context and persistence of reminders leads to the increase in EMA and improves the patterns of medication adherence. Figures 31b also reflects the same increase in EMA for various levels of reminders and persistence. On the other

hand, Figure 31c shows that if a person is 100% adherent to medication and follows all the reminders, then the EMA for SR and CAR is 100% as compared to EMA in the range of 63%-86% in case of NR.

Figure 32a shows the EMA of a person when he/she is 80% adherent to medication for NR, SR, and CAR (with 1, 2, 3 and 4 persistent reminders). Figure 32b represents that the person follows the reminders only 60% of the times. In the case of NR, the EMA_{NR} is in the range of 44%-64%. On the other hand, for SRs, EMA_{SR} ranges from 54%-71%. In case of CARs, EMA_{CAR} ranges from 65%-77% (NP=1); 74%-80% (NP=2); 77%-79% (NP=3); 79%-80% (NP=4).

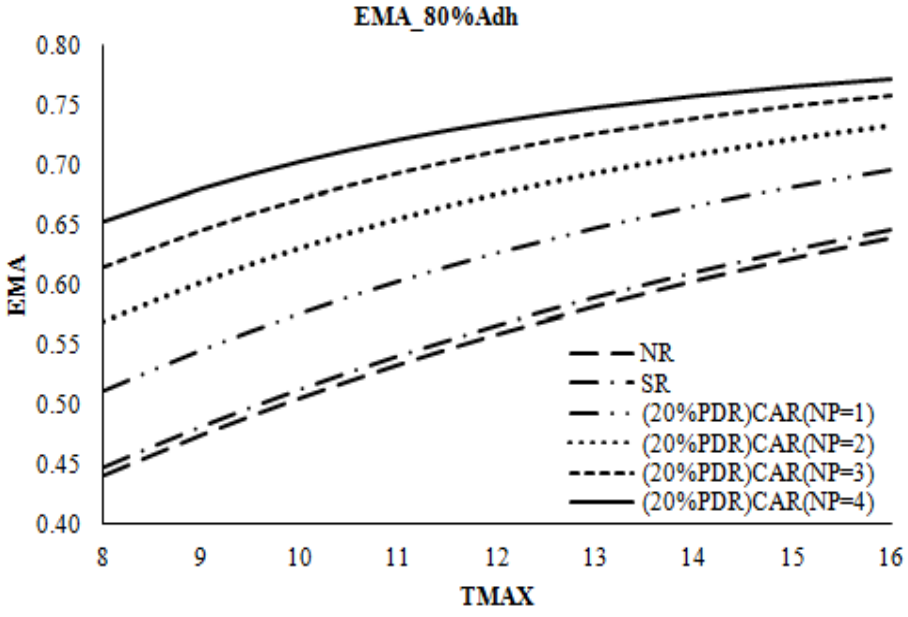


Figure 32a

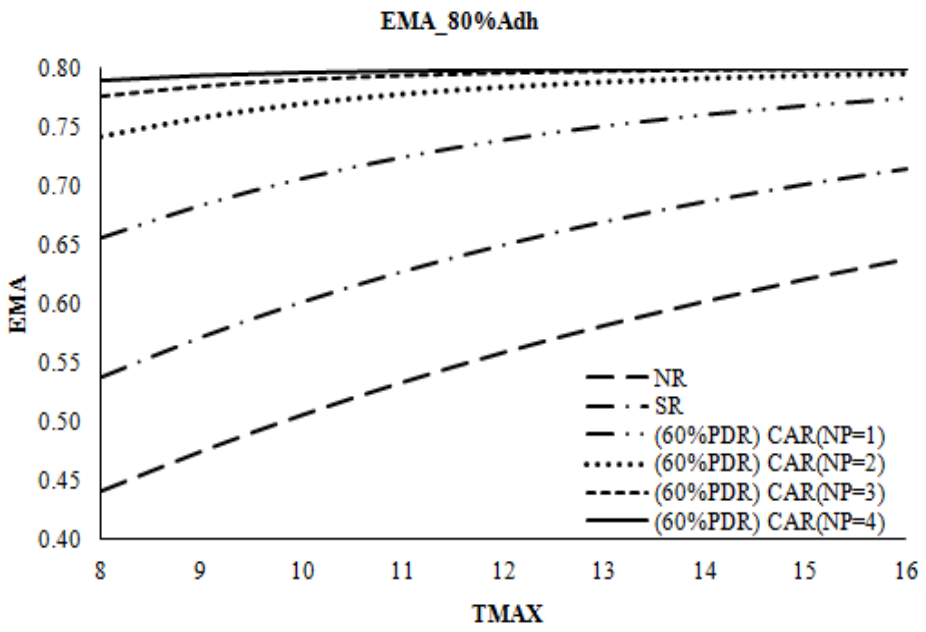


Figure 32b

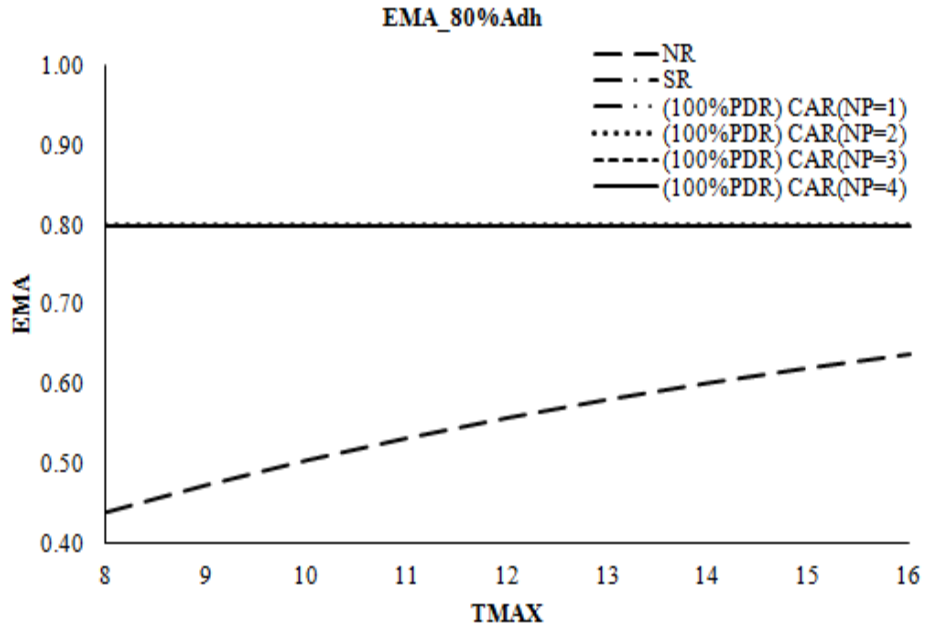


Figure 32c

Figure 32. Comparing EMA for NR, SR and CAR (AMA=80%)

So we can conclude that increase in context and persistence of reminders leads to the increase in EMA and improves the patterns of effective medication adherence. On the other hand, Figure 32c shows that if a person is 80% adherent to medication and follow all the reminders, then the EMA for SR and CAR is 80% as compared to EMA in the range of 44%-64% in case of NR.

Figure 33 shows the comparison of patterns of adherence for EMA with varied medication adherence, 2 persistent reminders and varied levels of dose consumption due to reminders.

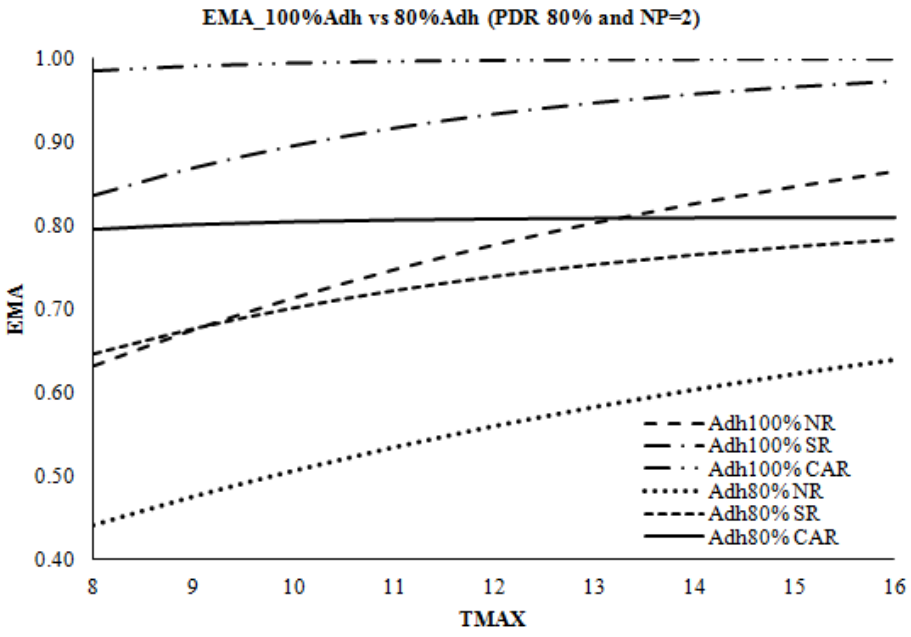


Figure 33a

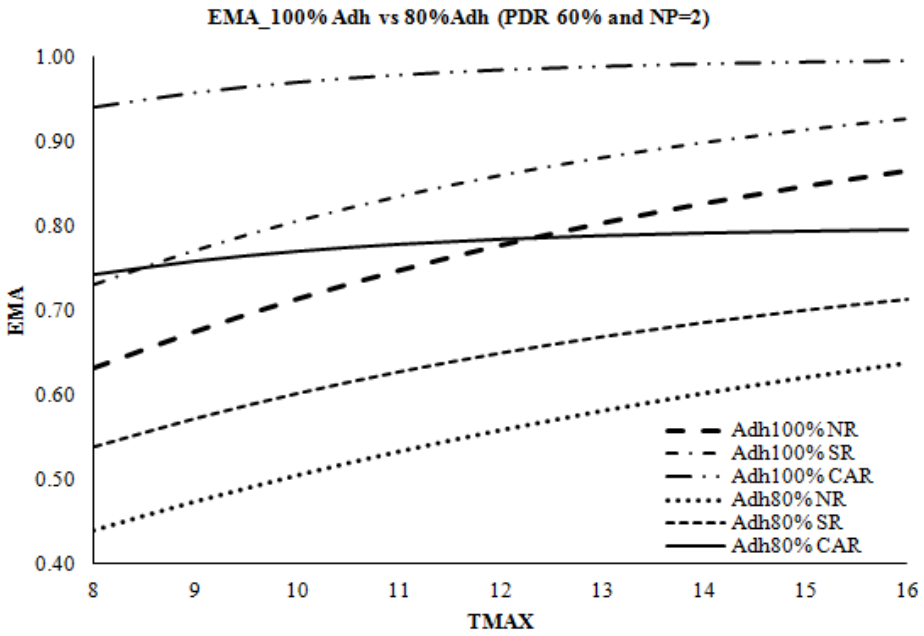


Figure 33b

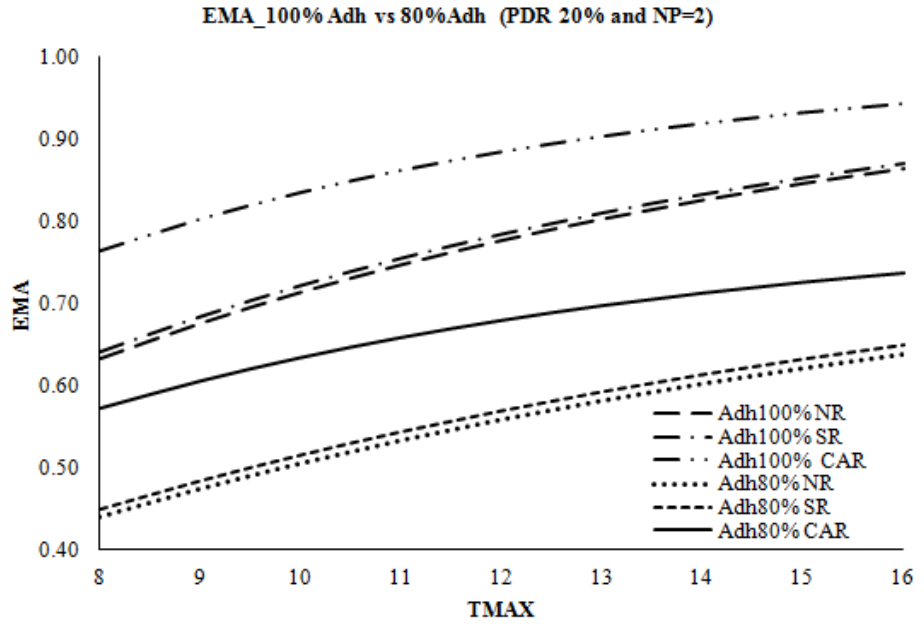


Figure 33c

Figure 33. EMA - (AMA=100% vs AMA80%); N_P=2; $P_{D\text{-}R}$= 80%, 60%, 20%

We can conclude from Figure 33a and 33b that at some point in time the patterns for CAR and SR coincide with each other for different PDR. For example, we can see that for N_P=2, AMA=80% and $P_{D\text{-}R}$=80% the pattern of adherence for simple reminders overlaps the pattern of adherence for context-aware reminders. Similarly, if the patient is 80% adherent to medication and takes the dose 80% of the time due to two persistent reminders, then the patient can achieve the same EMA as with 100% adherence to medications.

We observed similar results from Figure 34 and Figure 35 as above after varying other input parameters such as dosing rate (λ), the number of reminders, and the probability of dose taking after a reminder. In Figure 34 and Figure 35, 3DD and 2DD represent 3 doses per day and 2 doses per day respectively.

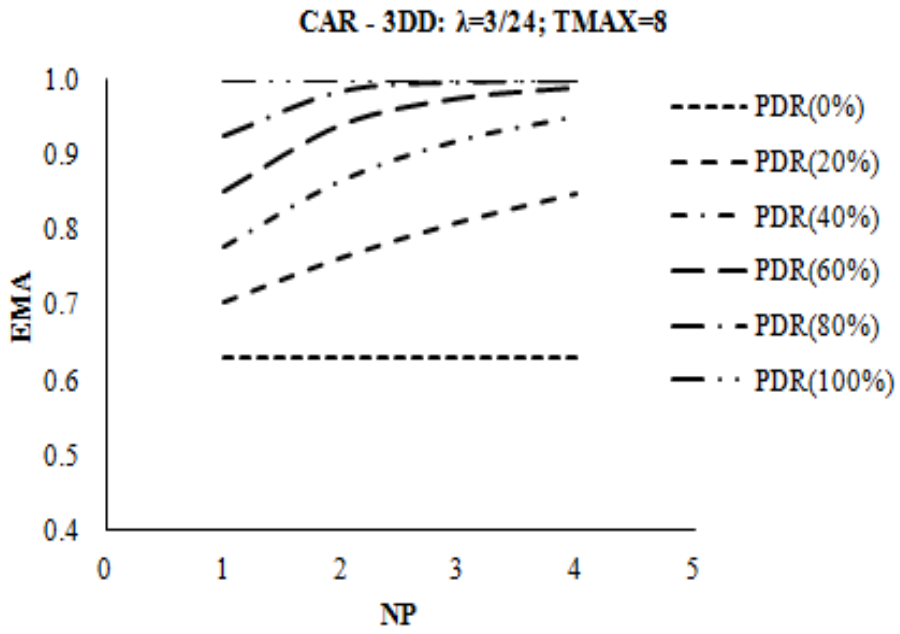


Figure 34. Impact of Np on EMA for varying PDR

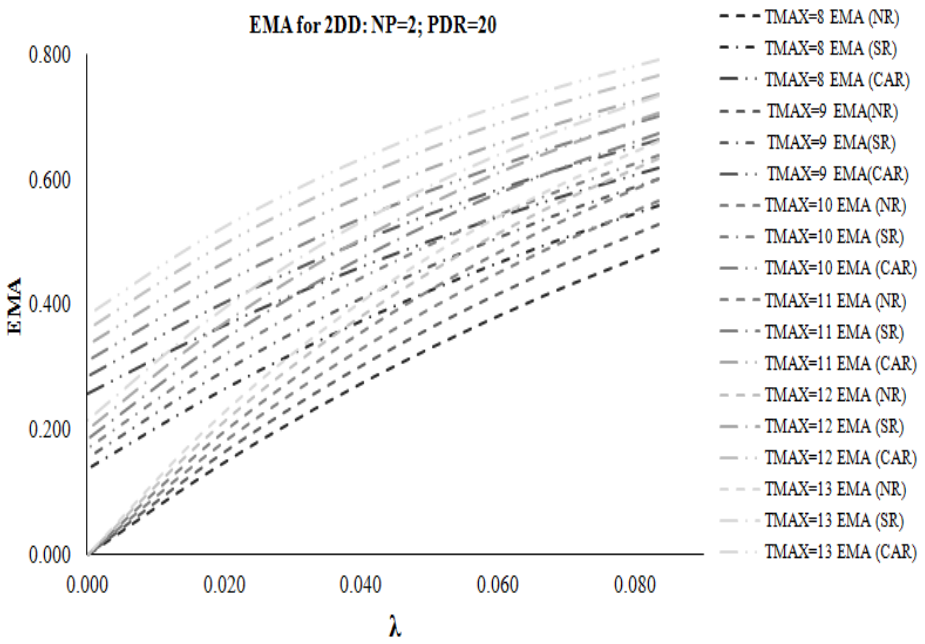


Figure 35. Impact of lambda on EMA with varying T_{MAX}

5.3.3 Undesirable dose event (UDE)

Figure 36 shows the results for UDE. UDE can be a problem as higher UDE can lead to drug toxicity and/or adverse side effects, thus affecting the future adherence to medications. UDE is increased by simple and persistent reminders, and even when CAR is not highly reliable.

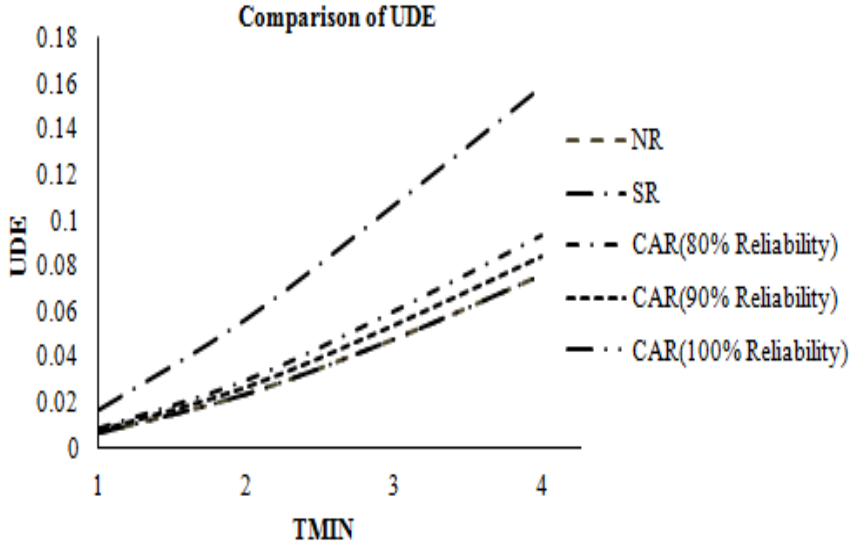


Figure 36. Comparison of UDE for NR, SR, and CAR

Results show that the pattern of adherence has a significant impact on EMA. Also, higher levels of EMA can be achieved for more flexible medication regimen, such as those with higher values of maximum interdose-time. It is also possible for a patient with lower average adherence but a desirable pattern of adherence to have higher EMA than a patient with higher AMA and less desirable pattern. In the case of interventions, results show that (1) simple and persistent reminders can improve EMA, but lead to higher UDE in some cases; (2) context-aware reminders can improve EMA without increasing UDE.

5.3.4 Effective Medication Adherence for Multiple Medication

To evaluate the effective medication adherence for multiple medication (M) in a day, with multiple doses of each medicine, we evaluated $EMA_{(SR)\,M}$ and $EMA_{(CAR)\,M}$. This will compare the EMA for simple and persistence reminders and context-aware reminders to see which intervention works better to improve EMA when patient is consuming multiple medications in a day. EMA is weighted average of EMA of individual medicines based on whether the medicine is primary or secondary. For the weighted average, the T_{MAX} is considered in the range of 12hrs to 18hrs because during this time interval all 3 medicines have effective dosing times. However, individually the T_{MAX} varies from 12hrs to 24hrs for N_{R1}; 6hrs to 18hrs for N_{R2}; and 5hrs to 20hrs for N_{R3}.

Case 1: Patient is prescribed three independent medicines in a day with all three medicines having the same dosing rate.

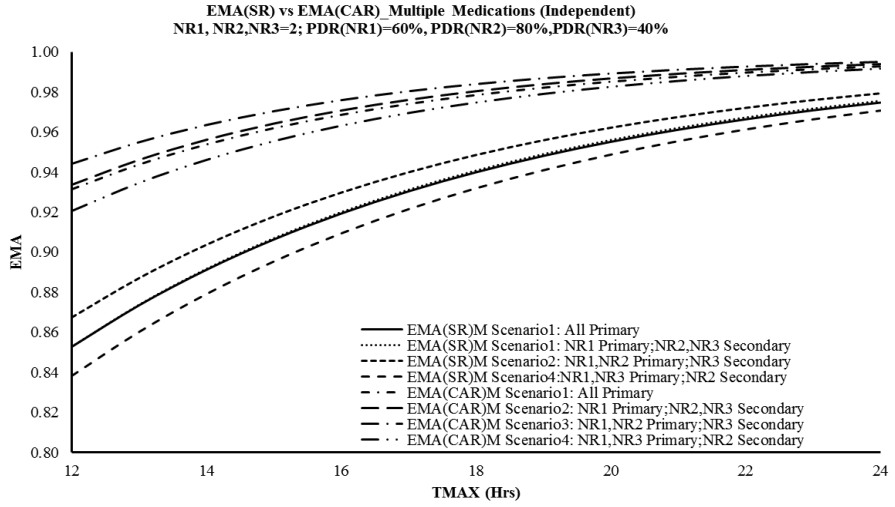


Figure 37. Comparing EMA for SR and CAR (multiple medications) – Case1

Case 2: Patient is prescribed three independent medicines in a day with two medicines having the same dosing rate and one with different dosing rate.

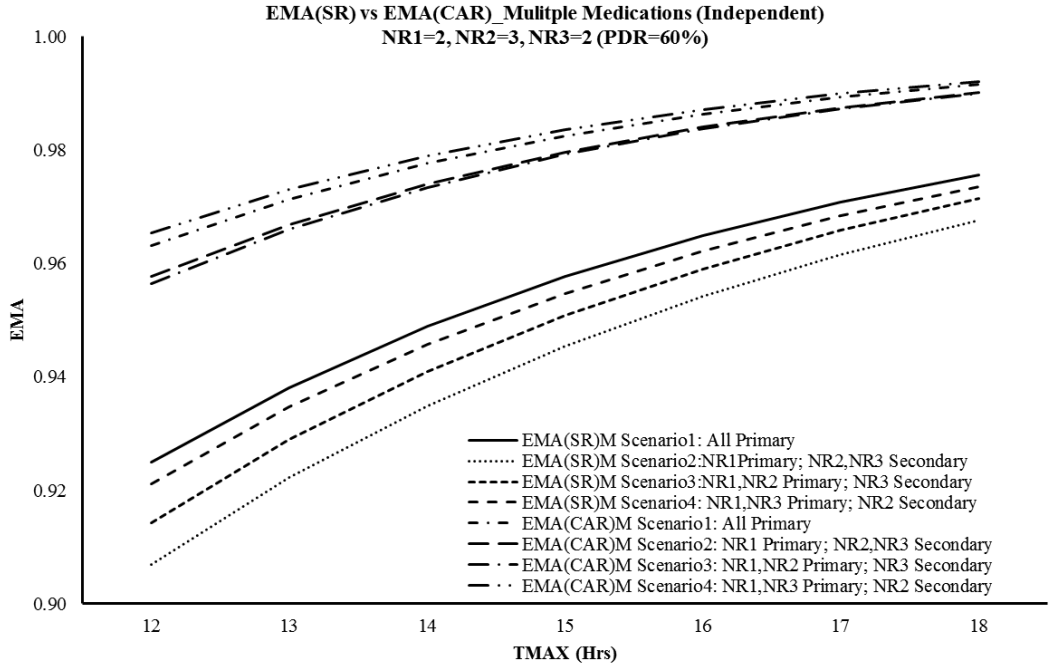


Figure 38. Comparing EMA for SR and CAR (multiple medications) – Case2

Case 3: Patient is prescribed three independent medicines in a day with all three medicines having different dosing rate.

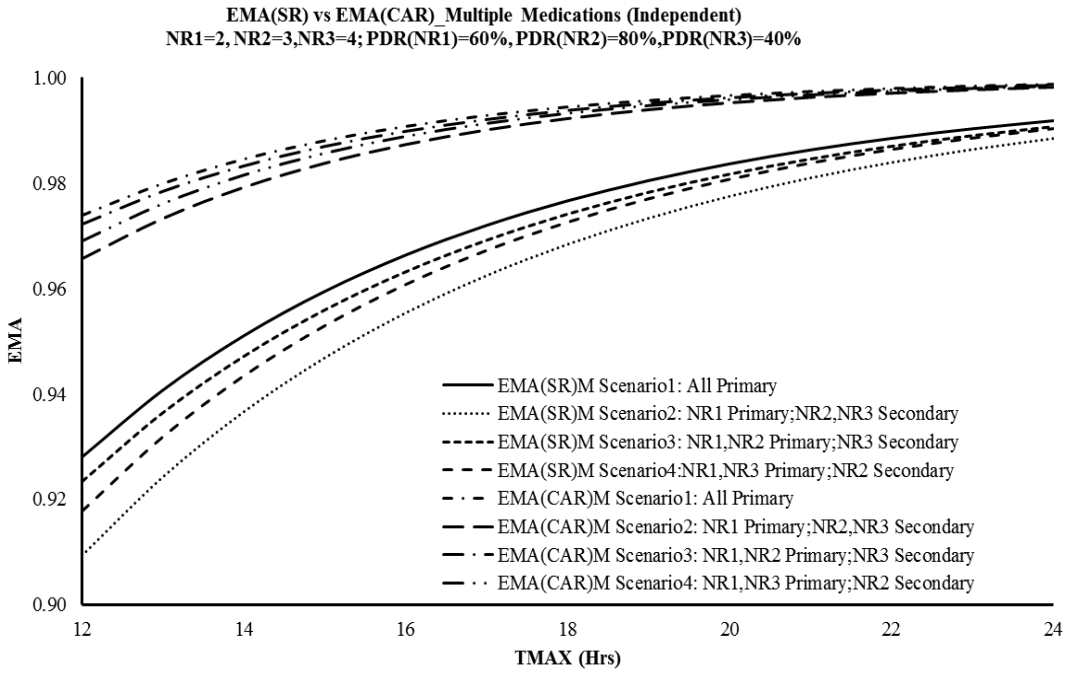


Figure 39. Comparing EMA for SR and CAR (multiple medications) – Case3

5.3.5 Healthcare cost

Healthcare cost for nonadherent patients comprises of medical and drug cost. When a simple and persistent intervention is administered to a nonadherent patient, it helps in improving the medication adherence. However, due to additional undesirable dose event and cost of intervention, it increases the healthcare cost to some extent. Still the analysis shows that simple and persistent reminders bring the healthcare cost by approximately 15% to 20% (HCCOST_SR Scenario I and HCCOST-SR Scenario II in Figure 40). On the other hand, smart interventions improve the effectiveness of medication adherence as well as reduce the healthcare cost by 39%

(HCCOST-CAR Scenario I). Analysis of healthcare cost is conducted based on the data available in Sokol (2005) for the all-disease cost (medical and drug cost).

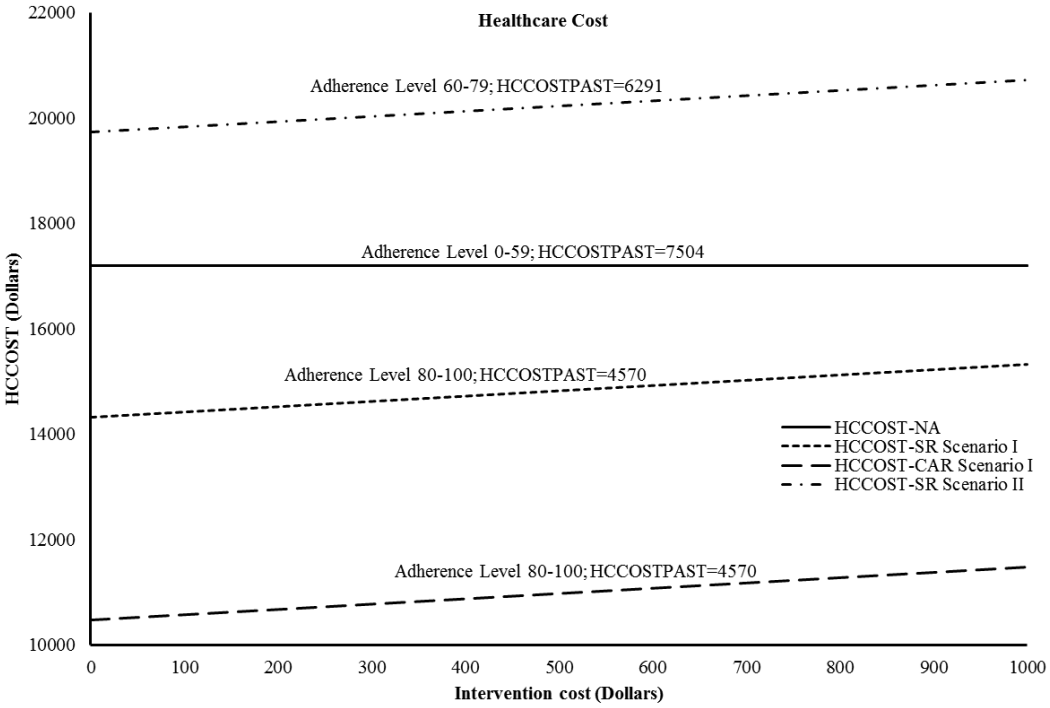


Figure 40. Comparison of healthcare cost saving

Section 5.4 Propositions

5.4.1 Proposition 1

Context-aware Reminders will always outperform Simple and Persistent Reminders in improving Effective Medication Adherence.

EMA is higher for context-aware reminder (CAR) as compared to simple and persistent reminders (SR).

Since equation 14 is $\boldsymbol{EMA_{CAR} = AMA_{NEW\text{-}CAR} \times [1 - ((P_{ND\text{-}R})^{\lambda T_{MAX} N_P} \times e^{-\lambda T_{MAX}})]}$

And equation 9 is $\mathbf{EMA_{SR} = AMA_{NEW\text{-}SR} \times (1 - (P_{ND\text{-}R})^{Q} [e^{-\lambda T_{MAX}}])}$

So for,

$$[\boldsymbol{AMA_{NEW\text{-}CAR}} \times [\mathbf{1} - ((\boldsymbol{P_{ND\text{-}R}})^{\boldsymbol{\lambda T_{MAX} N_P}} \times \boldsymbol{e}^{-\boldsymbol{\lambda T_{MAX}}})]] > [\mathbf{AMA_{NEW\text{-}SR}} \times (\mathbf{1} - (\boldsymbol{P_{ND\text{-}R}})^{\boldsymbol{Q}} [\boldsymbol{e}^{-\boldsymbol{\lambda T_{MAX}}}])]$$

Either, $\boldsymbol{AMA_{NEW\text{-}CAR}} > \mathbf{AMA_{NEW\text{-}SR}}$

Or, $\boldsymbol{\lambda T_{MAX} N_P} > Q$ i.e., $\frac{\mathbf{N_R}}{\mathbf{24}} \mathbf{T_{MAX}} \boldsymbol{N_P} > \frac{\boldsymbol{T_{MAX}}}{\mathbf{24}} \boldsymbol{N_R}$

i.e., $\boldsymbol{N_P} > \mathbf{1}$ which is true by definition. **Therefore,** $\boldsymbol{EMA_{CAR}} > \boldsymbol{EMA_{SR}}$

Results represented in Figure 31, Figure 32, and Figure 33 aligns with analysis of Proposition 1.

5.4.2 Proposition 2

Simple and Persistent Reminders will generate more UDE than Context-aware Reminders.

Equation 10 is:

$$\boldsymbol{UDE_{TOTAL}} = \boldsymbol{Prob}\big((\boldsymbol{T_{I+1}} - \boldsymbol{T_I}) < \boldsymbol{T_{MIN}}\big)$$

$$= [\mathbf{1} - \boldsymbol{\lambda T_{MIN}}] \times \left[(\boldsymbol{\lambda T_{MIN}})^2 \times \frac{\boldsymbol{e}^{-\boldsymbol{\lambda T_{MIN}}}}{\mathbf{2!}}\right] + \boldsymbol{\lambda T_{MIN}} \times \boldsymbol{P_{D\text{-}R}} \times \left[(\boldsymbol{\lambda T_{MIN}}) \times \boldsymbol{e}^{-\boldsymbol{\lambda T_{MIN}}}\right]$$

Equation 15 is: $\mathbf{Prob}\big((\mathbf{T_{I+1}} - \mathbf{T_I}) < \mathbf{T_{MIN}}\big) = (\boldsymbol{\lambda T_{MIN}})^2 \times \frac{\mathbf{e}^{-\boldsymbol{\lambda T_{MIN}}}}{\mathbf{2!}}$

Comparing equation 10 and equation 15,

$$[\mathbf{1} - \boldsymbol{\lambda T_{MIN}}] \times \left[(\boldsymbol{\lambda T_{MIN}})^2 \times \frac{\boldsymbol{e}^{-\boldsymbol{\lambda T_{MIN}}}}{\mathbf{2!}}\right] + \boldsymbol{\lambda T_{MIN}} \times \boldsymbol{P_{D\text{-}R}} \times \left[(\boldsymbol{\lambda T_{MIN}}) \times \boldsymbol{e}^{-\boldsymbol{\lambda T_{MIN}}}\right]$$

$$> (\boldsymbol{\lambda T_{MIN}})^2 \times \frac{\mathbf{e}^{-\boldsymbol{\lambda T_{MIN}}}}{\mathbf{2!}}$$

OR, $\left[\frac{(\mathbf{1}-\boldsymbol{\lambda T_{MIN}})}{\mathbf{2}} + \boldsymbol{P_{D\text{-}R}}\right] > \frac{\mathbf{1}}{\mathbf{2}}$

OR, $\left[\frac{\mathbf{1}}{\mathbf{2}} - \frac{\boldsymbol{\lambda T_{MIN}}}{\mathbf{2}} + \boldsymbol{P_{D\text{-}R}}\right] > \frac{\mathbf{1}}{\mathbf{2}}$

OR, $\left[\boldsymbol{P_{D\text{-}R}} - \frac{\boldsymbol{\lambda T_{MIN}}}{\mathbf{2}}\right] > \frac{\mathbf{1}}{\mathbf{2}} - \frac{\mathbf{1}}{\mathbf{2}}$

OR, $\left[\boldsymbol{P_{D\text{-}R}} - \frac{\boldsymbol{\lambda T_{MIN}}}{\mathbf{2}}\right] > \mathbf{0}$

Therefore, $\boldsymbol{P_{D\text{-}R} > \frac{\lambda T_{MIN}}{2}}$

For example, $\boldsymbol{\lambda = \frac{3}{24}, T_{MIN} = 1\text{-}4hr, Then\ P_{D\text{-}R} >}$

$\boldsymbol{\frac{1}{4}, i.e., 25\%\ chances\ of\ taking\ medication\ due\ to\ reminders.}$

Results represented in Figure 36 where the undesirable dose event for 3 different scenarios is compared aligns with analysis of Proposition 2.

5.4.3 Proposition 3

The EMA will be minimum when the probability of consuming dose due to reminder is minimum and maximum interdose-time between doses is as prescribed.

Using equation 9, we can derive the lowest value for EMA, i.e., EMA_{MIN} for persistent reminders.

$$\mathbf{EMA_{MIN\text{-}SR} = AMA_{NEW} \times \left(1 - (P_{ND\text{-}R})^{Q}\left[e^{-\lambda T_{MAX}}\right]\right)}$$

$$\mathbf{= Min[(AMA + (1 - P_{ND\text{-}R}) \times \lambda T_{MAX}), 1] \times \left(1 - (P_{ND\text{-}R})^{Q}\left[e^{-\lambda T_{MAX}}\right]\right)}$$

The variables used in this equation are as follows:

$$\mathbf{AMA, P_{ND\text{-}R}, \lambda T_{MAX}\ and\ Q\ where\ Q = \lambda T_{MAX}}$$

For EMA to be minimum:

i. It is desirable that $\mathbf{(1 - P_{ND\text{-}R}) \times \lambda T_{MAX}}$ should be minimum, and

ii. It is required that $\mathbf{1 - (P_{ND\text{-}R})^{Q}\left[e^{-\lambda T_{MAX}}\right] = 1 - (P_{ND\text{-}R})^{\lambda T_{MAX}}\left[e^{-\lambda T_{MAX}}\right] = 1 - \left(\frac{P_{ND\text{-}R}}{e}\right)^{\lambda T_{MAX}}}$ is minimum.

Alternatively, we can say $\boldsymbol{\left(\frac{P_{ND\text{-}R}}{e}\right)^{\lambda T_{MAX}}}$ should be maximum. It implies, $\mathbf{P_{ND\text{-}R}}$ should be maximum AND/OR $\mathbf{\lambda T_{MAX}}$ should be close to zero. Using equation 14, we can derive the lowest value for EMA, i.e., EMA_{MIN} for context-aware reminders.

$$\boldsymbol{EMA_{MIN\text{-}CAR} = AMA_{NEW} \times \left(1 - [(P_{ND\text{-}R})^{\lambda T_{MAX}}]^{N_P} \times [e^{-\lambda T_{MAX}}]\right)}$$

$$\boldsymbol{= \mathbf{Min}[(\mathbf{AMA} + (1 - \mathbf{P_{ND\text{-}R}})^{\mathbf{N_P}})), 1] \times [1 - ((P_{ND\text{-}R})^{\lambda T_{MAX} N_P} \times e^{-\lambda T_{MAX}})]}$$

Since equation 14 is $\boldsymbol{EMA_{CAR} = AMA_{NEW} \times [1 - ((P_{ND\text{-}R})^{\lambda T_{MAX} N_P} \times e^{-\lambda T_{MAX}})]}$

Moreover, equation 4 is $\boldsymbol{EMA = AMA \times (1 - DNE) = AMA \times (1 - e^{-\lambda T_{MAX}})}$

We know that, $\boldsymbol{AMA_{NEW} \geq AMA.}$ Using equation 14 and 4 we can say that following condition must be true, i.e., $\boldsymbol{(P_{ND\text{-}R})^{\lambda T_{MAX} N_P} < 1}$

$\Rightarrow \textit{Since, } \boldsymbol{P_{ND\text{-}R} < 1} \textit{ So following equation must be true, i.e., } \boldsymbol{\lambda T_{MAX} N_P > 1}$

Now we know that λ is the average arrival rate, and T_{MAX} varies from 8 hours to 16 hours. Also, N_P is always greater than 1 being the Number of reminders per missing dose event. It implies $\boldsymbol{\lambda T_{MAX} N_P > 1}$ holds true. Detailed analysis of results shown in Figure 31, Figure 32, and Figure 33 confirms with Proposition 3.

5.4.4 Proposition 4

The UDE is maximum when the minimum gap between doses is equal to or greater than the regular gap between medications.

Evaluating equation 10 (UDE for simple and persistent reminders) for finding UDE_{MAX}

$$\boldsymbol{UDE_{TOTAL} = [1 - \lambda T_{MIN}] \times \left[(\lambda T_{MIN})^2 \times \frac{e^{-\lambda T_{MIN}}}{2!}\right] + [\lambda T_{MIN} \times P_{D\text{-}R}] \times \left[(\lambda T_{MIN}) \times e^{-\lambda T_{MIN}}\right]}$$

Since UDE is a probability, this can have a maximum value of 1.

Let us consider following three parameters if the prescribed doses are 3 in an interval of 8 hours: $\lambda = \frac{N_R}{24}$ $\quad T_{MIN} = (Min, Max)$ $\quad P_{D\text{-}R} = (0, \ldots\ldots 1)$

UDE_{MAX} will be .368 when minimum gap between medications is equal to the regular gap between medications, i.e., when $\lambda = \frac{3}{24}$, $T_{MIN} = 8$, $P_{D\text{-}R} = 1$

It holds true for 2doses/day at 12hrs intervals as well as 4doses/day at 5 hrs interval. We can have higher value of UDE beyond the regular gap between medications, but $[\mathbf{1} - \boldsymbol{\lambda}\mathbf{T_{MIN}}] \times \left[(\boldsymbol{\lambda}\mathbf{T_{MIN}})^{\mathbf{2}} \times \frac{e^{-\lambda T_{MIN}}}{\mathbf{2!}}\right]$ component (the probability of patient taking two doses when no reminder came) of UDE becomes negative too. After analyzing results represented in Figure 36, we can confirm the analysis of Proposition 4.

5.4.5 Proposition 5

The maximum healthcare savings due to context-aware reminders is always higher than simple persistent reminders when there are no failures.

Since equation 16a is: $\mathbf{HC_{COST_{NA}}} = (\mathbf{HC_{COST\text{-}PAST}}) \times (\mathbf{1.05})^{\mathbf{N}}$

Equation 16b is: $\mathbf{HC_{COST_{SR}}} = (\mathbf{HC_{COST\text{-}PAST}}) \times (\mathbf{1.05})^{\mathbf{N}} \times (\mathbf{1} + \mathbf{UDE_{SR}}) + \mathbf{INTVN_{COST\text{-}SR}}$

Equation 16c is: $\mathbf{HC_{COST_{CAR}}} = (\mathbf{HC_{COST\text{-}PAST}}) \times (\mathbf{1.05})^{\mathbf{N}} + \mathbf{INTVN_{COST\text{-}CAR}}$

Therefore, from equation 16b and 16c we can see that the healthcare cost due to simple persistent reminders includes the additional cost for UDE as compared to healthcare costs due to context-aware reminder. Also, the intervention cost ($INTVN_{COST}$) varies for context-aware reminders as compared to simple persistent reminders. Results represented in Figure 40 helps us in a detailed analysis of Proposition 5.

Chapter 6. Conclusion

Improving the rate of medication adherence is a serious concern. Most of the studies on improving medication adherence focus on one or more interventions and measure average rate of medication adherence. Although the average rate of medication adherence is useful, we note that patients could achieve the same average medication adherence value with widely different consumption patterns including those where patients have not consumed any doses for several days and then taken multiple doses or doses that are more frequent. In this research, we focus on the idea that in addition to the average rate of medication adherence, the patterns of adherence and effective medication adherence should also be studied. These are more likely to be a better predictor of outcomes than average medication adherence alone.

Using design science research (DSR) approach we have developed a model for smart interventions as health IT artifact. We have leveraged behavior change techniques (BCTs) based on behavior change theories to design smart intervention. Because of the need for real time requirements for the system, we are also focusing on hierarchical control system theory and reference model architecture (RMA). The benefit of using this design will be allowing an intervention to be administered dynamically on a need basis. A key distinction from existing systems is that the developed artifact leverages probabilistic measure instead of static schedule. We have developed a health IT artifact with intelligence and persistence for the reminders.

Interventions that stimulate better adherence to essential medications even slightly may meaningfully improve public health (Friedman et al. 1996; Haynes et al. 2005). The uniqueness of our health IT artifact, termed MEMA, is that it does not create a schedule of administering the interventions but decides the next administration of the intervention dynamically. It creates a schedule of prescribed dosing events at the time of prescription and also registers actual dosing

event of the patient during prescription. A probable rate of effective medication adherence (EMA) generates at each dosing event of the patient and the prescribed dosing event. Based on the value of EMA, an appropriate type of intervention is chosen and scheduled either before or at the next dosing event for the patient. It may also happen that intervention is not deemed necessary for the next prescribed dosing event if the patient is 100% following the prescribed dosing regimen. The type of intervention denotes the priority we associate to the next scheduled intervention in maintaining the EMA above a specified threshold (depending on the type of care and therapy received). It will consider the dosing frequency and time for a particular dosing regimen. In this way, the context-aware reminders provided by MEMA will not lead to the undesirable dose event (UDE).

We have evaluated and validated the artifact using analytical model and empirically evaluated the effectiveness of the health IT artifact by having domain experts assess the simple and smart intervention. Two categories of domain experts considered are the healthcare provider and health IT experts. Focus is explicitly on the experts' reasoning about their preferences between the existing and our smart interventions, and on relating that reasoning to the proposed health IT artifact. This evaluation provides the insights for interventions preferred by experts. As discussed in section 5.2, domain experts prefer smart intervention as compared to simple intervention. There is one limitation of concern to the experts that is the reliability of the health IT system. Patient-provider concordance is also mentioned by some of the experts as one the factor for effectiveness of the smart intervention. The smart intervention is developed considering the patient-provider concordance during the medication therapy/persistence.

The results have significant implication for the healthcare system and researchers studying medication adherence and interventions. The patterns of adherence will be useful in studying

effective medication adherence (EMA) for patients to improve medication adherence. Our results show that (1) simple interventions can improve the pattern of adherence and the average rate of medication adherence, but can also increase the probability of undesirable dose events sometimes; (2) smart interventions can improve both the pattern and average value of adherence without increasing the undesirable dose events.

The results of our analysis have significant implications for healthcare providers, patients, insurance companies, and health IT researchers interested in improving healthcare delivery and outcomes**.** Higher levels of effective adherence can be achieved for more flexible medication regimen, such as those with higher values of maximum interdose-time. It is also possible for a patient with lower average adherence but a more desirable pattern of adherence to have higher effective medication adherence than a patient with higher average adherence with a less desirable pattern of adherence. Also, the smart intervention will work for patients who are willing and can take medication when reminded.

Section 6.1 Research Questions and Discussion

The design science research process followed in this research occurred in phases, and each phase was instrumental in arriving at the conclusions discussed herein. This research recognized the problem of nonadherence and the tremendous impact it has has upon financial and treatment outcomes, especially among chronic patients prescribed self-administered medications. The problem of nonadherence has been prevalent and very little progress in improving the rate of medication adherence has been achieved so far. The perspective this research carried during literature reviews to identify possible solutions to this problem was to revisit the fundamental question related to this problem i.e. what it meant to be nonadherent and the bearing it had on the

medication adherence. Analysis of this fundamental question provided greater insight into the effectiveness of medication adherence and arrived at the research problem.

This research examined how patterns of medication adherence impact effective medication adherence (EMA)? The outcome of this examination was a measure of effective medication adherence (EMA) that could capture the effectiveness of medication adherence within the medication persistence. So far, measurements were for average medication adherence that one could arrive at only towards the end of medication persistence. Improving the rate of medication adherence needs interventions that are effective for the healthcare providers to administer and patients to follow. Based upon the measure of EMA, this research developed a health IT model for effective medication adherence that could allow the healthcare providers to administer smart interventions. The overall usefulness of smart interventions with results on improving effective medication adherence and reducing healthcare costs is validated.

The guiding questions at various stages of DSR process are revisited to assess the knowledge gained at each stage:

• **Awareness of Problem: If interventions to medication nonadherence can improve medication adherence, why such interventions are not effective*?*** Nonadherence is a multidimensional problem, and current measure of adherence does not support intervention within the period of medication persistence where it can be effectively intervened.

• **Suggestion: How can the effectiveness of interventions be improved?** By enabling healthcare providers to assist patients in improving their medication adherence and adopting the use of smart interventions that are based on effective medication adherence and provide the ability to intervene when there is a need. EMA generates at the actual dose event and the prescribed dose events.

• **Development: How closely does the new model represent the original model/design of the available interventions?** The new model for MEMA is an enhancement to existing model and augments the existing design with real time intelligent decision system.

• **Evaluation: What are the limiting conditions for the effectiveness of interventions utilizing new model?** Besides the theoretical limits to improving the effective medication adherence, there are practical limitations like developing a classification for the thresholds that EMA should never fall below or for accessing the impact on a specific prescription based on medicines administered. Development of classification for different medication regimen is an identified future research.

• **Conclusion: Do the smart interventions improve effectiveness of medication adherence?** Health Behavior Change Theories indicate so, and validations using the sample data proved that smart interventions improve medication adherence overall and also improve the effectiveness of medication adherence.

Section 6.2 Research Contribution

6.2.1 Contribution to Information Systems

Baskerville and Myers (2002) suggested that the "potential audience for IS field includes scholars in any field that is vitally concerned with the development, use, and application of information technology and systems" (p. 8). They have specifically mentioned this potential in medical fields (Baskerville and Myers 2002 pp. 8). The healthcare industry poses important social challenges and interesting research possibilities for researchers interested in the development and use of information systems and technologies (Agarwal et al. 2010; Chiasson and Davidson 2004; Romanow et al. 2012). We have leveraged the in-depth knowledge of an IS

researcher to influence healthcare practice (Agarwal et al. 2010) by increasing effectiveness of interventions, improving medication adherence and advancing the behavior change techniques.

Without the use of information technology (IT), measuring medication adherence can be onerous, with feasibility and cost being barriers. Innovations in health IT utilizing the IS advancements can increase the feasibility of monitoring, accuracy, and widespread usage of medication adherence tools (Williams et al. 2014). Using IS/IT perspective and application of behavior change theories (behavior change techniques) we have developed an IT based smart intervention to address the multidimensional issue of medication adherence. Smart intervention helps in improving medication adherence which further helps in minimizing the healthcare cost, improving the healthcare quality and advancing behavior change techniques.

This research contributes a health IT domain specific artifact to the DSR community. The artifact developed in this study solves a specific problem of low medication adherence among chronic patients prescribed self-administered medications. The artifact is made a general artifact (Iivari 2015) by using some of the requirements and design processes presented in this research. Finally, the research adds to the IS knowledge base by providing the theory based smart interventions based on BCTs and RMA for improving the medication adherence.

6.2.2 Contribution to Health IT

This research focuses on the effectiveness of medication adherence and the impact of medication behavior on the overall effectiveness of treatment outcome. Specifically, we propose that pattern of adherence along with average medication adherence is a better predictor of health outcomes. Effective medication adherence captures the context for smart interventions that helps increase the rate of medication adherence and lower the healthcare costs. Propositions 1 through

5 are validated design rules for the development of smart interventions and can be useful for future research related to medication adherence and development of new interventions.

The developed model can be utilized to create, implement and evaluate health IT artifacts for health and wellness, and daily activity monitoring. Although our work can lead to numerous types of health IT artifacts and related interventions, here we briefly discuss two such examples.

1. Health and wellness: The health IT artifact can be generalized for dieticians to create dietary charts for patients to track health and wellness. These dietary charts updatesare updated in the medication management server, and a copy is provided to patients. In this way, a three way interaction and adherence to the diet can be tracked and improved by providing smart interventions through the modified system.
2. Daily activity monitoring: The health IT artifact for physiotherapists is used for assisting patients to manage pain and follow daily exercise routines. It administers Smart interventions by managing the interaction between medication management server (which will store the exercise schedule provided by physiotherapist and routine followed by patients), patient and physiotherapists.

The theory based smart intervention improves medication behavior among nonadherent patients. The effect of smart interventions on medication behavior can enrich the knowledge base for Health Behavior Change Theories. New medication behaviors can be examined and can lead to further theory and behavior change techniques development.

Section 6.3 Limitations and Future Research

The current design has the limitation that patient should be willing to take medication as the interventions designed for prescribed self-administered medications. Regarding artifact evaluation, it can be further extended by conducting a field study where the modeled artifact can

be made accessible to patients and healthcare provider to use. It will help in empirical validation of the artifact. The ability of patients to interact with mobile devices and applications are studied in determining the effectiveness of interventions for medication adherence. This research is also cognizant that deciding the 'Type of intervention' requires extensive study of therapy regimens, medication behaviors, and medical conditions. It can become an active research topic. The future work can involve

1. comparing patterns of adherence for different conditions: acute vs. chronic,
2. comparing patterns of adherence for chronic conditions over long time,
3. studying the patterns of people living alone vs. people living with a caregiver, and
4. designing highly personalized context-aware interventions for patients based on pattern as well as average medication adherence and the patient's condition.

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Appendices

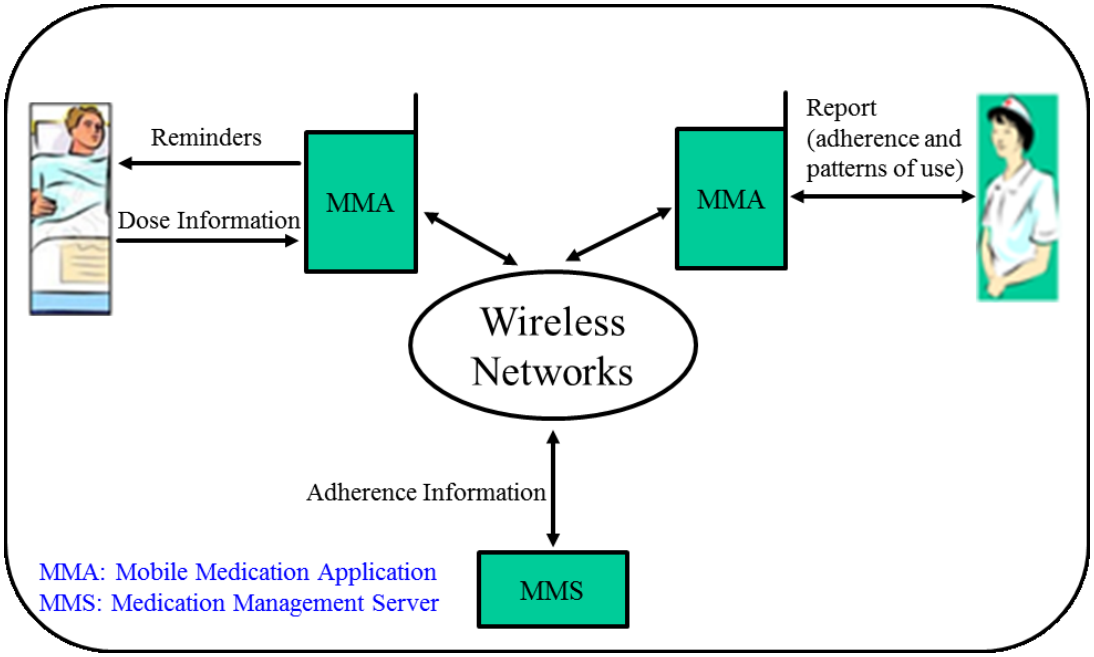
A1. Empirical evaluation form used by domain experts

Instructions for Expert

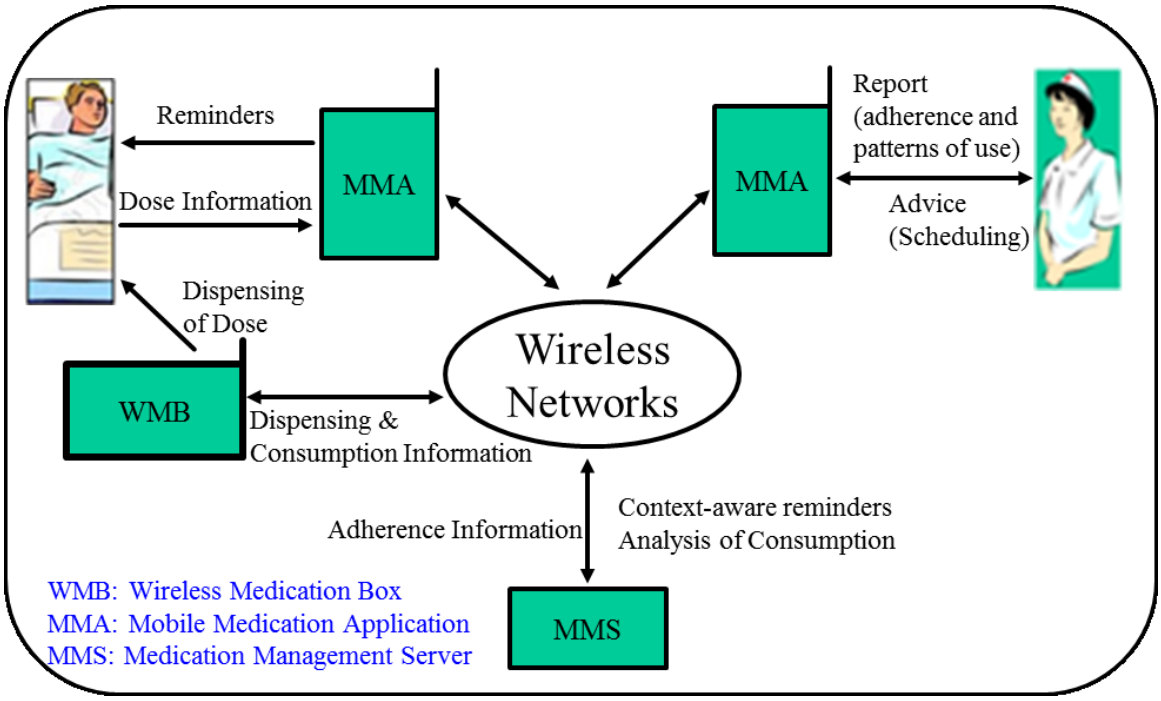
There are two artifacts (Table 1) and their respective specifications. These artifacts constitute the interventions for improving medication adherence among chronic disease patients. Artifact1 provides simple interventions/reminders to patients to take medications based on the prescription information provided by the healthcare professional and dosing information provided by the patient. Artifact2 provides smart interventions based on the prescription information provided by the healthcare professional and dosing information provided by the patient. Artifact2 includes some additional information, which is missing in Artifact1. So please examine Artifact1 and Artifact2 for improving medication adherence and answer the questions in Table 2.

Note: We are aware of that Artifact2 is still partial and some information is missing. We ask that you base your responses on the interventions as presented.

Table 1



Artifact1(Simple intervention)



Artifact2(Smart Intervention)

Table 2	
Questions	**Response**
(1) What differences can be identified between the two artifacts?	
(2) What questions could be asked to clarify the reasons for these differences?	
(3) Which of the two might be more useful or realistic based on your general knowledge of the domain?	
(4) Which one of these is more reliable or less likely to fail?	
(5) Which one of these will lead to overdose/over medication?	

IRB Outcome Letter for Non-Human Subject Research

INSTITUTIONAL REVIEW BOARD

Mail: P.O. Box 3999
Atlanta, Georgia 30302-3999
Phone: 404/413-3500
Fax: 404/413-3504

In Person: Dahlberg Hall
30 Courtland St, Suite 217

April 14, 2016

Principal Investigator: Upkar Varshney

Key Personnel: Hong, Shuguang, Ph.D.; Singh, Neetu; Varshney, Upkar

Study Department: Computer Information Systems

Study Title: Smart Interventions for Effective Medication Adherence

Submission Type: Application for Designation of Not Human Subjects Research

IRB Number: H16560

Reference Number: 338336

Thank you for your application for Designation of Not Human Subjects Research. Based on the information you've provided, the submission has been determined to be not human subjects' research.

Please do not hesitate to contact the Office of Research Integrity if you have any questions or concerns.

Sincerely,

Shelia L. White, IRB Member

Federal Wide Assurance Number: 00000129

A2 Analytical Model Implementation Using Excel

A2.1 Effective Medication Adherence (EMA) for Single Medication, Multiple Doses

Simple and Persistent Reminder

Number of Prescribed Doses in a day (3 at 8 Hr Intervals) (NR)	Event (k)	Average Arrival rate (λ)	Observed time (t as TMAX)	Prob. Of taking dose due to reminders (PD-R)	Prob. of not taking dose due to reminders (PND-R)	No. of reminders came during last TMAX Q=[TMAX/(24/NR)]	Prob of Number of doses in last TMAX (PND-R)^Q	Mean $\mu = (\lambda * t)$	Prob of No. of doses after the last reminder Prob(k) $=((\mu^k)*((e)^{-\mu}))/k!$	Prob that gap between doses exceeded the max interdose time Prob{(TI+1-TI) > TMAX) =[(PND-R)^Q] *[Prob(k)]	AMANew =MIN((AMA + (1-P_{ND-R}). T_{MAX}/(24/ N_R)), 100)	EMA_{st} = AMA_{n-1} -(AMA_{n-1} * [Prob{(TI+1-TI) > TMAX)])
3	0	0.125	8	0.000	1.000	1.000	1.000	1.000	0.368	0.368	1.000	0.632
3	0	0.125	9	0.000	1.000	1.125	1.000	1.125	0.325	0.325	1.000	0.675
3	0	0.125	10	0.000	1.000	1.250	1.000	1.250	0.287	0.287	1.000	0.713
3	0	0.125	11	0.000	1.000	1.375	1.000	1.375	0.253	0.253	1.000	0.747
3	0	0.125	12	0.000	1.000	1.500	1.000	1.500	0.223	0.223	1.000	0.777
3	0	0.125	13	0.000	1.000	1.625	1.000	1.625	0.197	0.197	1.000	0.803
3	0	0.125	14	0.000	1.000	1.750	1.000	1.750	0.174	0.174	1.000	0.826
3	0	0.125	15	0.000	1.000	1.875	1.000	1.875	0.153	0.153	1.000	0.847
3	0	0.125	16	0.000	1.000	2.000	1.000	2.000	0.135	0.135	1.000	0.865
3	0	0.125	8	0.200	0.800	1.000	0.800	1.000	0.368	0.294	1.000	0.706
3	0	0.125	9	0.200	0.800	1.125	0.778	1.125	0.325	0.253	1.000	0.747
3	0	0.125	10	0.200	0.800	1.250	0.757	1.250	0.287	0.217	1.000	0.783
3	0	0.125	11	0.200	0.800	1.375	0.736	1.375	0.253	0.186	1.000	0.814
3	0	0.125	12	0.200	0.800	1.500	0.716	1.500	0.223	0.160	1.000	0.840
3	0	0.125	13	0.200	0.800	1.625	0.696	1.625	0.197	0.137	1.000	0.863
3	0	0.125	14	0.200	0.800	1.750	0.677	1.750	0.174	0.118	1.000	0.882
3	0	0.125	15	0.200	0.800	1.875	0.658	1.875	0.153	0.101	1.000	0.899
3	0	0.125	16	0.200	0.800	2.000	0.640	2.000	0.135	0.087	1.000	0.913
3	0	0.125	8	0.400	0.600	1.000	0.600	1.000	0.368	0.221	1.000	0.779
3	0	0.125	9	0.400	0.600	1.125	0.563	1.125	0.325	0.183	1.000	0.817
3	0	0.125	10	0.400	0.600	1.250	0.528	1.250	0.287	0.151	1.000	0.849
3	0	0.125	11	0.400	0.600	1.375	0.495	1.375	0.253	0.125	1.000	0.875
3	0	0.125	12	0.400	0.600	1.500	0.465	1.500	0.223	0.104	1.000	0.896
3	0	0.125	13	0.400	0.600	1.625	0.436	1.625	0.197	0.086	1.000	0.914
3	0	0.125	14	0.400	0.600	1.750	0.409	1.750	0.174	0.071	1.000	0.929
3	0	0.125	15	0.400	0.600	1.875	0.384	1.875	0.153	0.059	1.000	0.941
3	0	0.125	16	0.400	0.600	2.000	0.360	2.000	0.135	0.049	1.000	0.951
3	0	0.125	8	0.600	0.400	1.000	0.400	1.000	0.368	0.147	1.000	0.853
3	0	0.125	9	0.600	0.400	1.125	0.357	1.125	0.325	0.116	1.000	0.884
3	0	0.125	10	0.600	0.400	1.250	0.318	1.250	0.287	0.091	1.000	0.909
3	0	0.125	11	0.600	0.400	1.375	0.284	1.375	0.253	0.072	1.000	0.928
3	0	0.125	12	0.600	0.400	1.500	0.253	1.500	0.223	0.056	1.000	0.944
3	0	0.125	13	0.600	0.400	1.625	0.226	1.625	0.197	0.044	1.000	0.956
3	0	0.125	14	0.600	0.400	1.750	0.201	1.750	0.174	0.035	1.000	0.965
3	0	0.125	15	0.600	0.400	1.875	0.179	1.875	0.153	0.028	1.000	0.972
3	0	0.125	16	0.600	0.400	2.000	0.160	2.000	0.135	0.022	1.000	0.978
3	0	0.125	8	0.800	0.200	1.000	0.200	1.000	0.368	0.074	1.000	0.926
3	0	0.125	9	0.800	0.200	1.125	0.164	1.125	0.325	0.053	1.000	0.947
3	0	0.125	10	0.800	0.200	1.250	0.134	1.250	0.287	0.038	1.000	0.962
3	0	0.125	11	0.800	0.200	1.375	0.109	1.375	0.253	0.028	1.000	0.972
3	0	0.125	12	0.800	0.200	1.500	0.089	1.500	0.223	0.020	1.000	0.980
3	0	0.125	13	0.800	0.200	1.625	0.073	1.625	0.197	0.014	1.000	0.986
3	0	0.125	14	0.800	0.200	1.750	0.060	1.750	0.174	0.010	1.000	0.990
3	0	0.125	15	0.800	0.200	1.875	0.049	1.875	0.153	0.008	1.000	0.992
3	0	0.125	16	0.800	0.200	2.000	0.040	2.000	0.135	0.005	1.000	0.995
3	0	0.125	8	1.000	0.000	1.000	0.000	1.000	0.368	0.000	1.000	1.000
3	0	0.125	9	1.000	0.000	1.125	0.000	1.125	0.325	0.000	1.000	1.000
3	0	0.125	10	1.000	0.000	1.250	0.000	1.250	0.287	0.000	1.000	1.000
3	0	0.125	11	1.000	0.000	1.375	0.000	1.375	0.253	0.000	1.000	1.000
3	0	0.125	12	1.000	0.000	1.500	0.000	1.500	0.223	0.000	1.000	1.000
3	0	0.125	13	1.000	0.000	1.625	0.000	1.625	0.197	0.000	1.000	1.000
3	0	0.125	14	1.000	0.000	1.750	0.000	1.750	0.174	0.000	1.000	1.000
3	0	0.125	15	1.000	0.000	1.875	0.000	1.875	0.153	0.000	1.000	1.000
3	0	0.125	16	1.000	0.000	2.000	0.000	2.000	0.135	0.000	1.000	1.000

Number of Prescribed Doses in a day (3 at 8 Hr Intervals) (NR)	Event (k)	Average Arrival rate (λ)	Observed time (t as TMAX)	Prob. Of taking dose due to reminders (PD-R)	Prob. of not taking dose due to reminders (PND-R)	No. of reminders came during last TMAX Q=[TMAX/(24/NR)]	Prob of Number of doses in last TMAX (PND-R)^Q	Mean μ= (λ*t)	Prob of No. of doses after the last reminder Prob(k) =((μ^k)*((e)^-μ))/k!	Prob that gap between doses exceeded the max interdose time Prob((TI+1-TI) > TMAX) =[(PND-R)^Q] *[Prob(k)]	AMANew =MIN((AMA + (1-P_{ND-R}). T_{MAX}/(24/ N_R)), 100)	EMA_{SS} = AMA_{n-1} -(AMA_{n-1} * [Prob((TI+1-TI) > TMAX)])
3	0	0.100	8	0.000	1.000	1.000	1.000	0.800	0.449	0.449	0.800	0.44
3	0	0.100	9	0.000	1.000	1.125	1.000	0.900	0.407	0.407	0.800	0.47
3	0	0.100	10	0.000	1.000	1.250	1.000	1.000	0.368	0.368	0.800	0.50
3	0	0.100	11	0.000	1.000	1.375	1.000	1.100	0.333	0.333	0.800	0.53
3	0	0.100	12	0.000	1.000	1.500	1.000	1.200	0.301	0.301	0.800	0.55
3	0	0.100	13	0.000	1.000	1.625	1.000	1.300	0.273	0.273	0.800	0.58
3	0	0.100	14	0.000	1.000	1.750	1.000	1.400	0.247	0.247	0.800	0.60
3	0	0.100	15	0.000	1.000	1.875	1.000	1.500	0.223	0.223	0.800	0.62
3	0	0.100	16	0.000	1.000	2.000	1.000	1.600	0.202	0.202	0.800	0.63
3	0	0.100	8	0.200	0.800	1.000	0.800	0.800	0.449	0.359	0.802	0.51
3	0	0.100	9	0.200	0.800	1.125	0.778	0.900	0.407	0.316	0.802	0.54
3	0	0.100	10	0.200	0.800	1.250	0.757	1.000	0.368	0.278	0.803	0.57
3	0	0.100	11	0.200	0.800	1.375	0.736	1.100	0.333	0.245	0.803	0.60
3	0	0.100	12	0.200	0.800	1.500	0.716	1.200	0.301	0.216	0.803	0.63
3	0	0.100	13	0.200	0.800	1.625	0.696	1.300	0.273	0.190	0.803	0.65
3	0	0.100	14	0.200	0.800	1.750	0.677	1.400	0.247	0.167	0.804	0.66
3	0	0.100	15	0.200	0.800	1.875	0.658	1.500	0.223	0.147	0.804	0.68
3	0	0.100	16	0.200	0.800	2.000	0.640	1.600	0.202	0.129	0.804	0.70
3	0	0.100	8	0.400	0.600	1.000	0.600	0.800	0.449	0.270	0.804	0.58
3	0	0.100	9	0.400	0.600	1.125	0.563	0.900	0.407	0.229	0.805	0.62
3	0	0.100	10	0.400	0.600	1.250	0.528	1.000	0.368	0.194	0.805	0.64
3	0	0.100	11	0.400	0.600	1.375	0.495	1.100	0.333	0.165	0.806	0.67
3	0	0.100	12	0.400	0.600	1.500	0.465	1.200	0.301	0.140	0.806	0.69
3	0	0.100	13	0.400	0.600	1.625	0.436	1.300	0.273	0.119	0.807	0.7
3	0	0.100	14	0.400	0.600	1.750	0.409	1.400	0.247	0.101	0.807	0.72
3	0	0.100	15	0.400	0.600	1.875	0.384	1.500	0.223	0.086	0.808	0.73
3	0	0.100	16	0.400	0.600	2.000	0.360	1.600	0.202	0.073	0.808	0.74
3	0	0.100	8	0.600	0.400	1.000	0.400	0.800	0.449	0.180	0.806	0.66
3	0	0.100	9	0.600	0.400	1.125	0.357	0.900	0.407	0.145	0.807	0.69
3	0	0.100	10	0.600	0.400	1.250	0.318	1.000	0.368	0.117	0.808	0.71
3	0	0.100	11	0.600	0.400	1.375	0.284	1.100	0.333	0.094	0.808	0.73
3	0	0.100	12	0.600	0.400	1.500	0.253	1.200	0.301	0.076	0.809	0.74
3	0	0.100	13	0.600	0.400	1.625	0.226	1.300	0.273	0.061	0.810	0.76
3	0	0.100	14	0.600	0.400	1.750	0.201	1.400	0.247	0.050	0.811	0.77
3	0	0.100	15	0.600	0.400	1.875	0.179	1.500	0.223	0.040	0.811	0.77
3	0	0.100	16	0.600	0.400	2.000	0.160	1.600	0.202	0.032	0.812	0.78
3	0	0.100	8	0.800	0.200	1.000	0.200	0.800	0.449	0.090	0.808	0.73
3	0	0.100	9	0.800	0.200	1.125	0.164	0.900	0.407	0.066	0.809	0.75
3	0	0.100	10	0.800	0.200	1.250	0.134	1.000	0.368	0.049	0.810	0.77
3	0	0.100	11	0.800	0.200	1.375	0.109	1.100	0.333	0.036	0.811	0.78
3	0	0.100	12	0.800	0.200	1.500	0.089	1.200	0.301	0.027	0.812	0.79
3	0	0.100	13	0.800	0.200	1.625	0.073	1.300	0.273	0.020	0.813	0.79
3	0	0.100	14	0.800	0.200	1.750	0.060	1.400	0.247	0.015	0.814	0.80
3	0	0.100	15	0.800	0.200	1.875	0.049	1.500	0.223	0.011	0.815	0.80
3	0	0.100	16	0.800	0.200	2.000	0.040	1.600	0.202	0.008	0.816	0.80
3	0	0.100	8	1.000	0.000	1.000	0.000	0.800	0.449	0.000	0.810	0.81
3	0	0.100	9	1.000	0.000	1.125	0.000	0.900	0.407	0.000	0.811	0.8
3	0	0.100	10	1.000	0.000	1.250	0.000	1.000	0.368	0.000	0.813	0.81
3	0	0.100	11	1.000	0.000	1.375	0.000	1.100	0.333	0.000	0.814	0.81
3	0	0.100	12	1.000	0.000	1.500	0.000	1.200	0.301	0.000	0.815	0.81
3	0	0.100	13	1.000	0.000	1.625	0.000	1.300	0.273	0.000	0.816	0.81
3	0	0.100	14	1.000	0.000	1.750	0.000	1.400	0.247	0.000	0.818	0.81
3	0	0.100	15	1.000	0.000	1.875	0.000	1.500	0.223	0.000	0.819	0.81
3	0	0.100	16	1.000	0.000	2.000	0.000	1.600	0.202	0.000	0.820	0.82

Context-aware Reminder

Number of Prescribed Doses in a day (3 at 8 Hr Intervals) (N_R)	Persistent Reminder N_P	Event (k)	Average Arrival rate (λ)	Observed time (t as TMAX)	Prob. Of taking dose due to reminders ($P_{D\text{-}R}$)	Prob. of not taking dose due to reminders ($P_{ND\text{-}R}$)	No. of reminders came during last TMAX Q=NP*[TMAX/(24/NR)]	Prob of Number of doses in last TMAX ($P_{ND\text{-}R}$)^Q	Mean $\mu=(\lambda*t)$	Prob of No. of doses after the last reminder Prob(k) =((μ^k)*((e)^-μ))/k!	Prob that gap between doses exceeded the max interdose time Prob((TI+1-TI) > TMAX) =[($P_{ND\text{-}R}$)^Np] *[Prob(k)]	MA-new =MIN((MA + (1-($P_{ND\text{-}R}$)^Np)),100)/100	EMA$_{CAR}$ = MA-new- MA-new * Prob((TI+1-TI) > TMAX)
3	2	0	0.125	8	0.000	1.000	2.000	1.000	1.000	0.368	0.368	1.000	0.632
3	2	0	0.125	9	0.000	1.000	2.250	1.000	1.125	0.325	0.325	1.000	0.675
3	2	0	0.125	10	0.000	1.000	2.500	1.000	1.250	0.287	0.287	1.000	0.713
3	2	0	0.125	11	0.000	1.000	2.750	1.000	1.375	0.253	0.253	1.000	0.747
3	2	0	0.125	12	0.000	1.000	3.000	1.000	1.500	0.223	0.223	1.000	0.777
3	2	0	0.125	13	0.000	1.000	3.250	1.000	1.625	0.197	0.197	1.000	0.803
3	2	0	0.125	14	0.000	1.000	3.500	1.000	1.750	0.174	0.174	1.000	0.826
3	2	0	0.125	15	0.000	1.000	3.750	1.000	1.875	0.153	0.153	1.000	0.847
3	2	0	0.125	16	0.000	1.000	4.000	1.000	2.000	0.135	0.135	1.000	0.865
3	2	0	0.125	8	0.200	0.800	2.000	0.640	1.000	0.368	0.235	1.000	0.765
3	2	0	0.125	9	0.200	0.800	2.250	0.605	1.125	0.325	0.197	1.000	0.803
3	2	0	0.125	10	0.200	0.800	2.500	0.572	1.250	0.287	0.164	1.000	0.836
3	2	0	0.125	11	0.200	0.800	2.750	0.541	1.375	0.253	0.137	1.000	0.863
3	2	0	0.125	12	0.200	0.800	3.000	0.512	1.500	0.223	0.114	1.000	0.886
3	2	0	0.125	13	0.200	0.800	3.250	0.484	1.625	0.197	0.095	1.000	0.905
3	2	0	0.125	14	0.200	0.800	3.500	0.458	1.750	0.174	0.080	1.000	0.920
3	2	0	0.125	15	0.200	0.800	3.750	0.433	1.875	0.153	0.066	1.000	0.934
3	2	0	0.125	16	0.200	0.800	4.000	0.410	2.000	0.135	0.055	1.000	0.945
3	2	0	0.125	8	0.400	0.600	2.000	0.360	1.000	0.368	0.132	1.000	0.868
3	2	0	0.125	9	0.400	0.600	2.250	0.317	1.125	0.325	0.103	1.000	0.897
3	2	0	0.125	10	0.400	0.600	2.500	0.279	1.250	0.287	0.080	1.000	0.920
3	2	0	0.125	11	0.400	0.600	2.750	0.245	1.375	0.253	0.062	1.000	0.938
3	2	0	0.125	12	0.400	0.600	3.000	0.216	1.500	0.223	0.048	1.000	0.952
3	2	0	0.125	13	0.400	0.600	3.250	0.190	1.625	0.197	0.037	1.000	0.963
3	2	0	0.125	14	0.400	0.600	3.500	0.167	1.750	0.174	0.029	1.000	0.971
3	2	0	0.125	15	0.400	0.600	3.750	0.147	1.875	0.153	0.023	1.000	0.977
3	2	0	0.125	16	0.400	0.600	4.000	0.130	2.000	0.135	0.018	1.000	0.982
3	2	0	0.125	8	0.600	0.400	2.000	0.160	1.000	0.368	0.059	1.000	0.941
3	2	0	0.125	9	0.600	0.400	2.250	0.127	1.125	0.325	0.041	1.000	0.959
3	2	0	0.125	10	0.600	0.400	2.500	0.101	1.250	0.287	0.029	1.000	0.971
3	2	0	0.125	11	0.600	0.400	2.750	0.080	1.375	0.253	0.020	1.000	0.980
3	2	0	0.125	12	0.600	0.400	3.000	0.064	1.500	0.223	0.014	1.000	0.986
3	2	0	0.125	13	0.600	0.400	3.250	0.051	1.625	0.197	0.010	1.000	0.990
3	2	0	0.125	14	0.600	0.400	3.500	0.040	1.750	0.174	0.007	1.000	0.993
3	2	0	0.125	15	0.600	0.400	3.750	0.032	1.875	0.153	0.005	1.000	0.995
3	2	0	0.125	16	0.600	0.400	4.000	0.026	2.000	0.135	0.003	1.000	0.997
3	2	0	0.125	8	0.800	0.200	2.000	0.040	1.000	0.368	0.015	1.000	0.985
3	2	0	0.125	9	0.800	0.200	2.250	0.027	1.125	0.325	0.009	1.000	0.991
3	2	0	0.125	10	0.800	0.200	2.500	0.018	1.250	0.287	0.005	1.000	0.995
3	2	0	0.125	11	0.800	0.200	2.750	0.012	1.375	0.253	0.003	1.000	0.997
3	2	0	0.125	12	0.800	0.200	3.000	0.008	1.500	0.223	0.002	1.000	0.998
3	2	0	0.125	13	0.800	0.200	3.250	0.005	1.625	0.197	0.001	1.000	0.999
3	2	0	0.125	14	0.800	0.200	3.500	0.004	1.750	0.174	0.001	1.000	0.999
3	2	0	0.125	15	0.800	0.200	3.750	0.002	1.875	0.153	0.000	1.000	1.000
3	2	0	0.125	16	0.800	0.200	4.000	0.002	2.000	0.135	0.000	1.000	1.000
3	2	0	0.125	8	1.000	0.000	2.000	0.000	1.000	0.368	0.000	1.000	1.000
3	2	0	0.125	9	1.000	0.000	2.250	0.000	1.125	0.325	0.000	1.000	1.000
3	2	0	0.125	10	1.000	0.000	2.500	0.000	1.250	0.287	0.000	1.000	1.000
3	2	0	0.125	11	1.000	0.000	2.750	0.000	1.375	0.253	0.000	1.000	1.000
3	2	0	0.125	12	1.000	0.000	3.000	0.000	1.500	0.223	0.000	1.000	1.000
3	2	0	0.125	13	1.000	0.000	3.250	0.000	1.625	0.197	0.000	1.000	1.000
3	2	0	0.125	14	1.000	0.000	3.500	0.000	1.750	0.174	0.000	1.000	1.000
3	2	0	0.125	15	1.000	0.000	3.750	0.000	1.875	0.153	0.000	1.000	1.000
3	2	0	0.125	16	1.000	0.000	4.000	0.000	2.000	0.135	0.000	1.000	1.000

Number of Prescribed Doses in a day (3 at 8 Hr Intervals) (N_R)	Persistent Reminder N_P	Event (k)	Average Arrival rate (λ)	Observed time (t as TMAX)	Prob. Of taking dose due to reminders ($P_{D\text{-}R}$)	Prob. of not taking dose due to reminders ($P_{ND\text{-}R}$)	No. of reminders came during last TMAX Q=NP*[TMAX/(24/NR)]	Prob of Number of doses in last TMAX ($P_{ND\text{-}R}$)*Q	Mean $\mu=(\lambda*t)$	Prob of No. of doses after the last reminder Prob(k) =((μ^k)*((e)^-μ))/k!	Prob that gap between doses exceeded the max interdose time Prob([TI+1-TI) > TMAX) =[($P_{ND\text{-}R}$)*Np)]^Q]*[Prob(k)]	MA-new =MIN((MA + (1-($P_{ND\text{-}R}$)*Np)),100)/100	EMA_{CAR} = MA-new- MA-new * Prob([TI+1-TI) > TMAX)
3	2	0	0.100	8	0.000	1.000	2.000	1.000	0.800	0.449	0.449	0.800	0.441
3	2	0	0.100	9	0.000	1.000	2.250	1.000	0.900	0.407	0.407	0.800	0.475
3	2	0	0.100	10	0.000	1.000	2.500	1.000	1.000	0.368	0.368	0.800	0.506
3	2	0	0.100	11	0.000	1.000	2.750	1.000	1.100	0.333	0.333	0.800	0.534
3	2	0	0.100	12	0.000	1.000	3.000	1.000	1.200	0.301	0.301	0.800	0.559
3	2	0	0.100	13	0.000	1.000	3.250	1.000	1.300	0.273	0.273	0.800	0.582
3	2	0	0.100	14	0.000	1.000	3.500	1.000	1.400	0.247	0.247	0.800	0.603
3	2	0	0.100	15	0.000	1.000	3.750	1.000	1.500	0.223	0.223	0.800	0.621
3	2	0	0.100	16	0.000	1.000	4.000	1.000	1.600	0.202	0.202	0.800	0.638
3	2	0	0.100	8	0.200	0.800	2.000	0.640	0.800	0.449	0.288	0.804	0.573
3	2	0	0.100	9	0.200	0.800	2.250	0.605	0.900	0.407	0.246	0.804	0.606
3	2	0	0.100	10	0.200	0.800	2.500	0.572	1.000	0.368	0.211	0.804	0.634
3	2	0	0.100	11	0.200	0.800	2.750	0.541	1.100	0.333	0.180	0.804	0.659
3	2	0	0.100	12	0.200	0.800	3.000	0.512	1.200	0.301	0.154	0.804	0.680
3	2	0	0.100	13	0.200	0.800	3.250	0.484	1.300	0.273	0.132	0.804	0.698
3	2	0	0.100	14	0.200	0.800	3.500	0.458	1.400	0.247	0.113	0.804	0.713
3	2	0	0.100	15	0.200	0.800	3.750	0.433	1.500	0.223	0.097	0.804	0.726
3	2	0	0.100	16	0.200	0.800	4.000	0.410	1.600	0.202	0.083	0.804	0.737
3	2	0	0.100	8	0.400	0.600	2.000	0.360	0.800	0.449	0.162	0.806	0.676
3	2	0	0.100	9	0.400	0.600	2.250	0.317	0.900	0.407	0.129	0.806	0.703
3	2	0	0.100	10	0.400	0.600	2.500	0.279	1.000	0.368	0.103	0.806	0.724
3	2	0	0.100	11	0.400	0.600	2.750	0.245	1.100	0.333	0.082	0.806	0.741
3	2	0	0.100	12	0.400	0.600	3.000	0.216	1.200	0.301	0.065	0.806	0.754
3	2	0	0.100	13	0.400	0.600	3.250	0.190	1.300	0.273	0.052	0.806	0.765
3	2	0	0.100	14	0.400	0.600	3.500	0.167	1.400	0.247	0.041	0.806	0.773
3	2	0	0.100	15	0.400	0.600	3.750	0.147	1.500	0.223	0.033	0.806	0.780
3	2	0	0.100	16	0.400	0.600	4.000	0.130	1.600	0.202	0.026	0.806	0.785
3	2	0	0.100	8	0.600	0.400	2.000	0.160	0.800	0.449	0.072	0.808	0.750
3	2	0	0.100	9	0.600	0.400	2.250	0.127	0.900	0.407	0.052	0.808	0.767
3	2	0	0.100	10	0.600	0.400	2.500	0.101	1.000	0.368	0.037	0.808	0.778
3	2	0	0.100	11	0.600	0.400	2.750	0.080	1.100	0.333	0.027	0.808	0.787
3	2	0	0.100	12	0.600	0.400	3.000	0.064	1.200	0.301	0.019	0.808	0.793
3	2	0	0.100	13	0.600	0.400	3.250	0.051	1.300	0.273	0.014	0.808	0.797
3	2	0	0.100	14	0.600	0.400	3.500	0.040	1.400	0.247	0.010	0.808	0.800
3	2	0	0.100	15	0.600	0.400	3.750	0.032	1.500	0.223	0.007	0.808	0.803
3	2	0	0.100	16	0.600	0.400	4.000	0.026	1.600	0.202	0.005	0.808	0.804
3	2	0	0.100	8	0.800	0.200	2.000	0.040	0.800	0.449	0.018	0.810	0.795
3	2	0	0.100	9	0.800	0.200	2.250	0.027	0.900	0.407	0.011	0.810	0.801
3	2	0	0.100	10	0.800	0.200	2.500	0.018	1.000	0.368	0.007	0.810	0.804
3	2	0	0.100	11	0.800	0.200	2.750	0.012	1.100	0.333	0.004	0.810	0.806
3	2	0	0.100	12	0.800	0.200	3.000	0.008	1.200	0.301	0.002	0.810	0.808
3	2	0	0.100	13	0.800	0.200	3.250	0.005	1.300	0.273	0.001	0.810	0.808
3	2	0	0.100	14	0.800	0.200	3.500	0.004	1.400	0.247	0.001	0.810	0.809
3	2	0	0.100	15	0.800	0.200	3.750	0.002	1.500	0.223	0.001	0.810	0.809
3	2	0	0.100	16	0.800	0.200	4.000	0.002	1.600	0.202	0.000	0.810	0.809
3	2	0	0.100	8	1.000	0.000	2.000	0.000	0.800	0.449	0.000	0.810	0.810
3	2	0	0.100	9	1.000	0.000	2.250	0.000	0.900	0.407	0.000	0.810	0.810
3	2	0	0.100	10	1.000	0.000	2.500	0.000	1.000	0.368	0.000	0.810	0.810
3	2	0	0.100	11	1.000	0.000	2.750	0.000	1.100	0.333	0.000	0.810	0.810
3	2	0	0.100	12	1.000	0.000	3.000	0.000	1.200	0.301	0.000	0.810	0.810
3	2	0	0.100	13	1.000	0.000	3.250	0.000	1.300	0.273	0.000	0.810	0.810
3	2	0	0.100	14	1.000	0.000	3.500	0.000	1.400	0.247	0.000	0.810	0.810
3	2	0	0.100	15	1.000	0.000	3.750	0.000	1.500	0.223	0.000	0.810	0.810
3	2	0	0.100	16	1.000	0.000	4.000	0.000	1.600	0.202	0.000	0.810	0.810

A2.2Effective Medication Adherence for Multiple Medication, Multiple Doses

Simple and Persistent Reminder Vs Context-aware Reminder

Observed time (t or TMAX n)	EMA1 for MR1-2, λ=-.083	EMA2 for MR2-2, λ=-.083	EMA3 for MR3-2, λ=-.083	Scenario1(SC1):All equal/primary A11	A12	A13	EMA$_H$-A11"EMA1+A12 "EMA2+A13"EMA3	Scenario2 (SC2):MR1 Primary/MR2, MR3 Secondary A21	A22	A23	EMA$_H$-A21"EMA1+A22 "EMA2+A23"EMA3	Scenario3(SC3):MR1, MR2 Primary/MR3 Secondary A31	A32	A33	EMA^H-A31"EMA1+A32 "EMA2+A33"EMA3	Scenario4(SC4):MR1, MR3 Primary/MR2 Secondary A31	A32	A33	EMA$_H$-A31"EMA1+A32"EMA2+A33"EMA3
12	0.941	0.985	0.868	0.33	0.33	0.33	0.931	0.50	0.25	0.25	0.934	0.40	0.40	0.20	0.944	0.40	0.20	0.40	0.921
13	0.954	0.990	0.888	0.33	0.33	0.33	0.944	0.50	0.25	0.25	0.946	0.40	0.40	0.20	0.955	0.40	0.20	0.40	0.935
14	0.963	0.993	0.905	0.33	0.33	0.33	0.954	0.50	0.25	0.25	0.956	0.40	0.40	0.20	0.963	0.40	0.20	0.40	0.946
15	0.971	0.995	0.920	0.33	0.33	0.33	0.962	0.50	0.25	0.25	0.964	0.40	0.40	0.20	0.970	0.40	0.20	0.40	0.955
16	0.977	0.996	0.932	0.33	0.33	0.33	0.969	0.50	0.25	0.25	0.971	0.40	0.40	0.20	0.976	0.40	0.20	0.40	0.963
17	0.982	0.997	0.943	0.33	0.33	0.33	0.974	0.50	0.25	0.25	0.976	0.40	0.40	0.20	0.980	0.40	0.20	0.40	0.969
18	0.986	0.998	0.952	0.33	0.33	0.33	0.979	0.50	0.25	0.25	0.980	0.40	0.40	0.20	0.984	0.40	0.20	0.40	0.975
19	0.989	0.999	0.959	0.33	0.33	0.33	0.982	0.50	0.25	0.25	0.984	0.40	0.40	0.20	0.987	0.40	0.20	0.40	0.979
20	0.991	0.999	0.966	0.33	0.33	0.33	0.985	0.50	0.25	0.25	0.987	0.40	0.40	0.20	0.989	0.40	0.20	0.40	0.982
21	0.993	0.999	0.971	0.33	0.33	0.33	0.988	0.50	0.25	0.25	0.989	0.40	0.40	0.20	0.991	0.40	0.20	0.40	0.985
22	0.994	1.000	0.975	0.33	0.33	0.33	0.990	0.50	0.25	0.25	0.991	0.40	0.40	0.20	0.993	0.40	0.20	0.40	0.988
23	0.996	1.000	0.979	0.33	0.33	0.33	0.992	0.50	0.25	0.25	0.993	0.40	0.40	0.20	0.994	0.40	0.20	0.40	0.990
24	0.997	1.000	0.982	0.33	0.33	0.33	0.993	0.50	0.25	0.25	0.994	0.40	0.40	0.20	0.995	0.40	0.20	0.40	0.992
12	0.853	0.926	0.779	0.33	0.33	0.33	0.853	0.50	0.25	0.25	0.853	0.40	0.40	0.20	0.868	0.40	0.20	0.40	0.838
13	0.875	0.941	0.805	0.33	0.33	0.33	0.874	0.50	0.25	0.25	0.874	0.40	0.40	0.20	0.887	0.40	0.20	0.40	0.860
14	0.893	0.952	0.828	0.33	0.33	0.33	0.891	0.50	0.25	0.25	0.892	0.40	0.40	0.20	0.904	0.40	0.20	0.40	0.879
15	0.909	0.962	0.849	0.33	0.33	0.33	0.906	0.50	0.25	0.25	0.907	0.40	0.40	0.20	0.918	0.40	0.20	0.40	0.895
16	0.922	0.969	0.867	0.33	0.33	0.33	0.919	0.50	0.25	0.25	0.920	0.40	0.40	0.20	0.930	0.40	0.20	0.40	0.909
17	0.934	0.975	0.882	0.33	0.33	0.33	0.930	0.50	0.25	0.25	0.931	0.40	0.40	0.20	0.940	0.40	0.20	0.40	0.922
18	0.944	0.980	0.896	0.33	0.33	0.33	0.940	0.50	0.25	0.25	0.941	0.40	0.40	0.20	0.949	0.40	0.20	0.40	0.932
19	0.952	0.984	0.909	0.33	0.33	0.33	0.948	0.50	0.25	0.25	0.949	0.40	0.40	0.20	0.956	0.40	0.20	0.40	0.941
20	0.959	0.987	0.919	0.33	0.33	0.33	0.955	0.50	0.25	0.25	0.956	0.40	0.40	0.20	0.962	0.40	0.20	0.40	0.949
21	0.965	0.990	0.929	0.33	0.33	0.33	0.961	0.50	0.25	0.25	0.962	0.40	0.40	0.20	0.968	0.40	0.20	0.40	0.956
22	0.970	0.992	0.937	0.33	0.33	0.33	0.966	0.50	0.25	0.25	0.967	0.40	0.40	0.20	0.972	0.40	0.20	0.40	0.961
23	0.975	0.993	0.945	0.33	0.33	0.33	0.971	0.50	0.25	0.25	0.972	0.40	0.40	0.20	0.976	0.40	0.20	0.40	0.966
24	0.978	0.995	0.951	0.33	0.33	0.33	0.975	0.50	0.25	0.25	0.976	0.40	0.40	0.20	0.979	0.40	0.20	0.40	0.971
12	0.853	0.980	0.951	0.33	0.33	0.33	0.928	0.50	0.25	0.25	0.909	0.40	0.40	0.20	0.923	0.40	0.20	0.40	0.918
13	0.875	0.986	0.962	0.33	0.33	0.33	0.941	0.50	0.25	0.25	0.924	0.40	0.40	0.20	0.936	0.40	0.20	0.40	0.932
14	0.893	0.990	0.971	0.33	0.33	0.33	0.951	0.50	0.25	0.25	0.937	0.40	0.40	0.20	0.947	0.40	0.20	0.40	0.943
15	0.909	0.992	0.977	0.33	0.33	0.33	0.959	0.50	0.25	0.25	0.947	0.40	0.40	0.20	0.956	0.40	0.20	0.40	0.953
16	0.922	0.995	0.982	0.33	0.33	0.33	0.966	0.50	0.25	0.25	0.955	0.40	0.40	0.20	0.963	0.40	0.20	0.40	0.961
17	0.934	0.996	0.986	0.33	0.33	0.33	0.972	0.50	0.25	0.25	0.962	0.40	0.40	0.20	0.969	0.40	0.20	0.40	0.967
18	0.944	0.997	0.989	0.33	0.33	0.33	0.977	0.50	0.25	0.25	0.968	0.40	0.40	0.20	0.974	0.40	0.20	0.40	0.973
19	0.952	0.998	0.992	0.33	0.33	0.33	0.980	0.50	0.25	0.25	0.973	0.40	0.40	0.20	0.978	0.40	0.20	0.40	0.977
20	0.959	0.999	0.994	0.33	0.33	0.33	0.984	0.50	0.25	0.25	0.978	0.40	0.40	0.20	0.982	0.40	0.20	0.40	0.981
21	0.965	0.999	0.995	0.33	0.33	0.33	0.986	0.50	0.25	0.25	0.981	0.40	0.40	0.20	0.985	0.40	0.20	0.40	0.984
22	0.970	0.999	0.996	0.33	0.33	0.33	0.989	0.50	0.25	0.25	0.984	0.40	0.40	0.20	0.987	0.40	0.20	0.40	0.986
23	0.975	0.999	0.997	0.33	0.33	0.33	0.990	0.50	0.25	0.25	0.986	0.40	0.40	0.20	0.989	0.40	0.20	0.40	0.989
24	0.978	1.000	0.998	0.33	0.33	0.33	0.992	0.50	0.25	0.25	0.988	0.40	0.40	0.20	0.991	0.40	0.20	0.40	0.990
12	0.941	0.998	0.982	0.33	0.33	0.33	0.974	0.50	0.25	0.25	0.966	0.40	0.40	0.20	0.972	0.40	0.20	0.40	0.969
13	0.954	0.999	0.987	0.33	0.33	0.33	0.980	0.50	0.25	0.25	0.973	0.40	0.40	0.20	0.978	0.40	0.20	0.40	0.976
14	0.963	0.999	0.991	0.33	0.33	0.33	0.985	0.50	0.25	0.25	0.979	0.40	0.40	0.20	0.983	0.40	0.20	0.40	0.982
15	0.971	1.000	0.994	0.33	0.33	0.33	0.988	0.50	0.25	0.25	0.984	0.40	0.40	0.20	0.987	0.40	0.20	0.40	0.986
16	0.977	1.000	0.995	0.33	0.33	0.33	0.991	0.50	0.25	0.25	0.987	0.40	0.40	0.20	0.990	0.40	0.20	0.40	0.989
17	0.982	1.000	0.997	0.33	0.33	0.33	0.993	0.50	0.25	0.25	0.990	0.40	0.40	0.20	0.992	0.40	0.20	0.40	0.991
18	0.986	1.000	0.998	0.33	0.33	0.33	0.994	0.50	0.25	0.25	0.992	0.40	0.40	0.20	0.994	0.40	0.20	0.40	0.993
19	0.989	1.000	0.998	0.33	0.33	0.33	0.996	0.50	0.25	0.25	0.994	0.40	0.40	0.20	0.995	0.40	0.20	0.40	0.995
20	0.991	1.000	0.999	0.33	0.33	0.33	0.997	0.50	0.25	0.25	0.995	0.40	0.40	0.20	0.996	0.40	0.20	0.40	0.996
21	0.993	1.000	0.999	0.33	0.33	0.33	0.997	0.50	0.25	0.25	0.996	0.40	0.40	0.20	0.997	0.40	0.20	0.40	0.997
22	0.994	1.000	0.999	0.33	0.33	0.33	0.998	0.50	0.25	0.25	0.997	0.40	0.40	0.20	0.998	0.40	0.20	0.40	0.998
23	0.996	1.000	1.000	0.33	0.33	0.33	0.998	0.50	0.25	0.25	0.998	0.40	0.40	0.20	0.998	0.40	0.20	0.40	0.998
24	0.997	1.000	1.000	0.33	0.33	0.33	0.999	0.50	0.25	0.25	0.998	0.40	0.40	0.20	0.999	0.40	0.20	0.40	0.998
12	0.853	0.944	0.978	0.33	0.33	0.33	0.925	0.50	0.25	0.25	0.907	0.40	0.40	0.20	0.914	0.40	0.20	0.40	0.921
13	0.875	0.956	0.984	0.33	0.33	0.33	0.938	0.50	0.25	0.25	0.922	0.40	0.40	0.20	0.929	0.40	0.20	0.40	0.935
14	0.893	0.965	0.989	0.33	0.33	0.33	0.949	0.50	0.25	0.25	0.935	0.40	0.40	0.20	0.941	0.40	0.20	0.40	0.946
15	0.909	0.972	0.992	0.33	0.33	0.33	0.958	0.50	0.25	0.25	0.945	0.40	0.40	0.20	0.951	0.40	0.20	0.40	0.955
16	0.922	0.978	0.994	0.33	0.33	0.33	0.965	0.50	0.25	0.25	0.954	0.40	0.40	0.20	0.959	0.40	0.20	0.40	0.962
17	0.934	0.983	0.996	0.33	0.33	0.33	0.971	0.50	0.25	0.25	0.962	0.40	0.40	0.20	0.966	0.40	0.20	0.40	0.968
18	0.944	0.987	0.997	0.33	0.33	0.33	0.976	0.50	0.25	0.25	0.968	0.40	0.40	0.20	0.971	0.40	0.20	0.40	0.973
12	0.941	0.952	0.997	0.33	0.33	0.33	0.963	0.50	0.25	0.25	0.958	0.40	0.40	0.20	0.956	0.40	0.20	0.40	0.965
13	0.954	0.963	0.998	0.33	0.33	0.33	0.971	0.50	0.25	0.25	0.967	0.40	0.40	0.20	0.966	0.40	0.20	0.40	0.973
14	0.963	0.971	0.999	0.33	0.33	0.33	0.978	0.50	0.25	0.25	0.974	0.40	0.40	0.20	0.973	0.40	0.20	0.40	0.979
15	0.971	0.977	0.999	0.33	0.33	0.33	0.983	0.50	0.25	0.25	0.980	0.40	0.40	0.20	0.979	0.40	0.20	0.40	0.984
16	0.977	0.982	0.999	0.33	0.33	0.33	0.986	0.50	0.25	0.25	0.984	0.40	0.40	0.20	0.984	0.40	0.20	0.40	0.987
17	0.982	0.986	1.000	0.33	0.33	0.33	0.989	0.50	0.25	0.25	0.987	0.40	0.40	0.20	0.987	0.40	0.20	0.40	0.990
18	0.986	0.989	1.000	0.33	0.33	0.33	0.992	0.50	0.25	0.25	0.990	0.40	0.40	0.20	0.990	0.40	0.20	0.40	0.992

A2.3 Undesirable Dose Event

Number of Prescribed Doses in a day (2 at 12 Hr Intervals) (N_{R1})	Event (k)	Average Arrival rate (λ)	T_{MIN}	Prob. Of taking dose due to reminders (P_{D-R})	Prob. of not taking dose due to reminders (P_{ND-R})	(λ^*T_{MIN})	$e^{-\lambda^*T_{MIN}}$	($\lambda^*T_{MIN}*P_{D-R}$)	$UDE_{BASE(k)} = Prob[(T_{(k+1)N} - T_{(k)N}) < T_{UDE(k)}]$ $UDE_{BASE(k)} = (\lambda_R \times t_k)^{2k} \times \frac{e^{-\lambda_R t_k}}{k!}$ for $k = 2$ and $t_k = T_{UDE(k)}$	UDE1	$UDE_k = Prob[(T_{(k+1)N} - T_{(k)N}) < T_{UDE(k)}]$ $UDE_k = \frac{1}{2}(\lambda_R \times T_{UDE(k)})^2 \times e^{-\lambda_R T_{UDE(k)}}$	UDE2	$\left[1 - \lambda_R T_{UDE(k)}\right] \times \left[(\lambda_R \times T_{UDE(k)})^2 \times \frac{e^{-\lambda_R T_{UDE(k)}}}{2!}\right]$	$\left[\lambda_R T_{UDE(k)} \times P_{D-R(k)}\right] \times \left[(\lambda_R \times T_{UDE(k)})^2 \times e^{-\lambda_R T_{UDE(k)}}\right]$	$UDE_{(EP)k} = \left[1 - (\lambda_R T_{UDE(k)}) \left[(\lambda_R T_{UDE(k)})^2 \times \frac{e^{-\lambda_R T_{UDE(k)}}}{2}\right]\right] \times \left[\lambda_R T_{UDE(k)} \times P_{D-R(k)}\right] \times \left[(\lambda_R \times T_{UDE(k)})^2 \times e^{-\lambda_R T_{UDE(k)}}\right]$	UDE3	$UDE_{(EP)k} = UDE_{(TOTAL)k} - UDE_{BASE)k}$	UDE4
3	0	0.013	8	1.000	0.000	0.100	0.905	0.100	0.003	0.005	0.004	0.003	0.013	0.004
3	0	0.113	8	1.000	0.000	0.900	0.407	0.900	0.329	0.165	0.016	0.329	0.346	0.016
3	0	0.119	8	1.000	0.000	0.950	0.387	0.950	0.343	0.175	0.009	0.343	0.358	0.009
3	0	0.123	8	1.000	0.000	0.980	0.375	0.980	0.360	0.180	0.004	0.360	0.364	0.004
3	0	0.125	8	1.000	0.000	1.000	0.368	1.000	0.368	0.184	0.000	0.368	0.368	0.000
3	0	0.125	1	1.000	0.000	0.125	0.882	0.125	0.014	0.007	0.006	0.014	0.020	0.006
3	0	0.125	2	1.000	0.000	0.250	0.779	0.250	0.049	0.024	0.018	0.049	0.067	0.018
3	0	0.125	3	1.000	0.000	0.375	0.687	0.375	0.097	0.048	0.030	0.097	0.127	0.030
3	0	0.125	4	1.000	0.000	0.500	0.607	0.500	0.152	0.076	0.038	0.152	0.190	0.038
3	0	0.125	8	1.000	0.000	1.000	0.368	1.000	0.368	0.184	0.000	0.368	0.368	0.000
3	0	0.125	1	1.000	0.000	0.125	0.882	0.125	0.014	0.007	0.006	0.014	0.020	0.006
3	0	0.125	2	1.000	0.000	0.250	0.779	0.250	0.049	0.024	0.018	0.049	0.067	0.018
3	0	0.125	3	1.000	0.000	0.375	0.687	0.375	0.097	0.048	0.030	0.097	0.127	0.030
3	0	0.125	4	1.000	0.000	0.500	0.607	0.500	0.152	0.076	0.038	0.152	0.190	0.038
3	0	0.125	5	1.000	0.000	0.625	0.535	0.625	0.203	0.105	0.039	0.203	0.248	0.039
3	0	0.125	6	1.000	0.000	0.750	0.472	0.750	0.266	0.133	0.033	0.266	0.299	0.033
3	0	0.125	7	1.000	0.000	0.875	0.417	0.875	0.319	0.160	0.020	0.319	0.339	0.020
3	0	0.125	8	1.000	0.000	1.000	0.368	1.000	0.368	0.184	0.000	0.368	0.368	0.000
3	0	0.125	9	1.000	0.000	1.125	0.325	1.125	0.411	0.205	-0.026	0.411	0.385	-0.026
3	0	0.125	10	1.000	0.000	1.250	0.287	1.250	0.448	0.224	-0.056	0.448	0.392	-0.056
3	0	0.125	11	1.000	0.000	1.375	0.253	1.375	0.478	0.239	-0.090	0.478	0.388	-0.090
3	0	0.125	12	1.000	0.000	1.500	0.223	1.500	0.502	0.251	-0.126	0.502	0.377	-0.126
4	0	0.167	1	1.000	0.000	0.167	0.846	0.167	0.024	0.012	0.010	0.024	0.033	0.010
4	0	0.167	2	1.000	0.000	0.333	0.717	0.333	0.080	0.040	0.027	0.080	0.106	0.027
4	0	0.167	3	1.000	0.000	0.500	0.607	0.500	0.152	0.076	0.038	0.152	0.190	0.038
4	0	0.167	4	1.000	0.000	0.667	0.513	0.667	0.228	0.114	0.038	0.228	0.266	0.038
4	0	0.167	5	1.000	0.000	0.833	0.435	0.833	0.302	0.151	0.025	0.302	0.327	0.025
4	0	0.167	6	1.000	0.000	1.000	0.368	1.000	0.368	0.184	0.000	0.368	0.368	0.000
4	0	0.167	7	1.000	0.000	1.167	0.311	1.167	0.424	0.212	-0.035	0.424	0.389	-0.035
4	0	0.167	8	1.000	0.000	1.333	0.264	1.333	0.469	0.234	-0.078	0.469	0.391	-0.078
4	0	0.167	9	1.000	0.000	1.500	0.223	1.500	0.502	0.251	-0.126	0.502	0.377	-0.126
4	0	0.167	10	1.000	0.000	1.667	0.189	1.667	0.525	0.262	-0.175	0.525	0.350	-0.175
4	0	0.167	11	1.000	0.000	1.833	0.160	1.833	0.537	0.269	-0.224	0.537	0.313	-0.224
4	0	0.167	12	1.000	0.000	2.000	0.135	2.000	0.541	0.271	-0.271	0.541	0.271	-0.271
2	0	0.083	1	1.000	0.000	0.083	0.920	0.083	0.006	0.003	0.003	0.006	0.009	0.003
2	0	0.083	2	1.000	0.000	0.167	0.846	0.167	0.024	0.012	0.010	0.024	0.033	0.010
2	0	0.083	3	1.000	0.000	0.250	0.779	0.250	0.049	0.024	0.018	0.049	0.067	0.018
2	0	0.083	4	1.000	0.000	0.333	0.717	0.333	0.080	0.040	0.027	0.080	0.106	0.027
2	0	0.083	5	1.000	0.000	0.417	0.659	0.417	0.114	0.057	0.033	0.114	0.148	0.033
2	0	0.083	6	1.000	0.000	0.500	0.607	0.500	0.152	0.076	0.038	0.152	0.190	0.038
2	0	0.083	7	1.000	0.000	0.583	0.558	0.583	0.190	0.095	0.040	0.190	0.229	0.040
2	0	0.083	8	1.000	0.000	0.667	0.513	0.667	0.228	0.114	0.038	0.228	0.266	0.038
2	0	0.083	9	1.000	0.000	0.750	0.472	0.750	0.266	0.133	0.033	0.266	0.299	0.033
2	0	0.083	10	1.000	0.000	0.833	0.435	0.833	0.302	0.151	0.025	0.302	0.327	0.025
2	0	0.083	11	1.000	0.000	0.917	0.400	0.917	0.336	0.168	0.014	0.336	0.350	0.014
2	0	0.083	12	1.000	0.000	1.000	0.368	1.000	0.368	0.184	0.000	0.368	0.368	0.000

A2.4 Healthcare cost

Healthcare cost Nonadherent, Simple Intervention and Smart Intervention

Scenario I	$HC_{COST\text{-}PAST}$	N (Nth gear	(1.05)$^{\blacksquare}$	UDE_{SR}	1+ UDE_{SR}	$INTVN_{COST\text{-}SR}$	$INTVN_{COST\ CAR}$	$HC_{COST_{NA}}$	$HC_{COST_{SR}}$	$HC_{COST_{CAR}}$
Adherence Level 0-59	7504	17	2.29					17200		
Adherence Level 80-100 (Simple and Persistent Reminder-SR)	4570	17	2.29	0.368	1.368	0			14329	
	4570	17	2.29	0.368	1.368	100			14429	
	4570	17	2.29	0.368	1.368	200			14529	
	4570	17	2.29	0.368	1.368	300			14629	
	4570	17	2.29	0.368	1.368	400			14729	
	4570	17	2.29	0.368	1.368	500			14829	
	4570	17	2.29	0.368	1.368	600			14929	
	4570	17	2.29	0.368	1.368	700			15029	
	4570	17	2.29	0.368	1.368	800			15129	
	4570	17	2.29	0.368	1.368	900			15229	
	4570	17	2.29	0.368	1.368	1000			15329	
Adherence Level 80-100 (Context-aware reminder-CAR)	4570	17	2.29				0			10475
	4570	17	2.29				100			10575
	4570	17	2.29				200			10675
	4570	17	2.29				300			10775
	4570	17	2.29				400			10875
	4570	17	2.29				500			10975
	4570	17	2.29				600			11075
	4570	17	2.29				700			11175
	4570	17	2.29				800			11275
	4570	17	2.29				900			11375
	4570	17	2.29				1000			11475

Scenario II	$HC_{COST\text{-}PAST}$	(Nth gear since	(1.05)$^{\blacksquare}$	UDE_{SR}	1+ UDE_{SR}	$INTVN_{COST\text{-}SR}$	$INTVN_{COST\ CAR}$	$HC_{COST_{NA}}$	$HC_{COST_{SR}}$	$HC_{COST_{CAR}}$
Adherence Level 0-59	7504	17	2.29					17200		
Adherence Level 60-79 (Simple and Persistent Reminder-SR)	6291	17	2.29	0.368	1.368	0			19725	
	6291	17	2.29	0.368	1.368	100			19825	
	6291	17	2.29	0.368	1.368	200			19925	
	6291	17	2.29	0.368	1.368	300			20025	
	6291	17	2.29	0.368	1.368	400			20125	
	6291	17	2.29	0.368	1.368	500			20225	
	6291	17	2.29	0.368	1.368	600			20325	
	6291	17	2.29	0.368	1.368	700			20425	
	6291	17	2.29	0.368	1.368	800			20525	
	6291	17	2.29	0.368	1.368	900			20625	
	6291	17	2.29	0.368	1.368	1000			20725	
Adherence Level 80-100 (Context-aware reminder-CAR)	4570	17	2.29				0			10475
	4570	17	2.29				100			10575
	4570	17	2.29				200			10675
	4570	17	2.29				300			10775
	4570	17	2.29				400			10875
	4570	17	2.29				500			10975
	4570	17	2.29				600			11075
	4570	17	2.29				700			11175
	4570	17	2.29				800			11275
	4570	17	2.29				900			11375
	4570	17	2.29				1000			11475

A3 Theoretical Background

A3.1 Factors reported affecting medication adherence (Meducation 2006)

1. SOCIAL AND ECONOMIC DIMENSION

• Limited English language proficiency
• Low health literacy
• Lack of family or social support network
• Unstable living conditions; homelessness
• Burdensome schedule
• Limited access to healthcare facilities
• Lack of healthcare insurance
• Inability or difficulty accessing pharmacy
• Medication cost
• Cultural and lay beliefs about illness and treatment
• Elder abuse

2. HEALTHCARE SYSTEM DIMENSION

• Provider-patient relationship
• Provider communication skills
• Disparity between the health beliefs of the healthcare provider and those of the patient
• Lack of positive reinforcement from the healthcare provider
• Weak capacity of the system to educate patients and provide follow-up
• Lack of knowledge on adherence and of effective interventions for improving it
• Patient information materials are written at too high literacy level
• Restricted formularies; changing medications covered on formularies
• High drug costs, copayments, or both
• Poor access or missed appointments
• Long wait times
• Lack of continuity of care

3. CONDITION-RELATED DIMENSION

• Chronic conditions
• Lack of symptoms
• Severity of symptoms
• Depression
• Psychotic disorders
• Mental retardation/developmental disability

4. THERAPY-RELATED DIMENSION

• Complexity of medication regimen (number of daily doses; number of concurrent medications)
• Treatment requires mastery of certain techniques (injections, inhalers)
• Duration of therapy
• Frequent changes in medication regimen
• Lack of immediate benefit of therapy
• Medications with social stigma attached to use
• Actual or perceived unpleasant side effects
• Treatment interferes with lifestyle or requires significant behavioral changes

5. PATIENT-RELATED DIMENSION

Physical Factors

• Visual impairment
• Hearing impairment
• Cognitive impairment

• Impaired mobility or dexterity • Swallowing problems **Psychological/Behavioral Factors** • Knowledge about disease • Perceived risk/susceptibility to disease • Understanding reason medication is needed • Expectations or attitudes toward treatment • Perceived benefit of treatment • Confidence in ability to follow treatment regimen • Motivation • Fear of possible adverse effects • Fear of dependence • Feeling stigmatized by the disease • Frustration with healthcare providers • Psychosocial stress, anxiety, anger • Alcohol or substance abuse

A3.2 Models and Concepts for Health Behavior Change

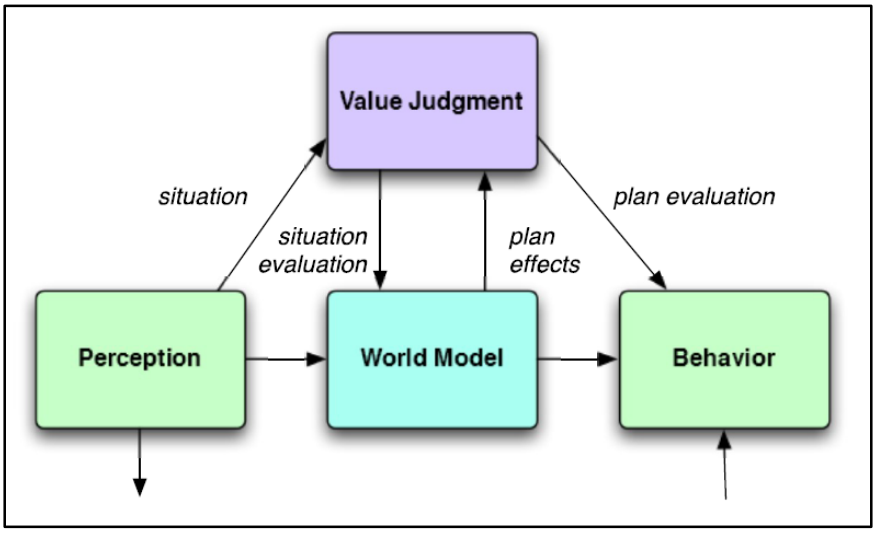
(Revere and Dunbar 2001)

Concept	Definition	Application
Health Belief Model (Rosenstock et al. 1994)**:**		
Perceived susceptibility	One's opinion of chances of getting a condition	Personalize risk based on a person's features or behavior.
Perceived severity	One's opinion of how serious a condition and its consequences are	Specify consequences of the risk and the condition.
Perceived benefits	One's opinion of the efficacy of the advised action to reduce risk or seriousness of impact	Define action to take; how, where, when; clarify the positive effects to be expected.
Perceived barriers	One's opinion of the tangible and psycho- logical costs of the action	Identify and reduce barriers through reassurance, incentives, assistance.
Cues to action	Strategies to activate "readiness."	Provide how-to information, promote awareness, and provide reminders.
Self-efficacy	Confidence in one's ability to take action	Provide training, guidance in performing an action.
Stages-of-Change Model (Prochaska and Diclemente 1983)**:**		
Pre-contemplation	Unaware of problem hasn't thought about changes	Increase awareness of the need for change, personalizes information on risks and benefits.
Contemplation	Thinking about change, in the near future.	Motivate, encourage to make specific plans.
Preparation	Making a plan to change	Assist in developing concrete action plans, setting gradual goals.
Action	Implementation of specific action plans	Assist with feedback, problem solving, social support, reinforcement.
Maintenance	Continuation of desirable actions, or repeating periodic recommended step(s)	Assist in coping, reminders, finding alternatives, avoiding slips/relapses (as applicable).
Theory of Planned Behavior (Godin and Kok 1996) **and Theory of Reasoned Action** (Ajzen and Fishbein 1975)**:**		
Behavioral intention	Perceived likelihood of performing the behavior; prerequisite for action	Define action; identify how much effort one is planning to exert to reach the goal.
Attitude	One's favorable or unfavorable evaluation of the behavior	Identify outcomes of action.
Behavioral belief	Belief that behavioral performance is associated with certain attributes or outcomes	Provide information about outcomes; clarify positive effects to be expected.
Normative belief	Subjective belief regarding approval or disapproval of the behavior	Identify barriers and advantages of behavior.
Subjective norm	Influence of perceived social pressure; weighted by one's motivation to comply with perceived expectations	Identify specific groups or individuals of influence; identify how much their approval or disapproval affects action.
Perceived behavioral control (Theory of Reasoned Action only)	One's perception of how easy or difficult it will be to act	Incorporate information about likely results of action in advice.
Social Cognitive Theory (Bandura 1977)**:**		

Concept	Definition	Application
Reciprocal determinism	Behavior changes result from interaction between individual and environment	Work to change the environment.
Behavioral capability	Knowledge and skills to influence behavior	Provide information and training about action.
Expectations	Beliefs about likely results of action	Incorporate information about likely results of action into advice.
Self-efficacy	Confidence in ability to take action and persist in action	Point out strengths; use persuasion and encouragement; approach behavior change in small steps.
Observational learning	Beliefs based on observing others	Point out others' experience; identifies role models.
Reinforcement	Responses to a person's behavior that increase or decrease chances of recurrence	Provide incentives, rewards, praise; encourage self-reward.

A3.3a Theoretical analysis of cognition

(Model Proposed by Albus and Meystel (1996))



A3.3b Control Techniques

(Control Theory 2016)

Control Technique	Description
Adaptive control	Uses on-line identification of the process parameters, or modification of controller gains, thereby obtaining strong robustness properties. Adaptive controls were applied for the first time in the aerospace industry in the 1950s and have found particular success in that field.
Hierarchical control system	A type of control system in which a set of devices and governing software is arranged in a hierarchical tree. When the links in the tree are implemented by a computer network, then that hierarchical control system is also a form of networked control system
Intelligent control	Uses various AI computing approaches like neural networks, Bayesian probability, fuzzy logic, machine learning, evolutionary computation and genetic algorithms to control a dynamic system
Optimal control	A particular control technique in which the control signal optimizes a certain "cost index": for example, in the case of a satellite, the jet thrusts needed to bring it to the desired trajectory that consumes the least amount of fuel
Robust control	Deals explicitly with uncertainty in its approach to controller design. Controllers designed using robust control methods tend to be able to cope with small differences between the true system and the nominal model used for design.
Stochastic control	Deals with control design with uncertainty in the model. In typical stochastic control problems, it is assumed that there exist random noise and disturbances in the model and the controller, and the control design must take into account these random deviations
Energy-shaping control	View the plant and the controller as energy transformation devices. The control strategy is formulated regarding interconnection (in a power-preserving manner) to achieve the desired behavior.
Self-organized criticality control	May be defined as attempts to interfere in the processes by which the self-organized system dissipates energy.