

AN ONTOLOGY FOR FORMAL REPRESENTATION OF MEDICATION
ADHERENCE-RELATED KNOWLEDGE:
CASE STUDY IN BREAST CANCER

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DEDICATION

All glory to God Almighty, my Creator, my strong pillar, my source of inspiration, wisdom, knowledge, and understanding. His mercy is with me throughout my life and ever more in this study.

I dedicate this dissertation to the memory of my father, who would have been happy to see this work completed. I also dedicate it to my husband and my lovely kids. From the bottom of my heart, thank you for making my dream become a reality.

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Medication non-adherence is a major healthcare problem that negatively impacts the health and productivity of individuals and society as a whole. Reasons for medication non-adherence are multi-faced, with no clear-cut solution. Adherence to medication remains a difficult area to study, due to inconsistencies in representing medication-adherence behavior data that poses a challenge to humans and today's computer technology related to interpreting and synthesizing such complex information. Developing a consistent conceptual framework to medication adherence is needed to facilitate domain understanding, sharing, and communicating, as well as enabling researchers to formally compare the findings of studies in systematic reviews.

The goal of this research is to create a common language that bridges human and computer technology by developing a controlled structured vocabulary of medication adherence behavior—"Medication Adherence Behavior Ontology" (MAB-Ontology) using breast cancer as a case study to inform and evaluate the proposed ontology and demonstrating its application to real-world situation. The intention is for MAB-Ontology to be developed against the background of a philosophical analysis of terms, such as belief, and desire to be human, computer-understandable, and interoperable with other systems that support scientific research.

The design process for MAB-Ontology carried out using the METHONTOLOGY method incorporated with the Basic Formal Ontology (BFO) principles of best practice. This approach introduces a novel knowledge acquisition step that guides capturing

medication-adherence-related data from different knowledge sources, including adherence assessment, adherence determinants, adherence theories, adherence taxonomies, and tacit knowledge source types. These sources were analyzed using a systematic approach that involved some questions applied to all source types to guide data extraction and inform domain conceptualization. A set of intermediate representations involving tables and graphs was used to allow for domain evaluation before implementation. The resulting ontology included 629 classes, 529 individuals, 51 object property, and 2 data property.

The intermediate representation was formalized into OWL using Protégé. The MAB-Ontology was evaluated through competency questions, use-case scenario, face validity and was found to satisfy the requirement specification. This study provides a unified method for developing a computerized-based adherence model that can be applied among various disease groups and different drug categories.

Karl F. MacDorman, Ph.D., Chair

TABLE OF CONTENTS

LIST OF TABLES	xii
LIST OF FIGURES	xiii
LIST OF ABBREVIATIONS.....	xiv
CHAPTER ONE: INTRODUCTION AND BACKGROUND	1
1.1 Problem Statement.....	9
1.2 Proposed Solution.....	11
1.3 Aims and Objectives.....	11
1.4 Significance of the Study.....	12
1.5 Rationale.....	13
1.6 Description of the Chapters	14
1.7 Protection of Human Subjects	15
CHAPTER TWO: LITERATURE REVIEWS.....	16
2.1 Reasons for Non-Adherence to Tamoxifen and Aromatase Inhibitors.....	16
2.1.1 Introduction.....	16
2.1.2 Methods.....	18
2.1.3 Results.....	21
2.1.4 Discussion.....	30
2.1.5 Limitations.....	32
2.1.6 Conclusion.....	32
2.2 The Impact of Information Technology on Behavior Change.....	33
2.2.1 Introduction.....	33
2.2.2 Methods.....	36
2.2.3 Results.....	39
2.2.4 Discussion.....	59
2.2.5 Limitations.....	66
2.2.6 Implications.....	67
2.2.7 Conclusion.....	68
2.3 Ontologies and Knowledge Representation.....	69
2.3.1 What is an Ontology?.....	70
2.3.2 Ontology's Impact on the Biomedical Field.....	71
2.3.3 Ontology Developing Approach.....	77
2.3.4 Methodologies Comparison.....	81
2.3.5 Principles of Ontology Design.....	86
2.3.6 Upper-Level Ontology.....	87
CHAPTER THREE: GUIDING PRINCIPLE FOR ONTOLOGY DEVELOPMENT	90
3.1 Domain Specification.....	92
3.1.1 The Purpose of the Ontology.....	93
3.1.2 Approaches for Ontology Building.....	93
3.1.3 Scope of the Ontology.....	93
3.2 Knowledge Acquisition.....	94
3.2.1 Knowledge Sources.....	94
3.2.2 Source Selection.....	95
3.2.3 Searching Strategy.....	96
3.2.4 Source Analysis.....	102

3.3 Knowledge Structuring Using Set of Intermediate Representations	103
3.3.1 Building a Glossary of Terms	103
3.3.2 Knowledge Representation Using Triplet.....	106
3.3.3 Building the MAB Hierarchy.....	107
3.3.4 Hierarchy of MAB-Ontology Based on BFO	109
3.3.5 Building Relations	115
3.4 Ontology Integration.....	120
3.5 Model Formalization.....	120
3.6 Evaluation	122
3.6.1 Face Validity of Intermediate Representations.....	122
3.6.2 Competency Questions	123
3.6.3 Consistency Checking.....	123
3.6.4 Compliance with the OBO Foundry Principle.....	124
3.6.5 Compliance with the METHONTOLOGY Methodology.....	124
CHAPTER FOUR: RESULTS AND DISCUSSION OF MAB-ONTOLOGY	125
4.1 Domain Specification.....	125
4.1.1 The Purpose of the Ontology.....	125
4.1.2 Approaches for Ontology Building.....	131
4.1.3 The Scope of the Ontology	131
4.2 Knowledge Acquisition	132
4.2.1 Source Selection.....	132
4.2.2 Source Analysis	139
4.3 Knowledge Structuring Using Set of Intermediate Representations	148
4.3.1 Building a Glossary of Terms	148
4.3.2 Knowledge Representation Using Triples	153
4.3.3 Building the MAB Hierarchy.....	156
4.3.4 Building the MAB Hierarchy Based on BFO	157
4.4 Model Integration.....	206
4.5 Model Formalization.....	207
4.6 MAB-Ontology Evaluation.....	210
4.6.1 Face Validity of Intermediate Representation	210
4.6.2 Competency Question.....	213
4.6.3 Use Case Scenario.....	226
4.6.4 Consistency Checking.....	227
4.6.5 Compliance with OBO Foundry.....	227
4.6.6 Compliance with METHONTOLOGY.....	229
4.6.7 Expandability Testing.....	230
CHAPTER FIVE: CONCLUSION AND FUTURE WORK.....	236
5.1 Conclusion	236
5.2 Impact of the Research.....	237
5.3 Challenges in the Development of MAB-Ontology	238
5.4 Future Work	239
APPENDICES	240
Appendix 1.....	240
Appendix 2.....	242
Appendix 3.....	261

REFERENCES 299
CURRICULUM VITAE

LIST OF TABLES

Table 1 Studies Assessing Reasons for Non-adherence to TAM or AIs	26
Table 2 Summary of the Review Results Based on Types of IT Platforms.	40
Table 3 Impact of IT Platforms Among Different Disorders	46
Table 4 Impact of IT Platforms on Patient Engagement.....	49
Table 5 Impact of IT Platforms and Theories of Health Behavior	52
Table 6 Patient Engagement and Theories of Health Behavior	53
Table 7 Impact of IT Platforms and Methods to Measure Health	54
Table 8 Impact of IT Platforms and Usability	57
Table 9 Patient Engagement and Usability	58
Table 10 The Criteria for Methodology Selection	84
Table 11 Use Case Scenario Flow	130
Table 12 Theories Identified in the Included Review.....	134
Table 13 Source Selection Examples.....	138
Table 14 Medication Adherence Assay Literature Source Type	140
Table 15 Determinants of Medication Adherence Literature Source Type	141
Table 16 Theory of Adherence Change Source Type.....	142
Table 17 Medication Adherence Data Standard Source Type.....	143
Table 18 Medication Adherence-Related Terms Source Type.....	146
Table 19 Tacit Knowledge Source Type	147
Table 20 Building a Glossary of Terms.....	149
Table 21 Knowledge Representation Using Triples.	154
Table 22 Listing of Leveraged Ontology.....	206
Table 23 Adherence to the OBO Foundry Principles.	228
Table 24 Adherence to the METHONTOLOGY Method	230

LIST OF FIGURES

Figure 1 Articles Identified During the Search for Relevant Literature	20
Figure 2 Flow Diagram of Included and Excluded Studies	39
Figure 3 MAB-Ontology Methodology Overview	92
Figure 4 Medication Adherence Assessment Literature	97
Figure 5 Theory of Adherence Change Literature	100
Figure 6 Theory of Adherence Change Among Books and Websites	100
Figure 7 The Hierarchy for BFO	109
Figure 8 The Realizable Entity Hierarchy for BFO	115
Figure 9 Medication Adherence Source Types to Intermediate Representation	139
Figure 10 Knowledge Representation in Triples	154
Figure 11 Linda’s Belief Instantiates at Different Times	166
Figure 12 The Belief Structure Under BFO	169
Figure 13 The Mental Disposition Structure Under BFO	171
Figure 14 Measurement Under BFO	172
Figure 15 Medication Adherence Process	176
Figure 16 Treatment Process	177
Figure 17 Medication Adherence Assay	188
Figure 18 Drug Concentration Assay	189
Figure 19 Direct Observation Assay	190
Figure 20 Dosing Event Recording	191
Figure 21 Pill Counting	192
Figure 22 Self-Reported Medication Adherence Assessment	193
Figure 23 Prescription Refill Assessment	194
Figure 24 Behavior Change Intervention	197
Figure 25 Medication Adherence Intervention	198
Figure 26 Adherence Determinate Finding	200
Figure 27 Conclusion Based on Data About Causal Belief	204
Figure 28 Conclusion Based on Data About Adherence Pattern	205
Figure 29 MAB-Ontology Viewed in Protégé	208
Figure 30 Class extraction process using OntoFox	208
Figure 31 Object Properties and Data Properties in the MAB-Ontology	209
Figure 32 Factors Impact Medication Adherence Process	211
Figure 33 Breast Cancer Patient and Disease Categories	212
Figure 34 Adherence Influencing Factors	213
Figure 35 Psychological Determinants of Medication Adherence	214
Figure 36 Determinants Influence 60 Year-old Patients Taking Tamoxifen	215
Figure 37 Patient Discontinues Tamoxifen Due to Side Effects	216
Figure 38 Behavioral Change Techniques Used to Change Medication Adherence	217
Figure 39 Information Technologies Used to Change Medication Adherence	217
Figure 40 Methods Used to Measure Medication Adherence	218
Figure 41 Direct Methods Used to Measure Medication Adherence	219
Figure 42 Methods Used to Measure Medication Adherence Among Patient 1	219
Figure 43 Questionnaires Used to Measure Adherence to Endocrine Therapy	220
Figure 44 Questionnaires Used to Measure Only Medication Adherence Behavior	220

Figure 45 Questionnaires Measure Medication Adherence Behavior and Barriers	221
Figure 46 Behavioral Theories Used for Medication Adherence Intervention.....	222
Figure 47 MAB-Ontology for Theory of Planned Behavior Constructs	223
Figure 48 Theories That Include Constructs Represent Behavior Capability Belief.....	223
Figure 49 Patients at Risk of Non-adherence	224
Figure 50 Sixty Year-old Breast Cancer Patient at Risk for Non-adherence	224
Figure 51 MAB-Ontology for Non-adherent Patients	225
Figure 52 MAB-Ontology for Medication Adherence Risk Factors	225
Figure 53 Factors That Influence Adherence in the First Three Months.....	226
Figure 54 Consistency Checking	227
Figure 55 TAB-Ontology.....	232
Figure 56 Factors with Negative Value	233
Figure 57 Technology Discontinuation	234
Figure 58 Expanding MAB-Ontology	235

LIST OF ABBREVIATIONS

American Nursing Association (ANA)
Application Programming Interface (API)
Ascertaining Barriers to Compliance Project (ABC)
Aromatase Inhibitors (AIs),
Basic Formal Ontology (BFO)
Behavior Change Technique (BCT)
Centers for Medicare and Medicaid Services (CMS)
Comparative Effectiveness Research (CER)
Critical Appraisal Skills Programme (CASP)
Current Procedural Terminology (CPT)
Diagnostic Related Group (DRG)
Domain Ontology for Linguistic and Cognitive Engineering (DOLCE)
Electronic Health Records (EHRs)
Health Belief Model (HBM)
Electronic Drug Monitoring Systems (EDMs)
Foundational Model of Anatomy (FMA)
Health and Human Services (HHS)
Health Information Technology (HIT)
Information Technology (IT)
Institutional Review Boards (IRBs)
International Classification of Disease (current version, ICD-10)
International Organization for Standardization (ISO)
KBSI IDEF5 Methodology
Knowledge Representation (KR)
Logical Observation Identifiers Names and Codes (LOINC)
Medication Adherence Behavior Ontology (MAB-Ontology)
Medication Event Monitoring System (MEMS)
Mobile Health (mHealth)
National Coordinator for Health Information Technology (ONC)
National Center for Biomedical Ontology (NCBO)
Biomedical Ontologies Foundry (OBO)
Ontology Design Patterns (ODP)
Open Knowledge Base Connectivity (OKBC)
Protection Motivation Theory (PMT)
Personal Health Records (PHRs)
Reasoned Action (TRA)
SENSUS-Based Methodology Short Message Service (SMS)
Social-cognitive Theory (SCT)
Stage of Change (SOC)
Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT)
Tamoxifen (TAM)
Theory of Planned Behavior (TPB)
Transtheoretical Model (TTM)
Uniform Resource Identifiers (URIs)

Unified Medical Language System (UMLS)
Visual Understanding Environment (VUE)
World Health Organization (WHO)

CHAPTER ONE: INTRODUCTION AND BACKGROUND

Despite progress in medical science leading to new therapies for acute, chronic, and fatal diseases, such as AIDS and cancers, full benefits of these treatments have not been realized (Sawesi, Carpenter, & Jones, 2014). This is primarily due to non-adherence leading to poor clinical outcomes, treatment failure, and ineffective therapies (Sedjo & Devine, 2011; Williams, Mertz, & Wilkins, 2014). Medication non-adherence—“the extent to which patients are not taking their medications as prescribed by their healthcare provider (Meichenbaum & Turk, 1987)”—is a major problem that produces an “invisible epidemic,” unknown to patients and unrecognized by caregivers, clinicians, pharmacists, and healthcare systems as a whole (Haider et al., 2014; Kaufman & Birks, 2009).

Medication non-adherence is estimated to cause approximately 125,000 deaths and at least 10% of hospitalizations annually (Viswanathan et al., 2012). Based on the Centers for Disease Control and Prevention’s (CDC) leading causes for the numbers of deaths in 2017, medication non-adherence would rank as sixth. Between \$100-\$300 billion in annual unnecessary medical costs are attributed to medication non-adherence (Cutler, Fernandez-Llimos, Frommer, Benrimoj, & Garcia-Cardenas, 2018; Iuga & McGuire, 2014; Nasseh, Frazee, Visaria, Vlahiotis, & Tian, 2012; Williams et al., 2014). More than 1.6 billion annual prescriptions dispensed in the U.S. are not taken as prescribed (Williams et al., 2014). And, among patients with chronic diseases, it is even higher. These patients require long-term, possibly lifelong medications to control symptoms and prevent complications.

Medication adherence among breast cancer patients exemplifies these challenges. Two types of hormone-based therapies, tamoxifen (TAM) and aromatase inhibitors (AIs),

have reduced disease recurrence and mortality rates among women with breast cancer, provided the regimens are adhered to for at least five years (Nekhlyudov, Li, Ross-Degnan, & Wagner, 2011). However, studies show that around half of breast cancer patients fail to adhere to hormone treatment, risking clinical responses below expected standards (Banning, 2012; Chlebowski & Geller, 2007; Doggrell, 2011; Gotay & Dunn, 2011; Hadji, 2010; Verma, Madarnas, Sehdev, Martin, & Bajcar, 2011). While side effects are the main reason for medication non-adherence (Henry et al., 2013; Kadakia, Kidwell, et al., 2016; Kadakia, Snyder, et al., 2016; Sawesi, Carpenter, & Jones, 2014), co-morbidity, patient-provider relationship, forgetfulness, and patients' perceptions and beliefs have been cited as contributing to non-compliance: specifically TAM and AIs (Sawesi, Carpenter, & Jones, 2014).

Adherence research has been spurred by the proliferation of information technology (IT) innovations in the healthcare system. Medication non-adherence offers the health information technology (HIT) community the opportunity to devise tools and solutions that assist medication adherence and enhance quality of life and improve population health. Several HITs have been used to understand, explore, measure, and improve medication adherence. The U.S. Department of Health and Human Services (HHS), via the Office of the National Coordinator for Health Information Technology (ONC) and the Centers for Medicare and Medicaid Services (CMS), supports using HIT applications to improve medication adherence and medication management through various programs, such as certified electronic health records (EHRs), the Medicare and Medicaid EHR Incentive Program, and adoption of consumer-based tools that motivate the patient and caregiver to participate in medication adherence (Williams

et al., 2014). Studies reveal that hospital HIT enhances storage and retrieval of patient information via electronic health records (EHRs) (Buntin, Burke, Hoaglin, & Blumenthal, 2011). For example, EHRs enable healthcare providers to assess medication adherence by linking electronic prescription information from the e-prescribing system with pharmacy-fill information. Healthcare providers can also track medication adherence using electronic drug monitoring systems (EDMs), such as personal health records (PHRs) and patient portals, and use electronic pillboxes and medication event monitoring systems (MEMS) (Williams et al., 2014). As a result, a growing volume of heterogeneous data (Shaban-Nejad, Lavigne, Okhmatovskaia, & Buckeridge, 2016) from heterogeneous sources store data having different meaning in different formats with the need to move it from place to place among healthcare providers, payers, and beneficiaries.

Although medication adherence varies based on patient demographics, behavioral dimensions, the nature of the disease, the type of drug, and its duration, it differs highly by heterogeneity in data and clinical terminologies that represent this domain (Bramwell et al., 2009; Sawesi, Carpenter, & Jones, 2014). The lack of uniformity in terminology used to describe and measure medication adherence behavior and factors impacting a patient's adherence impede the integration, analysis, interpretation, usefulness, and synthesis of the medication adherence-related data (Verma et al., 2011). This problem leads to fragmented, non-interoperable healthcare information systems in terms of comparative effectiveness research (CER). Consequently, it limits data dissemination due to underdeveloped domain standards that can facilitate both human and computer understanding, analysis, and sharing. The domain of medication adherence behavior has many challenges that need to be overcome in order to achieve a standardized, shareable

information network that can successfully “interoperate” and allow research and treatment to inform one another.

Inconsistencies in terminology and definitions of medication adherence are a challenge. The terms adherence, compliance, persistence, and concordance are often used interchangeably (Hugtenburg, Timmers, Elders, Vervloet, & Dijk, 2013). However, each has a different meaning/measurement and reflects a variety of views on the relationship between patient, healthcare provider, and how the medicine has been filled and taken. Medication compliance, for example, is defined as the “extent to which the patient follows the recommendations of the prescriber” (Hugtenburg, Timmers, Elders, Vervloet, & Dijk, 2013). In this instance, the behavior seems to have a negative association that is subservient to prescribers. There is no regard for patient autonomy and self-efficacy, as the patient has to comply with medication regimens regardless of their suitability (Chakrabarti, 2014). Non-compliance in this context represents the patient’s maladaptation behavior when he/she refuses to comply. Failure to comply may not always be harmful; while many treatments can cause severe side-effects, non-compliance to a medication can be considered a protective behavior. Therefore, while compliance is possibly useful in defining and measuring patient behavior, it fails to address all the reasons for patient non-compliance.

Medication adherence, the preferred term, now replaces compliance and is defined as the “extent to which medication intake behavior corresponds with the recommendations of the healthcare provider (Sabaté, 2003).” This implies that the patient can actively choose the most suitable treatment plan (Organization, 2014). This definition emphasizes the patient partnership or engagement in the treatment processes and decision

making. Thus, the patient will not be blamed for a treatment plan failure if he/she does not adhere to the medication regimen. Although this definition addresses the patient's role in treatment decisions, it creates conceptual confusion that generates a measurement problem. As it implies the need for agreement between the patient and the healthcare provider, it also requires methods to measure this agreement. Moreover, it lacks the normative agenda, i.e., whether adhering to medication is good or bad (Chakrabarti, 2014). Therefore, the term "concordance" has evolved to mean the "normative agenda" of taking medication. It is defined as "the agreement between the prescriber and patient on the purpose and use of the medication (Vrijens et al., 2012)"; it describes the patient-prescriber relationship, in which a consensus about how taking medication will be reached by including the patient's perspective and his or her own views on taking medication. Although concordance can solve the normative agenda, it creates an ethical dilemma for the healthcare provider when a patient's decision threatens him/herself (i.e., patient selects the treatment based on preference, not on scientific evidence).

"Persistence," also mentioned in the literature, refers to medication-taking behavior. It refers to "the length of time between the first and last dose (Vrijens et al., 2012)," implying how long the patient remains on a medication regimen. While these terms are used as synonyms, they do not consistently define. They hold different meanings and reflect different views about the role of patients in treatment plans, as well as the relationship between patients and healthcare providers; they do not include the entire range of data sources for adherence—i.e., medication initiation or discontinuation behavior (Cramer et al., 2008; Organization, 2014).

Medication non-adherence can take a variety of forms; there is no unilateral category as to their types. The World Health Organization (WHO), for example, classifies medication non-adherence into: (1) Erratic non-adherence (patient forgets dose; patient inconsistently follows the health professional's instructions, such as incorrect time, dose, and frequency); and (2) Intelligent non-adherence (patient purposely alters, discontinues, or even fails to fill the prescription (Sabaté, 2003)). Williams (2014) formalized non-adherence types differently: (1) Primary non-adherence (patient does not obtain the prescribed medication), (2) Discontinuation (patient stops taking the medication), (3) Compromised execution (medication inconsistent with provider's instructions) (Williams et al., 2014). Another non-adherence category is: (1) Intentional non-adherence (patient actively fails to follow prescribed treatment recommendations, and (2) Unintentional non-adherence (unplanned behavior for not taking the prescribed treatment) (Hugtenburg, Timmers, Elders, Vervloet, & Dijk, 2013).

Medication non-adherence was also categorized based on factors or determinants that contribute to adherence behavior called "dimensions" (Figure 1) by WHO (WHO, 2003) and is referred to as patient-related factors; therapy-related factors; social and economic factors; disease-related factors; and the healthcare system. Munro et al. classifies these same factors under four different themes: structural, personal, social context, and health service (Munro et al., 2007). Selinger et al. (2013) used different categorizations to represent medication adherence: influencing factors through a modifiable and non-modifiable category. Among these dimensions, the patient can fall into more than one category at a given time. Therefore, since these dimensions are potential causes of medication non-adherence, they can help healthcare providers

understand the reasons for non-adherence and effectively collaborate with patients to overcome barriers (Shah et al., 2009).

Medication non-adherence can be explained through the use of behavioral theories. However, theoretical constructs were found to overlap in many areas, making the inconsistent use of terminology involved with determining and deciding which theories would be the most precise in explaining the difficulty challenging to the health-related behavior. For example, the perceived benefits of HBM, named as perceived outcome expectancy in SCT; and perceived barriers in HBM, termed as perceived cost in self-regulatory theory. Also, the construct of self-efficacy—a person’s belief in his/her ability to self-manage and overcome boundaries, used in the Social Cognitive Theory (SCT), Protection Motivation Theory (PMT), Theory of Planned Behavior (TPB), Health Belief Model (HBM), and Self-Regulation Theory (Leventhal & Cameron, 1987). This term holds the same meaning with the phrase, “perceived behavioral control”— meaning an individual’s belief about his/her ability to produce a performance that influences events that affect his/her life (Ajzen, 2002). Both self-efficacy and perceived behavioral control pertain to a belief in one’s ability to perform a behavior and have control over that behavior. It does not refer to controlling the outcomes or events. However, “perceived behavioral control” in the theory of planned behavior may have been misleading; it has been intended to refer to the belief that performing a behavior affords control over achievement of an outcome, which is not the intended meaning. It has also been used to measure external constraints on behavior, while self-efficacy has been used to measure internal control factors (Gustafson et al., 2001). There is a lack of clarity about the definition and measurement of these terms and under what category they exist in reality.

Many studies either neglect these terms, assuming the reader knows their meaning, or inconsistently define them. Examining their nature and under what category they exist is essential for data sharing. All medication adherence researchers and clinicians pretty much need the same data. This data must have the same meaning and context to be understandable and shared. Belief, as an example, is defined in several ways in the literature. (i) Belief is a feeling (Hume, 2003): to believe that Tamoxifen will prevent the recurrence of breast cancer is to have a special kind of feeling linked with this statement. (ii) Belief is a mental state (Davidson, 1989): having the belief that Tamoxifen prevents the recurrence of breast cancer is being in a state of belief about this proposition. (iii) Belief is something an individual holds (Eynde, Corte, & Verschaffel, 2002): to believe that Tamoxifen prevents breast cancer is to have a material entity in the brain representing this proposition. (iv) Belief is a metacognitive process in which an individual believes in knowledge and knowing (Hofer, 2004): to believe that Tamoxifen prevents breast cancer is to believe and know this as fact. The belief is an event or episode. Therefore, in order to predict and explain an individual's behavior and design better behavioral intervention, such terms need to be represented consistently in common schema in order to be sharable and interoperable. To circumvent these obstacles, such diverse information requires the ability to integrate, analyze, interpret, organize, and be stored in interconnected computer repositories, so that it would be available to anyone, anywhere in the world, at any point in time (Arp, Smith, & Spear, 2015). There is a need for some way to explicitly specifying the semantics for each terminology in an unambiguous fashion—a novel framework that represents and investigates the existing knowledge and hidden patterns from the data.

1.1 Problem Statement

Evidence-based practice needs to produce and access current best evidence to understand and make decisions related to better ways to overcome and improve the patient medication-adherence problem. The main reasons for collecting medication adherence data are to facilitate the conversation among healthcare providers regarding the non-adherence issue and the reasons behind this problematic behavior. These reasons need to be documented to enable behavioral change. Medication non-adherence documentation lexically varies and is represented by numerous semantics (Turchin et al., 2008). Clinicians, informaticians, and researchers sometimes use terms inconsistently and define them imprecisely (Andrade, Kahler, Frech, & Chan, Arnold 2006). Other terms lack understanding as to their nature and the categorical classes they subsumed, such as in the case of cognitive constructs used in behavioral theories.

These inconsistencies in definition, measurement, and the reporting of medication adherence-related information make it challenging to determine the best interventions and treatment plans and impede the evidence-based practice process. Also, using different computer technologies to standardize, encode, and store these results creates serious obstacles to better access, interoperability, and reusing of data and information (Arp et al., 2015). Arp, Smith, and Spear (2015) state, “It is the diversity of data, not the quantity, that poses the primary challenge in making use of electronic medical data and information (Arp et al., 2015).” Constructing definitions and classifying this heterogeneous information in a way that avoids these idiosyncrasies is what is needed to improve domain knowledge interoperability and improve consistency in data description.

Discussing medication adherence domain, in general, Jack BW (2009) stated, “If there was a standard instrument that existed, it would be nice to report adherence in a standard way if there was a standard or accepted tool that is used. It would be nice if our project used a similar standard, so it means something around the country (Blake, 2016).” Complicated knowledge, such as that related to medication adherence mentioned in previous sections, presents challenges in information representation. For example, the terms beliefs, desires, motives, emotion, and intentions, all lack clarity about what kind of entities they are. The term adherence could also be problematic. It may represent different ideas, can be understood and used in various contexts, or describes different phenomena.

Such inconsistent use of terminology would render the term useless in systems with the goals of automating information sharing, facilitating re-use of information, and supporting building new knowledge. The uniformity of concepts and language used to describe medication adherence and theoretical constructs would further enhance comparing and combining results and aiding in developing effective and efficient intervention strategies to improve medication adherence (Cramer et al., 2008). Uniform concepts and language will facilitate communication across medication adherence disciplines and among healthcare providers and patients. Accordingly, the problem statement is formally stated as:

Representation of medication adherence-related knowledge using ontology as a formal representational tool is needed to facilitate domain understandability, interoperability, and comparative effectiveness research.

1.2 Proposed Solution

Representing knowledge related to medication-adherence behavior with ontology is proposed as a step toward improving clinical data interoperability, understanding and formalizing a knowledge-related domain, and evidence-based care. Consequently, it can support the development and implementation of medication adherence applications. At a high level, it involves building standard and formal definitions of concepts and their use to enable the reuse of derived knowledge and facilitate the connection of databases and datasets in the medication adherence domain.

In past years, considerable research has related to using ontologies as an information tool for knowledge representation. They are used to provide a shared understanding of a domain, both for computers and humans, by modeling concepts and relationships within a domain, enhancing interoperability, and reusing data and knowledge (Bailey, McMullin, & Coble, 2001; Bodenreider & Stevens, 2006; Gruber, 1995; M. Musen, 2008; M. A. Musen, 1999) to support multiple clinical tasks (Beale & Heard, 2007; Borycki & Kushniruk, 2006; Dao, Marin, & Tho, 2007; Islam, Brandeau, & Das, 2006). However, what has not been explored was representing medication adherence-related knowledge based on ontologies.

1.3 Aims and Objectives

Based on the aforementioned problem description, specific research aims of this dissertation are as follows:

- 1- Develop a formal representation of medication adherence-related knowledge using breast cancer as a case study. This model represents theoretical constructs that influence medication-adherence behavior, methods used to assess medication

adherence, and behavioral change intervention using information technology platforms to enhance medication adherence.

- a. Identify key foundational medication-adherence behavior-domain sources.
- b. Identify definitions and metrics for terms related to medication-adherence behavior.
- c. Develop an intermediate representation of medication adherence domain using tables and graphs.
- d. Formalize the conceptual model using the ontology editor Protégé.

2- Validate the ontological model by experts using the Face Validity Technique.

1.4 Significance of the Study

Inconsistencies with representing medication-adherence behavior data pose a challenge for humans and computers to use, interpret, and synthesize such complex information. Data quality and consistency are important, not only for communicating, coordinating, and reporting healthcare, but also for ensuring patient safety (Fenton, Giannangelo, Kallem, & Scichilone, 2007). Currently, medication-adherence behavior data is siloed, the terms are not standardized, and the information is fragmented across different sources. Developing a consistent conceptual framework will enhance the consistency and generalizability of medication-adherence research and facilitate domain understanding, sharing, and communicating, and enable researchers to formally compare study findings in systematic reviews.

Moreover, such a model can be used to facilitate retrieval and analysis of medication-adherence information, automated data annotation and integration, semantic interoperability between data sets, and automated reasoning and knowledge generation.

Internet searches based on this proposed ontology will be able to retrieve all relevant data from different data sources. Also, ontologies are machine-readable and can enable automated programs, such as data mining, to intelligently access and analyze information and, therefore, derive meaningful data patterns and extract new knowledge. Also, as new, hidden relationships are identified among different aspects of medication adherence in the knowledge representation process, this will motivate researchers to conduct additional studies on these important topics.

1.5 Rationale

Studies of patients who fail to take their medication, which can result in serious problems, have been documented for decades in the literature. Yet, these studies offer few solutions. This kind of behavior increases patients' chances of worsening their disease, increasing the chance of the cancer returning, and very possibly resulting in death (Sabaté, 2003). Healthcare providers largely view this behavior as a binary event, with two outcomes: patients either take or do not take their medication (Samarth & Grant, 2009).

This view of the problem omits the behavioral change aspect. It risks taking an authoritarian/paternalistic approach to how we view patients who refuse to adhere to their medication regimen. This assumption could reflect patients not complying due to a low level of understanding the repercussions of not taking their medications or their simply forgetting to take it. While these reasons are accurate in some situations, non-adherence is far broader and may not be as obvious to healthcare providers. A key reason to gather information about the importance of patients adhering to their medications is to start a conversation with a health provider that addresses issues, such as side effects, cost of the

medication, and discovering other behavioral and psychological reasons why patients fail to comply with their medication regimens. Capturing and understanding these underlying reasons, respecting patient choices, and discussing them is necessary in order to help patients become medication adherent.

Building a common language (biomedical ontology) that can be shared across different biological and medical domains takes time. It is a difficult process, as documented by the scope and collective effort of well-known ontology projects, such as Gene Ontology (Harris et al., 2004). Attaining a consensus as to the terms and definitions used by different domain experts requires negotiation and ongoing iterations. As a result, this project serves as a foundational step towards developing a refined Medication Adherence Behavior (MAB-Ontology) that can interact with other ontologies. It is designed to serve as a methods model and first-iteration artifact that the domain can interact with and refine/improve. In this way, a comprehensive systematic review approach needs to use sources rooted in research and practice to grasp the important concepts of domain communication. A wide variety of sources, combined with different methods designed to fulfill validity criteria, assures that steps taken, and documented results provide an accurate approach and meaningful contribution to the effort.

1.6 Description of the Chapters

Chapter 2—Includes three reviews: (1) Reasons for non-adherence to tamoxifen and aromatase inhibitors for the treatment of breast cancer: a literature review (Sawesi, Carpenter, & Jones, 2014). This part discusses the complexity and challenges of medication adherence behavior using breast cancer as a case study to narrow down the domain. It addresses important factors that impact adherence to adjuvant hormone

therapy. (2) The impact of information technology on patient engagement and health behavior change: a systematic review of the literature (Sawesi, Rashrash, Phalakornkule, Carpenter, & Jones, 2016). This section provides an overview of the different information technology platforms used to improve, sustain, and change health-related behavior. (3) Ontology and knowledge representation. This section defines ontology, its role in the biomedical domain, and the different methodologies used to develop ontologies.

Chapter 3—Chronicles the methodologies used to construct a formal knowledge representation for the Medication Adherence Behavior ontology (MAB-Ontology). It describes the steps taken to formalize medication adherence knowledge, the methods used to validate this knowledge, and the resulting model.

Chapter 4—Provides results based on the selected methodology and describes the outcome of each step.

Chapter 5—Links the results to the problem statement, implications, next steps, and limitations of the approach. It also recaps conclusions and contributions.

1.7 Protection of Human Subjects

This study was approved by the Indiana University Institutional Review Boards (IRBs). Human subjects' protection was required for the validation aim: Face Validity. It was designated as Non-Human Subject Research, because it was not subject to FDA or common-rule definitions of human subject research. This research involved use of informal meeting procedures with committee members not considered subjects for this research and did not place them at risk for criminal or civil liability or damage their financial standing, employability, or reputation (Appendix 1).

CHAPTER TWO: LITERATURE REVIEWS

This dissertation is primarily informed by three areas of literature: Medication adherence behavior, technology adoption to change patient behavior, and knowledge representation with ontology. Medication adherence literature provides knowledge about factors that affect medication adherence using breast cancer as a case study and the way in which these factors are categorized (Sawesi, Carpenter, & Jones, 2014). Biomedical informatics technologies literature provides knowledge regarding technology used to impact patient behavior, and the behavioral theories have been used to guide the design and assess the outcomes (Sawesi, Rashrash, Phalakornkule, Carpenter, & Jones, 2016). Ontology and knowledge representation literature provides the foundation required to create a formal representation for medication adherence behavior-related knowledge using ontology. It reviews the key topics of relevance to biomedical ontologies including: philosophical approaches of ontology; ambiguity in medical terminologies; benefits of ontology; existing biomedical ontologies; and methodologies used for ontology development and evaluation, which informed the methodology used in this dissertation.

2.1 Reasons for Non-Adherence to Tamoxifen and Aromatase Inhibitors

2.1.1 Introduction

Breast cancer is the most prevalent type of cancer among women worldwide (Coulter, Parsons, & Askham, 2008). Treatment commonly includes estrogen-suppressive or ablative medications. Two types of hormone-based therapies (i.e., tamoxifen [TAM] and aromatase inhibitors [AIs]) have been shown to decrease disease recurrence and mortality rates (Nekhlyudov et al., 2011). TAM works by inhibiting estrogen action, and AIs work by inhibiting the aromatase enzyme-mediated peripheral

conversion of androgen to estrogen (Johnston & Dowsett, 2003). TAM is used to treat pre-, peri-, or postmenopausal women with hormone receptor–positive breast cancer, and AIs are used to treat postmenopausal women with hormone receptor–positive breast cancer (Herk-Sukel et al., 2010).

TAM and AIs have the potential to provide significant levels of clinical benefit if patients adhere to the regimens for the pre- scribed time period, which is usually a number of years. However, many women with breast cancer do not follow the protocol. Intentional and unintentional non-adherence to therapies persists and undermines the effectiveness of those therapies (Sedjo & Devine, 2011). Many patients with chronic diseases rarely follow their medication regimens, including patients with cancer who may be regarded as highly motivated because of the clinical consequences associated with non-adherence to the medication (Chlebowski & Geller, 2007). Healthcare providers should encourage women with breast cancer to adhere to the recommended dosage of TAM or AI at prescribed times each day and over the recommended time period. Randomized placebo-controlled research studies testing the efficacy of TAM and AI therapies have reported non-adherence as a study limitation (Bramwell et al., 2009; Bramwell et al., 2009; Chlebowski & Geller, 2007; Dezentjé et al., 2010; Lin, Zhang, & Manson, 2011; Partridge et al., 2008). As a result of the apparent widespread lack of adherence, considerable effort has been made to develop interventions that can effectively enhance adherence rates. One approach to help increase the chances of medication adherence is to use information technology. Health information technology can potentially improve the timely and complete information flow between patients and healthcare providers, and it can identify and address gaps in patients' medication usage

(Parekh, 2011). Companies have devised many different types of electronic tools (e.g., computer-based interactive healthcare programs, short message service [SMS] alerts, drug compliance monitors) as a way to address the problem. Mobile health (mHealth) technology provides healthcare providers greater power to ensure adherence and reduce the adverse health and economic consequences associated with the problem. Simple phone counseling interventions have demonstrated improved adherence to mammography and adjuvant chemotherapy (Champion, Skinner, & Foster, 2000; Gotay & Dunn, 2011). However, each intervention has its advantages and disadvantages. To achieve the therapeutic goals of TAM and AIs when designing an intervention, the reasons for poor adherence or non-adherence should be clearly identified to tailor the intervention (Grunfeld, Hunter, Sikka, & Mittal, 2005). The purpose of the current systematic review is to evaluate the reasons for and factors associated with non-adherence to TAM and AI therapies among women with breast cancer.

2.1.2 Methods

Defining adherence categories in the current review, medication adherence is conceptualized as encompassing medication compliance and persistence. Medication compliance was considered to be measured if the study assessed administered medication doses per defined period of time or the proportion of the prescribed doses taken in a given time interval (Cramer et al., 2008). Patient self-reporting, electronic monitoring, pill count, and prescription refill records are common measurement tools related to medication compliance. Medication persistence was measured if the study assessed the duration from initiation to discontinuation of therapy (Cramer et al., 2008). Medication

persistence can be evaluated according to the duration and as a time-dependent rate (e.g., the percentage of patients who are still adherent five-years post-treatment).

1. Search strategy.

A literature search was conducted using electronic databases (i.e., CINAHL®, PsycINFO, and PubMed). The search was limited to English-language studies published in peer-reviewed journals from January 1990 to October 2011. Key words and medical subject headings initially used to identify relevant studies included breast cancer, medication adherence, medication non-adherence, medication compliance, medication non-compliance, and medication persistence. Additional relevant key words were identified during some of the electronic searches, including breast cancer regimens and treatment regimens. All three databases were searched using similar strategies and refined according to initial search results from some databases. The authors also searched reference lists from all included studies and relevant reviews. Titles and abstracts were screened to identify articles included in the review. Full articles from potentially relevant studies were then retrieved and assessed for eligibility based on the inclusion criteria. The same researcher twice reviewed all included and excluded studies.

2. Inclusion criteria.

Inclusion criteria for the review were (a) the study described specific reasons for medication non-adherence, (b) the study was written in the English language, (c) medication adherence outcomes were specifically reported, (d) participants received treatment regimens that included TAM or AIs, and (e) participants had a diagnosis of only breast cancer. Studies were excluded from the review if (a) participants had other types of cancer, (b) medication adherence outcomes were not reported, (c) the study was

written in a language other than English, or (d) the study evaluated adherence to variables other than TAM or AI therapy (e.g., appointments kept, chemotherapy, radiation).

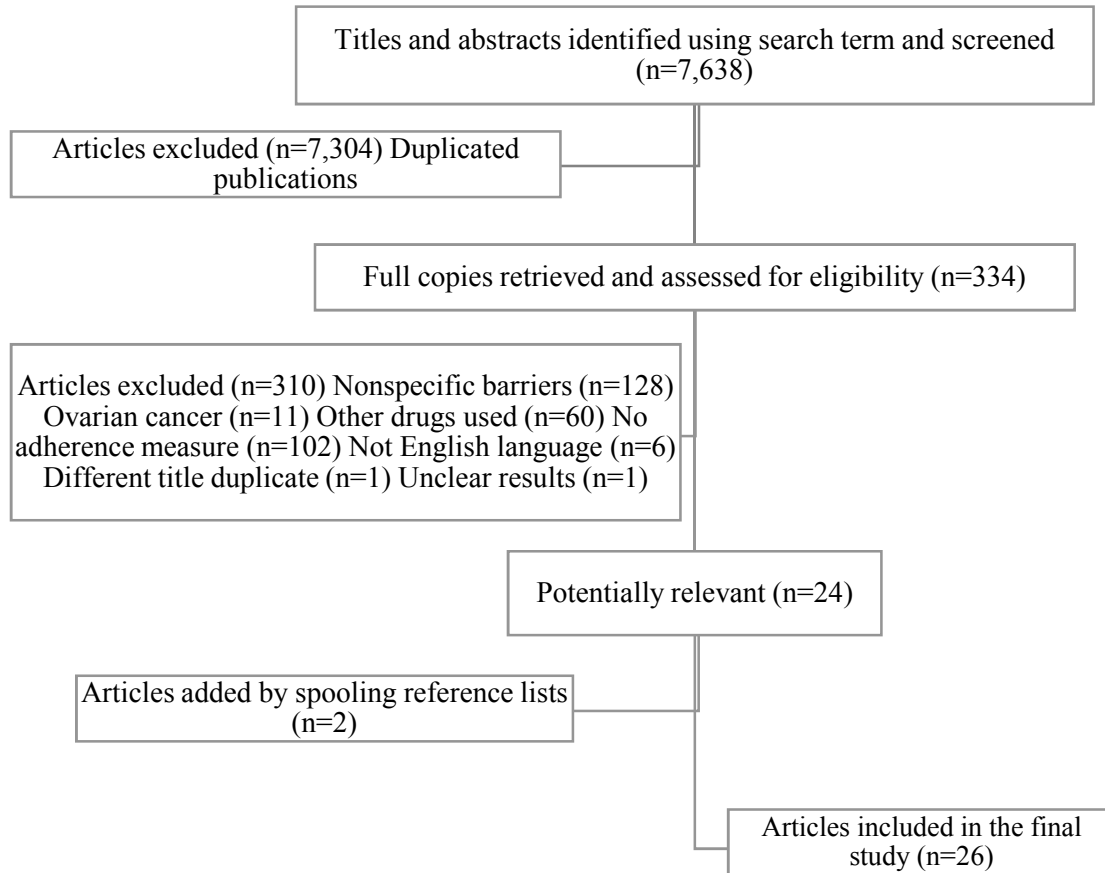


Figure 1 Articles Identified During the Search for Relevant Literature

3. Data extraction.

From each relevant study, information was extracted into a review table.

Variables included names of authors, title of the article, year, country of origin, study design, study duration, age of participants, sample size, stage of cancer, adjuvant drugs used, gender, adherence measures, adherence outcomes, and reasons for non-adherence.

2.1.3 Results

The three electronic databases yielded 7,638 research articles (CINAHL = 6,035, PsycINFO = 978, PubMed = 625) (Figure 1). After manual screening of the articles' titles and abstracts, a total of 7,304 articles were excluded; 2,513 were duplicate publications, and 4,791 were irrelevant. Of the remaining 334 full articles retrieved for eligibility, 24 met the inclusion criteria and were included in the review. Reference lists of the 24 articles were reviewed, and two more articles were identified for a total of 26 articles used. The majority of the included studies were conducted in the United States (n = 14) and published from 2001-2011 (n = 25). With the exception of two studies that included men, all other studies were conducted with only female participants because of the nature of the breast cancer diagnosis. Sample sizes varied greatly, ranging from 26-22,160 participants. Participants' ages ranged from 16-95 years, and the study duration ranged from 12 months to five years. Most studies evaluated the reasons for non-adherence to TAM therapy exclusively (n = 15). Only two studies evaluated non-adherence to AIs exclusively. Nine studies included both types of adjuvant therapies. Studies primarily used self-report questionnaires and abstraction of the patients' medical records to collect data on non-adherence. Two studies collected adherence data through direct interviews with participants, and two studies evaluated the reliability of data-collecting tools with suggestions for using an additional confirmatory assessment tool (Atkins & Fallowfield, 2006) (Lash, Fox, Westrup, Fink, & Silliman, 2006).

Reasons for non-adherence were grouped into five dimensions (i.e., patient-related factors, therapy-related factors, healthcare system factors, socioeconomic factors, and disease factors) based on the World Health Organization (2003) report on medication

adherence. Seventeen individual themes of medication factors were recorded in 26 studies (Table 1).

1. Patient-related factors.

Six patient-related factors were found, including patients' beliefs toward TAM and AIs, patients' knowledge about the disease, forgetfulness, smoking, age, and race or ethnicity. Negative beliefs and patients' negative perceptions related to TAM and AIs contributed to failure to initiate the medications' regimen (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004; Grunfeld et al., 2005; Lash et al., 2006; Oguntola, Adeoti, & Akanbi, 2011; Pellegrini et al., 2010). In a study conducted by Pellegrini et al. (2010) to assess women's perceptions and experience toward adjuvant TAM therapy, the women who were interviewed about their TAM regimen had branded the TAM therapy as "hormone treatment" and "anti-hormonal." In that scenario, the women cited their past negative experiences with hormone-based contraceptives as the primary reason for their refusal to initiate or adhere to ongoing TAM therapy. A lack of information (e.g., how the disease develops, effective ways to manage the disease, specific information about the medication prescribed such as dose specification, duration specification, timing specification) was found to be a significant barrier in medication adherence (Pellegrini et al., 2010; Ziller et al., 2009). Forgetfulness was acknowledged as the single most important factor in medication non-adherence (Atkins & Fallowfield, 2006; Grunfeld et al., 2005; Kirk & Hudis, 2008; Murthy, Bharia, & Sarin, 2002; Waterhouse, Calzone, Mele, & Brenner, 1993). One study found that patients who smoked were less likely to be adherent to the therapy (Maurice, Howell, Evans, O'Neil, & Scobie, 2006). Twelve articles found that patients younger than age 45 years or older than age 85 years exhibited

higher rates of TAM non-adherence (Atkins & Fallowfield, 2006; Hershman et al., 2010; Huiart, Dell'Aniello, & Suissa, 2011; Kahn, Schneider, Malin, Adams, & Epstein, 2007; Ma et al., 2008; McCowan et al., 2008; Neugut et al., 2011; Oguntola et al., 2011; Owusu et al., 2008; Partridge, Wang, Winer, & Avorn, 2003; Sedjo & Devine, 2011; van Herk-Sukel et al., 2010). In Nekhlyudov et al.'s (2011) study, women older than age 60 years were found to be less compliant than other age groups. Five studies found that minority patients were less adherent than their Caucasian counterparts (Bhosle, 2007; Hershman et al., 2010; Ma et al., 2008; Neugut et al., 2011; Partridge et al., 2003).

2. Therapy-related factors.

Four therapy-related factors (i.e., therapy duration, side effects, additional prescribed medications, and perceived interference) were found to help explain why women with breast cancer failed to adhere to adjuvant TAM and AI therapies. The long duration of therapy interfered with medication persistence. In one study, patients found a five-year TAM regimen to be too long (Bramwell et al., 2009). Nine of the studies found that unpleasant side effects (e.g., hot flashes, vaginal bleeding, interrupted menstrual cycles, nausea with vomiting, body weakness) altered patients' compliance (Bramwell et al., 2009; Demissie, Silliman, & Lash, 2001; Fink et al., 2004; Grunfeld et al., 2005; Kahn et al., 2007; Kirk & Hudis, 2008; Lash et al., 2006; Oguntola et al., 2011; Owusu et al., 2008). Two studies found that an increased number of prescriptions was associated with an increased adherence rate (Lash et al., 2006; Maurice et al., 2006). Those results contradicted two other studies that found that a greater number of daily doses and number of concurrent medications were associated with non-adherence (McCowan et al., 2008; Neugut et al., 2011). One study found that patients who perceived that TAM or AI

treatment interfered with their lifestyles and abilities to function normally led to ceasing treatment (Bramwell et al., 2009).

3. Healthcare system factors.

Only one healthcare system factor was found. The patient/ provider relationship appeared to play a significant role in adherence to TAM and AIs. A good relationship between the patient and healthcare provider was found to have a positive impact on adherence rates (Güth et al., 2008; Kahn et al., 2007; Kirk & Hudis, 2008; Partridge et al., 2003; Pellegrini et al., 2010; Sedjo & Devine, 2011).

4. Socioeconomic factors.

Four socioeconomic factors (i.e., medication cost, work complexity, religious practices, and marital status) have been observed as reasons for poor adherence to TAM and AIs. Cost of medications may be significant enough to cause unintentional non-adherence among patients with economic problems (Kirk & Hudis, 2008; Neugut et al., 2011; Oguntola et al., 2011; Sedjo & Devine, 2011). In one study, a burdensome work schedule was associated with decreased adherence rates. Type of occupation also was a reason for medication non-compliance because being outside of the home and traveling may have altered adherence rates (Oguntola et al., 2011). Religious practices were found to be a reason for non-adherence, because fasting on specific days during the year prevented patients from adhering to their treatment (Murthy et al., 2002). Two studies found marital status to be a barrier for medication adherence; being unmarried was associated with a higher probability of medication non-adherence and having a family support network was reported to be a facilitator of adherence (Hershman et al., 2010; Neugut et al., 2011).

5. Disease-related factors.

Two disease-related factors (i.e., comorbidities and disease stage) were found. Comorbid illnesses, such as diabetes and hypertension, are a common problem that may cause poor adherence to TAM and AIs therapies (Hershman et al., 2010; Neugut et al., 2011; Oguntola et al., 2011; Owusu et al., 2008; Partridge et al., 2003; Sedjo & Devine, 2011; Herk-Sukel et al., 2010). In two studies, the patients' stage of breast cancer was found to be a significant reason for non-adherence to TAM or AIs, with greater non-adherence associated with later disease stages (Ma et al., 2008; Oguntola et al., 2011).

Table 1 Studies Assessing Reasons for Non-adherence to TAM or AIs

Study	Design	Length (Years)	Sample	Non-adherence Rate		Measure
				TAM	AI	
Atkins & Fallowfield, 2006	Semi structured interview	–	131 patients with a median age of 59.4 years	54%	61%	SR
Bhosle, 2007	Retrospective cohort	1	206 pairs of patients with stage I–IV cancer, with a median age of 66.6 years	34%	29%	MPR
Bramwell et al., 2009	Randomized, controlled trial	5	672 patients with stage I, II, and IIIA cancer, with an age range of 29–58 years	31%	–	RxRR
Demissie et al., 2001	Prospective cohort	3	303 patients with stage I–II cancer, aged 55 years or older	15%	–	SR
Fink et al., 2004	Cohort	2	597 patients with stage I–III cancer, aged 65 years or older	17%	–	SR
Grunfeld et al., 2005	Survey	2.75	110 patients with a median age of 56.3 years	13%	–	MARS-5

Güth et al., 2008	Follow-up	5	325 patients (n = 206 TAM) with stage I–III cancer, with a median age of 67.3 years	11%		MR
Hershman et al., 2010	Cohort	4.5	8,769 patients with stage I–III cancer, with a median age of 62 years	30%	28% (year 1) 50% (year 5)	RxRR
Huiart et al., 2011	Cohort	5	13,479 participants with age of 62 years	31%	19%	MPR
Kahn et al., 2007	Prospective cohort	4	881 patients with stage I–II cancer, with an age range of 21–80 years	21%	–	SR
Kirk & Hudis, 2008a	Survey	–	542 patients (n = 7 male) with stage I–IV cancer, with an age range of 21–80	43%		SR
Lash et al., 2006	Follow-up	5	462 patients with stage I–IIIA cancer, aged 65 years or older	31%	–	SR
Ma et al., 2008	Retrospective cohort	5	1,769 patients aged 54 years	37%	–	SR, RxRR
Maurice et al., 2006	Case-control trial	5	533 patients aged 48 years	29%	–	MEMS

McCowan et al., 2008	Cohort	5	2,080 patients with stage I–IV cancer, with a median age of 61.4 years	20%	–	RxRR
Murthy et al., 2002	Survey	5	53 patients	62%	–	SR
Nekhlyudov et al., 2011	Cohort	5	2,207 patients with early-stage cancer, aged 18 years or older	> 70%		MPR
Neugut et al., 2011	Retrospective cohort	2	22,160 patients with early-stage cancer, aged 50 years or older	–	9%– 10%	RxRR
Oguntola et al., 2011a	Cohort	1	115 patients (n = 6 male) with stage I–IV cancer, aged 45 years or younger and 65 years or older	25%	–	SR
Owusu et al., 2008	Cohort	5	961 patients with stage I–IIB cancer, aged 65 years or older	49%	–	RxRR
Partridge et al., 2003	Cohort	4	2,378 patients with early-stage cancer, aged 75 years	25% (year 1) 50% (year 4)	–	RxRR

Pellegrini et al., 2010	Qualitative, semi-structured interview	–	34 patients with early-stage cancer, aged from 35–65 years	18%	–	SR
Sedjo & Devine, 2011	Retrospective cohort	1	13,593 patients, with a median age of 55.5 years	–	23%	MPR
van Herk-Sukel et al., 2010	Cohort	5	1,451 patients with stage I–IIIA cancer, aged 35 years or younger and 70 years or older	44%–51%		RxRR
Waterhouse et al., 1993	Prospective cohort	5.8	26 patients with stage I–IV cancer, aged from 42–86 years	17% PC; 29% MEMS	–	SR, PC, MEMS
Ziller et al., 2009	Retrospective cohort	1	100 patients (n = 72 AIs, n = 65 TAM, n = 39 ANA)	0% SR; 20% MPR	0% SR; 31% MPR	SR, MPR
<p>a Studies included male participants. AI—aromatase inhibitor; ANA—anastrozole; MARS-5—Medication Adherence Report Scale; MEMS—Medication Event Monitoring System; MPR— medication possession ratio; MR—medical record; PC—pill count; RxRR—prescription refill records; SR—self-report questionnaire; TAM—tamoxifen.</p>						

2.1.4 Discussion

Most published studies reviewed the reasons for non-adherence to adjuvant TAM but not AIs. No single study independently explained the reasons for non-adherence to the therapies because factors contributing to non-adherence are multifaceted. No single factor can clearly explain non-adherence. Nurses play a key role in addressing identified contributing factors. Nurses can help patients find financial aid to fill prescriptions, manage side effects, improve self-management of comorbidities, facilitate the patient/provider relationship, and help patients identify strategies to address forgetfulness or change perceptions and beliefs. At a global level, certain therapies may become more important predictors of non-adherence. For example, most patients with breast cancer living in developed countries have adequate access to medications because most have medical or commercial insurance coverage, suggesting that cost may not be a detrimental factor. However, in a study done in an African population, financial constraints and side effects were the most viable reasons for non-adherence (Oguntola et al., 2011). When designing health interventions to improve adherence, the relative weight of each factor should be carefully assessed and considered within a larger environmental context.

The importance of decision making in TAM and AI adherence should not be underestimated. One study found that patients with breast cancer who are given adequate medical support are more likely to adhere to recommended regimens (Kahn et al., 2007). Nurses can help facilitate patient-centered healthcare services, which may positively influence adherence. In addition, nurses can support patients' involvement in the decision-making process to initiate TAM therapy.

The main limitation in almost all of the reviewed studies was that most data were self-reported. Waterhouse et al. (1993) questioned the validity of the method, citing it as relatively subjective and erroneous. In an effort to investigate adherence behavior to oral TAM, Waterhouse et al. (1993) argued that conventional methods of collecting non-adherence data, such as self-reporting and pill counting, significantly overrate the extent to which patients adhere to their regimens and suggested the use of microelectronic monitoring to track patients' adherence behaviors. That monitoring system can be used to obtain confirmatory or complementary data. The integration of microelectronics into the TAM drug package can effectively and continuously monitor patient interaction with the drug package. Although it does not guarantee data on drug entry into the body, it can effectively provide data on missed doses and dosage timing. In a study of 26 patients on TAM, comparisons were made using three parallel measuring tools: patient self-reporting questionnaires, remainder pill counting, and the Medication Event Monitoring System (MEMS) (Waterhouse et al., 1993). MEMS includes a microprocessor in the cap of a bottle that records each time it is opened; date, time, and duration of bottle openings are downloaded for later retrieval on a computer. TAM adherence data collected from patients' self-reporting was highest, followed by remainder pill counting, with MEMS data indicating the lowest adherence. Those findings suggest that conventional self-reporting and remainder pill counting may not be the most reliable methods. In the current review, it became apparent that some factors related to non-adherence were much more important than others. However, the reasons for non-adherence to TAM and AI breast cancer therapies are multifaceted because no single study established an independent factor that effectively explained the frequently observed non-adherence to

the two most common breast cancer therapies. The authors' findings indicate that many barriers to adherence could be amenable to change if targeted with mHealth interventions. Implementing mHealth has the potential to enable behavior change and improve health outcomes (Free et al., 2013; Qiang, Yamamichi, Hausman, Altman, & Unit, 2011; Thirumurthy & Lester, 2012). The cost of mobile phone use has declined dramatically, and availability of easy-to-use software programs has increased. For example, SMS reminders may readily help patients to adhere to treatment by overcoming forgetfulness. SMS alerts can reach across geographic boundaries and be used to educate and improve patient knowledge. mHealth interventions designed by nurses or other healthcare professionals can be viewed as a way to support patients and healthcare providers in a convenient and cost-effective way (Mair, Hiscock, & Beaton, 2008).

2.1.5 Limitations

Limitations of the current review include a focus on English-language articles and its focus on only TAM and AI for breast cancer treatment in the adjuvant setting. The focus on English-language articles may have omitted some relevant reports. Use of TAM for breast cancer prevention was not explored, and additional factors may exist that uniquely affect non-adherence in that context.

2.1.6 Conclusion

Despite the proven benefits of TAM and AIs for breast cancer treatment, many patients with breast cancer adhere poorly to recommended regimens and others decline to initiate the therapies. Reasons for non-adherence are multifaceted, but a number of factors (e.g., patient/provider relationship, forgetfulness, fear of side effects, burden, additional prescribed medications, treatment interfering with lifestyle, scheduling

problems, patient beliefs and knowledge) may be improved by using mHealth interventions. Future studies should be performed that incorporate health information technology to evaluate the necessary steps and measures that can be taken to address the barriers to adherence.

2.2 The Impact of Information Technology on Behavior Change

2.2.1 Introduction

Patient engagement is currently considered the cornerstone of the healthcare system revolution for its positive impact on health outcomes and healthcare costs (Barello, Graffigna, Vegni, & Bosio, 2014; Coulter et al., 2008). A growing body of evidence demonstrates that lack of patient engagement is a major contributor to preventable deaths. In fact, it is estimated that 40% of deaths in the United States are caused by modifiable behavioral issues, including smoking, obesity, poor blood sugar control, poor blood pressure control, inadequate exercise, medication non-adherence, and neglect in attending follow-up medical appointments (Parekh, 2011). As a result, patients must be encouraged to become more involved with managing their own care. Frequent, real-time communication and feedback are essential in supporting health behavior change and empowering patient engagement in the healthcare process (Sundiata, Shonu, Thomas, & Angela, 2012). However, the traditional model of care delivery, a face-to-face interaction with an expert or trusted healthcare provider, can be implemented only with a small number of patients and thus has limited impact and limited reach (Bickmore & Giorgino, 2004). In an effort to reach and engage larger numbers of patients, researchers and clinicians have begun exploring the role of information technology (IT) platforms in patient engagement and health behavior change interventions (Bickmore & Giorgino,

2004; Vollmer et al., 2011). It is assumed that face-to face interaction in the traditional model can be mimicked by peer-to-peer or peer group support in social media.

IT platforms are being embraced as a way to enhance patient engagement in the healthcare process, improve quality of care, support healthcare safety, and provide cost-effective health services for patients (Or & Karsh, 2009; Sutcliffe et al., 2011; Vollmer et al., 2011; Webb, Joseph, Yardley, & Michie, 2010). Numerous IT platforms are used to motivate patient engagement in health behavior change including short message service (SMS)-capable mobile devices, Internet-based interventions, social media, and other online communication tools (de Jong, Ros, & Schrijvers, 2014; Martyn & Gallant, 2012; Winbush, McDougle, Labranche, Khan, & Tolliver, 2013). Previous systematic reviews have evaluated the potential benefit of IT platforms in managing different health conditions and how these platforms have been used to actively engage patients and change unhealthy patient behavior. A systematic review conducted to assess the effectiveness of IT platforms on physical activity and dietary behavior change found that 51% of studies showed positive results, although a significant proportion of the studies showed no significant effect (Norman et al., 2007). The reviewed interventions tended to focus on specific technology (e.g., desktop applications), while mobile devices, such as mobile phones and text messaging devices were not included. Similarly, Webb et al. reviewed 85 studies on the impact of Internet-based interventions on health behavior change and found small but significant effects on health-related behavior, especially with regards to interventions grounded in behavioral theory. Although the review mentioned that the effectiveness of Internet-based interventions was enhanced by using additional IT

methods, such as text messaging (SMS), it did not focus on the distinction between these different interventions (Webb et al., 2010).

In addition, a meta-analysis performed to investigate the effectiveness of Web-based interventions on health behavior changes found that Web-based interventions improve patient outcomes. This particular meta-analysis, however, referred only to Web-based interventions in specific problem areas and focused on a relatively narrow range of technologies (Wantland, Portillo, Holzemer, Slaughter, & McGhee, 2004). A recent systematic review that investigated the effectiveness of the IT platform on self-management among diabetic patients showed positive effects in 74% of studies (El-Gayar, Timsina, Nawar, & Eid, 2013). Another research study showed that successful health behavior interventions may contribute to understanding of health behavior theories and their appropriate use (Glanz & Bishop, 2010). Mobile-based interventions and web-based interventions developed based on health behavior theories are more likely to effectively change patient health behavior and maintain behavior change than non-theory-based interventions (DiClemente, Crosby, & Kegler, 2009; Ellis et al., 2004; Patrick et al., 2014; Webb et al., 2010).

Basing IT interventions on behavior theories can help test and detect why interventions succeed or fail (Rothman, 2004). Health behavioral theories can identify key determinants of the target behaviors and identify behavior change strategies essential to obtain desired health outcomes; this knowledge can then be transformed into specific behavioral strategies that patients can adapt in their daily life (Rothman, 2004). Conclusions drawn from these reviews are important; they provide insights but no clear answers about the effectiveness of IT platforms on patient engagement and behavior

change. They do not address which interventions are used most or are most effective with which theory or model when it comes to improving patients' health behaviors and patient engagement. IT platforms generally can have high potential benefits and some proven effects; however, specific components in several health conditions associated with success remain unclear. To better understand how to build a successful intervention that can engage patients to change their behavior meaningfully, we performed a systematic review. Review aims were to systematically determine (1) the impact of IT platforms used to promote patient engagement and to effect change in health behaviors and health outcomes, (2) behavioral theories or models applied as bases for developing these interventions and their impact on health outcomes, (3) different ways of measuring health outcomes, (4) usability, feasibility, and acceptability of these technologies among patients, and (5) challenges and research directions for implementing IT platforms to meaningfully impact patient engagement and health outcomes.

2.2.2 Methods

1. Search strategy and data source.

Electronic literature searches were performed using four databases: PubMed, Web of Science, PsycINFO, and Google Scholar. Google Scholar was searched because it had sufficiently wide coverage to be used instead of several databases (Howland, Wright, Boughan, & Roberts, 2009; Kennedy et al., 2012; Walters, 2007). The reference lists of retrieved articles from searches were screened for additional articles. Searches used the following medical subject headings (MeSH) terms in various combinations: patient engagement, health, promotion, behavior, digital, technology, email, Internet, web-based, cell phone, social media, computer, and intervention.

2. Inclusion and excluding criteria.

The following criteria were used to select the articles: (1) all types of study designs published in scientific journals between 2000 and December 2014 were included, excluding conference proceedings, book chapters, reviews, dissertations, and protocols. (2) Studies that evaluated and reported the impact of health information technology platforms on patients' health outcome, (3) studies that focused on disease management rather than more general health promotion including but not limited to patient education, symptom monitoring, medication adherence, diet, and physical activity, (4) studies that addressed patient engagement and health-related behavior change through the use of IT platforms such as social networking sites, mobile telephony, video and teleconferencing, email, SMS, and electronic monitoring, (5) studies that explored different factors affecting patient engagement and health behavior change were excluded, (6) studies that were published in languages other than English were excluded, (7) studies where the patient was not the main actor (i.e., studies that were clinician-focused), and (8) the methodological quality of articles was evaluated to establish their inclusion in the review using 10 items adopted from Critical Appraisal Skills Program (CASP) (Campbell et al., 2003; Trust, 2002). The criteria that were used in the quality assessment included (1) study name, (2) aims clearly stated, (3) appropriate research design, (4) appropriate recruitment strategy, (5) theories clearly stated, (6) usability tested within the study, (7) patient engagement part of study, (8) appropriate data collection method, (9) data analysis sufficiently rigorous, and (10) findings clearly stated. After the completion of the methodological quality assessment, the studies that met the criteria for the categories of

“good” were reviewed (i.e., bad=0-33%, satisfactory=34-66%, and good=67-100%) (Davids & Roman, 2014).

3. Data extraction.

Two investigators independently reviewed the titles and then abstracts. The same investigators read and screened for full text eligibility. Data extraction was carried out by one reviewer and was rechecked for accuracy by another reviewer. The reasons for exclusion were recorded. Discrepancies were resolved by joint probability of agreement (0.98) (El-Gayar et al., 2013). A meta-analysis was not feasible due to the varying data collection methods and outcome measures. Therefore, eligible studies were broken down and evaluated in a narrative format using some statistical analysis when feasible and summarized systematically according to the following key information abstracted from them: study details (including author name, year, country, and study design); study characteristics (including sample size and condition/disease); intervention details (including technology used and duration); and outcome details (including direct and indirect assessment methods); and impact of intervention, usability assessment, patient engagement, and theory used in interventions classified according to Leventhal (biomedical model, behavioral learning, communicative, cognitive theory, and self-regulative) (De Geest & Sabaté, 2003; Leventhal & Cameron, 1987; Munro, Lewin, Swart, & Volmink, 2007). The outcomes variable was classified into (1) positive impact in which health information technology platform was associated with improvement in one or more aspects of care and (2) no impact or no noticeable improvement or change in health outcomes. This was assessed based on the overall conclusion made by the authors of each study. Most studies used statistical methods to test hypotheses or describe

quantitative findings. Patient engagement was measured based on the overall conclusion. This was usually measured by timed patient log-ins, communication with the healthcare provider via secure message, or data download.

2.2.3 Results

1. Search and selection results.

Figure 2 shows the flow chart that describes the process of identifying the relevant literature. A separate comprehensive search using four databases yielded 2235 articles. Following removal of duplicates, our search identified 786 potentially relevant articles. These were scanned keeping 219 papers for full reading at full text level, of which 59 were screened and rejected, leaving 160 studies to be included in the review. Ten additional papers were included from the reference lists of retrieved articles. A total of 170 articles matched the initial search criteria.

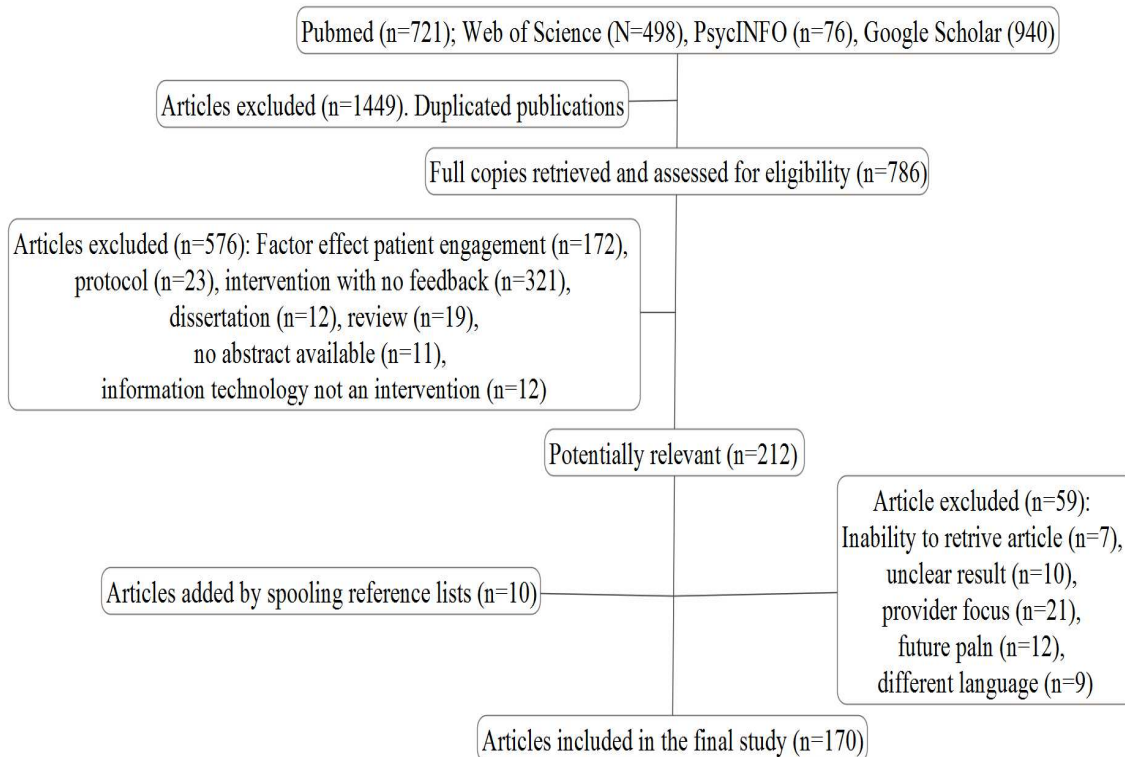


Figure 2 Flow Diagram of Included and Excluded Studies

2. Article characteristics.

Different categories of IT platforms were identified including Internet-based interventions (50.6%, 86/170), mobile-based interventions (25.9%, 44/170), social media (9.4%, 16/170), video game technology (3.5%, 6/170), and telemonitoring (10.6%, 18/170). Publication years ranged from 2000 to 2014, with an overall increase in articles published more recently (21.8%, 37/170 in 2014). The majority of studies were implemented in the United States (54.7%, 93/170). With respect to the different targeted disorders, hormonal disorders were most frequently targeted (22.4%, 38/170 studies, e.g., diabetes). The literature was dominated by randomized controlled trials (65.9%, 112/170). The duration of these studies ranged from 1 week to 48 months, and sample sizes ranged from 1-22,337 subjects. Articles included in this review were categorized in five topics based on study aims: impact of IT platform on health outcomes, patient engagement in health behavior change, theory of health behavior, ways to assess health outcomes, and usability assessment (Table 2).

Table 2 Summary of the Review Results Based on Types of IT Platforms.

Health condition, n (%)	Internet (n=86)	Phone (n=44)	Video- game (n=6)	Social network (n=16)	Tele- monitoring (n=18)
Bone, joint, and muscle disorders	3 (3)				
Brain, spinal cord, and nerve disorders	7 (8)	1 (2)	2 (33)	1 (6)	1 (6)
Cancer	5 (8)	2 (5)	1 (17)	2 (13)	2 (11)
Disorders of nutrition and metabolism	13 (15)	4 (9)	1 (17)	2 (13)	1 (6)
Ears, nose, and throat disorders		1 (2)			

Eye disorders					1 (6)
Health hazard	5 (6)	6 (14)			
Heart and blood vessel disorders	5 (6)	3 (7)			6 (33)
Hormonal disorders	20 (23)	11 (25)		4 (25)	3 (17)
Immune disorders	4 (5)	5 (11)		1 (6)	1 (6)
Lung and airway disorders	2 (2)	1 (2)	1 (17)	1 (6)	1 (6)
Mental health disorders	12 (14)	4 (9)	1 (17)	2 (13)	2 (11)
Skin disorders		1 (2)		1 (6)	
Women's health issues	3 (3)	1 (2)			
Not specified	7 (8)	4 (9)		2 (13)	
Country, n (%)					
Australia	7 (8)	5 (42)			
Austria					1 (6)
Bangladesh		1 (2)			
Canada	4 (5)				2 (11)
Chile	1 (1)				
China		1 (2)			
France		1 (2)			
Germany	3 (3)				
Israel				1 (6)	
Italy	1 (1)	1 (2)			
Japan	1 (1)			1 (6)	
Kenya		1 (2)			
Korea	1 (1)	1 (2)			1 (6)

Malaysia		1 (2)			
Netherlands	4 (5)		1 (17)		2 (11)
New Zealand		2 (5)			
Norway		1 (2)			
Poland					1 (6)
Russia		1 (2)			
Slovenia	1 (1)				
South Korea	2 (2)	4 (5)			
Spain		1 (2)			1 (6)
Sweden	2 (2)				
Switzerland					1 (6)
Taiwan	1 (1)				
United Kingdom	5 (6)	7 (16)	1 (17)		1 (6)
United States	53 (62)	14 (32)	4 (67)	14 (88)	8 (44)
Victoria		1 (2)			
Vietnam		1 (2)			
Study design, n (%)					
Randomized controlled trial	55 (64)	34(30)	2 (33)	7 (44)	14 (78)
Case study	2 (2)	1 (2)	2 (33)	2 (13)	
Cohort study	10 (12)	4 (5)	1 (17)	1 (6)	3 (17)
Cross-sectional analysis	8 (9)	1 (2)		5 (31)	1 (6)
Quasi-experimental trial	11 (13)	4 (5)	1 (17)	1 (6)	
Ways to measure health outcomes, n (%)					
Direct	28 (33)	20 (45)	3 (50)	1 (6)	6 (33)
Indirect	58 (67)	24 (55)	3 (50)	15 (94)	12 (67)

Impact of technology, n (%)					
Yes	75 (87)	41 (93)	6 (100)	13 (81)	16 (89)
No	11 (13)	3 (7)		3 (19)	2 (11)
Usability assessment, n (%)					
Yes	38 (44)	8 (18)	1 (17)	8 (50)	3 (17)
No	48 (56)	36 (82)	5 (83)	8 (50)	15 (83)
Patient engagement, n (%)					
Yes	68 (79)	38 (86)	6 (100)	13 (81)	16 (89)
No	18 (21)	6 (14)		3 (19)	2 (11)
Theory of behavior change, n (%)					
Biomedical theory (chronic model)	1 (1)				1 (6)
Behavioral learning theory	3 (3)				
Communication theories	5 (6)	5 (11)	2 (13)		
Cognitive theories	40 (47)	9(20)	2 (33)	2 (13)	1 (6)
Self-regulatory	6 (7)		1 (17)	2 (13)	
Not specified	31 (36)	30 (69)	3 (33)	10 (63)	16 (88)
Sample size, n	Min.	1	2	6	51
	Max.	13564	22337	375	1754
Duration	Min.	1 m	1 m	1 m	1 w
	Max.	48 m	16 m	3 m	36 m
	n/s	3	1	1	3

m=month, w=week, n/s=Not specified.

3. Impact of information technology platforms on health outcome.

Overall, IT platforms have been shown to improve health behavior among different disease categories (88.8%, 151/170), although the majority of the positive

impact has been shown among hormonal disorders (20.6%, 35/170) (Table 3). Among studies utilizing Internet-based platforms, 87% (75/86) of studies showed a significant impact on health outcomes. Studies also showed that the use of Internet-based tailored weight control programs was correlated with significant increases in weight loss (Adachi et al., 2007; Johnston, Massey, & DeVaneaux, 2012) and walking distance ($P < .05$) (Napolitano et al., 2003).

Similarly, mobile-based platforms showed significant effects on health outcomes (91%, 40/44). For example, a study examined use of text messages among patients with diabetes and found a significant decrease in HbA1C level, improved medication adherence, and decreased in emergency service use (Arora, Peters, Burner, Lam, & Menchine, 2014). Social media showed a positive impact on health outcomes (81%, 13/16). For example, one study indicated that Twitter usage among cancer patients was a valuable medium for sharing information, discussing treatments, and also acted as a psychological support (Sugawara et al., 2012). The use of Facebook has also been found to help improve asthma care (Winstead-Derlega et al., 2012).

As such, this review found that 100% (6/6) of studies had a positive impact on patient health behavior when implementing a video game as an intervention to change health behavior. A study concluded that video games can be implemented successfully among hyperfunctional voice disorder as a “voice therapeutic protocol,” a voice and speech therapy program including a set of vocal tasks using syllable repetitions and chanting of songs and phrases (King, Davis, Lehman, & Ruddy, 2012).

Furthermore, the literature showed that telemonitoring improved health outcomes (89%, 16/18). One telemonitoring-based study assessed the effects of a glucose

monitoring system on HbA1c levels in diabetic patients and found that usage of this system was correlated with a significant decrease in HbA1c ($P=.001$) (Tildesley, Mazanderani, & Ross, 2010). Another study evaluated the impact of home-based telemonitoring on patients with heart failure and showed a significant correlative improvement in patients' health outcomes (Kwon et al., 2004; Scherr et al., 2009).

In contrast, 11% of studies (19/170) showed no impact of using IT platforms on health behavior. Among studies using Internet-based platforms, 13% (11/86) did not find significant results. One study using a Web-based behavior change program found no differences in smoking abstinence rates at 3- and 6-month follow-up assessment (Danaher, Boles, Akers, Gordon, & Severson, 2006) and no maintenance of weight loss in an Internet-based intervention group compared to the study's control group (Steele, Mummery, & Dwyer, 2007). Also, 7% of (3/44) mobile phone studies reported non-significant impact (Arora et al., 2014; Benhamou et al., 2007; Chen, Fang, Chen, & Dai, 2008; Song et al., 2013). Two mobile phone platform studies did not find a significant reduction in HbA1c level among diabetic patients when SMS text messaging was used to manage their healthcare ($P<.10$) (Arora et al., 2014; Sugawara et al., 2012).

Moreover, 18% (3/16) of studies showed undesirable effects from using social media (Kaplan, Salzer, Solomon, Brusilovskiy, & Cousounis, 2011; Thackeray, Crookston, & West, 2013; Winstead-Derlega et al., 2012). For instance, Kaplan et al. found that psychiatric patients who participated in Internet peer support reported higher levels of distress compared to those who did not participate (Kaplan et al., 2011). The literature shows that 12% (2/18) of telemonitoring studies had no effect on health outcomes. One particular study found significant changes in neither readmission rate

(Wakefield et al., 2008) nor medication adherence (Ramaekers, Janssen-Boyne, Gorgels, & Vrijhoef, 2009) among patients with heart failure.

Table 3 Impact of IT Platforms Among Different Disorders

Disorders	Internet		Mobile		Social Media		Tele-monitoring		Video game			
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	T Yes	T No	T
Bone, joint, and muscle	3(3)									3 (2)		3 (2)
Brain, spinal cord & nerves	7(8)		1(2)			1 (6)	1(6)		2 (33)	11 (6)	1 (1)	12 (7)
Cancer	5 (6)		2 (5)		2 (13)		2 (11)		1 (17)	12 (7)		12 (7)
Nutrition and metabolism	10 (12)	3 (3)	4 (9)		2 (13)		1 (6)		1 (17)	18 (11)	3 (3)	21 (12)
Ears, nose & throat				1 (2)							1 (1)	1 (1)
Eye							1(6)			1(1)		1 (1)
Health hazard	4 (5)	1 (1)	6 (14)							10 (6)	1 (1)	11 (6)
Heart and blood vessel	4 (5)	1 (1)	3 (7)				4 (22)	2 (11)		11 (6)	3 (2)	14 (8)

Hormonal	19 (22)	1 (1)	9 (20)	2 (5)	4 (25)		3 (17)			35 (21)	3 (2)	38 (22)
Immune system	2 (2)	2 (2)	5 (11)			1 (6)	1 (6)			8 (5)	3 (2)	11 (6)
Lung and airway	2 (2)		1 (2)		1 (6)		1 (6)		1 (17)	6 (4)		6 (4)
Mental health	11 (13)	1 (1)	4 (9)		2 (13)		2 (11)		1 (17)	20 (12)	1 (1)	21 (12)
Not specified	5(6)	2 (2)	4 (9)		1 (6)	1 (6)				10 (6)	3 (2)	13 (8)
Skin			1(2)		1(6)					2(1)		2 (1)
Women's health	3 (3)		1 (2)							4 (2)		4 (2)
Total	75 (87)	11 (13)	41 (93)	3 (7)	13 (81)	3 (19)	16 (89)	2 (11)	6 (100)	151 (89)	19 (11)	170 (100)

T=Total, Yes=positive impact, No=no impact

4. Patient engagement.

In total, 82.9% (141/170) of studies reported improvement in patient engagement after using IT platforms (Table 4). Among Internet-based interventions, 79% (68/86) of studies reported a high level of patient engagement. For example, a research study reported that human immunodeficiency virus patients used the Internet-based intervention a majority of the time to access information and manage their health (Andrade et al., 2005; Shaw & Gant, 2002). Among studies using mobile-based interventions, 86% (38/44) reported improvement in patient engagement. One mobile-based intervention study found that text messaging enhanced successful engagement of

diabetic patients in their own healthcare. Patients were able to use this study's text message system for clinical data queries and communicating with healthcare providers (Franklin, Greene, Waller, Greene, & Pagliari, 2008). Similarly, 81% (13/16) of studies reported that social media was helpful in improving patient engagement. One study found that Facebook provided a forum for reporting personal experiences, asking questions, and receiving direct feedback for people living with diabetes (Thackeray et al., 2013). Another study showed that social media was helpful to individuals with lower patient activation (Magnezi, Bergman, & Grosberg, 2014; McKay, Glasgow, Feil, Boles, & Barrera, 2002; McKay, King, Eakin, Seeley, & Glasgow, 2001). In addition, it was found that video games could enhance patients' active participation in the healthcare process (100%, 6/6). One video game-based study demonstrated that a health-based video game could help build an effective client-therapist relationship, help structure sessions, and improve patient engagement in the therapeutic process (Coyle, Doherty, & Sharry, 2009; Jelsma, Geuze, Mombarg, & Smits-Engelsman, 2014).

Likewise, the literature showed that telemonitoring has been particularly useful for improving patient engagement remotely (88.8%, 16/18) (Chan, Callahan, Sheets, Moreno, & Malone, 2003; Galiano-Castillo et al., 2014; Gray et al., 2000; Kinney et al., 2014; Meiland et al., 2014; Price & Gros, 2014; Španiel et al., 2008), as traditional point-of-care-based ways to monitor patients are costly and difficult to implement (Weinstock et al., 2010). Overall, analysis showed significant correlations between patient engagement in healthcare and the impact of IT platforms ($\chi^2 = 39.8836$, $P < .001$). Only Internet-based platforms had a significant association between patient engagement and impact of technology on outcomes ($\chi^2 = 28.2558$, $P < .001$).

Table 4 Impact of IT Platforms on Patient Engagement

Engagement	Internet		Mobile		Social Media		Tele-monitoring		Video game	T Yes	T No	T
	Y	N	Y	N	Y	N	Y	N	Y			
Yes	66 (88)	2 (18)	36 (88)	2 (67)	12 (92)	1 (33)	15 (94)	1 (50)	6 (100)	135 (63)	6 (32)	141 (83)
No	9 (12)	9 (82)	5 (12)	1 (33)	1 (8)	2 (67)	1 (6)	1 (50)		16 (37)	13 (68)	29 (17)
Total	75 (100)	11 (100)	41 (100)	3	13 (100)	3 (100)	16 (100)	2 (100)	6 (100)	151 (100)	19 (100)	170 (100)

Y=Yes, N=No, Yes=positive impact, No=no impact.

5. Behavior theory

Overall results showed that 47.0% (80/170) of the literature explicitly referenced theory (Table 5). Among Internet-based interventions, 64% (55/86) of studies mentioned the use of behavior theories. Cognitive theories dominated this category (47%, 40/86). Further, 32% (14/44) of mobile-based intervention studies reported use of behavior theories. Cognitive theories were also the most widely used among this category (30%, 13/44) (Brendryen & Kraft, 2008; Franklin et al., 2008; Franklin, Waller, Pagliari, & Greene, 2006; Gold, Lim, Hellard, Hocking, & Keogh, 2010; Granholm, Ben-Zeev, Link, Bradshaw, & Holden, 2011; Hurling et al., 2007; Rodgers et al., 2005; Song et al., 2013; Stacy, Schwartz, Ershoff, & Shreve, 2009).

Moreover, 38% (6/16) of social media studies used behavior change theory. Social support, cognitive, and self-regulatory theories were the only models used in this category (Gabriele, Carpenter, Tate, & Fisher, 2011; Gustafson et al., 2001; Kaplan et al., 2011; Magnezi et al., 2014; Simon et al., 2011; Winstead-Derlega et al., 2012). The analysis showed 50% (3/6) of video-game platforms used behavior change theories, where the cognitive and self-regulatory theories are the only used (Bingham, Lahiri, & Ashikaga, 2012; Kato, Cole, Bradlyn, & Pollock, 2008). Only 11% (2/18) of telemonitoring studies used biomedical and cognitive theories (Green et al., 2008; Read, 2014). Literature showed that 89% (71/80) of studies with behavior theories had a significant impact on health outcomes. Only 11% (9/80) of telemonitoring studies explicitly referenced the use of behavior theories and showed no impact of technology on health outcomes.

The result failed to show any relationship between using behavior theory and the impact of technology on health outcomes ($\chi^2 = 0.008$, $P = .977$). The analysis also found no significant correlative relationship between behavior theory and patient engagement in healthcare ($\chi^2 = 0.3055$, $P = .580479$). However, there was a significant relationship between patient engagement and Internet-based interventions using behavior theories ($\chi^2 = 7.314$, $P = .0068$) (Table 6).

6. Methods to measure health outcomes.

Most studies used indirect ways (such as self-reports) to measure health outcomes (65.9%, 112/170). The literature showed that 57.6% (98/170) of studies showed a positive impact of IT platforms when the health outcomes were assessed using indirect ways. For example, self-reporting was used to assess whether a text message could increase smoking cessation (Rodgers et al., 2005), reduce methamphetamine use among human immunodeficiency virus patients (Reback et al., 2012), and to assess medication adherence among patients with congestive heart failure (Ramaekers et al., 2009). The analysis showed no significant association between ways to measure health outcomes and technology impact ($\chi^2 = 0.5793$, $P = .446603$) (Table 7).

Table 5 Impact of IT Platforms and Theories of Health Behavior

Behavior theory	Internet		Mobile		Social Media		Tele-monitoring		Video- game	T Y	T N	T
	Y	N	Y	N	Y	N	Y	N				
Biomedical theory	1 (1)						1 (6)			2 (1)		2 (1)
Behavioral learning theory	2 (2)	1 (1)								2 (1)	1 (1)	3 (2)
Communication	4 (5)	1 (1)	1 (2)		1 (6)	1 (6)				6 (4)	2 (1)	8 (5)
Cognitive theory	36(42)	4 (5)	12(27)	1 (2)	2 (13)		1 (6)		2 (33)	53(31)	5 (3)	58 (34)
Self-regulatory	5 (6)	1 (1)			2 (13)				1 (17)	8 (5)	1 (1)	9 (5)
Reported theory	48(56)	7 (8)	13(29)	1 (2)	5 (31)	1 (6)	2 (2)		3 (50)	71(42)	9 (5)	80 (47)
Theory not reported	27(31)	4 (5)	28(64)	2 (5)	8 (50)	2 (13)	14(78)	2 (11)	3 (50)	80(47)	10 (6)	90 (53)
Total	75 (87)	11 (13)	41 (93)	3 (7)	13 (81)	3 (19)	16 (89)	2 (11)	6 (100)	151 (89)	19 (11)	170 (100)

T=Total, Y=Yes, N=No, Yes=positive impact, No=no impact. Social cognitive theory (TPB, SOC, TTM, self-efficacy, information motivation, and behavioral skill). V-Game=video-game.

Table 6 Patient Engagement and Theories of Health Behavior

Behavior theory	Patient Engagement, n (%)											
	Internet		Mobile		Social Media		Tele-monitoring		Video-game			
	Y	N	Y	N	Y	N	Y	N	Y	T Y	T N	T
Biomedical theory	1 (1)						1 (6)			2 (1)		2 (1)
Behavioral learning theory	2 (2)	1 (1)								2 (1)	1 (1)	3 (2)
Communication	5 (6)		1 (2)		2 (13)					8 (5)		8 (5)
Cognitive theories	30 (35)	10 (12)	11 (25)	2 (5)	2 (13)		1 (6)		2 (33)	46 (27)	12 (7)	58 (34)
Self-regulatory	4 (5)	2 (2)			2 (13)				1 (17)	7 (4)	2 (1)	9 (5)
Total of used theory	42 (49)	13 (12)	12 (27)	2 (5)	6 (38)		2 (11)		3 (50)	65 (38)	15 (9)	80 (47)
Theory not reported	26 (30)	5 (2)	26 (59)	4 (9)	7 (44)	3 (19)	16 (89)	2 (11)	3 (50)	76 (45)	14 (8)	90 (53)
Total	68 (79)	18 (15)	38 (86)	6 (14)	13 (81)	3 (19)		2 (11)	6 (100)	141 (83)	29 (17)	170 (100)

T=Total, Y=Yes, N=No, Yes=positive impact, No=no impact, Cognitive theory=(TPB, SOC, TTM, self-efficacy, information motivation, and behavioral skill).

Table 7 Impact of IT Platforms and Methods to Measure Health

Methods to Measure Health Impact of Information Technology Platforms, n (%)												
Outcomes	Internet		Mobile		Social Media		Tele-monitoring		Video game			
	Y	N	Y	N	Y	N	Y	N	Y	T Y	T N	T
Direct	25 (29)	3 (3)	(41)	2 (5)	1 (6)		6 (33)		3 (50)	53 (31)	5 (3)	58 (34)
Indirect	50 (58)	8 (9)	23 (52)	1 (2)	12 (75)	3 (19)	10 (56)	2 (11)	3 (50)	98 (58)	14 (8)	112 (66)
Grand Total	75 (87)	11 (13)	41 (93)	3 (7)	3 (81)	(19)	16 (89)	2 (11)	6 (100)	151 (89)	19 (11)	170 (100)

T=Total, N=No, Yes=positive impact, No=no impact

7. Usability assessment.

Only 33.5% (57/170) of studies assessed the usability of IT platforms. Of those, the majority were considered by authors to be usable (89%, 51/57). Specifically, 75% (28/37) of Internet-based IT intervention studies showed positive health outcomes with usable interventions (Agarwal, Anderson, Zarate, & Ward, 2013; Bantum et al., 2014; Barnabei, O'Connor, Nimphius, Vierkant, & Eaker, 2008; Botts, Horan, & Thoms, 2011; Boudreaux et al., 2012; Buhrman et al., 2013; Claborn, Leffingwell, Miller, Meier, & Stephens, 2014; Feldman, Murtaugh, Pezzin, McDonald, & Peng, 2005; R. Glasgow et al., 2011; Glynn, Randolph, Garrick, & Lui, 2010; Gustafson et al., 2005; Gutierrez, Kindratt, Pagels, Foster, & Gimpel, 2014; Hasin, Aharonovich, & Greenstein, 2014; Irvine, Gelatt, Seeley, Macfarlane, & Gau, 2013; Iverson, Howard, & Penney, 2008; Krishna et al., 2003; Lee, Gray, & Lewis, 2010; Lewis, Gray, Freres, & Hornik, 2009; Lorig, Ritter, Laurent, & Plant, 2006; Osborn, Mayberry, Wallston, Johnson, & Elasy, 2013; Pandolfi et al., 2014; Rooke, Gates, Norberg, & Copeland, 2014; Ross, Moore, Earnest, Wittevrongel, & Lin, 2004; Steele et al., 2007; Urowitz et al., 2012; Van den Berg et al., 2007; Villegas et al., 2014; Winzelberg et al., 2000). In one study that gauged usability, Steele et al. performed a 3-month randomized controlled trial among 192 participants and found an Internet-based physical activity behavior change program to be usable, feasible, and acceptable among inactive participants (Steele et al., 2007). Mobile-based interventions also showed 75% (6/8) of usable interventions had a positive impact on health outcomes (Brendryen & Kraft, 2008; Harris et al., 2010; Hasin et al., 2014; Shrier, Rhoads, Burke, Walls, & Blood, 2014; Song et al., 2013; Tran & Houston, 2012).

In one study, SMS was found to be useful in helping patients to remember to take their medications and be engaged in treatment planning (Harris et al., 2010). SMS-based intervention was also found to be useful in promoting communication with healthcare providers by delivering, receiving health information, generating questions, and seeking information related to health conditions (Song et al., 2013). Moreover, 87% (7/8) of studies reported that the usability of social media-based interventions was positively correlated with good impact on health outcomes (Fisher & Clayton, 2012; Greene, Choudhry, Kilabuk, & Shrank, 2011; Magnezi et al., 2014; McKay et al., 2002; Sugawara et al., 2012; Thackeray et al., 2013; Winstead-Derlega et al., 2012). One particular social networking-related study found that online health-related social networking was useful and acceptable in chronic disease management (Magnezi et al., 2014).

In addition, one study reported the usability assessment in the video-game category and found that it was usable and had a positive impact among patients with hyperfunctional voice disorders (King et al., 2012). Overall, the analysis also found that telemonitoring also showed similar results (100%, 3/3). One telemonitoring-based study found that telecommunication-based reminder tools are useful for improving medication adherence (Boland et al., 2014). Although our results failed to report any relationship between usability of IT platforms and the impact on health outcomes ($P=.1065$), they showed significant association between usability and patient engagement in healthcare ($P=.0216$) (Fisher's exact test) (Tables 8-9).

Table 8 Impact of IT Platforms and Usability

Usability	Impact of Information Technology Platforms, n (%)											
	Internet		Mobile		Social Media		Tele-monitoring		Video game			
	Y	N	Y	N	Y	N	Y	N	Y	T N	T N	T
Usable	28 (33)	4 (5)	6 (14)	2 (5)	5 (31)	2 (13)	3 (17)		1 (17)	43 (25)	8 (5)	51 (30)
Not usable	1 (1)	4 (5)			1 (6)					4 (2)	2 (1)	6 (4)
Total of assessed usability	29 (34)	8 (9)	6 (14)	2 (5)	6 (38)	2 (13)	3 (17)		1 (17)	12 (7)	45 (26)	57 (34)
Not assessed usability	46 (53)	3 (3)	35 (80)	1 (2)	7 (44)	1 (6)	13 (72)	2 (11)	5 (83)	7 (4)	106 (62)	113 (66)
Grand total	75 (87)	11 (13)	41 (93)	3 (7)	13 (81)	3 (19)	16 (89)	2 (11)	6 (100)	19 (11)	151 (89)	170 (100)

T=Total, N=No, Yes=positive impact, No=no impact.

Table 9 Patient Engagement and Usability

Usability	Impact of Information Technology Platforms, n (%)											
	Internet		Mobile		Social Media		Tele-monitoring		Video-game			
	Y	N	Y	N	Y	N	Y	N	Y	T Y	TY	T
Usability assessed (usable)	26 (30)	6 (7)	7 (16)	1 (2)	5 (31)	2 (13)	3 (17)		1 (17)	41 (24)	9 (5)	51 (30)
Usability assessed (not usable)	1 (1)	4 (5)			1 (6)					2 (1)	4 (2)	6 (4)
Total usability assessed	27 (31)	10 (12)	7 (16)	1 (2)	6 (38)	2 (13)	3 (17)		1 (17)	43 (25)	13 (8)	57 (34)
Not assessed	41 (48)	8 (9)	31 (70)	5 (11)	7 (44)	1 (6)	13 (72)	2 (11)	5 (83)	97 (57)	16 (9)	113 (66)
Grand total	68 (79)	18 (21)	38 (86)	6 (14)	13 (81)	3 (19)	16 (89)	2 (11)	6 (100)	141 (83)	29 (17)	170 (100)

T=Total, N=No, Yes=positive impact, No=no impact

2.2.4 Discussion

1. Impact of IT platforms on health outcomes.

Overall, this review indicated that IT platform-based health interventions had a great impact on patients' health outcomes in the United States and in other nations. IT-based health interventions have been viewed as driving positive health behavior change through patient engagement with most technology platforms. IT-based health interventions also provide necessary information and advice and counseling related to certain diseases and conditions, such as mental disorders (Bond, Burr, Wolf, & Feldt, 2010; Buhrman, Fältenhag, Ström, & Andersson, 2004; Christensen, Griffiths, & Jorm, 2004; Herbst et al., 2014; Houston, Cooper, & Ford, 2002; Kerr et al., 2008; Rotondi et al., 2010; Roy & Gillett, 2008), asthma (Baptist et al., 2011; Bingham et al., 2012; Chan et al., 2003; Krishna et al., 2003; Nguyen et al., 2008; Ostojic et al., 2005), obesity (Johnson & Wardle, 2011; Johnston et al., 2012; Kornman et al., 2010; Napolitano et al., 2003; Park & Kim, 2012; Kevin Patrick et al., 2009; Petersen, Sill, Lu, Young, & Edington, 2008; Steinberg et al., 2014; Tate, Jackvony, & Wing, 2006; Turner-McGrievy & Tate, 2014; Ware et al., 2008), smoking (Boudreaux et al., 2012; Bramley et al., 2005; Brendryen & Kraft, 2008; Danaher et al., 2006; McKay, Danaher, Seeley, Lichtenstein, & Gau, 2008; Richardson et al., 2013; Rodgers et al., 2005; Strecher et al., 2008), diabetes (Bell, Fonda, Walker, Schmidt, & Vigersky, 2012; Cho et al., 2006; Fonda, McMahon, Gomes, Hickson, & Conlin, 2009; Kim & Jeong, 2007; Kim & Kim, 2008; McCarrier et al., 2009; McMahon et al., 2005; Meigs et al., 2003; Quinn et al., 2008; Ralston et al., 2009; Rami, Popow, Horn, Waldhoer, & Schober, 2006; Smith et al., 2004; Tasker, Gibson, Franklin, Gregor, & Greene, 2007; Weppner et al., 2010; Winbush et al.,

2013; Yoon & Kim, 2008), sleep disorder (Espie et al., 2012), hypertension (Kiselev, Gridnev, Shvartz, Posnenkova, & Dovgalevsky, 2012; Park & Kim, 2012; Park, Kim, & Kim, 2009), cancer (Bantum et al., 2014; Galiano-Castillo et al., 2014; Ginsburg et al., 2014; Gustafson et al., 2001; Gustafson et al., 2005; Kato et al., 2008; Kinney et al., 2014; Lee et al., 2010; Lewis et al., 2009; McCann, Maguire, Miller, & Kearney, 2009; Sugawara et al., 2012; Zernicke et al., 2014), thereby encouraging healthy living (Adachi et al., 2007; Christensen et al., 2010; Gabriele et al., 2011; Johnston et al., 2012; Oh, Jorm, & Wright, 2009; Tate et al., 2006). Moreover, these interventions enable patients to be engaged in self-monitoring, thereby directing patients toward healthy eating, enhancing attendance rate (Downer, Meara, & Da Costa, 2005; Farmer, Brook, McSorley, Murphy, & Mohamed, 2014; Kay-Lambkin, Baker, Lewin, & Carr, 2011; Liew et al., 2009; McInnes et al., 2014; Sims et al., 2012; Stockwell et al., 2012; Strecher et al., 2008), improving medication adherence (Glasgow et al., 2012; Heisler et al., 2014; Heyworth et al., 2014; Kay-Lambkin et al., 2011; Meglic et al., 2010; Parr, Kavanagh, Young, & Mitchell, 2011; Santschi, Wuerzner, Schneider, Bugnon, & Burnier, 2007; Vilella et al., 2004), increasing knowledge about disease and treatment (Arora et al., 2014; Christensen et al., 2004; Feldman et al., 2005; Heisler et al., 2014; Irvine et al., 2013; Kato et al., 2008; Krishna et al., 2003; Kulkarni, Wright, & Kingdom, 2014; Pandolfi et al., 2014; Rotondi et al., 2010; Song et al., 2013; Vaart et al., 2014; Wakefield et al., 2008), and enhancing exercise use (Aikens, Zivin, Trivedi, & Piette, 2014; Bantum et al., 2014; Bentley & Richardson, 2014; Claborn et al., 2014; Glasgow et al., 2011; Helander, Kaipainen, Korhonen, & Wansink, 2014; Hunter et al., 2008; Jelsma et al., 2014; Johnson & Wardle, 2011; Keyserling et al., 2014; Kim & Kang, 2006; Kiselev et

al., 2012; Kornman et al., 2010; Napolitano et al., 2003; Nguyen et al., 2008; Kevin Patrick et al., 2009; Petersen et al., 2008; Plotnikoff, McCargar, Wilson, & Loucaides, 2005; Steinberg et al., 2014; ter Huurne, Postel, de Haan, Drossaert, & DeJong, 2013; Turner-McGrievy & Tate, 2014; Ware et al., 2008; Zernicke et al., 2014). Online coaching by specialists enables patients to recover quickly, ensuring that the pain they experience is reduced (Buhrman et al., 2013; Trautmann & Kröner-Herwig, 2008), and doctor-patient communications are made readily available (Furber et al., 2011; Greysen, Khanna, Jacolbia, Lee, & Auerbach, 2014; Idriss, Kvedar, & Watson, 2009; Lancioni et al., 2012; Lee, Yeh, Liu, & Chen, 2007; McCann et al., 2009; Schnall, Wantland, Velez, Cato, & Jia, 2014; Sciamanna et al., 2006; Simon et al., 2011).

Apart from Internet-based technologies, mobile phone technologies have been used extensively to engage patients and ensure there is patient health behavior change. Mobile phone technologies engage patients by using SMS to contact them and provide necessary health information. This technology can be very effective and efficient, since it is less expensive and therefore more people can afford it. Studies have shown that patients can receive health-related information, receive reminders of their healthcare attendance, as well as be encouraged to adhere to their treatment (Granholm et al., 2011; Green et al., 2008; Harris et al., 2010; Lester et al., 2010; Winstead-Derlega et al., 2012).

Social media outlets, such as Twitter and Facebook, can ensure patients get and exchange necessary health information (Sugawara et al., 2012; Thackeray et al., 2013). Video game and telemonitoring technologies served a similar purpose; these technologies tried to engage patients in order to provide necessary health information and provided a platform for helping patients adhere to treatment and helped patients actively become

involved in the treatment process. These technologies are of great importance to patients as well as helpful to healthcare providers, therefore ensuring effectiveness and efficiency. Although several studies demonstrated the positive impact of IT platform usage, others showed no impact (Arora et al., 2014; Benhamou et al., 2007; Claborn et al., 2014; Glynn et al., 2010; Gutierrez et al., 2014; Habibović et al., 2014; Helander et al., 2014; Kaplan et al., 2011; McCarrier et al., 2009; McInnes et al., 2013; McKay et al., 2008; Phillips et al., 2014; Ramaekers et al., 2009; Schweier et al., 2014; Steele et al., 2007; Thackeray et al., 2013; Wakefield et al., 2008; Williamson et al., 2006; Winstead-Derlega et al., 2012; Womble et al., 2004). This could be due to the timing of the follow-up assessments ranging from one extremely short follow-up timing (1 week) to a relatively long-term follow-up timing (48 months). The lack of consistency in follow-up timing made it unclear as to how long these effects on patient health last.

Moreover, the technology adoption rate may decline after a certain time period, thus diminishing its effectiveness after significant results at the beginning of the study. This occurred in a study by Williamson et al. who found that after two years of an IT-based intervention, the decrease in body weight did not differ between the intervention and control group (Leventhal & Cameron, 1987). Similarly, another research study found a slow decline in HbA1c at 3 months follow-up (1.22%) versus (1.09%) six month follow-up (Kim & Song, 2008; Kim & Jeong, 2007). Therefore, designing and evaluating IT platforms may become a significant challenge because researchers are dealing with a large volume of interventions that have different impacts on patient health behavior. Thus, several issues need to be addressed if such interventions are to be evaluated or

assessed, such as length of intervention, type of technology, usability of the technology, application of behavior theory, and how health outcomes are measured.

2. Patient engagement in healthcare using IT platforms.

Our review showed that IT platforms are playing a significant role in patient engagement. This review implies that higher patient participation in condition self-management was correlated with greater improvement in health outcomes. Many studies have shown that patients who actively participated in healthcare experience better health outcomes compared to less involved patients. One specific study showed a significant association between patient engagement using the Internet and weight loss at 6 months ($P < .001$) (Green et al., 2008). Another study reported that a text messaging could enhance patient engagement (Arora et al., 2014). Social networks can also be particularly helpful to individuals with lower patient activation (Magnezi et al., 2014).

Despite the evidence regarding the importance of patient engagement, it is challenging to draw solid conclusions. Many of the studies conducted qualitative surveys to measure patient engagement or relied solely on the number of times patients logged in or uploaded data to determine their engagement. However, system log-ins and upload and download data are not engagement. Patient engagement is basically about interaction and participation in managing one's health to achieve desired goals. Therefore, further research is needed to determine the best ways to measure patient engagement.

3. Association between usability of IT platforms and their impact.

The review found limited levels of evidence supporting the correlation between usability and impact of technology on health outcomes ($P = .1065$). Several factors may hinder the positive impact of technology on health outcomes other than usability issues.

Patients' willingness to participate in managing their healthcare could be one of the main reasons. The review found a significant relationship with patient engagement and impact of technology. It found also a significant positive correlation between patient engagement and usability of IT platforms. Even though the aim of this study was not to discover determinants of patient engagement, several issues were identified including unequal access to technology, technical issues, poor interface design, suboptimal message content, privacy and confidentiality issues (Baptist et al., 2011; Fisher & Clayton, 2012; Sims et al., 2012; Thackeray et al., 2013; Tran & Houston, 2012; Walker et al., 2011; Womble et al., 2004), and patients' self-perceived health illiteracy. The latter issue was seen in social media, where patients think such a discussion should be restricted to healthcare professionals (Thackeray et al., 2013). Also, the majority of technologies rely on patient-provider engagement from both sides to exchange information and manage health conditions, such as in two-way SMS, thus increasing burden on providers as well as patients. Moreover, in some countries like Sweden, information dissemination can be restricted by legal and ethical regulations for online patient-provider communication (Nordgreen et al., 2010). Therefore, more research on the usability and acceptability of these technologies and discovering the different factors that impact patient engagement and their meaningful use will be required in the future.

4. Association between technology impact and intervention grounded in behavior change theories.

This review found that only a limited number of specific behavioral theories and models were referenced among multiple articles inferring a theoretical design. This could imply that several IT interventions are designed in an ad hoc way, without using any

theoretical frameworks. This finding supports the results of a previous study showing the majority of mobile-based interventions used for improving medication adherence and disease management were developed without a theoretical basis (Riley et al., 2011). The review failed to detect any relationship between (1) behavioral theories and impact of technology or (2) theories and patient engagement. This could imply that existing theories/model were not developed to be used with these technologies. The review found a significant association between patient engagement in Internet-based interventions and use of behavior theories in these interventions ($\chi^2 = 7.3144$, $P = .00684$). This could imply that existing theories or models may have limited applicability. However, it was difficult to draw a clear conclusion whether or not using theory influenced intervention effectiveness. Possible reasons for the lack of theory may include the investigator not citing the theory, researchers' lack of knowledge of the theories, struggling to define appropriate theories, poorly operationalized theories, an absence of good evaluation methods and usability testing, and theories containing overlapping constructs and inconsistent use of terminology. For example, the construct of self-efficacy can be found in Social Cognitive Theory, Protection Motivation Theory, the Theory of Planned Behavior, the Health Belief Model, and Self-Regulation Theory. In addition, the simplicity of the interventions could be another reason for not including behavior theories. For example, reminding patients to take their treatment through text message appears simple and consistent with the "cue to action" constituent of many health behavior theories or models, but these theories were not always described. Our findings of the lack of association between use of theory and outcomes was based on the theory description within each published article and should be interpreted cautiously.

5. Association between methods measure health outcomes and the technologies impact.

Overall, slightly more than half of the reviewed articles had a positive impact when assessed with patient questionnaires, patient self-reports, pill counts, rates of prescription refills, assessment of patients' clinical response, and electronic medication monitors. Even though the way to measure health outcomes is an important factor in determining the impact of technology, the review failed to detect any relationship between methods used to measure health outcomes and the impact of technology. Therefore, further study is needed to replicate our results, because for each approach, there are different assumptions related to what data to collect, how to collect that data, and how to make decisions about success. Indirect methods may overestimate patient adherence. For instance, metformin treatment adherence can be monitored either by recording the number of times the medication bottle was opened, or alternately, adherence could be gauged by metformin plasma levels. Both health behaviors are part of the same behavioral class to control blood sugar levels. However, measuring metformin in blood is more effective at measuring adherence than recording the time when the bottle is opened because patients may open and close the bottle without taking any medication.

2.2.5 Limitations

Our review included some limitations. First, due to the heterogeneity of the research studies and the fact that some data were not available for certain types of interventions and their characteristics, some statistical tests could not be performed, hindering optimal quantitative assessment. Second, we excluded studies not written in English; this criterion might have omitted certain relevant research. Third, the majority of studies were performed in the United States, which limits generalizability of findings.

Finally, because of possible publication bias toward positive findings, our review may overestimate the actual impact of these technologies.

2.2.6 Implications

The results from this review reveal several practical applications worthy of future study: (i) Information technology platforms: It would be valuable to further evaluate IT platform-based interventions to form a more coherent picture of their effectiveness in encouraging patient engagement for the purpose of enhancing lasting health behavior change. A study with a long-time frame may be useful to draw a clear conclusion on the effectiveness of these technologies and to determine the best ways to guarantee positive long-term effects in patients. Also, due to low availability of studies meeting our criteria, we could not provide or conclude relationships between factors. Therefore, we recommend doing another review when there are more studies available in future. In future, we can increase the quality of the review by limiting sample size and study time frame. IT platform interventions reviewed in this study are mutually inclusive; they use different labels and contexts to describe the same concepts and lack of formal definitions. Therefore, a common framework for analyzing these concepts is needed. A framework with an ontological approach may serve this purpose. (ii) Patient engagement: The outreach and engagement period prior to the intervention enrollment are critical to the success of any intervention. Therefore, studies should consider that when implementing the interventions. A study assessing determinant of patient engagement is highly recommended. (iii) Usability. Assessment of user satisfaction toward IT platforms and their usability of these platforms are needed and could be done through qualitative evaluations of user opinions of the respective IT platform(s). (iv) Behavioral theories:

The literature also needs to focus more on referencing, selecting, and implementing behavioral theory to achieve the best possible impact. Reporting accurate information about interventions is essential to assessing the effectiveness of these interventions and facilitating their successful implementation. Also, new theories are needed to better understand how patients can participate and facilitate health behavior change, theories building on past conceptual and focus only on one aspect, a triangulation model would provide internally logical and comprehensible perception to achieve these goals.

(v) Methods measure outcomes: It would be valuable to further examine how different types of measurement could affect patient outcomes reported in the study. A comparison between direct and indirect methods could be helpful to draw a clear conclusion.

2.2.7 Conclusion

Based on our review, there is moderately strong evidence that IT platforms can engage patients in healthcare and improve health outcomes. The usefulness and acceptability of IT platforms can have great power in engagement and outcomes. Studies grounded in behavior theory appeared to show a positive impact on patient health behavior. To exploit the full potential of IT platforms in healthcare, new theories may be needed to better understand how patients can participate and facilitate health behavior change. Selecting appropriate ways to measure health behavior change and developing a common framework to analyze and understand the different components of IT platforms and their safety, effectiveness, efficiency, and acceptability will also be of great importance.

2.3 Ontologies and Knowledge Representation

Based on the review in section 2.1, medication-adherence behavior is multifactorial in its origin and is affected by interaction between individuals and situation factors (Sawesi, Carpenter, & Jones, 2014). Section 2.2 discussed the vast amount of information produced as a result of advancements in medication adherence in information technology. For medication adherence research activities to be ultimately effective in understanding, changing, or modifying such complex behavior, there needs to be knowledge aggregation from different resources, such as literature, clinical study results, and databases.

Currently, no single system capably covers the medication adherence domain completely. A fundamental reason for this gap relates to the inconsistency and lack of a strategy for representing knowledge related to the medication adherence domain. Medication adherence is measured in a variety of ways (e.g., self-report vs. drug concentration in body fluid). Although these represent different constructs or entities, they are labeled as medication adherence. Also, medication adherence and medication persistence are used interchangeably (Aronson, 2007) when they refer to different phenomena. Moreover, different labels can be used to refer to the same meaning, such as in case of some theoretical constructs (e.g., self-efficacy, perceived behavioral control, and locus of control). Therefore, developing an interoperable and standardized framework that enables the scientific community to contribute equally to the representation of the medication-adherence knowledge domain is necessary.

Knowledge representation is a surrogate for something tangible or intangible in the real world. It is a medium of human expression and computation (Blobel, 2006). It

facilitates our understanding, communicating, sharing, organizing, thinking, and reasoning about the thing in the real world (Davis, Shrobe, & Szolovits, 1993).

Knowledge representation in biomedical informatics refers to electronic models of real-world phenomena; an example is that knowledge representation represents patient-related information in electronic health records (EHRs).

To solve any problem or discover knowledge in a domain, the first step is to represent that knowledge in a way that it can be understood and shared by humans and computers (Chandrasegaran et al., 2013). An ontology is a form of knowledge representation about the real world or a part of it. It is one strategy that has been used in biomedical science to support knowledge aggregation. It is organized in hierarchical structures of a set of entities describing a domain that can be used as a foundation for knowledge base (Salem & Alfonse, 2008).

2.3.1 What is an Ontology?

Philosophically, the term “ontology” refers to the study of kinds of things that exist and their relation to each other. Barry Smith (2003) defined it as a “science of what is, of the kinds and structures of objects, properties, events, processes, and relations in every area of reality (Smith, 2003).”

In information science, Gruber defines ontology as a specification of conceptualization (Gruber, 1995). Although Gruber’s definition has been accepted by most ontological engineers, his concept-centric view assumed as a matter of course that ontology represents what is in humans’ minds, not what exists in reality. Ontology primarily concerns describing reality in its most general sense (Arp et al., 2015). Therefore, to avoid being misleading, this dissertation defines ontology as a formal

description of knowledge within a domain as a set of entities/terms on an abstract level and relations between those entities. An ontology, as applied in areas of biomedical science, is perceived as a given role in capturing a reality about a domain and allowing shareability and reusability of domain knowledge.

2.3.2 Ontology's Impact on the Biomedical Field

Applications for ontologies are broad, as they show value within a domain (Zhang & Bodenreider, 2007), across health systems (Anagnostakis, Tzima, Sakellaris, Fotiadis, & Likas, 2005), and in the facilitation of bench research to patient care (Tenenbaum et al., 2011). According to the National Center for Biomedical Ontology (NCBO), an ontology enables data aggregation, improves searching, and detects new associations that previously went undetected (Musen et al., 2012). A select number of studies have measured ontology's impact on biomedical research and patient care. Ontology's impact includes, but is not limited to: (1) understanding patient perception, (2) acquiring knowledge, (3) understanding patient behavior, (4) allowing the domain knowledge to be independent of technology, (5) structuring a relational database, and (6) standardizing or formalizing the domain. Each area is discussed below.

An ontology could be used to better understand patients' perceptions. In turn, these perceptions could then be transformed into a framework structure (Meghani & Houldin, 2007). In the same paper, ontology was used to acquire knowledge about how patients describe their cancer pain and learn how patients view pain (Meghani & Arkene, 2007). A study by McGrath (2002) also looked at how ontology was used to attain knowledge of an interesting domain through oral interviews (McGrath, 2002). A study by Brown (2006) demonstrated similar use for ontology. Brown's research team used an

ontology to better comprehend how patients waited for liver transplants (Brown, Sorrell, McClaren, & Creswell, 2006). A study by Bickmore, Schulman, and Sidner (2011) demonstrated that ontology has been used successfully to represent changes in health behavior. This study covered the Trans-theoretical Model, Motivational Interviewing as Applied to Exercise (walking) Promotion, and Diet (fruit and vegetable) Promotion (Bickmore, Schulman, & Sidner, 2011). Another study used an ontology to design computerized behavioral protocols to help individuals improve their behaviors (Lenert, Norman, Mailhot, & Patrick, 2005).

An ontology framework can also allow the domain knowledge to be independent of technology. This means that it can operate on multiple platforms, using a variety of capabilities (Farion et al., 2009). The ontology knowledge model allows for differentiation between logic knowledge and software design; it embodies a set of concepts and how they correlate into a hierarchical format that can be referenced in reasoning rules in machine learning. As a result, when knowledge is changed, reasoning changes without any work being done to the software system. Doyle, Ma, Groseclose, and Hopkins (2005) realized the benefits of ontologies and instituted the ontological knowledge base for public health surveillance. As a result of these characteristics, ontology benefits data sharing in Electronic Health Records (EHR). Ontology separates technology and medical knowledge. It allows patients' information to be shared across health institutions, irrespective of EHRs' operation or technology.

Ontology has played a significant role in linking a study's domain knowledge to standard terminology systems. The terminology servers Unified Medical Language System (UMLS), Systematized Nomenclature of Medicine (SNOMED), and Logical

Observation Identifiers Names and Codes (LOINC) are considered well-structured systems that, according to Cole (2004), offer standardized communication, documentation, and classification of health and medical vocabularies (Cole, Kanter, Cummins, Vostinar, & Naeymi-Rad, 2004). Despite these systems being built on a standard structured framework, in terms of their concepts, they are inconsistent and incompatible (Bolbel, Engel, & Pharow, 2006). A study by Ahmadian, Cornet, & Keizer (2009) investigated whether SNOMED CT adequately described the terms used in pre-operative assessment guidelines. These authors determined that 71% of the guidelines matched SNOMED, while 69% of 39 not-fully covered concepts violated a minimum of one SNOMED CT format. These researchers stated that ontology could potentially serve as a solution for formalizing SNOMED CT's guidelines. And, in Doan's 2009 research, ontology was instituted to examine the conceptual classifications of infectious diseases that were not presented in terminology systems (Doan, Kawazoe, Conway, & Collier, 2009). Fried et al. (2003) reported that no terminological systems, including current ICD10, READ, SNOMED, UMLS, or MeSH, supplied sufficient granularity of content or domain completeness for metadata in multimedia data within the Cardio domain (Friedl et al., 2003). Another example of ontology used in the terminology domain was found in a study by Elkin et al. (2005). In this instance, ontology contributed to building terminology structure for an automated system that provided clinical notes with classification in negation and propagation. When using ontologies, these terminology domains can share and integrate existing definitions and terminologies across multiple health levels (Pappa, Telonis, & Stergioulas, 2006). This is a requirement for semantic

interoperability, particularly in terms of knowledge representatives and terminologies (Blobel, 2007).

Medical ontology differs from those mentioned above in that ontology that is intended for terminology servers is built on static structures designed for knowledge reference. Its databases are built on language concepts; whereas, medical ontology merges all pertinent concepts, which, according to Jovic, Prcela, & Gamberger (2007), relate to five factors: diagnostics, treatment, clinical procedures, patient data, and outcome prediction. Ontology, in the environment of medicine/patient care, needs to consider temporal changes and factors, particularly when they apply to EHRs, because EHRs are patient-centered, longitudinal, comprehensive, and prospective (Garde, Knaup, Hovenga, & Heard, 2007). In addition, current ontology models need to be reusable and easily adapt to new changes. Furthermore, because stakeholders are present in medicine, ontologies need to be classified, based on their design purpose.

Other studies showed that ontologies are viable as a new tool to implement a knowledge framework that connects systems. Medicine is a complex system and ontologies can play a significant role, where studies need to focus on a special knowledge domain. To connect knowledge frameworks to a larger structure, ontologies must bridge similar interests. In a study by Capozzi and Lanzola (2009), in Italy, telemedicine was successfully built on a platform and was used for patients with Type I diabetes. Ontology served as pivotal knowledge that allowed for interaction connecting EMRs and domain knowledge of the study. Another researcher, Abidi (2009), showed ontology as allowing for specific clinical pathways to be computerized in prostate cancer. This researcher based ontology on the hypothesis of extending and blending nodes that served as

interclass intersections (Abidi, Butler, & Hussain, 2008). Abidi's study merged three unique clinical pathways into a single one. Comparably, in instances of heart failure, the developed ontology merged data from the ECG signal and heart image (Chiarugi et al., 2008).

An additional benefit of ontology is that it standardizes or formalizes the domain (Haschler, Skonetzki, Gausepohl, Linderkamp, & Wetter, 2004; Sobrado, Juan, Iker, Juan, & Diego, 2004). There is a difference between standardization and integration. It is the number of models that connect to the designs. With standardization, ontology can connect a significant number of models; it can also be designed without using any existing ontology. Lusignana (2003) incorporated ontologies into a study that developed a general quintessential theory for the subspecialty of Primary Care. In a study by Pellegrin et al., (2007), researchers built a method that represented and observed combined activities that occurred within the patient's management that team members could use to prepare for accreditation. However, no common guidelines were established for observation; therefore, the ICU team used ontologies to develop a framework for task observation. In turn, Haschler et al. (2004) went further and created an expanded oncology framework, known as HELEN, which was used to create clinical guidelines. This expanded framework served not only as a method for standardization, but it also became an adaptable process to change environments. Colantonio (2008) stated that ontology was constructed as a way to formalize the domain of chronic heart failure. The study further indicated that a main benefit of ontologies is that they allow for information-sharing across stakeholders and facilities. Fernandex (2004) indicated that ontology supports cardiology's conceptual frameworks in that it allows for a variety of

stakeholders and healthcare groups to exchange knowledge management and communication, with no need for any specific domain to be matched to a standard ontology (Fernandez et al., 2004; Goossen, Goossen-Baremans, & Van Der Zel, 2010).

Ontologies not only influence medical terminology, public health, and medicine, they also have an impact on healthcare management. Ontologies, when used by healthcare organizations, can fulfill many reference or guideline roles. Organizations and/or health facilities require their own ontology guidelines. Often they are not compatible with other facilities. A study by Dang et al. (2008) includes an ontological knowledge framework that addresses a variety of responsibilities, ranging from administrative to patient-care related. This framework captures all the critical knowledge needed to document complex personal events, ranging from patient care to insurance policies and drug prescriptions (Dang, Hedayati, Hampel, & Toklu, 2008). This differs from previous examples of ontologies, because it addresses a business perspective; yet, ontologies are also applicable to business rules and healthcare policies, and are applicable in the context of personalized patient care when supporting the composition and execution of an adaptive workflow system. This system incorporates functionalities that enable users to monitor and control the patient process and maintain any historical process data for future reference without relying on IT support. This study proposed creating an adaptive workflow system that could be managed by users without knowing the technical aspects. Furthermore, the software that was developed incorporated ontology's meta-data to gain an understanding of the specific domain's environment and its rules. In this instance, the process rules were separated from the business rules that

allowed this adaptive workflow system to bridge the healthcare needs and IT technology of any hospital environment as its first achievement.

2.3.3 Ontology Developing Approach

Considering the discussed benefits of ontology in the biomedical domain, several principles and methodologies have been proposed to build ontology. However, no specific standardized methods exist for developing an ontology (Smith et al., 2007), compared to ISO standards (Ceusters, Smith, & Goldberg, 2005). Ontological engineering, the field that studies methods and methodologies for building and using an ontology, is relatively young and has no standard methodologies built in or proven principles to guide ontology development (Pattueli, 2011). Ontologies are as unique as the domains they represent. Both a collaborative approach and a development trajectory are common features in ontology development (Bug et al., 2008; Cimino et al., 2009; Tudorache et al., 2010). This section discusses different methods used to build ontologies.

1. Methodology by Uschold and King (Jones, Bench-Capon, & Visser, 1998). The first methodology implemented for ontology developed by Uschold and King in 1995 based on experience as a result of developing an Enterprise Ontology—“an ontology for enterprise modeling processes.” It encompasses four steps:
 - a. Purpose identification: Identifying the purpose of the ontology, its domain, and intended users.
 - b. Ontology building: This step has three sub-processes: (i) Ontology capture-in, where key concepts and ideas from the ontology domain will be captured using bottom-up, top-down, or middle-out. (ii) Coding—Represents knowledge explicitly

- captured from the previous step. (iii) Integrates existing ontologies—using the existing ontology.
- c. Ontology evaluation: Makes technical judgment of the created ontology.
 - d. Ontology Documentation: Establishes a guideline for ontology documentation according to the purpose of the ontology.
2. TOVE Methodology (Grüninger & Fox, 1995): Based on experience gained through developing TOVE project ontology for the business domain by Gruninger and Fox in 1995, it involves several steps.
- a. Motivating scenario—may be a story problem or examples not addressed by existing ontologies.
 - b. Developing competency questions—a set of natural language questions used to measure the scope of the ontology.
 - c. Coding—specifies informal questions in a formal language.
 - d. Axioms specification—uses first-order logic using axioms to define terms and constraints for the property.
 - e. Evaluation—assesses competency by defining the condition under which answers to the competency questions are complete.
3. METHONTOLOGY method (Fernández-López, Gómez-Pérez, & Juristo, 1997): Developed within the Laboratory of Artificial Intelligence at the Polytechnic University of Madrid. Used when developing ontologies from scratch. It includes several activities and techniques to carry out these activities.
- a. Project management activity—involves three steps. (i) Planning—describes the tasks, methods, and time needed to perform an ontology. (ii) Control—ensures that planned

- tasks are completed, as intended. (iii) Quality assurance—guarantees the quality of the ontology is satisfactory.
- b. Development-oriented activities—involves several steps: (i) Specification: identifies the ontology’s purpose, intended user, and required degree of formality. (ii) Conceptualization: Uses informal representation to represent domain terms (i.e., concept, instances, relations). (iii) Formalization: transforms the informal model into a formal one. (iv) Implementation: Codifies the ontology in a formal language. (v) Maintenance: updates and corrects the ontology.
 - c. Support activities: this step includes a series of activities carried out simultaneously with development-oriented activities. It includes: (i) Knowledge acquisition: text analysis, expert interview, or other sources of knowledge. (ii) Evaluation: performs an ontology validation and verification. (iii) Integration: for uniformity across ontologies, definitions from other ontologies should be incorporated. (iv) Documentation: completed activities should be documented in order to control changes. (v) Configuration management: records all versions of the documentation.
4. KBSI IDEF5 Methodology (Jones et al., 1998): Proposed to assist in building, modification, and maintenance of ontologies. It involves general procedures with a set of guidelines:
- a. Organizing and scoping: the purpose and requirement of ontology.
 - b. Data collection: the raw data required to build the ontology is acquired using a typical technique, such as protocol or expert interview.
 - c. Data analysis: extracts the ontology from the results of the previous step.
 - d. Initial ontology development: initial description of kinds, relations, and properties.

- e. Ontology refinement and validation: proto-concept refined and tested iteratively.
5. The CYC methodology (Corcho, Fernández-López, & Gómez-Pérez, 2003):
 Developed by Lenat and Guha in 1990, it is based on experience from developing the CYC knowledge base. This method consists of two phases.
 - a. Manual knowledge codification: extracts knowledge by hand from different related resources.
 - b. Machine knowledge acquisition: new common-sense knowledge in this phase will be acquired with the help of natural language or machine-learning tools.
 6. 101 Methodology (Noy & McGuinness, 2001): Developed by Noy and Deborah, this methodology involves several steps:
 - a. Domain specification: determines the domain and scope of an ontology using competency questions.
 - b. Considers reusing an existing ontology.
 - c. Enumerates important terms in the ontology.
 - d. Defines classes and their hierarchy using top-down, bottom-up, or a combination.
 - e. Defines properties of classes.
 - f. Defines facets of the slot.
 - g. Defines instances.
 7. UPON Methodology (Iqbal, Murad, Mustapha, & Sharef, 2013): Derived from a unified software development process (UP), this methodology is use-case driven and consists of cycles, phases, iterations, and workflows. Each cycle contains four phases (inception, elaboration, construction, and transition). Each phase splits into iterations that contain five workflows.

8. The SENSUS-Based Methodology (Iqbal, Murad, et al., 2013): Based on the experience development of SENSUS Ontology, this methodology was developed at the Information Sciences Institute Natural Language Group. It includes terms from both a high- and medium-levels of abstraction and encompasses several steps:
 - a. Terms taken as seed.
 - b. Terms linked by hand to the SENSUS.
 - c. All concepts from seed to root.
 - d. Adds any terms relevant within the domain.
 - e. Adds the subtree under the node for nodes that have a large number of paths.
9. On-To-Knowledge (Corcho et al., 2003): Based on usage scenarios, this methodology includes identification of goals intended to be achieved:
 - a. Feasibility—identifies the problem and why an ontology is needed.
 - b. Kickoff—a semi-formal description of the ontology created from different sources, including by a domain expert.
 - c. Refinement—refining the semi-formal ontology created in the previous step by considering relevant knowledge sources: top-down and bottom-up approaches.
 - d. Evaluation—technology evaluations; user satisfaction evaluation; and ontology evaluation, using OntoClean as an example.
 - e. Application—testing develops an ontology in the productive system.
 - f. Ontology maintenance.

2.3.4 Methodologies Comparison

The scarcity of a standard methodology is one of the greatest issues in constructing an ontology. As a result, several criteria have been proposed to analyze and

compare methodologies used for ontology building. This comparison would be considered systematically-guided ontology building. A comparison of the nine methodologies mentioned in the previous section was carried out based on criteria developed by Fernández-López, & Asunción (2002), Gómez-Pérez, Fernández-López, & Corcho (2006), and as elaborated by Iqbal et al. (2013). The criteria is presented in Table 10 below and involves: (1) Type of development—there are three: namely, stage-based model (suitable when purpose and requirement are not clear), evolving prototype model (suitable when requirement needs modification over time), guidelines (focusing only on recommended tips or rules to make a better decision). (2) Support collaborative construction—when a team or group work on a single ontology simultaneously without restriction). (3) Support reusability—use of an existing ontology to prevent reinventing the wheel and focusing on quality, not quantity. (4) Interoperability—using upper-level ontology to facilitate communication between systems. (5) Application dependency—keeps in mind building on the basis of application. (6) Life-cycle recommendation—a set of stages through which the ontology moves during its specified life. (7) Strategy for identifying concepts—involves three types: namely, bottom-up, top-down, and middle-out approaches. (8) Details of the methodology—information on activities and techniques used in ontology development.

Results of the comparison show that the majority of methodologies are evolving prototype models, except for Enterprise mode and TOVE. They are stage-based models that are best when there is a clear purpose. The evolving prototype is suitable when the requirement is not clear initially and needs modification over time. The analysis shows that all the methodologies are isolation construction, except SENSUS, as the method

supports collaboration construction. Reusability is supported by all the methodologies except On-To-Knowledge. Seven of the methodologies are application-independent, wherein the designer has no assumption in mind regarding use of the ontology during the specification stage. METHONTOLOGY, UPON, and On-To-Knowledge proposed a life-cycle recommendation wherein the ontology moves during its life. Strategy for identifying the concept–Enterprise model, TOVE, METHONTOLOGY, UPON, SENSUS, and On-To-Knowledge all support the middle-out approach in identifying concepts that are candidates for ontology inclusion. Only METHONTOLOGY provides sufficient details pertaining to techniques and activities used in the ontology development process. This is considered one reason for the high adoption rate of this method in ontology building.

Table 10 The Criteria for Methodology Selection

Methodologies	Type of development	Collaborative construction	Reusability support	Degree of application dependency	Life cycle	Strategies for concept selection	Methodology details	Inter-operability support
Enterprise model approach	Stage-based	No	Yes	Application semi-independent	No	Middle-out strategy	Some details	No
TOVE	Stage-based	No	Yes	Application independent	No	Middle-out strategy	Some details	No
METHONTOLOGY	Evolving prototype	No	Yes	Application independent	Yes	Middle-out strategy	Sufficient details	No
KBSI IDEF5	Evolving prototype	No	Yes	Application independent	No	Not clear	Some details	No
CYC Methodology	Evolving prototype	No	Yes	Application independent	No	Not clear	Some details	No
101 Methodology	Evolving prototype	No	Yes	Application independent	No	Developer's consent	Some details	No

UPON	Evolving prototype	No	Yes	Application independent	Yes	Middle-out strategy	Some details	No
SENSUS	Does not mention any	Yes	Yes	Application semi-independent	NO	Bottom-up	Some details	Yes
On-To-Knowledge	Evolving prototype	No	No	Application independent	Yes	Middle-out strategy	Some details	No

2.3.5 Principles of Ontology Design

A comprehensive methodology for ontology development should involve principles to confirm the quality of the proposed ontology. Arp, Smith, and Spear highlighted in their book, *Building Ontology with Basic Formal Ontology*, (2015), the general principles that need to be kept in mind when developing an ontology (Arp et al., 2015). These principles are: (1) Realism—refers to the general feature of reality in the form of universals and relationships between these universals. (2) Perspectivism—the occurrence of several accurate descriptions of reality. (3) Fallibilism—the ability to revise an ontology. (4) Adequatism—a represented entity that should be taken seriously on its own, and is not considered to be reducible to another entity. (5) Reusability—refers to use of the existing ontology. (6) Balance utility and realism—refers to the fact that an ontology could be developed without restriction on its utility, as a short-term utility may impact its long-term utility. (7) Open-ended process—the ontology should be designed so that it can be expanded and modified over time. (8) Low-hanging-fruit—refers to defining general terms first, then represents more complex terms. For interoperability and reusability, the Open Biological and Biomedical Ontologies Foundry (OBO) and the NCBO (Smith et al., 2007) have developed “Best practices” in ontology design. The guidelines include several principles for collaborative, coordinated development and integration of biomedical ontologies (Smith et al., 2007). OBO Foundry Principles include: (1) Format—a common formal language. (2) URI—classes and relations should have Uniform Resource Identifiers (URIs). (3) Versioning—discloses ontology versioning through metadata to reflect changes made. (4) Documentation—on an ontology website, documents the ontology in sufficient quality and detail. (5) Users—shows evidence for multiple independent users.

(6) Authority locus—serves as a responsible leader and developer team/mechanism for contact and feedback. (7) Maintenance—the ontology should be maintained with appropriate regularity, rigorous quality, and a funding source. (8) License—the ontology should be openly available via the OBO foundry. (9) Content delineation—classes and relations should have clearly delineated content of acceptable precision. (10) Content coverage—a sufficient number of concepts and terms to cover domain. (11) Content Quality—both formal correctness and correctness of content. (12) Textual definition—textual and formal definitions for all class terms. (13) Naming conventions. (14) Relations—one method that represents relations by using an upper-level ontology, such as Basic Formal Ontology (BFO). (15) Conserved URIs—guarantees interoperability.

2.3.6 Upper-Level Ontology

Biomedical ontologies have increased dramatically based on escalating methods developed for their construction. The majority of these methods, however, do not support interoperability and knowledge sharing. As a result, many ontologies were built in isolation and without their intent to be integrated with other ontologies. Many lack formal definitions and are not based on formal logic. Using an upper ontology offers the highest level structural template related to interoperability between represented domains (Arp et al., 2015). As a unifying upper ontology, BFO was developed for biomedical domain ontologies. It ensures that all ontologic classes/entities are placed in the correct kind of hierarchy. Because of BFO's generality and the small size of its structure, many large projects and biomedical ontologies use BFO's as their upper-level ontology (Arp et al., 2015). This means that other ontologies are interoperable through BFO (Bug et al., 2008). More information on BFO entities will be discussed in the next chapter.

Summary

The literature was reviewed to evaluate factors impacting medication adherence and clarify how these factors relate to adherence behavior to enhance behavior change interventions. The review found medication adherence to be multidimensional and dynamic—impacted by intrapersonal, interpersonal, and contextual factors, thus making behavior change a complex problem. This complexity requires robust approaches for organizing and curating knowledge effectively to facilitate the accumulation and comparison of findings in the literature. Effectively accumulating knowledge is hindered by the inconsistent use of terminology and categorization. Although the literature adopted WHO dimensions to categorize factors that influence medication adherence, this category is not suitable for a computation representation of these factors, because of (i) a lack of uniformity in class categorization (e.g., side effects were represented in one study under patient-related, while in another study, it fell under medication-related); (ii) discrepancies in class hierarchy with some factors grouped directly with the main class (e.g., severity of disease fit under disease-related), while others had sub-categories (e.g., age under demographic-related); and (iii) lack of a concrete definition for the categories. It is essential to categorize and structure these factors to study complexity of medication behavior, allocate resources, and plan interventions. The resulting ontology can be used for decision support in medication adherence management programs.

Next, information technology platforms used to improve patients' behavior were reviewed. Although various platforms were used to improve patients' behavior, there was a need to understand causes of that behavior. The review examined behavioral theories or models that were applied to develop these interventions and their impact on health

outcomes. The literature review, however, shows that many articles are atheoretical or their theories are unspecified. Among studies that implemented theories, often theoretical constructs that describe the same concepts were unlabeled, concepts were found to lack formal definitions, and theories included overlapping constructs and inconsistent use of terminology. Such inconsistencies may limit the behavioral theories' application and evaluation, which impedes development of new theories.

Finally, biomedical informatics research related to ontology development was reviewed; it showed that ontology plays a significant role in analyzing, structuring, and implementing domain knowledge due to its ability to capture a common understanding. It was also used to facilitate the interoperability of heterogeneous information sources and enhanced communication between people and systems, as it provided terms, definitions, and relationships among these terms. The reviews discussed various methodologies and principles that were proposed and used to build and validate ontologies. They provided a brief comparison that would be helpful in deciding which approach would be more suitable to build the medication adherence behavior ontology. This section highlighted the importance of creating an ontology that can integrate and interoperate with other ontologies to facilitate knowledge sharing among experts.

CHAPTER THREE: GUIDING PRINCIPLE FOR ONTOLOGY DEVELOPMENT

Behavioral ontologies are difficult to engineer due to the vast and complex nature of behavior knowledge (Fabrigar, Petty, Smith, & Crites Jr, 2006). The instability of behavioral knowledge and constant changing in the behaviorist's understanding of this domain add further complications. Ontology development is a collaborative, iterative, and ongoing process, which implies involvement of various people with different viewpoints, making it difficult to define (Bilder et al., 2009). Although Medication-Adherence Behavior ontology (MAB-Ontology) represents the work and effort of a single author, it is designed to promote engagement with other biomedical ontology projects. MAB-Ontology is foundational, extensible, and requires continuing cooperation and curation to age gracefully (Cimino, 1998).

As described in chapter two section 2.3.3, no single methodology exists for developing ontologies. However, some criteria can be useful in guiding the methodology selection. Based on the criteria represented in Table 10, the METHONTOLOGY and UPON methodologies were considered the best candidates for developing the medication-adherence behavior ontology (MAB-Ontology). Both methods are application-independent, meaning there is no need for pre-assumption regarding their use to which the ontology will be put into knowledge-based systems. Moreover, they clearly recommend the life cycle that identifies a set of stages through which the ontology moves during its lifetime. They also adopt the middle-out approach to determine the most relevant terms as a first step before generating and specifying them. Unlike UPON, METHONTOLOGY provides adequate information about how information is gathered, organized, and evaluated through the ontology development life cycle. It also provides

sufficient detail on steps related to updating and correcting the implemented ontology. Moreover, METHONTOLOGY uses a set of intermediate representations (IR) to summarize knowledge into graphics and tables that can be understood by both domain experts and ontology developers. Although METHONTOLOGY and UPON methodologies support re-usability and make use of existing ontologies, they fail to support interoperability between systems.

Therefore, METHONTOLOGY was selected as the most suitable methodology for guiding development of the MAB-Ontology. In fact, modeling a domain requires a customized approach based on the domain's nature and purpose of the ontology to specify and represent the domain (Smith et al., 2007) and flexibility of the METHONTOLOGY methods, which allow its adoption to match the needs of the development of the medication-adherence behavior ontology (Prieto Ferrero, Lloret, & Palomar, 2014). It allows for the incorporation and use of upper-level ontology—the Basic Formal Ontology (BFO). Using BFO and following its principles is to guide domain ontology development and to support interoperability between the developed ontology and other ontologies (Arp et al., 2015). As a result, these methods entail six steps that have been adopted to develop a medication-adherence behavior ontology (Figure 3):

1. Domain specification by defining its purpose and scope.
2. Knowledge acquisition of a given domain.
3. Knowledge structuring and organizing within a set of Intermediate Representations (IRs).
4. Model Integration with the upper-level ontology and reusing existing ontologies.

5. Ontology concretization in a computer-tractable representational artifact (i.e., using formal language).
6. Ontology Evaluation during each phase of the process and between phases of the life cycle Methods Overview

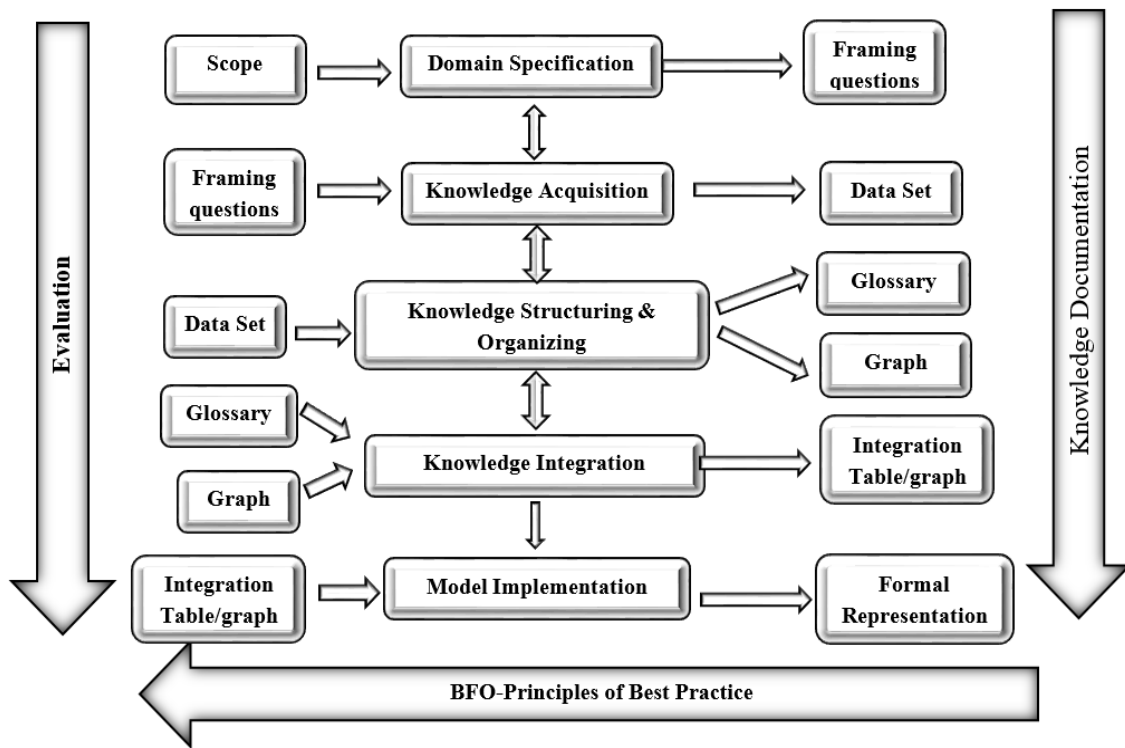


Figure 3 MAB-Ontology Methodology Overview

3.1 Domain specification

Domain specification is the first step in ontology building, wherein the purpose and scope of the ontology is defined. Defining use and scope of an ontology is essential to determining the ontology's complexity and the approach adopted for its development. The cost and complexity of building an ontology could vary, according to its use (Sang, 2009). This step is divided into three parts: (i) definition of the purpose of the ontology, including domain use and intended users; (ii) the approach taken for ontology building; and (iii) the scope of the ontology, including a set of terms represented.

3.1.1 The Purpose of the Ontology

This step precisely defines the goal the ontology of medication adherence domain for which it was created, its intended uses, and a scenario of use.

3.1.2 Approaches for Ontology Building

Three types of ontology building approaches existed; namely: The top-down approach, where the building process start with the most generic concepts and move to more specific concepts. The bottom-up approach, where the process moves from specific concepts to high-level abstractions (Francesconi, Montemagni, Peters, & Tiscornia, 2010). And, the middle-out approach, which is a combination of both approaches. It is an integration of theoretical modeling and text analysis that balances the level of detail, which, in turn, acquires knowledge, as needed (Fernández-López et al., 1997).

3.1.3 Scope of the Ontology

The scope of the ontology which is discussed in the next chapter (i.e., chapter four), is defined by using competency questions and use-case scenario. Competency questions are a list of natural language questions formulated on the motivation scenario (Grüninger & Fox, 1995). Use-case scenario uses to demonstrate an ontology application and is defined as an artifact that describes the expectation of the proposed ontology that should be satisfied after development (Grüninger & Fox, 1995; Iqbal, Mustapha, & Mohd. Yusoff, 2013). Both motivation scenario and competency questions are considered documents for the requirement specification; they are used to guide the scope of the ontology. That is why they are utilized to test the efficacy of ontology in answering those questions and solving the scenario problem.

3.2 Knowledge Acquisition

Knowledge acquisition involves identification of data, interpretation of this data (information), and analyzing and structuring this information (knowledge) for representation purposes (Mendonça, Coelho, de Andrade, & Almeida, 2012). It is an essential step for building an ontology. Through this step, insights into how medication adherence is realistically represented can be identified and modeled. To this end, resource availability is determined through exploring several areas of domain knowledge. This process is an iterative; it involves cycles of reviewing the literature and extracting information, as needed. Additional terms may be necessary to ensure the hierarchy's completeness.

3.2.1 Knowledge Sources

Several knowledge sources were investigated to ensure consistency, objectivity, and better quality of the developed ontology. (1) Scientific papers: Literature related to medication-adherence behavior that were systematically reviewed. The motivation behind using scientific papers was that they provide comprehensive and objective information on a complex and broad topic, such as medication-adherence behavior, which is beyond a single human expert (Ogundele, Moodley, Seebregts, & Pillay, 2015). Also, the rigorous process that a scientific paper went through before publication guarantees its validity as a source of knowledge used to build medication-adherence behavior. Moreover, scientific papers reflect complexity of the domain and its different perspectives, while also serving as a diverse representation of what the ontology intended to solve. Additionally, medical practice and decision making informed by knowledge was derived from clinical papers, which enhances ontology adoption and use. (2) Textbooks

also served as sources of domain understanding and modeling in this project, because they provided solid grounding in the subject and a basis for terms and definitions (Boyce & Pahl, 2007). (3) Online repositories of formal ontologies were perused to identify relevant terms in order to enhance ontology reusability and prevent reinventing the wheel: Ontobee- <http://www.ontobee.org/>, OBO Foundry-<http://www.obofoundry.org/>, and Bioportal- <https://bioportal.bioontology.org/>. (4) Domain-related experts were also consulted to strengthen understanding of domain content.

3.2.2 Source Selection

Sources were identified and clustered into categories based on project scope and aims. The first category was coded “Medication Adherence Assessment Literature,” which included key articles that describe different methods used to measure medication adherence. Category two was coded “Determinants of Medication Adherence Literature,” as this broad project will narrow in scope, based on a disease type. Therefore, only literature that discussed adherence to endocrine therapy among breast cancer patients was reviewed (chapter two, part one). Theories used to understand and change medication adherence were reviewed, collected, and grouped under “Theory of Behavioral Change.” “Medication Adherence Data Standard” was the code given to the: (a) taxonomy or categories for factors affecting medication adherence, such as five dimensions of the World Health Organization (WHO) category (Organization, 2014); (b) taxonomy used for medication adherence interventions, such as a Behavior Change Technique (BCT) project (Michie et al., 2013); and (c) taxonomy of medication adherence, such as Ascertaining Barriers to Compliance Project (ABC) (Vrijens et al., 2012). The sources under this category were analyzed for possible inclusion at this stage. The fifth category

was coded “Medication Adherence–Related Terms,” in which BioPortal, OBO Foundry, and Ontobee were reviewed to determine relevant terms and concepts used in similar conditions or situations. This step was taken to initially follow the principle of the OBO Foundry to ensure interoperability with existing ontologies and obtain feedback on the upper-level grouping, the level of granularity and terminology structure. Finally, domain experts—committee members—were consulted to enhance understanding of domain content. This diversity in the sources guaranteed domain knowledge saturation, as it elicited a vast set of terms from diverse source types that were carefully scrutinized for clear understanding.

3.2.3 Searching Strategy

1. Medication Adherence Assessment Literature Search Strategy.

Several electronic databases were employed to search Boolean phrases, namely “PubMed, Embase, and EBSCO.” CINAHL and PsycINFO were included when searching the EBSCO database (Figure 4). Conferences, dissertations, book chapters, letters, commentaries, reviews, case series, and case reports were not included in this category. Reference to related articles were also examined. MeSH index terms were used and included—(adherence OR compliance OR persistence OR concordance) AND (Tamoxifen OR Aromataze Inhibitors OR adjuvant hormone therapy) AND (adult OR elderly OR Women OR Men OR Female OR Male) AND (breast cancer) AND (assessment OR measurement OR direct assessment OR indirect assessment OR subjective assessment OR objective assessment OR monitoring device OR electronic device OR self-monitor OR self-monitoring OR drug monitoring OR self-administration OR reminders OR management OR process outcomes OR managing OR administration

OR drug administration schedule OR medication possession ratios OR self-report OR gap OR measurement). A comprehensive search strategy was implemented to avoid missing potentially relevant information. An article was included if the study abstract was available, the study's design and methods were clearly described, or the article measured adherence among breast cancer patients as a primary outcome. Articles reporting clinical outcomes as indicators of medication adherence were not included, because many other factors, other than adherence, could influence clinical outcomes. If an article reported medication adherence or a persistence rate and that described methods used to calculate adherence levels, it was included. The search was conducted for English-language publications between 2000 and 2017. The feature, Endnote, was used to sort and remove duplicates. Relevant terms were extracted and inserted in a structured sheet using Microsoft Excel. Terms were organized based on source type.

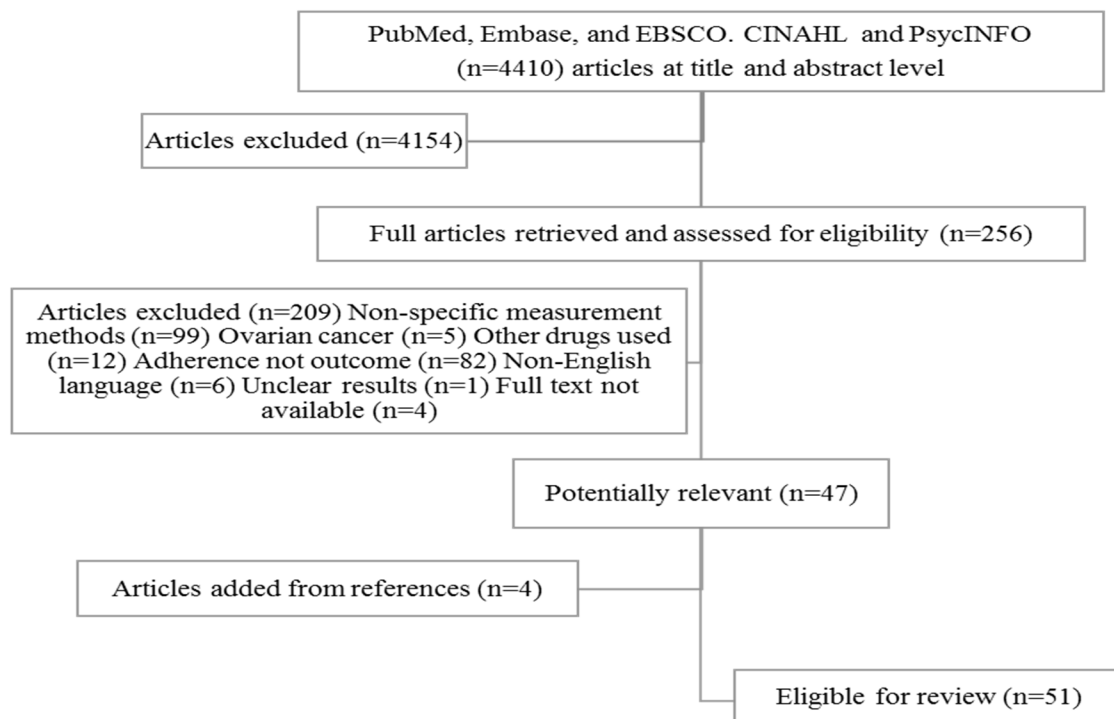


Figure 4 Medication Adherence Assessment Literature

2. Determinants of Medication Adherence Literature Search Strategy.

The searching strategy for the factors impact medication adherence among breast cancer women was discussed in chapter two section 2.1.

3. Theory of Behavioral Change Literature.

Two strategies were implemented to search for theories used for medication adherence: First, a systematic review was carried out to investigate the theories/model used to understand, sustain, or modify long-term medication adherence (Figure 5). MEDLINE, CINAHL, PsycINFO, ScienceDirect, and ERIC, were searched using the Medical Subject Headings (MeSH) terms “adherence [OR] compliance to medication [AND] theories [OR] models [AND] chronic disease” from the start date of each database through August 31, 2017. Chronic disease categories were chosen, because of their high global burden (Hamine, Gerth-Guyette, Faulx, Green, & Ginsburg, 2015).

Eligibility criteria for this review included: (i) Titles and abstracts were searched in an effort to limit search specificity and minimize the volume of literature, because behavioral theories are a broad and complex domain. Thus, theory or model needed to be mentioned explicitly in the title or abstract. (ii) Studies eligible for inclusion needed to mention theory about medication adherence behavior (i.e., studies using theory to understand medication adherence, determine factors impacting medication adherence, or reference designed interventions that increased/sustained medication adherence). (iii) Articles failing to show a clear methodology were excluded. (iv) Narrative reviews, descriptive studies, books, case-studies, letters, reports, conferences, commentaries, theses, and dissertations were not included at this stage. (vi) Search strategy related to publication date was not restricted to a specific date. All articles were included up to the

date of the search—August 31, 2017. (vii) If medication adherence proved to be the outcome, those articles were selected. (viii) Studies were excluded if they used theoretical constructs from different theories to create frameworks, such as theoretical Domain framework. Data extraction included: author(s), journal, country of study, type of study (intervention, evaluation, review), study design (qualitative, quantitative, mixed methods), diseases category, behavior measured (direct, indirect, subjective, objective), theory name, constructs name, measurement of adherence and theoretical constructs, stage of adherence (initiation or continuation), and theory role (guiding intervention, understanding determinant of behavior, evaluation of behavior or intervention).

Once a list of medication adherence theories was extracted from the review implemented in the previous step, the second strategy was conducted. This step included a manual search in Google for each theory or model, reviewing it for originality (Figure 6). The goal of reviewing the original theory or model was to investigate the relationship between theoretical constructs and whether the first author defined measurement criteria. Out of 12 books, two textbooks qualified for inclusion as a guide for theoretical constructs extract: *ABC of Behaviour Change Theories*(Michie, West, Campbell, Brown, & Gainforth, 2014) and *Cognitive and Behavioral Theories in Clinical Practice*.(Kazantzis, Reinecke, & Freeman, 2010). Two out of four behavioral-related websites browsed for behavioral theories and theoretical constructs were selected—Grid-Enabled Measures Database <https://www.gembeta.org/Public/Home.aspx> and Nursing Theories a companion to nursing theories models <http://currentnursing.com/nursingtheory/>.

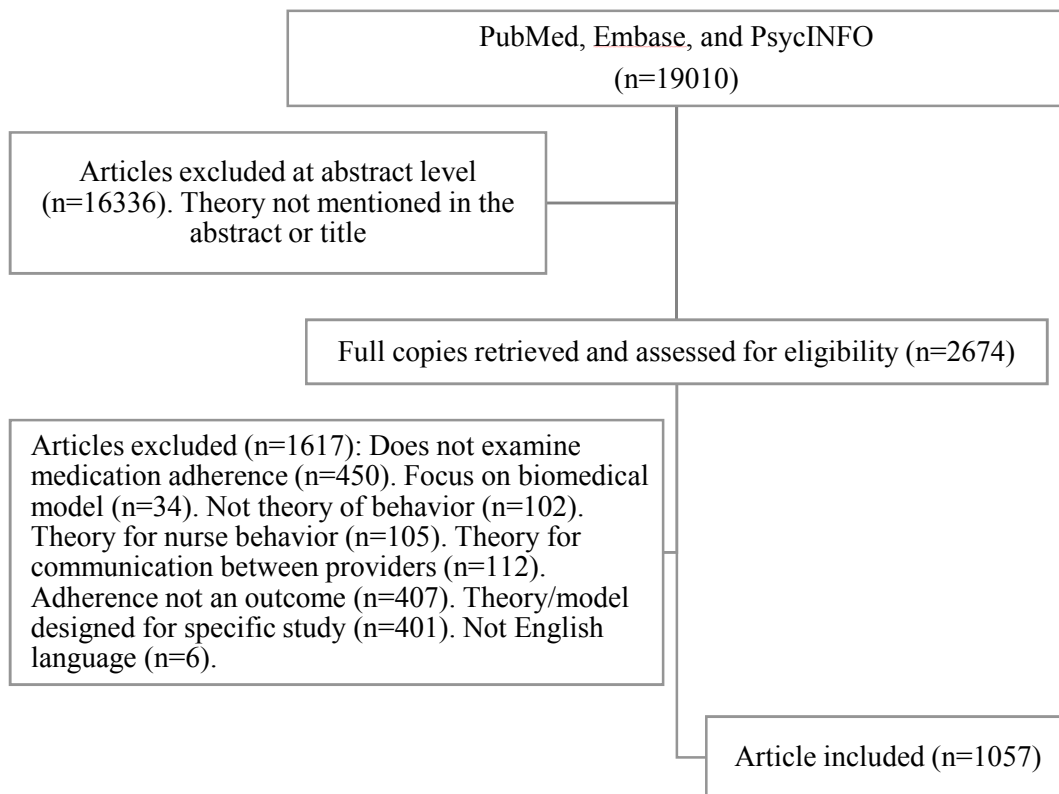


Figure 5 Theory of Adherence Change Literature

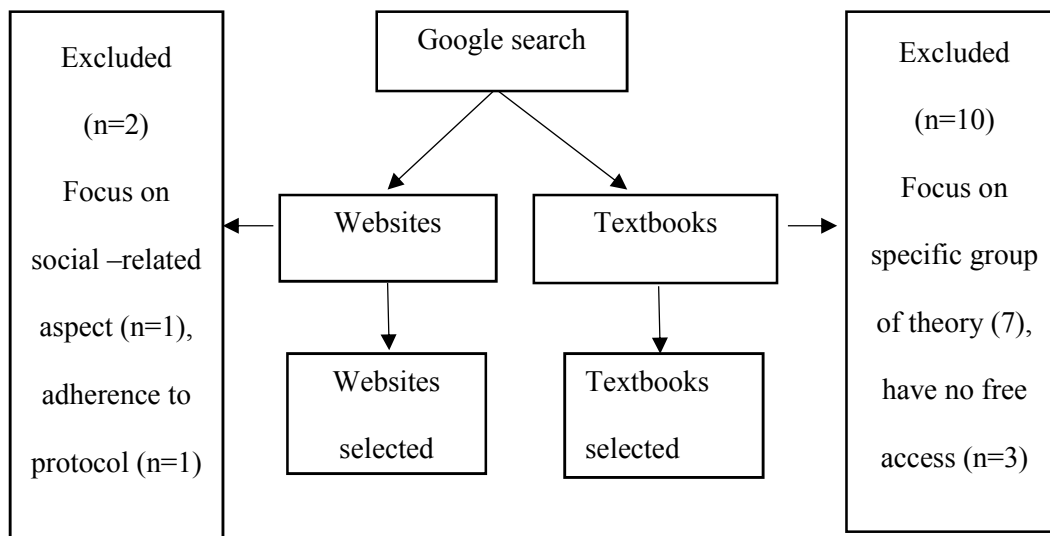


Figure 6 Theory of Adherence Change Among Books and Websites

4. Medication Adherence Data Standard.

This step included analyzing WHO's five dimensions to medication adherence (Sabaté, 2003); the Behavior Change Technique (BCT) project (Michie et al., 2013); and the Ascertaining Barriers to Compliance Project (ABC) (Vrijens et al., 2012) to determine possible relevant classes and relationships. WHO's five dimensions included patient-, disease-, medication-, socioeconomic-, and healthcare system-related medication adherence. Each dimension represents several interacting constructs. BCT includes 93 intervention strategy categories to improve medication adherence. All the terms extracted—12 categories—related to medication adherence were considered for inclusion in this step. The ABC project was also considered. The names and definitions/descriptions related to medication adherence behavior were extracted for further analyses and inclusion consideration.

5. Medication Adherence–Related Terms.

Three ontology repositories namely, Bioportal, Ontobee and OBO Foundry, were searched for relevant terms to determine how data was standardized in similar or related domains and what similar classifications and relationships existed. They were then nominated for inclusion. If a term was represented differently between two ontologies, both representations were extracted for further analysis in the next step.

6. Tacit Knowledge.

A discussion with the committee members was conducted to acquire the domain terminologies and understand information and data structures. Information was collected by writing notes and taking a picture of knowledge presented on the blackboard or on paper. The information was then transcribed and analyzed.

3.2.4 Source Analysis

Select sources were analyzed using a systematic approach involving questions applied to all source types. These questions were designed to guide data extraction and inform domain conceptualization. The framing questions were broadly outlined to capture general information in the same way that conceptualization captures high-level domain knowledge. Using the same questions against each source type ensured generalizability and strengthened the knowledge that was covered. If information was missed in one source type, another would address it.

The following questions were created to reflect project aims:

1. How is medication adherence described/defined in the source type?
2. How is medication adherence measured in the source type?
3. How is medication adherence impacted by the source type?
4. How is intervention described in the source type and what does it contain?
5. What are critical themes and concepts regarding MAB research in this source type?

The answers to the above questions were analyzed and categorized against each source type in a structured data sheet to abstract the summary of general terms from the different sources. For example, phrases, such as “initiation non-adherence,” appeared in several articles. This implies that this term was an important domain concept to be included in the knowledge representation step. To ensure relevance, authoritative source selections were nominated for each source type. For example, the phrase, “Initiation non-adherence,” was included as a source of “Medication Adherence Assay Literature” source type, as was found in a paper by Cramer et al. (2008). When the terms were extracted, an OBO/BFO principle for building ontology followed (chapter two part three). The

principle of low-hanging fruit was adopted whenever possible, wherein, more general and simple universal terms and their relations were extracted first, then more complex terms were identified (Arp et al., 2015).

3.3 Knowledge Structuring Using Set of Intermediate Representations

This step's title changed from "Knowledge Conceptualization" as named in METHONTOLOGY method to "Knowledge Structuring." Because the term "conceptualization," could be misleading, as it may refer to cognitive representation. The term "concept" was defined as "unique units of thought (Arp et al., 2015)." Based on this, the definition of "medication adherence," for example, would be "unique units of thought in which the patient correctly follows the medical advice." The representational model of medication-adherence behavior, however, represents the reality; for example, scientific papers, books, and databases, but not what was in the developer's mind. The goal of the ontology is to describe the reality that corresponds with the general terms used by scientists, not to the concept that is in people's minds (Arp et al., 2015).

To this end, a set of intermediate representations involving tables and graphs were developed to bridge the gap between reality of the domain and languages in which the ontology was formalized. This step allowed for domain evaluation before implementation. A resulting structure describes the problem and its solution in terms of domain vocabulary identified independent of any implementation language. Several activities were involved in this step.

3.3.1 Building a Glossary of Terms

The glossary included all terms, their synonyms, definitions/descriptions, and types (e.g., type/universal, relation, instance). A summary of relevant terms or phrases

extracted from all source types, which were represented in the data structure sheet, were merged, analyzed, collected, and listed in a “glossary” using “Microsoft Excel Sheet” to facilitate the analysis. “Merging” refers to grouping or putting all synonyms together to remove redundancies, as different terms may describe the same entity. For instance, terms, such as a drug, medicine, and regimen, refer to the same word, “medication.” “Analyzing” includes two steps; it specifies parts of speech (verb versus noun) and defines the exact meaning of terms. To specify terms as parts of speech, an object-subject-predicate strategy was carried out (more information in the next section). Since a term can have multiple meanings, it was examined carefully. For example, “treatment” may refer to a medication/drug or a process of care, such as surgery. Therefore, medication adherence or medication-taking behavior, for example, cannot be a subclass of treatment unless both terms specified and carefully defined.

BFO principles for ontology design were followed when building the glossary of terms. The definition was borrowed from an equivalent entry into another ontology. If no matching or equivalent definitions existed, a dictionary-based definition, books, or literature was consulted, or a creative definition was applied. To adopt or give a definition to terms, the definition must explain, clearly and coherently, the important distinguishing features that make the term what it is. Some definitions lack clarity and are not coherent, such as the case for “European,” where it is defined in SNOMED as “European is an ethnic group.” The “is-a” means it is a “subtype of.” Therefore, every instance of European must reference an ethnic group (Arp, 2010). Also, the definition may be circular, meaning a term is defined in the definition. For example, the term “coping behavior quality” in Ontology of Biological Attributes at

<https://bioportal.bioontology.org/ontologies/OBA> means “coping behavior quality” is defined as the “quality of coping behavior.” The term, “Expectancy,” listed in the National Cancer Institute Thesaurus at <http://purl.bioontology.org/ontology/NCIT>, is defined as “something expected, especially the value.” “Desire” is also defined as “a desire to have an act occur,” according to the Health Level Seven Reference Implementation Model, Version 3 at <http://purl.bioontology.org/ontology/HL7>. Another problem with the definition is confusion around its perception versus reality. An example found in BRIDG was an “adverse event is an observation of a change in the state of a subject that is assessed as being untoward (Arp, 2010).” These kinds of definitions lead to confusion between what exists in reality and what is a subjective mental representation. Additionally, another mistake that could occur if the term is defined based on its ontology-use, such an error being found in the Medical Subject Headings (MeSH) database, where “National Socialism” was defined as “a MeSH Descriptor,” created confusion with National Socialism as an actual political movement (Arp, 2010).

In order to avoid these types of problems, an Aristotelian definition was adopted when the definition was formulated or even adopted, wherein “A is B, which is C.” A is a child (subclass_of) B in the taxonomic hierarchy and C refers to the defining characteristic of what elects those Bs that are As. For example, a human (A) is an animal (B) who is rational (C). Here, the distinction was made about all other sibling classes (child_of B), such as a Cat is an animal, but is not rational. So, for someone to be a member of a class of humans, it is necessary and sufficient to be an animal and rational. Anything that fulfills these conditions is a human. Any intersubstitutable terms having this definition were followed. For example, “breast cancer is_a cancer located in the

breast,” (Schriml et al., 2011) where cancer is defined as “a disease of cellular proliferation that is malignant and primary, characterized by uncontrolled cellular proliferation, and local cell invasion and metastasis (Schriml et al., 2011). Therefore, breast cancer is “a disease of cellular proliferation that is malignant and primary, characterized by uncontrolled cellular proliferation, local cell invasion, and metastasis that is located in the breast.” The inspiration behind using an Aristotelian definition is to provide a consistent format for definitions’ representation, thus facilitating interoperability and reusability regardless of the domain at issue. Also, it facilitates the computational inferences that are essential for researchers using computational systems (Arp, 2010).

3.3.2 Knowledge Representation Using Triplet

The terms extracted from the previous step are represented in the triplet of “subject, predicate, and object.” Subject refers to the entity to be described (i.e., what or whom the sentence is about); predicate defines the type of relation that exists between the subject and object; it always contains a verb, tells something about the subject, and connects the subject with the object. And the object is an entity or value describing the subject through the relation that connects them (Christophe, Bernard, & Coatanéa, 2010). Anything can be described using this simple triple. The subject of one triple could become an object of another triple, or vice versa. The entities can participate in different relations and play different roles in these relations. For example, the predicate “title” associates this dissertation (the subject) with its title, “An Ontology for Formal Representation of Medication Adherence: Case Study in Breast Cancer” (the object).

3.3.3 Building the MAB Hierarchy

After the terms have been selected, defined in the glossary, and represented in triplets, a hierarchy among the terms was developed. All terms were grouped into either types, instances, or relations. Term levels in hierarchy were specified (i.e., if the general universals/types are defined initially, such as medication adherence, then more specific terms were created, such as initiation adherence and implementation adherence. Every instance of implementation adherence also served as an instance of medication adherence. Terms at the lower level need to adhere to all characteristics that are asserted to be true in the ontology from their parents. “A is B.” Class B is a subclass of A, if and only if each instance of Class B is also an instance of Class A (Gómez-Pérez, Fernández, & Vicente, 1996). As mentioned previously, this inheritance ensures logical consistency when the terms are defined and guarantees clear differentiations among the levels of abstractness within the ontology and the likelihood of automated reasoning (Arp, 2010). Since the Basic Formal Ontology (BFO)—an upper-level (formal, domain-neutral) ontology, is used to support creation of a lower-level domain ontology, “Medication Adherence Behavior ontology (MAB-Ontology),” some definitions need to be adjusted. For, example, Belief is a disposition that is realized by process. A disposition is a class under the realizable entity in BFO. The BFO framework for an MAB-Ontology contains MAB-Ontology terms mapped to or defined based on BFO neutral terms and relations between terms. Based on the BFO, the terms and relation can be primitive or defined.

1. Primitive and defined terms

Primitive terms are basic to our understanding of reality. They cannot be defined in a non-circular fashion; instead, they should be elucidated or exemplified or use an

axiom to be explained (Arp et al., 2015). For example, “entity” in BFO is defined as anything that exists or has existed or will exist, such as medication, the process of taking medication, the patient who takes medication, and information that resulted from assessing medication-taking behavior.

Defined terms are those terms defined by using primitive terms or other previously-defined terms. For example, “breast cancer” can be defined as “a thoracic cancer that originates in the mammary gland.” (Schriml, 2016) Such a definition is built from another predefined term, “thoracic cancer,” which, in its term, is defined as “an organ system cancer located in the thoracic cavity that develops in the different types of cells within the lungs, as well as less common cancers of the esophagus, trachea, or chest wall.” (Schriml, 2016) BFO-defined terms are based on an Aristotle’s definition adopted when building the glossary in the previous step, wherein $A = \text{Def. } B$, which differentiates D s. A is the term to be defined, B is an immediate parent in the hierarchy, and D is the differentiating criteria specifying what it is about certain B s in virtue of which they are A s. For example, “medication adherence management” is a planned process of monitoring and supporting patient adherence to medication by healthcare systems, providers, patients, and their social networks. “Consciousness raising” is a type of management of the adherence process; it is defined as a “management of the adherence process in which the patient was provided with information, feedback or confrontation about the causes, consequences, and alternatives for problem behavior.”

2. Primitive and defined relations

Primitive relations are those relations that cannot be defined and must be accepted as primitive, such as “instance of” relation. This type of relation holds some particulars

(i.e., individual) and some universals (i.e., type). This relation cannot be defined. Its meaning, however, can be elucidated by example or axiom. This relation takes the form of “a” is_instance_of “A” in which “a” represents an individual or a particular in class “A.” For example, “missed dose” is_instance_of “medication adherence” and “medication possession ratio” is_instance_of “medication possession measurement. More types of primitive relations will be discussed in the next section. (ii) Defined relations are those explained or defined by using other primitive or defined relations or terms. For example, “A” is_a “B” =def. A and B are universals, and for all of a (if a is an instance_of A, then a is an instance_of B). Therefore, breast cancer is_a thoracic cancer. Breast and thoracic cancer are universals for all breast cancer instances (if ductal carcinoma *in situ* is_instance_of breast cancer, then ductal carcinoma *in situ* is_instance_of thoracic cancer).

3.3.4 Hierarchy of MAB-Ontology Based on BFO

Based on BFO, entities in reality are classified into two general groups: continuant entities and occurrent entities, as shown in Figure 7.

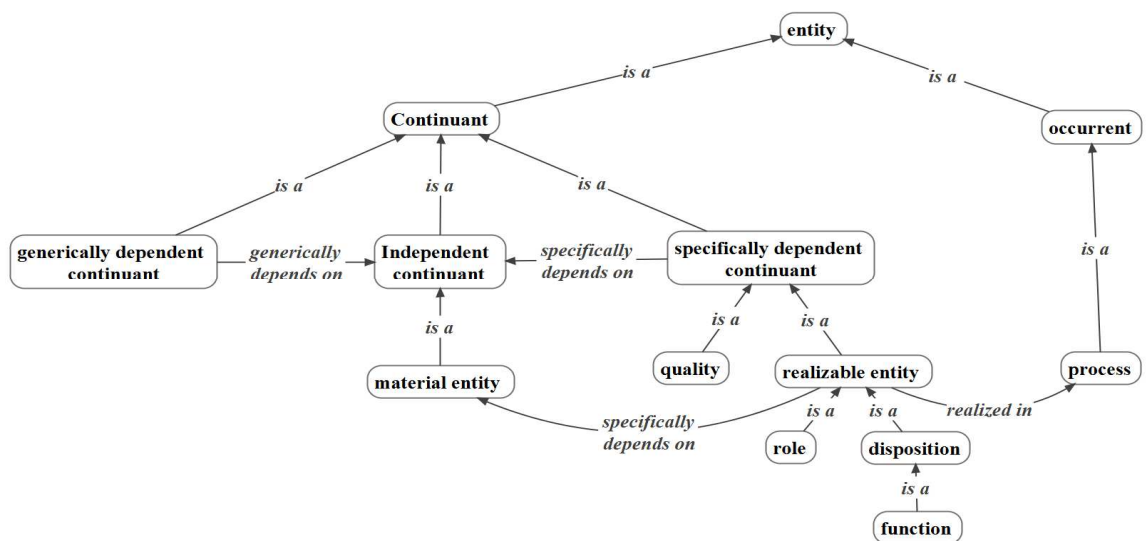


Figure 7 The Hierarchy for BFO

3.3.4.1 Occurrent Entities

Occurrent entities unfold themselves in time or they are the instantaneous boundaries of such entities (for example, a beginning or an ending), or they are temporal or spatiotemporal regions, where such entities occupy_temporal_regions or occupy_spatiotemporal_regions (Arp et al., 2015). Occurrent entities are categorized into four types: process, temporal region, process boundary, and spatiotemporal region. For purposes of this dissertation, only process and temporal region are defined.

1. Process

Process is an occurrent entity that exists in time by occurring or happening. It has temporal parts, such as a beginning, middle, and end, and always depends on some or at least one material entity (Arp et al., 2015). An example is a process of medication adherence, or the process of measuring medication adherence. Being has temporal parts, which means that there is no instance in time during which this process would exist as a whole. Instead, it unfolds along a series of temporal parts, such as taking medication in the morning, taking it in the evening, or the first minute of taking medication. The formal definition is: P is a process = Def. p is an occurrent that has temporal proper parts, and for some time, t , p s-depend_s_on some material entity at t (Smith et al., 2012).

2. Temporal Region

Temporal region is an occurrent entity that is a part of time, as defined relative to some reference frame. Temporal region with extent is a one-dimensional temporal region. If it is not with extent, it is a zero-dimension temporal region. The temporal region does not have a closure axiom, because the subclasses do not exhaust all possibilities (Smith et al., 2012)—for example, five years of continuously taking Tamoxifen.

3.3.4.2 Continuant Entities

Continuant entities are those “entities that persist, endure, or continue to exist through time while maintaining their identity.” (Arp et al., 2015) A person is a continuant entity who persists his/her identity through time, no matter what happens throughout his/her life. He/she may gain weight, lose weight, lose a leg, or gain an artificial leg, yet he or she still perseveres an identity through time. Continuant entities categorize into independent, specific-dependent or generic-dependent continuants, as shown in Figure 7.

1. Independent Continuant Entities

Independent continuant entities do not depend on other entities. They are the bearer of specific and generic dependent entities (Arp et al., 2015) and are categorized into two types: namely, material and immaterial entities. A person is an example of an independent continuant who bears the patient role at a specific time. A person bears a biological sex (female or male). Breast cells bear cancer. A Medication Event Monitoring System (MEMS) (Sterns, Hughes, Masstandrea, & Smith, 2014) bears the function of recording the time and date each time the container is opened and closed. A pharmacy or hospital computer bears record of medication refills as a PDF or another format. Formal definition: B is an independent continuant = Def. b is a continuant that is such that there is no c and no t, such that b s-depend_s_on c at t (Arp et al., 2015).

a- Material Entities: Material entities are independent continuant entities that have a portion of matter as part (Arp et al., 2015), such as a person, the chest of a person, cell, a collection of cells, MEMS, or Drug.

b- Immaterial Entities: Immaterial entities are independent continuant entities that contains no material entities as parts (Arp et al., 2015), such as the surface of a cell or the surface of an organ.

2. Dependent Continuant Entities

Dependent continuant entities are continuant entities that depend on other existing entities in order to exist (Arp et al., 2015), such as in the previous example. For the role of being a patient to exist, it must be someone who exists and has this role at a time when he/she is sick. For a patient record or file to exist, there must be a computer or other technology that exists to bear this file. Dependent continuants are two types: specific or generic dependent continuants.

a- Specific Dependent Continuant Entities

Specific dependent continuants are dependent continuant entities (i.e., realizable entities and qualities) that depend on one or more specific independent continuants to exist and they cannot migrate from one bearer to another. If this independent continuant, upon which it depends ceases to exist, then this specific independent continuant entity will also cease to exist (Arp et al., 2015). For example, a function of MEMS is to record the date and time when Lori opens and closes the cap. It will not exist if the MEMS did not exist. Lori's low education level will not exist if she did not exist. Formal definition: B is a specifically-dependent continuant = Def. b is a continuant and there an independent continuant c that is not a spatial region and, as such, b s-dependes_on c at every time of t during the course of b's existence (Arp et al., 2015). (i) Realizable entities: Realizable entities are specifically dependent continuant entities that inhere in or have an independent continuant entity as their bearer, and whose instances require process in

order to be realized (manifested, executed, actualized) (Arp et al., 2015), as shown in Figure 8. For example, the role of being a patient, the function of MEMS, or the disposition certain people have to develop breast cancer.

(1) Role: Role is an external, grounded, realizable entity that inheres in specific dependent entities (the bearer) under special physical, social, or institutional sets of circumstances (i.e., external to the bearer) in which this bearer's physical makeup does not have to be changed if the role ceased to exist (Arp et al., 2015). For example, the role of being a patient under certain circumstances, such as being under the care of a physician or healthcare provider. Once this role has ceased treatment, the person's physical make does not change. Formal definition: *b* is a role that means: *b* is a realizable entity and *b* exists, because there is some single bearer that is in some special physical, social, or institutional set of circumstances in which this bearer does not have to be and *b* is not such that, if it ceases to exist, then the physical makeup of the bearer is thereby changed (Smith et al., 2012).

(2) Disposition: Disposition is an internal, grounded, realizable entity, a specific dependent entity that inheres in independent continuant entity (the bearer) under special physical circumstances (i.e., internal to the bearer) wherein the bearer's physical makeup has to be changed if the disposition ceases to exist (Arp et al., 2015). For example, the disposition to have breast cancer or breast cells or tissues under certain physical circumstances (e.g., a gene mutation). If the breast cancer ceased to exist, the physical makeup of breast cells or tissues would change. Formal definition: *b* is a disposition means: *b* is a realizable entity and *b*'s bearer is some material entity and *b* is such that, if it ceases to exist, then its bearer is physically changed, and *b*'s realization would occur when and because this bearer is in some special physical circumstances. Therefore, this

realization would occur in virtue of the bearer's physical makeup (Smith et al., 2012).

Function: Function is a disposition that exists in virtue of the bearer's physical makeup and this physical makeup is something the bearer possesses, because it came into being, either through evolution (in the case of natural biological entities) or through intentional design (in the case of artifacts), in order to realize processes of a certain type (Arp et al., 2015). For example, an aromatase inhibitor's function, such as Anastrozole (i.e., drug class), is to interfere with the action of aromatase, in order to reduce the production of estrogenic steroid hormones. In turn, the function of MEMS is to record the date and time the medication is taken every time the patient opens the cap. (ii) Quality: Quality is a specifically dependent continuant that, unlike a realizable entity, does not require any further process in order to be realized (Arp et al., 2015). For example, the patient's age, biological sex, level of education, the size of the tablet, the color of the tablet, and the taste of the tablet. The quality of a ridged entity means that if an entity is a quality at any time that it exists, then it is a quality every time that it exists. Formal definition: b quality_of c at $t = \text{Def. } b$ is a quality and c is an independent continuant that is not a spatial region, and b s-depends_on c at t (Smith et al., 2012).

b- Generically Dependent Continuant Entities

Generically dependent continuant entities rely on one or more independent continuant entities (i.e., they can migrate from one bearer to another), which can serve as their bearer (Arp et al., 2015). For example, a PDF file that contains a medication refill date and time from a pharmacy computer can migrate to a hospital computer. For this file to exist, there must be some physical storage device where it was saved (in this case, either a pharmacy computer, hospital computer, or physician's laptop). Formal definition:

B is a generically-dependent continuant = Def. b is a continuant that g-depends_on for one or more other entities (Smith et al., 2012).

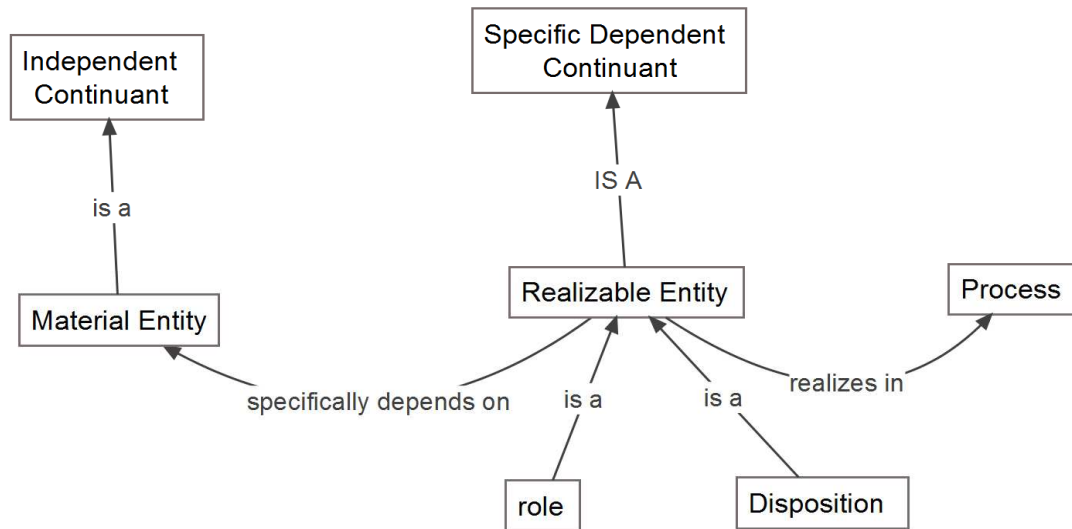


Figure 8 The Realizable Entity Hierarchy for BFO

3.3.5 Building Relations

The hierarchies defined in the previous step are connected via relations. Besides the “is_a” relations that are applied to build the hierarchy, further relations used to define BFO were adopted from the BFO 2 reference (relation ontology (RO)) (Smith et al., 2012) for building the MAB-Ontology. Based on BFO, three types of relations were used at this level: relations that hold between two universals, such as a “belief about capability ‘is_a’ belief;” relations that hold between instance and universal, such as “this patient ‘is_instance of’ patient;” or relations that hold between two particles, such as “this leg is_part of this patient.” Having these kinds of relations allows for use of the ontology in combination with information about particulars in the world to reason about those particulars. The outcome of this step is to build a table of relations. It involves relation

name, definition, source of the relation (domain), target of the relation (range), inverse relation, and relation property or characteristics.

3.3.5.1 Relations/Property Characteristics

1) Reflexivity: to say that relation R is reflexive is to say anything A bears relation R to something else. B also bears that relation to itself (Smith et al., 2012). For example, “knows” is a reflexive relation. Lori knows her physician, Jacob. Then Lori must know herself, too. If relation “is_a” is reflexive relation and a person is_a human, then the person must be a person, too. Relation “being the same age as” is reflexive, and with Lori “being the same age as” her physician, Jacob, at t, then Lori must be the same age as herself at t.

2) Symmetry: to say that a relation R is symmetric is to say that if A stands in relation R to B, then B also stands in R to A (Smith et al., 2012). For example, if relation adjacent_to is symmetric (on the instance level) and cell₁ is adjacent_to cell₂, then cell₂ must be adjacent_to cell₁.

3) Transitivity: to say that relation R is transitive is to say that if A stands in relation R to B, and B stands in relation R to C, then A also stands in relation R to C (Smith et al., 2012). For example, if a relation is_a transitive, and medication adherence is_a behavior, and behavior is_a process, then medication adherence is_a process, too.

4) Antisymmetric: To say that relation R is antisymmetric is to say that if A bears R relation to B and B bears R relation to A, then A and B are identical (Smith et al., 2012). If not, then they cannot hold this relation. For example, if part_of relation is antisymmetric, and cognitive process is part_of emotional process, then cognitive process and emotional process are identical (in this case, they cannot be identical).

3.3.5.2 MAB-Ontology Relation Based on BFO

This section represents some of the relations used in MAB-Ontology. A complete list of the included relations is tabulated in the next chapter.

1) “is_a” relation: is relation used to relate subtypes in BFO to their parent type and can be transitive, reflexive, or antisymmetric. This relation is defined using primitive relation “instance_of.” For example, medication adherence is_a medication-taking behavior.

Every instance_of medication adherence is_instance of medication-taking behavior. For example, a missed dose is_instance of medication adherence, then it is an instance_of medication-taking behavior. Formal definition: $A \text{ is_a } B = \text{Def. for every instance of } a, \text{ if } a \text{ is an instance_of } A, \text{ then } a \text{ is an instance of } B$ (Smith et al., 2012).

2) “instance_of relation”: a relation that holds between particulars and universals/types. It is used to relate instance to the continuant and occurrent universals/types as follows:

$c \text{ instance_of } C \text{ at } t$ means: that the particular continuant entity c instantiates the universal C at t (Smith et al., 2012). For example, a high school diploma is an instance of educational level. $p \text{ instance_of } P$ means: that the particular occurrent entity p instantiates the universal P (Smith et al., 2012). For example, a missed dose is an instance of medication adherence.

3) “part_of” relation: a relation used to relate two continuants or two occurrents and can be transitive, reflexive, or antisymmetric. $b \text{ continuant_part_of } c \text{ at } t = \text{Def. } b \text{ is a part of } c \text{ at } t \text{ and } t \text{ is a time and } b \text{ and } c \text{ are continuant}$ (Smith et al., 2012). For example, questions are part of a questionnaire. $b \text{ occurrent_part_of } c = \text{Def. } b \text{ is a part of } c \text{ and } b \text{ and } c \text{ are occurrents}$ (Smith et al., 2012). For example, the cognitive process is part of the emotional process.

4) “specifically depends on” relation: a relation used to specify the existence of conditions that hold between two particular entities, such that the first entity cannot exist without the second entity. For example, the patient role specifically depends on the patient; MEMS function of the recording date and time specifically depends on MEMS; belief specifically depends on mental function anatomical structure. Formal definition: a “specifically depends on” b=Def. a is an entity, b is an entity, and a exists only if b exists (Smith et al., 2012).

5) “generic depends on” relation: a relation specifies the existence of conditions that hold between a particular entity and one or more other entities. For example, refill record (i.e., pharmacy record) generically depends on computer systems, such as the pharmacy and hospital system (EHR) that host it. It exists as long as some records are stored in a computer system. Formal definition: a generically depends on b_1, \dots = Def. a is an entity, b_1, \dots are entities, and a exists only if one or more of b_1, \dots exists (Smith et al., 2012).

6) “bears” relation: a relation that can be used instead of “specific depends on” and “generic depends on” relations. For example, a person bears a patient role at t; MEMS bears MEMS function in recording the date and time every time a cap opens; disorder bears breast cancer. Formal definition: a bears b= Def. a is an entity, b is an entity, and either b specifically depends on a or b generically depends on a (Smith et al., 2012).

7) “inheres_in” relation: a relation that holds between a specific dependent continuant and an independent continuant that is not a spatial region. For example, the active role of the patient to participate in decision-making inheres in the patient at t. Formal definition: b bearer_of c at t =Def. c s-depends_on b at t and b is an independent continuant that is not a spatial region (Smith et al., 2012).

8) “quality_of” relation: a relation that holds between quality and independent continuant that is not a spatial region. For example, Lori’s level of education is a quality of Lori.

Formal definition: $b \text{ quality_of } c \text{ at } t = \text{Def. } b \text{ is a quality and } c \text{ is an independent continuant that is not a spatial region and } b \text{ s-depends_on } c \text{ at } t$ (Smith et al., 2012).

9) “realized in” relation: A relation that holds between realizable entity and process.

Some entities are manifested only when they participate in certain kinds of processes. For example, belief is a realized entity that is realized in bodily processes (which include mental and behavioral processes) in which there exists some material entity (i.e., mental-function-related anatomical structure/executive-function-related anatomical structure) such that belief specifically depends on it; MEMS function in calculating the date and time is a function that inheres in MEMS and is realized in the adherence assessment process; the patient’s role is realized in the healthcare process. Formal definition: $a \text{ realized in } b = \text{Def. } a \text{ is an entity (i.e., realized entity), } b \text{ is a process, and there exists some entity } c \text{ such that } a \text{ specifically depends on, and } a \text{ is fully present or exhibited when } c \text{ participates in } b$ (Smith et al., 2012).

10) “preceded by” relation: a relation that holds between two processes in which one occurs before the other and the latter starts when the first ends and it can be transitive.

For example, the medication initiation phase starts to occur before the continuation phase or medication filling/refilling process occurs after the medication prescribing process.

Formal definition: $p' \text{ is preceded by a process } p \text{ if and only if the last temporal instant of } p \text{ is earlier than the first temporal instant of } p'$ and a process p' is immediately preceded by a process p if and only if there exists a temporal instant where both the first instant of p' and the last instant of p exist (Smith et al., 2012).

11)“has_participant” relation: a relation that holds between a process and a continuant entity in which the continuant is somehow involved in the process. For example, behavioral change information technology intervention has some platforms or devices as participant. Formal definition: P has_participant C=Def. for every particular occurrence of p, if p is an instance of P, then there is some c and sometimes t, such that a c instance of C at t and p has_participant c at t (Smith et al., 2012).

3.4 Ontology Integration

This step occurred side-by-side with previous steps, where reusing the existing definition was considered. The OBO Foundry Ontology Library, Ontobee, and the Biportal servers searched to leverage entities that were identified from other ontologies into the MAB-Ontology. The criteria selected to be included was a class label where: (1) the selected term definition must be consistent with the MAB-Ontology term definition (synonym). (2) The ontology of the selected match term must be mapped to BFO. The class was imported using Ontofox—“a web-based ontology tool that fetches ontology terms and axioms.” Ontofox supports ontology reuse (<http://ontofox.hegroup.org/>). It allows users to input terms, fetch selected properties, annotations, and certain classes of related terms from source ontologies and saves the results using the RDF/XML serialization of OWL” (Xiang, Courtot, Brinkman, Ruttenberg, & He, 2010).

3.5 Model Formalization

Intermediate Representation (IR) is an iterative artifact that contains information needed to create an ontology (Gómez-Pérez et al., 1996). Since IR is not an ontology, the resulting model was built manually using Protégé (<http://protege.stanford.edu/>) to formalize the entities and relations into an OWL for computation. Protégé is a tool that

provides interfaces for easy structure, navigation, and query of the ontology. It aligns with the NCBO toolkit, which allows for easy importing/exporting, merging, leveraging, and sharing; for example, with the BioPortal library of more than 270 ontologies. It also ensures integration, harmonization, and leveraging opportunities (Noy et al., 2009). Plug-in reasoners validate its use, which allows inferences related to the ontology to be made so as to demonstrate whether the design's structure can successfully create instances, commonly referred to as "consistency checking" (where it conducts a new entity assertion that yields instances consistent with the logic of other instances) (Horridge & Bechhofer, 2011; Peters & Consortium, 2009). Protégé tools can also allow "subsumption testing." This test determines whether a class can be a subclass of another (Horridge, Knublauch, Rector, Stevens, & Wroe, 2004). Additional examples of Protégé reasoning encompass "satisfiability" (meaning, does an entity meet first-order logic of a hierarchy and properties) and "retrieval" (have all instances of a class been found). Protégé also provides plug-in reasoners that accomplish these tasks; they can show structural consistency and check/test descriptive logic via information retrieval and by validating the ontology's content (Aranguren, 2005). Pellet, Fact++, HermiT, and increasingly, Elk, are the common reasoners used in Protégé (Kazakov, Krötzsch, & Simancik, 2014). Lastly, Protégé's various storage formats (OWL, RDF, XML, and HTML) allow for flexibility in how they are shared and applied. Being able to store Protégé in these formatting languages helps Protégé-developed ontologies that conform to Semantic Web standards set by the W3C (Horridge & Bechhofer, 2011) and offer human-readable options. Therefore, all the terms and hierarchies built in the first steps, as well as the definitions given for each class and property, were entered into Protégé manually. As

mentioned earlier, an Aristotelian definition followed beside the best principles that include applying the essential feature, avoiding a circulatory definition, applying for an appropriate extension, avoiding obscure and figurative language, and avoiding negative terms, when possible (Copi, Cohen, & Flage, 2007).

3.6 Evaluation

Ontology evaluation methods classify into three types: Direct evaluation, in which the structure and content validate; application-based evaluation, in which an application develops using ontology; and analysis-based evaluation, which evaluates the ontology as a tool in scientific data analysis (Hoehndorf, Dumontier, & Gkoutos, 2012). This project fell under “Direct Evaluation,” in which the domain representation and structure were evaluated against the purpose for which it was developed and ensured its consistency.

3.6.1 Face Validity of Intermediate Representations

Since committee members are experts in the domains of breast cancer, medication adherence behavior, and ontology, they participated in validating the content and Intermediate Representations. Two committee members who are experts in breast cancer and medication adherence-related knowledge validated the content in the intermediate representation model, while the ontology expert validated the model structure, consistency of relationship, and formal presentation of the MAB-Ontology. This study was exempted by the Institutional Review Board (IRB) (Appendix 1). (a) Content validity. The IR model and its content was validated using an iterative face validity technique. An informal meeting with committee members was conducted to discuss model content. The validation process was carried out to check if the model represented the medication-adherence behavior domain (i.e., represented valid entities and valid

structure). (b) Structure validity. An expert in ontology validated the model structure in an iterative process. The class hierarchy, relationships, and consistency with upper-level ontology were validated. The model was adjusted based on the evaluator's feedback.

3.6.2 Competency Questions

Competency questions are a list of natural language questions formulated based on the motivation scenario (Grüninger & Fox, 1995). Motivation scenario is defined as an artifact that describes the expectation of the proposed ontology that should be satisfied after development (Grüninger & Fox, 1995; Iqbal, Mustapha, et al., 2013). Both the motivation scenario and competency questions are considered to be documents for the requirement specification; they are used to guide the scope of the ontology. That is why they are utilized to test the efficacy of the ontology in answering those questions and solving the scenario problem. This type of evaluation is used to evaluate the semantic query of the ontology—what the system intended to answer. Protégé editing tool provide a query interface for assembling and executing queries. First, the ontology query was developed, then executed on the ontology to produce an answer to the question. This answer was evaluated manually for correctness and comprehensiveness.

3.6.3 Consistency Checking

This type of evaluation was used to check for consistency of the ontology. The reasoning module of Protégé, such as Hermit and Pellet, can be used to check for logical consistency of the ontology. If there is any inconsistency, the reasoners will highlight the source of the error in red. Accordingly, it must be corrected until the ontology is logically consistent (Ogundele et al., 2015).

3.6.4 Compliance with the OBO Foundry Principle

The ontology that was developed followed the OBO Foundry Principles explained in chapter two. At the end, the model was validated for adherence to the principles.

3.6.5 Compliance with the METHONTOLOGY Methodology

The ontology-driven approach is based on the METHONTOLOGY methodology. An evaluation for adherence to the methodology was carried out, and justification for non-compliance was reported.

Summary

This chapter presented the methodological approach used for developing a medication adherence behavior ontology (MAP-Ontology). Six steps were introduced to capture, structure, evaluate, and implement a medication-adherence behavior ontology that can be accessed, queried, navigated, and used for several applications, such as in a decision support system, to predict adherence risk among specific disease types or as a repository for factors influencing medication adherence.

The chapter discussed how flexibility of the METHONTOLOGY methodology allows the BFO principles to be incorporated into the development lifecycle. This step was taken to increase interoperability of the developed ontology with other existing ontologies. The chapter presented the different searching strategies implemented to gather the information needed to build the ontology. This strategy was used to provide a broader, more objective perspective on the medication adherence domain. The chapter also discussed several evaluation methods used to evaluate each step.

CHAPTER FOUR: RESULTS AND DISCUSSION OF MAB-ONTOLOGY

Brief descriptions of results based on the methodology approach mentioned in chapter three are presented in the following sections. This chapter describes the six steps of the METHONTOLOGY approach and the Basic Formal Ontology (BFO) principles incorporated in each step. The six steps are: domain specification, knowledge acquisition, knowledge structure, integration with other ontologies, implementation in a formal language, and evaluation steps. These processes are mapped to the project aims described in chapter one:

1. Develop a formal ontology framework for medication adherence behavior using breast cancer as a case study. This model represented medication adherence behavior, factors that impact medication adherence from a theoretical perspective, methodologies used to assess medication adherence, and technologies used to enhance medication adherence.
 - a. Identify key foundational medication-adherence behavior domain sources.
 - b. Identify definitions and metrics for terms related to medication-adherence behavior.
 - c. Organize and structure the acquired knowledge using tables and graphs.
 - d. Formalize the conceptual model using the ontology editor Protégé.
2. Validate the ontological model by experts using the Face Validity Technique.

4.1 Domain Specification

4.1.1 The Purpose of the Ontology

The general purpose of the MAB-Ontology is to serve as a reference that comprehensively represents the domain of medication adherence using breast cancer as a case study. This developed ontology aims to eliminate or at least minimize terminological

confusion and move towards a common and shared understanding that improves communication, sharing, interoperability, and reusability. Thus, the MAB-Ontology should capture different factors that impact medication adherence in a consistent manner, the methods used to measure adherence behavior, and interventions used to improve or sustain medication adherence behavior. For example, the negative effects of low self-efficacy on medication initiation, or the positive impact of persuasive intervention using a mobile application on medication adherence. The MAB-Ontology should not only enable access to such information, but it should also enhance the query and navigation of this information. In brief, MAB-Ontology can be used when information about factors that impact adherence are required in intervention development, decision making, detection risk for non-adherence, capturing current and future findings from medication adherence-related publications, etc.

a. Deriving the Competency Questions.

Examples of informal competency questions generated for the scope of MAB-Ontology are:

CQ1: Is it possible to search the MAB-Ontology for factors that impact medication adherence?

CQ1a: Is it possible to search the MAB-Ontology for only cognitive-related factors that impact medication adherence?

CQ1b: Is it possible to search the MAB-Ontology for only medication-related factors that impact medication adherence?

CQ1c: Is it possible to search the MAB-Ontology for only disease-related factors that impact medication adherence?

CQ1d: Is it possible to search the MAB-Ontology for only economic-related factors that impact medication adherence?

CQ1e: Is it possible to search the MAB-Ontology for only demographic-related factors that impact medication adherence?

CQ1f: Is it possible to search the MAB-Ontology for only geographic-related factors that impact medication adherence?

CQ1g: Is it possible to search the MAB-Ontology for only health care system-related factors that impact medication adherence?

CQ1h: Is it possible to search the MAB-Ontology for only health literacy-related factors that impact medication adherence?

CQ1i: Is it possible to search the MAB-Ontology for only lifestyle-related factors that impact medication adherence?

CQ1j: Is it possible to search the MAB-Ontology for only social-related factors that impact medication adherence?

CQ1k: Is it possible to search the MAB-Ontology for only technology use-related factors that impact medication adherence?

CQ1l: Is it possible to search the MAB-Ontology for medication adherence risk factors among breast cancer patients?

CQ1m: Is it possible to search the MAB-Ontology for factors that influence medication adherence among patients who are 60 years old and taking tamoxifen?

CQ1n: Is it possible to search the MAB-Ontology for a patient who discontinues his medication due to tamoxifen side effects?

CQ1o: Is it possible to search the MAB-Ontology for a patient who discontinues his medication due to fasting during some days?

CQ1p: Is it possible to search the MAB-Ontology for a patient who discontinues his medication due to the cost of tamoxifen?

CQ2: Is it possible to search the MAB-Ontology for behavioral interventions used to change/sustain medication adherence?

CQ2a: Is it possible to search the MAB-Ontology for Information Technology platforms that use to change/sustain medication adherence?

CQ3: Is it possible to search the MAB-Ontology for methods used to measure medication adherence?

CQ3a: Is it possible to search the MAB-Ontology for direct methods used to measure medication adherence?

CQ3b: Is it possible to search the MAB-Ontology for indirect methods used to measure medication adherence?

CQ3c: Is it possible to search the MAB-Ontology for assays used to measure medication adherence?

CQ3d: Is it possible to search the MAB-Ontology for methods used to measure medication adherence among patients?

CQ3e: Is it possible to search the MAB-Ontology for questionnaires used to measure only medication adherence behavior?

CQ3f: Is it possible to search the MAB-Ontology for questionnaires used to measure medication adherence behavior, along with barrier impact medication adherence?

CQ3g: Is it possible to search the MAB-Ontology for questionnaires used to measure both barriers and beliefs that impact medication adherence?

CQ3h: Is it possible to search the MAB-Ontology for questionnaires used to measure only beliefs associated with medication adherence behavior?

CQ4: Is it possible to search the MAB-Ontology for theories used as a part of a plan specification for medication adherence intervention development?

CQ4a: Is it possible to search the MAB-Ontology for theoretical constructs for each theory?

CQ4b: Is it possible to search the MAB-Ontology for theories that include constructs that represent behavior capability belief?

CQ4c: Is it possible to search the MAB-Ontology for theories that include constructs that represent behavior capability belief and behavior consequences belief?

CQ5: Is it possible to search the MAB-Ontology for patients who are at risk for non-adherence?

CQ4d: Is it possible to search the MAB-Ontology for 60 year-old breast cancer patients who is at risk for non-adherence?

CQ6: Is it possible to search the MAB-Ontology for non-adherent patients?

CQ7: Is it possible to search the MAB-Ontology for medication adherence risk factors?

b. Use Case Scenario

Use case scenario describes expectations that the MAB-Ontology should comply with after development. A use case scenario was created to represent users who can access the MAB-Ontology to support their tasks. They can make requests to the MAB-Ontology and the results will be the required output that is needed to further carry out

expected tasks. Table 11 shows the use case template adopted from the object-oriented technology to represent the basic flow of the event. The motivation behind using this template is that it represents information in a concise way and does not require prior experience for understanding IT (Iqbal, Mustapha, et al., 2013).

Table 11 Use Case Scenario Flow

Description	Describes how a user can input a formal query in the Protégé query tab.
Actors	User and Protégé
Preconditions	<p>Installed Protégé</p> <p>The MAB-Ontology is loaded into the environment.</p> <p>The user is familiar with the formal query language, such as DL.</p>
Basic flow of events	<p>Protégé is initialized.</p> <p>The user inputs a query into the query tab using formal language, i.e., DL.</p> <p>After the query is entered, the user presses the execution button.</p> <p>The system searches the MAB-Ontology for the suitable answer.</p> <p>The answer/answers are showed on the screen.</p> <p>If another query is requested, the procedure will be repeated.</p>
Post-conditions	<p>Successful execution: The correct answer will be received from the system.</p> <p>Failure to execute: Two cases give “No results”:</p> <ul style="list-style-type: none"> • If the formal query was entered incorrectly (query syntax), then No results will be shown. • If the query was inputted correctly, but No results displays; this means the query is out of the scope of the MAB-Ontology.

The Use case Scenario: A program officer planning to design a new intervention to improve medication adherence among breast cancer patients uses information technology platforms. The data gathered by the program officer at the point of care is an indication that there is a high number of fluctuations in the adherence rate among the breast cancer population in the first three months. The program officer does not understand the reasons for this discrepancy. He or she wishes to identify a list of the potential factors that influence the adherence rate among breast cancer patients in the first three months. He or she requires this knowledge in order to develop a proper intervention plan that will reduce the rate of non-adherence among this population.

4.1.2 Approaches for Ontology Building

The middle-out approach to ontology building was used to build the MAB-Ontology. It is a combination of top-down and bottom-up strategies. It is an integration of theoretical modeling and text analysis, in which the most commonly used general terms are extracted first, then the more concrete and abstract entities—“terms and relations”—are extracted from other ontologies and textual resources. This method gives balance in terms of the level of detail.

4.1.3 The Scope of the Ontology

The scope of the ontology reflects the knowledge domain covered by the MAB-Ontology. Adherence behavior is defined by the World Health Organization (WHO) as “the extent to which a person’s behavior—taking medication, following a diet, and executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider.” (Sabaté, 2003) Such a definition is applied to different behaviors and regulatory topics. It includes adherence to all recommendations, such as lifestyle, diet,

physical activity, preventive screening, follow-up, and vaccination. The goal of the MAB-Ontology is to represent knowledge related to adherence to medication only. It is also not possible to cover all aspects of medication adherence, such as all diseases, medications groups, and interventions used to impact medication adherence. Therefore, the scope of the MAB-Ontology is on medication adherence among breast cancer patients taking endocrine hormonal therapy and using information technology to improve their medication adherence. The motivation for this selection has already been discussed in chapter one. This ontology includes factors that impact medication adherence, the methods used to assess adherence, and the interventions used to improve adherence.

4.2 Knowledge Acquisition

As specified in chapter three, several reviews were conducted to extract the important terms that needed to be represented in the MAB-Ontology. In this section, a brief discussion of the important terms extracted from those reviews are included.

4.2.1 Source Selection

This section includes sources that were used to extract the terms needed to represent MAB-Ontology. In chapter two, two reviews (Sawesi, Carpenter, & Jones, 2014; Sawesi, Rashrash, Phalakornkule, Carpenter, & Jones, 2016) were conducted to gain background and detect a gap in the literature—the outcomes that the literature uses to extract the terms needed to build an MAB-Ontology. In this section, two additional literature reviews were conducted to extract terms needed for MAB-Ontology representation:

1. Medication adherence-related theory

The extracted articles were analyzed based on the studies' characteristics: study design, country of study, disease type, theory, constructs, target direction of behavior (increase adherence, maintain adherence), constructs measurement methods, adherence measurement methods, stage of adherence (initiation if less than three months, continuation if more than three months), theory object (i.e., explain adherence, conceptualize the factors affecting patients' adherence, theory testing, intervention developing), and the number of medications prescribed. Table 12 includes theories identified from the extracted articles, the name of the lead author and the date that theory was originally described, frequency of occurrence in the selected articles, and the objective of the theory in the study. A total of 1,057 out of 19,010 articles were included and 47 theories were detected from those articles. The results showed that 51% (n=539) of the studies used quantitative methods, 24% were carried out in the USA (n=253), diabetes mellitus was the most cited disease type (n=200; 19%), the majority of theories were intervention application (n=798; 75%), the majority of studies targeted diabetes (n=240; 44%), the majority of studies used theory as an intervention (n=687, 65%), 88% (n=930) of studies were used to measure theoretical concepts by using a questionnaire, 74% (n=782) of the studies measured adherence using a self-report, and the majority of the studies (67%, n=708) used theory at the continuation stage. Construct characteristics: 441 constructs were extracted from the 47 theories. After de-duplication, 220 concepts were included for further analysis. Terms were grouped into 40 concepts based on their meaning. Fifteen themes were assigned for those constructs as general terms: antecedent of behavior consequence belief, behavior capability belief, behavior consequences belief,

behavior regulation, behavior reinforcement, emotion, environment influence, goal, habit, intention, knowledge, skill, motivation, social influence, technology influence, and memory. Each term gives a definition and the full list is inserted in Protégé. Out of 441 constructs, only 47 related to medication adherence at the initiation phase.

Table 12 Theories Identified in the Included Review

Theory/model	First author, year	Frequency	Role of theory
Health belief model	Rosenstock, 1950	108	E, C, T, I
Theory of reasoned action	Fishbein, 1975	57	E, C, T, I
Theory of planned behavior	Ajzen, 1991	56	E, C, T, I
Health promotion model	Pender, 1982	63	E, C, T, I
Social cognitive theory	Bandura, 1997	40	E, C, T, I
Protection motivation theory	Rogers, 1983	34	E, C, T, I
Social ecological model	McLeroy, 1988	11	E, C, T, I
Motivational interviewing	Miller, 2002	165	E, C, T, I
Rogers' client-centered counseling	Rogers, 1957	40	I
Cognitive dissonance theory	Festinger, 1957	3	I
Stages of change model	Prochaska, 1983	158	E, I
Consciousness raising		2	I
Self-determination theory	Deci, 1985	20	I
Information-motivation-behavioral skills	Fisher, 1992	48	E, C, T, I
Self-regulation/common sense model	Kanfer, 1986	32	E, C, T, I
Self-management theory	Ryan, 2009	96	E, C, T, I
Operant conditioning theory	Skinner, 1938	2	I

Classical conditioning theory	Pavlov, 1988	1	I
Behavioral learning theory	Skinner	31	I
Behavioral modification theory	Skinner, 1970	2	I
Orem's self-care theory	Orem, 1959	3	I
Problem-solving theory	Newell, 1972	21	I
Adult learning theory	Knowles, 1913	16	I
PRECEDE/PROCEED	Green, 1974	2	I
Diffusion of innovations	Rogers, 1962	39	I
Interpersonal theory	Peplau's	10	I
Main determinants of health model	Dahlgren, 1991	7	I
Social action theory	Ewart, 1991	17	I
Social marketing theory	Baran, 2003	1	I
Roy adaptation model	Roy,	1	I
Elaboration likelihood model	Petty, 1986	1	I
Learned resourcefulness	Rosenbaum, 1983	2	I
Empowerment theory	Zimmerman, 2000	11	I
Attitude, social influence, and self-efficacy (ASE) model	Nuwaha, 2002	9	E, C, T, I
I-change model	De Vries, 1988	2	I
The ecological model	Bronfenbrenner, 1977	16	I
Extended parallel process model	Witte, 1992	2	I
Model of goal-directed behavior	Bagozzi, 1998	2	I
Goal-framing theory	Lindenberg, 2007	1	I
Goal-setting theory	Locke, 1968	16	I

Health action process approach	Schwarzer, 1992	16	I
Integrated theory of health behavior change	Ryan, 2009	5	E, C, T, I
Precaution adoption process model	Weinstein, 1988	2	I
Prospect theory	Kahneman, 1979	2	I
Regulatory fit theory	Higgins, 2000	11	I
Relapse prevention	Marlatt, 1980	40	I
Theory acceptance model	Venkatesh, 1989	25	I

E=explain adherence, C=conceptualize factors affecting patients' adherence, T=theory testing, I=intervention developing

1. Methods used to measure medication adherence.

In this review, 51 articles about breast cancer as a disease contained clear methods to measure medication adherence. The main characteristics included are: study design, patient group, number of participants, and methods used to measure adherence. Methods used to measure adherence were grouped into direct and indirect methods. Direct measurement is defined as a medication adherence assessment that uses direct observation and/or an analyte assay to detect the presence of a drug in an extended organism. It includes methods, such as measuring drug concentration in body fluid, usually blood or urine, detecting biologic markers that are given with the drug, and direct observation of the patient administering the drug. Indirect methods, on the other hand, are defined as a medication adherence assessment in which the medication taking process measures using objective and/or subjective intermediary measurement methods. The subjective methods include self-reporting methods that depend on the observer's personal judgment and feelings as to how well the medication was taken, such as interviews and questionnaires. The objective methods include a prescription record review and pill

counting methods. Seventy-five percent (n=38) of studies used subjective measurement to measure adherence, of which the self-report measurement (n=29, 76%) was the most frequently used method. Among studies using objective methods, medication event monitoring systems were the most frequently used methods (n=8, 62%). This study provides the necessary measurement-related terms that are to be represented in the MAB-Ontology.

To this end, the literature reviews discussed above, along with those in chapter two, were used to manually extract terms and phrases and create a list of classes and properties (i.e., high-level classes for an upper hierarchy and sub-classes representing more specific details). Therefore, all sources were grouped and categorized into six source types based on the project's aims, as mentioned in the previous chapter. (i) Medication adherence assessment source type, (ii) medication adherence determinants source type, (iii) medication adherence behavioral theories source type, (iv) medication adherence data standards source type, (v) biomedical ontology repositories source type, and (vi) domain experts source type. For each source type, the related information was extracted based on predefined questions. Table 13 shows the category of knowledge source types, resources description, and the number included under each category (i.e., articles, textbooks, websites, repositories, human resources), use of each source type (e.g., for definition, categorization, reusability), and examples of the source extracted under the mentioned category. For example, under the category medication adherence assessment literature, 51 articles were reviewed in order to extract terms, definitions, components, interventions, and any other characterization of medication adherence found in the research. An example of an article extracted under this category is provided.

Table 13 Source Selection Examples

Knowledge Source Type	Resources and Number	Use	Source Example
Medication Adherence Assessment Literature	Journal articles (51)	Terms, definitions, interventions, characterization of adherence research	Steinberg et al., 2014
Determinants of Medication Adherence Literature	Journal articles (26)	Characterization of medication adherence among breast cancer research	Sedjo & Devine, 2011
Theories of Adherence Change	Journal articles (1057), books (2)	Theoretical concepts (terms/phrases)	Arora et al., 2014
Medication Adherence Data Standard	Research, project (3), and book (1)	Categorization, taxonomy of MAB	BCT project (Michie et al., 2013), ABC project (Vrijens et al., 2012)
Medication Adherence- Related Terms	Ontology repositories (n=3), Bioportal OBO foundry, and Ontobee	Related terms, data structure, and levels of granularity	Human disease ontology (Schriml et al., 2011), drug ontology (Hanna et al., 2013), emotion ontology (Hastings et al., 2011).
Tacit Knowledge	Domain-related experts (3)	Domain terminology, information, and data structure.	JC and JJ

4.2.2 Source Analysis

Figure 9 shows eligible studies included from each source type and the number of terms/phrases extracted. The extraction process started by identifying general terms most commonly used, then generalizing and specializing them. For each eligible study, the information resulted from answering all five questions discussed in the methodology chapter; they were then categorized and displayed in tables as shown in Tables 14-19, with full tables for all source types attached in Appendix 2. The questions are: (i) How is medication adherence described/defined in the source type? (ii) How is medication adherence measured in the source type? (iii) How is medication adherence impacted in the source type? (iv) What impact is medication adherence in the source type? (v) What are the critical themes and concepts concerning MAB research in this source type?

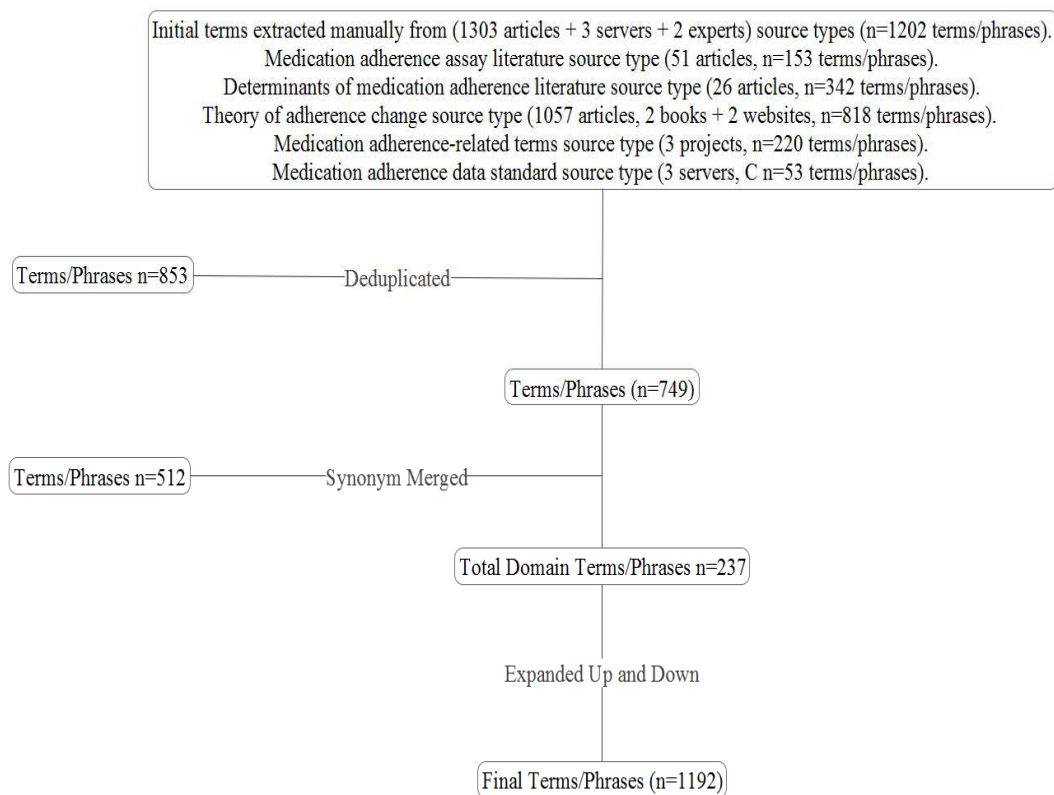


Figure 9 Medication Adherence Source Types to Intermediate Representation

Table 14 Medication Adherence Assay Literature Source Type

Source type	Atkins & Fallowfield, 2006	Huiart et al., 2011	Nekhlyudov et al., 2011
How is medication adherence described/defined in the source type?	Process, behavior, skip dose.	Behavior, medication management, medication taking, number of events.	Behavior, number of refills.
How is medication adherence measured in the source type?	Persistence, gap, questionnaire, self-reporting.	Electronic monitoring, Prescription refill records.	Medication possession ratio, objective measurement.
How is medication adherence impacted in the source type?	Beliefs, age, knowledge, forgetfulness, smoking, side effect, ethnicity, duration.	Disease stage, age, perceived interference, additional prescribed medications.	Medication cost, work complexity, religious practices, and marital status.
How is intervention described and what is contained in the source type?	Plan, treatment, knowledge, interview.	Technology, prescription simplicity, feedback, and social support.	Reminder, message, intervention.
What are the critical themes, concepts concerning MAB research in this source type?	Granularity of adherence factor, intervention component, measurements.	Stage of breast cancer, adherence range.	Length of adherence treatment class, impact type, intervention goal.

Table 15 Determinants of Medication Adherence Literature Source Type

Source type	Kahn et al., 2007	Oguntola et al., 2011	Pellegrini et al., 2010
How is medication adherence described/defined in the source type?	Behavior, self-management, self-regulation.	Planned process, misuse, suboptimal use.	Behavior, skipped dose, missed dose, discontinuation, drug management.
How is medication adherence measured in the source type?	Self-reporting, and electronic monitoring.	Monitoring, questionnaire.	Subjective, objective.
How is medication adherence impacted in the source type?	Patient-related, medication-related, healthcare-related, socioeconomic-related factors.	Beliefs, age, side effects, medication cost, schedule burden, comorbidity, disease stage.	Beliefs, knowledge, social impact, healthcare relations, communication.
How is intervention described and what is contained in the source type?	Service delivered through technology, mobile app, the Internet.	Structured interview, health belief model, education, feedback, monitoring.	Knowledge, education, session, text message.
What are the critical themes, concepts concerning MAB research in this source type?	Behavior, intervention, duration, outcome, healthcare engagement, direct & indirect assay, technology-related, patient related factors.	Disease stage, efficacy, impact type, stage of cancer. Long-term and short-term.	Drug class, type of cancer estrogen receptor-positive breast cancer.

Table 16 Theory of Adherence Change Source Type

Source type	Arora (2014)	Boland et al., (2014)	Granholm (2012)
How is medication adherence described/ defined in the source type?	Behavior, process, habit, initiation, continuation.	Adherence, behavior, quality of life, missed dose. Non-continue.	Decision-making, problem recognition, stop taking.
How is medication adherence measured in the source type?	Self-reporting, pill count.	Indirect, questionnaire	Monitoring.
How is medication adherence impacted in the source type?	Information searching, prior knowledge, novelty, past experience, confirmation of expectation, perceived alternative, evaluation process, attitude, antecedent, dissatisfaction, perceived knowledge, skills, social impact, belief, awareness, reinforcement, health	Cognitive dissonance, social learning, self-regulation, social rule, experience, social norm, cue to action, behavioral belief, barrier, facilitator, modifying factor, motivation, coping, expectancy, ease of	Capability, behavior, intervention, threat, intention, goal, relapse, environment, desire, attitude, self-determinant, feeling, self-care, ability, fear,

	consequence, perceived behavioral control, emotion.	use, communication, usefulness, autonomy.	opportunity, socioeconomic.
How is intervention described and what does it contain in the source type?	Treatment theory, knowledge, social support, emotion, motivation, belief change, reinforcement, feedback, goal, environment, self-regulation.	Telemonitoring, theory, constructs, stage of adherence, disease type, intervention session, days covered.	Mobile, reminder, social cognitive theory.
What are the critical themes, concepts concerning MAB research in this source type?	Behavior time, belief, emotion granularity, desire, intention, awareness, decision making, information processing, planned study, goal of study, intervention.	Adherence rate, comorbidity, components, theoretical construct.	Adopter, social interaction, severity, initiation, discontinuation.

Table 17 Medication Adherence Data Standard Source Type

Source type	WHO dimensions (Coulter et al., 2008)	BCT project (Michie et al., 2013)	ABC project (Vrijens et al., 2012)
How is medication adherence described/defined	Multidimensional, behavior, activity taking medication as recommended,	Behavior, typology	Process, typology, initiation, discontinuation, implementation, persistence,

in the source type?	agreed-on recommendations.		management of adherence.
How is medication adherence measured in the source type?	Subjective ratings, questionnaires, objective strategies, biochemical measurement, dose-response curve, pharmacy databases.	n/a	Time from prescription until first dose is taken, time from initiation until discontinuation, the proportion of prescribed drugs taken.
How is medication adherence impacted in the source type?	Five dimensions (the full list is in Appendix 2): patient-related factors, socioeconomic factors, therapy-related factors, disease related factors, healthcare system-related factors.	Knowledge, skills, social role, belief about capability, optimism, belief about consequences, goals, reinforcement, intention, memory, decision process, environment, social influence, emotion, behavioral regulation.	Socio-economic-related, healthcare-related, condition-related, therapy-related, patient-related, demographics, medicines use, health status, affordability, adherence, optimism, beliefs, self-efficacy, health service use, social support, illness, perceptions, income.
What are the components of medication	Role-play, education, support, communication, habit	Goal setting, problem-solving, planning, behavior discrepancy,	Education, knowledge, video, simplify dose, drug delivery systems,

<p>adherence intervention in the source type?</p>	<p>maintaining, comorbidity treating as depression, motivation.</p>	<p>monitoring, feedback, social support, reward, education, incentive. consequences, social comparison, cue to action, learning, habit formation, graded task, restructuring environment, learning, punishment, self-belief, persuasion.</p>	<p>patient assistance programs, adherence enhancing, packaging, reminder, pill organizing, telephone support, text message reminder, Internet based, low literacy intervention, low resources intervention, aged intervention.</p>
<p>What are the critical themes, concepts concerning MAB research in this source type?</p>	<p>Behavior, subjective measurement, objective measurement, patient-related factors, treatment-related, disease-related, healthcare system-related, socioeconomic-related, intervention component granularity.</p>	<p>Knowledge granularity, belief granularity, social impact granularity, emotion granularity, reinforcement, environment granularity, goal, component.</p>	<p>Intervention content granularity, adherence typology, adherence measurement granularity, factors granularity.</p>

n/a: not applicable

Table 18 Medication Adherence-Related Terms Source Type

Source type	OBO foundry http://www.obofoundry.org	Bioportal https://bioportal.bioontology.org	Ontobee http://www.ontobee.org
How is medication adherence described/defined in the source type?	Patient compliance, attitude to health, behavior.	Patient compliance, attitude to health, health behavior, behavior, pharmacology, medication management.	Patient compliance, attitude to health, behavior, medication taking, drug administration, medical intervention.
How is medication adherence measured in the source type?	Degree of medication taking, direct-observed therapy, medication tracking device.	Direct-observed therapy, medication tracking device.	Direct-observed therapy, medication tracking device.
How is medication adherence impacted in the source type?	n/a	Incorrect dose administration, omitted dose, error drug administration, overdose, under dose, ease of use of medication.	n/a

What are the components of medication adherence intervention in the source type?	n/a	Medication therapy management, medical device usage for medical intervention, medication knowledge, take medication at correct time, take medication as prescribed.	n/a
What are the critical themes, concepts concerning MAB research in this source type?	Upper-level, leveraging.	Adherence type, direct, indirect measurements, drug error, mode of delivery, type of intervention, management process.	Disposition measurement, process quality.

n/a: not applicable

Table 19 Tacit Knowledge Source Type

Source type	Experts 1 (JJ)	Expert 2 (JC)
How is medication adherence described/defined in the source type?	Initiation, continuation and discontinuation	Initiation and continuation.
How is medication adherence measured in the source type?	n/d	n/d

How is medication adherence impacted in the source type?	Knowledge category, motivation	Patient-related: demographic, psychological, physical; therapy-related: complexity, side effects; condition-related: disease stage, severity, comorbidity; social and economic factors: language, literacy, social support, living conditions, cost; healthcare-related: patient-provider relationship.
How is intervention described and what does it contain in the source type?	n/d	n/d
What are the critical themes, concepts concerning MAB research in this source type?	Process, knowledge granularity, motivation.	Granularity of factors, assay.

n/d: not discussed

4.3 Knowledge Structuring Using Set of Intermediate Representations

The terms and phrases extracted from the previous step were organized, structured, and represented informally using tables and graphs.

4.3.1 Building a Glossary of Terms

Terms extracted and listed in the previous step were de-duplicated and synonym-specified, with a definition of the terms adopted or created, type of terms defined (e.g., noun or verb), and source of the definition cited. Table 20 is an example of a glossary of terms; a full table with terms extracted is in Appendix 2.

Table 20 Building a Glossary of Terms

Term/Phrase	Descriptive Factor(s)	Definition	Type	Definition Source
Behavior	Behavioral process, activity	Patterned activity of a whole organism in a manner dependent upon some combination of that organism's internal state and external conditions.	Noun	MFO http://www.ontobee.org/
Medication adherence	Medication-taking behavior; behavioral response to medication, medication compliance	Behavior associated with the consumption or use of a chemical substance with presumed curative, preventive, or medicinal value in accordance with the provider's recommendation concerning the timing, dosage, frequency, and duration.	Noun	Sawesi
Duration of treatment course	Length of therapy	The period from start to the end of a treatment course.	Noun	APOLLO_SV http://www.ontobee.org/
Adherence rate		Percentage of doses taken as prescribed from initiation of the medication or start of observation, until stopping the medication or ending the observation.	Noun	Hugtenburg, Timmers, Elders, Vervloet, & van Dijk, 2013

Habituation	Habit	A condition resulting from repeating the consumption or use of a chemical substance presumed curative, preventive, or having a medicinal value with a desire (but not a compulsion) to continue taking the medication for the sense of improved well-being or to prevent disease recurrence, which it engenders; no tendency to miss or skip the dose; postpone the dose; or stop the dose for whatever reason without provider recommendation.	Noun	Sawesi
Impact	Affect, effect, influence	A relation that holds between two entities: one has influence over the other, such as a connection between behavioral determinant and the behavior in question. This impact can be positive, negative, or neutral.	Verb	Sawesi
Determinant	Factor	Anything that contributes causally to a result.	Noun	https://www.mcamillandictionary.com/us

New prescription	New medication	A prescription that includes a new medication or therapy that has not been used before by the patient to treat the current disease or condition.	Noun	Sawesi
Defined number of days		Number of days in which the prescription is presumed to be dispensed after it has been ordered. The commonly used days are 30 or 60.	Noun	Sawesi
Management of adherence process	Monitoring, supporting	The process of monitoring and supporting patients' adherence to medications by healthcare systems, providers, patients, and their social networks.	Noun	Vrijens et al., 2013
Behavioral intervention	Behavioral technique	Psychological or behavior intervention is a combination of program elements, strategies, or modalities designed to influence psychological or behavioral processes or outcomes.	Noun	Eagle_i resource ontology http://www.ontobee.org
Drug concentration measurement		An assay that is used to measure the drug concentration in body fluid, such as blood and urine.	Noun	Sawesi

Medication possession ratio (MPR)		Ratio of the number of days for which a patient has medication on-hand divided by the total number of days a patient was observed. Used for refill adherence.	Noun	Raebel, Schmittziel, Karter, Konieczny, & Steiner, 2013
Prescription	Written instruction	A document that represents verbal or written orders given by an authorized person instructing a patient to obtain and use a medical device, prescription, or undergo a procedure.	Noun	NCI Thesaurus http://www.onctobee.org
Patient	Sick person	A role that inheres in a person and is realized by the process of being under the care of a physician or healthcare provider.	Noun	OBI http://www.onctobee.org
Healthcare encounter	Patient present at healthcare system	A temporarily-connected healthcare process that has as its participants an organization or person realizing the healthcare provider role and a person realizing the patient role. The healthcare provider role and patient are realized during the healthcare encounter.	Noun	OBI http://www.onctobee.org

Belief		A mental disposition that is realized in a mental process.	Noun	Sawesi
Occurrent belief	Thinking	A mental process that realizes the dispositional belief. It is a process of bringing belief to the conscious.	Noun	Sawesi

4.3.2 Knowledge Representation Using Triples

The terms extracted and listed in the glossary have been structured in triples of Subject-predicate and object. These triples model those of the dictionary, wherein the meaning of the terms define using statements. The subject refers to the entity to be described, while the predicate defines a type of relation that exists between the subject and object. It is the subject attributes, with the object being an entity or value that describes the subject via being in relation with it. Figure 10 shows an example of this: Medication adherence behavior influenced by medication adherence determinants. Medication adherence behavior is an entity that is being described, influenced is relation with what exists between the entities; whereas, the medication adherence determinant is a value of this relationship. An instance of a triple could be a subject of other triples. For example, medication adherence behavior regulated by medication adherence intervention. Additionally, an object of one triple can be the subject of another, such as medication adherence determinant targeted by medication adherence intervention, or a subject of one triple can be an object of another, such as medication adherence intervention regulates medication adherence behavior. In this example, an inverse relation was used, but other relations could serve the same explanation, as shown in Table 21.

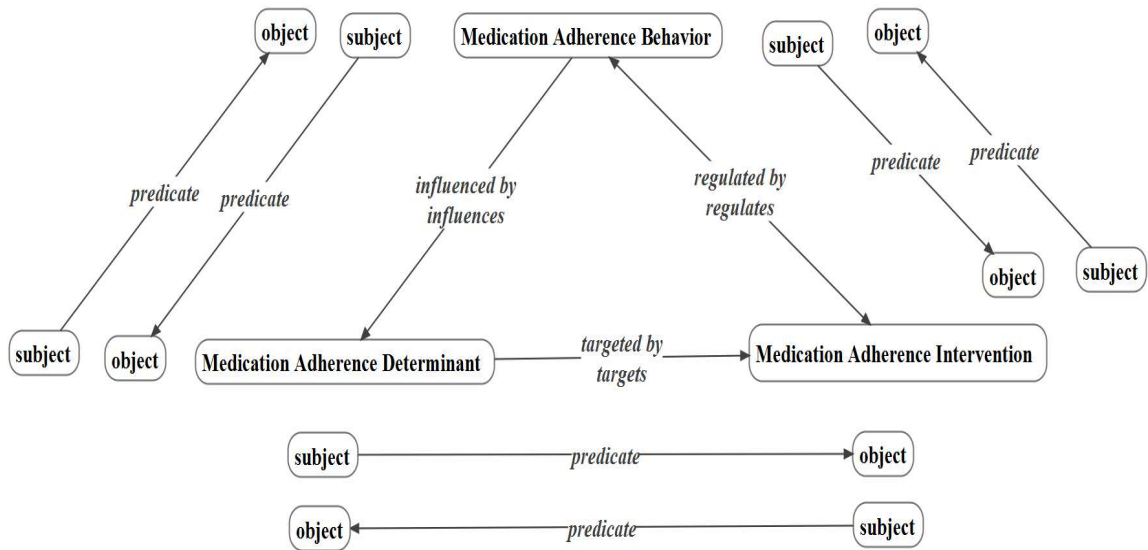


Figure 10 Knowledge Representation in Triples

Table 21 Knowledge Representation Using Triples.

Subject	Object	Predicate
Patient	Has	Breast cancer
Breast cancer	Is a	Disease
Disease	Has subtype	Breast cancer disease
Breast cancer	Has stages	Breast cancer stages
Breast cancer stages	Treated by	Breast cancer treatment
Breast cancer treatment	Specified by	Breast cancer treatment protocol
Breast cancer treatment protocol	Includes	Specified medication recommendation
Specified medication recommendation	Has specified	Medication dose specification, medication time specification, medication duration specification, medication frequency specification

Medication dose specification, medication time specification, medication duration specification, medication frequency specification	Participates in	Medication adherence process
Medication adherence process	Is a	Behavior process
Behavior process	Has participant some	Patient
Patient	Participates in	Healthcare process
Healthcare process	Has participant some	Physician
Medication	Prescribed to	Patient
Physician	Orders	Prescription
Prescription	Contains	Instruction about medication
Instruction about medication	Targeted some/ is about	Patient
Patient	Bears	Belief
Belief	Is a	Mental state
Mental state	Has subtype some	Belief
Belief	Targeted by	Psychological and behavioral intervention
Behavioral intervention	Influences	Patient adherence to medication
Patient adherence to medication	Is about	Patient
Patient	Takes	Medication
Medication	Has subtype	Tamoxifen
Tamoxifen	Has role	Selective estrogen receptor modulators (SERMs)

Selective estrogen receptor modulators (SERMs)	Realizes in	Preventing estrogen from binding (estrogen antagonist)
Preventing estrogen from binding (estrogen antagonist)	Has output	Reduces the risk of breast cancer recurrence
Reduces the risk of breast cancer recurrence	Is a	Finding
Finding	Is about	Patient
Patient	Participates in	Information technology-based intervention
Information technology-based intervention	Has part some	Technology mode of delivery
Technology mode of delivery	Has participant some	Technology
Technology	Bears some	Information technology platform
Information technology platform	Has part some	Information technology platform objective

4.3.3 Building the MAB Hierarchy

The triples created in the previous step facilitated knowledge representation in a hierarchy. As mentioned earlier, it acts like a dictionary. However, such a dictionary-like ontology can be understood only by a single system (as in the case of the English dictionary): only people who know English can understand the meaning. It is the same with the ontology: other systems cannot understand the meaning of the word and share it. Therefore, in order to facilitate interoperability, an upper-level of information is needed. Therefore, these triples need to be restructured and mapped with the BFO upper-level ontology. Not only does it need map terms to an upper level, but it also must adhere to

the BFO principles mentioned in chapter three. Therefore, the next step involves restructuring the extracted knowledge based on the reality—a philosophical perspective use towards defining the nature of each term as it exists in reality.

4.3.4 Building the MAB Hierarchy based on BFO

To define medication adherence, there is a need for defining the entities involved in this process based on BFO structure. As shown in Figure 10, behavioral determinants play a central role in medication adherence and behavioral interventions designed to target these psychological determinants. Therefore, it is important to define the nature of these entities using BFO structure.

4.3.4.1 Continuant Entity

I. Independent Continuant Entity

a. Material Entity.

MAB-Ontology involves several entities that fit under this category. In this section, a few examples are provided, while the full entities are formally represented in Protégé and are attached in Appendix 3. The hierarchy of classes adopted from other ontologies were extracted using OntoFox, <http://ontofox.hegroup.org/>.

1. Human, human being, or homo sapiens

Patients, healthcare providers, or others involved in the treatment process are categorized under this class according to the role they play or have. The hierarchy of homo sapiens was adopted from the NCBI Organismal classification.

<http://www.ontobee.org/ontology/NCBITaxon>. For example, human breast cancer patient=Def. A human who bears the breast cancer patient role. Healthcare provider =Def. A human who bears the healthcare provider role. Oncologist= Def. A healthcare

provider who bears the oncologist's role. Adherent patient=Def. A patient who has a medication adherence percentage greater than 80%, meaning there is material entity a (patient), process p (measurement of medication adherence), scalar measurement m (rate of adherence-80%), measurement unit label (percent) l, value (80) v and adherent patient

- participates in p
 - p has output m
 - m has label l
 - m has value v

2. Drug tablet

Drug tablet= Def. "A solid object, typically a discoid, spheroid, or elliptic-cylindrical shape or approximation thereof that bears a clinical drug role." This class has been adopted from Drug Ontology <http://www.ontobee.org/ontology/DRON> and includes several subclasses. For example, Anastrozole Oral Tablet= Def. A drug product that bears some active-ingredient role and has a granular part of some Anastrozole. Therefore, Anastrozole 1 MG Oral Tablet can be defined as= Def. An Anastrozole oral tablet where there exists some material entity b (anastrozole), role r (active ingredient role), quality q (mass), measurement unit m, value v (equal 1) and Anastrozole 1 MG Oral Tablet:

- has part b
- bears r and q
 - q has m
 - m has v

3. Device

Device=Def. “A material entity that is designed to perform a function in a scientific investigation but is not a reagent.” This definition was borrowed from Ontology for Biomedical Investigations <http://www.ontobee.org/ontology/OBI> to include MAB-Ontology-related devices. For example, Medication Event Monitoring System (MEMS)=Def. A device that bears MEMS function and is realized in the process of the medication adherence measurement process. This means there is a material entity *m*, function *f*, process *p* and Medication Event Monitoring System:

- bears *f*
- participates in *p*

4. Material anatomical structure

Material anatomical structure=Def. An anatomical entity that has mass adopted from the UBERON ontology <http://purl.obolibrary.org/obo/UBERON>. This class includes the subclass Multi-cellular anatomical structure=Def. “A material anatomical entity that has more than one cell as a part,” which includes several subclasses that represent the body organ. The reason for including this class is to relate disease to its location; for example, breast cancer is located in the breast. Also, to include mental functioning anatomical structure as subclass (will be discussed under disposition). It is adopted from Mental Functioning Ontology <http://www.ontobee.org/ontology/MF>. Mental functioning anatomical structure=Def. An anatomical structure in which there inheres the disposition to be the agent of a mental process. This means that there is a material entity *a* (mental functioning anatomical structure), disposition *d* (mental disposition), process *p* and, the mental functioning anatomical structure

- bears d
- d realized in p

II. Specific Dependent Continuant Entity

a. Realizable Entity

1. Role

Patient role=Def. A role which inheres in a person and is realized by the process of being under the care of a physician or healthcare provider. Adopted from Ontology of Biomedical Investigations <http://www.ontobee.org/ontology/OBI>. This means that there is role r (patient role), material entity a (patient), process p (healthcare process), and patient role

- inheres in a
 - a participates in p

Drug role=Any substance that, when absorbed into a living organism, may modify one or more of its functions. Adopted from Chemical Entities of Biological Interest <http://www.ontobee.org/ontology/CHEBI>. For example, estrogen receptor antagonist role=Def. A role that inheres in Tamoxifen and realizes in some process, such as the estrogen-binding process. This means that there is a role r (drug role), material entity a (Tamoxifen), process p (estrogen binding process) and drug role

- inheres in a
 - a participates in p

Oncologist role=Def. A role that inheres in the physician by which the physician diagnoses and treats patients with cancer. This means that there is a role r (oncologist

role), material entity a (physician), process p (cancer treatment process), and oncologist role r

- inheres in a
 - a participates in p

b. Disposition.

Disease=Def. A disposition (i) to undergo pathological processes that (ii) exist in an organism because of one or more disorders in that organism. This class has been adopted from the Ontology for General Medical Science

<http://www.ontobee.org/ontology/OGMS> to define breast cancer, the disease class categorized to include a class named disease of cellular proliferation= Def. A disease that is characterized by abnormally rapid cell division. This definition has been adopted from Human Disease Ontology (DOID) <http://www.ontobee.org/ontology/DOID>. Under this class, cancer class is represented and defined as= Def. A disease of cellular proliferation that is malignant and primary, characterized by uncontrolled cellular proliferation, local cell invasion, and metastasis. Cancer has two subclasses: cell type and organ system. Accordingly, breast cancer is defined as=Def. A cancer that is located in the breast. This means there is a disposition c (cancer), anatomical entity m (breast), and breast cancer

- subtype of c
- inheres in m

Cognitive or psychological factors: Psychological determinants, which include belief, motive, desire, fear, knowledge, intention, perception, feeling, thought, etc., are defined in the literature as mental states (Apperly, 2010; Call & Tomasello, 1999; De Villiers, 2007; Perugini & Bagozzi, 2004). A mental state is a state of mind that an agent

is in (Symons, Peterson, Slaughter, Roche, & Doyle, 2005): having a belief, desire, motive, etc., is being in the state. The question here is, under what BFO category does the mental state belong? Is it occurrent or continuant? If, for example, a mental state is categorized as an occurrent entity, do all the above-mentioned determinants satisfy the condition to be a member of that class of mental states? To answer this question, there needs to be a need for understanding the nature and distinguishing features that are unique only to this mental-state class. Philosophers argue that a mental state has two important features namely, intentionality and consciousness.

1. A mental state is intentional; it—“has intentionality” (Searle, 1979).

Two definitions were found related to intentionality. (i) One meaning of intentionality is aboutness or directedness (Bourget & Mendelovici, 2016). It is impossible to have a belief without referring to something or being about something. If a patient believes that medication causes side effects, then his or her belief is about the medication. This intentionality does not necessary exist, as the person may have a belief about something that does not exist in reality, such as, my son believes that Spiderman lives in California. His belief about Spiderman, even though Spiderman does not exist, is a mental state. (ii) Another meaning for intentionality is carrying information about something (Dretske, 1980). Pain and other symptoms are considered mental states. It does not make sense to say what pain is about, but it does make sense to say that pain carries information about what is happening in this patient’s body. This information does not need to exist. Some patients may have phantom sensations after breast amputation. Belief can also carry information, but other entities cannot, such as desire. In this case, an intentional mental state can be define as “a mental state that is either about some entity or

carries information about some entity.” These entities do not need to exist. Given this definition, all the entities mentioned above satisfy this condition and can be a member of a mental state class. But such a definition will allow other entities to be members of this class, such as non-living things. Books and pictures, for example, carry information about something. Are they considered mental states? Therefore, this feature is not unique to mental states.

2. A mental state is a state of consciousness or awareness.

It means that they do not persist through periods of loss of consciousness or sleep. Feeling pain, for example, is consciousness; once the person falls sleep or goes under anesthesia, he or she is not aware of the pain. It is the same with emotions. A person can be anxious and depressed while conscious. He or she may, however, lose this awareness for some time when being distracted by an important call or visit by a loved one. This duration of unconsciousness is what philosophers call a “genuine duration” (James, 1904) that occurs when conscious is interrupted by other events, then resumes after the distraction has been suppressed. Philosophers claim that consciousness is “something that it is like to be in” (Fabrega, 2000; Ornstein, 1972; Quilty-Dunn, & Mandelbaum, 2017). For example, a person may be in a cheerful or joyful state. Once a question is asked about what state patient “A” is in today, simply answer, patient “A” is in a state of depression, a bad mood, etc. This feature works for some psychological determinants mentioned above, but not all. For example, knowledge—a justified true belief (Schmitt, 2006)—is not conscious and cannot cease to exist simply because one falls sleep or lacks awareness. The person may forget some knowledge but does not exhibit a genuine duration. A person may have knowledge for the entirety of his or her life that cannot be interrupted

by some objects or events that distract attention and later resume that knowledge once the distraction has terminated. Belief, too, is not conscious and has no “genuine duration.” Intention (the tendency to act—not intentionality) also persists through time. A person may have the intention to do something for years and does not lose that intention when he or she falls asleep or has a genuine duration. Also, for consciousness to be “something to be in,” it does not work for all of mental states. For example, belief, knowledge, and desire. You cannot say this person is in a belief state or a knowledge state. The literature claims that consciousness is occurrent and part of all mental processes (Hastings, Smith, Ceusters, Jensen, & Mulligan, 2012). Since consciousness is a dynamic process (Aikens et al., 2014) and an inseparable part of all mental processes (Hastings, Smith, Ceusters, Jensen, & Mulligan, 2012), then mental state is a process. However, the state obtains not happening or taking place. How can a state be an occurrent? Based on what has been mentioned in chapter three, to be an occurrent, entities must unfold themselves in time. States do not unfold or evolve through time; they exist in the instantiation of properties in objects, as shown in Figure 11. Objects do not change their state over time; instead, a series of states are followed—one state is followed by another. Following this case of consciousness must mean following in time; one event follows another in temporal order. States have no temporal parts; for example, temperature and height. It makes no sense to say the early or latter part of the patient having the temperature or height he does. An event, on the other hand, has temporal parts and cannot be wholly present throughout each moment of its existence. Instead, for every moment an event is happening, there are temporal parts that exist. This is not true with state. Consider a state that instantiates property over a particular period of time. For each moment the state exists, the property

and the particular are wholly present, and if the particular ceases to have this property, then it undergoes a change of state. The change itself is occurrent, but the state is not an occurrent.

A mental state cannot be occurrent or at least occurrent cannot be its unique feature. For example, philosophers have said that belief is conscious and is categorized as a process (Österholm, 2010). When a belief is formed through perception, judgment, thinking, or other mental processes, it is stored in the memory and executed when needed. A belief can guide action by using it in reasoning, planning, and making a decision. For such an entity to serve this role, it is supposed to be a continuant and persist through time. Pitt (2016), in his paper, “Conscious Belief,” states that “to believe that p is to think that p while taking p to be the case—while accepting or endorsing that p.” He claims that such conscious endorses the content that p is a conscious belief. But how can the same belief be conscious (occurrent belief) and unconscious (continuant belief)? Belief is not just a matter of taking something as being the case for a period of time, relating belief to knowledge, and the similar role it plays in impacting an individual’s behavior and reasoning. Why is there no such an occurrent knowledge, while there is an occurrent belief? People bring their knowledge to mind when they need to. It is the same for belief. What does it mean to bring “A” to the mind or consciousness? This refers to the fact that there is an entity—“belief”—that participates in occurrent conscious, and by its participation, it is realized. Such an occurrent conscious could be a cognitive process, such as thinking, reasoning, judging, or decision-making. So, when we measure belief, we measure its realization either through behavioral observation or by asking an individual about his belief about x. This individual will answer the question based on his

or her belief (i.e., the continuant belief). Therefore, the claim that all mental states are consciousness and occurrent would be implausible, because it denies claim that there are some mental states that are not occurrent or conscious.

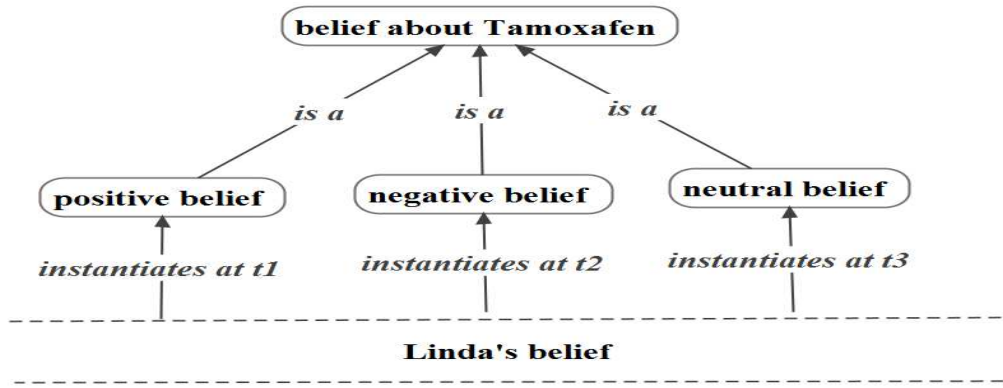


Figure 11 Linda’s Belief Instantiates at Different Times

To this end, it is impossible to define the above-mentioned determinants as mental states, or find an appropriate category for mental state under BFO, as the nature and feature of mental status are controversial and not clearly defined in the literature. Therefore, in this dissertation, each entity is treated and defined individually, based on its nature, if occurrent and continuant, without grouping each under the same category, such as mental state.

Based on BFO, entities must be either occurrent or continuant, and since a cognitive entity as a belief is not occurrent based on the above explanation, it categorized under continuant. Two options are considered for this project to categorize belief under BFO: (i) belief that “A” is a proposition that is stored in long-term memory. This means that belief is an object (material entity). (ii) Belief that “A” is a realizable entity that inheres in an independent continuant entity whose instances require process in order to be realized.

First, belief is an object. It is not unusual to see belief as something an individual may have. One way to interpret this is to consider belief as a proposition or statement “A” that is stored in the mental system, or as some in the literature name it, the belief box (Schiffer, 2006). So, to believe that “Tamoxifen can prevent breast cancer recurrence if taken for at least 5 years” is to have a representation/proposition with content that “Tamoxifen can prevent breast cancer recurrence if taken for at least 5 years” is stored in the brain and is ready to be activated when needed, such as when the patient is prescribed Tamoxifen and has to decide whether or not to take it. Although some neuroimaging literature neglects that there is any brain structure that can be mapped to the mental process, others prove the opposite. The amygdala, for example, has proven to be the “fear area,” and the anterior cingulate is the “conflict area” (Poldrack, 2010). For a belief to be a cognitive representation, it needs to be stored somewhere in the brain. Let’s say (belief area). But the problem here is in what form can the belief be represented? The representation—“patient belief that Tamoxifen can prevent breast cancer recurrence if taken for at least 5 years”—can be represented in many forms, such as beliefs that Tamoxifen can prevent breast cancer recurrence if taken for 4, 3, or 2 years, or more than one year. Likewise, the patient may believe that Tamoxifen is an antineoplastic and inhibits estrogen. The list could be expanded. The question is how many representations for a single proposition? If there is only one representation and the other is derived, which one? And, how could we know? Also, in what structure is this belief represented? Some cognitive scientists claim that belief representation can be in the form of language (Harman, 1973), while others say map-like representation (Camp, 2007) or sensorimotor representation (Gelder, 1990). If one of these representational structures is accepted, then

it will take the form of a yes-no phenomenon. The belief either exists or not, but what about the “in-between” belief? The belief in something and it acting differently as a result. For example, a patient who asserts that he or she can take medication on time, no matter what, and yet shows behavior indicative of the inability to control their behavior. Does the brain have both of those structures? Also, what about whether there is an individual who has a pattern behavior of knowing for a specific belief x but has a different underlying structure? Do we still consider that this individual believes that x?

Second assumption, belief is a disposition. To believe some particular proposition is to be disposed toward a certain act (i.e., behavior or thought) under certain circumstances. For example, to believe that Tamoxifen causes side effects is to be disposed not to fill the prescription if the physician prescribed it, to ask the physician for an alternative upon visiting him or her, to stop taking Tamoxifen if it is time for administration, or “to bring what you believe to conscious”—judgment or thinking—using this belief to answer the question about your belief. A person can be disposed to thinking about Tamoxifen’s benefits if he or she is going to make a specific-related decision, answer a question in a questionnaire, or judge with someone, build a new belief, etc. Therefore, belief is a multi-tracking entity in which an individual can be realized in many ways while holding the belief that x. To this end, even if the individual uses consider belief as a disposition, the material entity that bears such a disposition is still needed, therefore, belief is classified as a disposition. A disposition means that it is a realizable entity (realized by process) and specifically depends on (i.e., inheres in) some independent entity –material entity (i.e., belief area- or mental-functioning anatomical structure (term adopted from Mental Functioning Ontology (Hastings et al., 2012;

Schurz, Aichhorn, Martin, & Perner, 2013)). Mental functioning anatomical structure, as defined under material entity, above, is that part of an individual that bears mental disposition to be a participant in one or more actions (thought or behavior). Mental functioning anatomical structure can include subtypes, such as neurotransmitter, assumed to be a bearer of belief disposition (Harris, Sheth, & Cohen, 2008). If this disposition ceases to exist, then its bearer (i.e., the neurotransmitter) will physically change. Formal definition=Def. Belief is a disposition that realizes in process (behavioral or mental processes) and inheres (i.e., specifically depends on) in mental functioning anatomical structure, and belief is such that, if it ceases to exist, then its bearer is physically changed. Figure 12 shows this process, which means there are disposition d (belief), material entity a (mental functioning anatomical structure), process p (behavioral or mental processes) and belief

- Inheres in a
- Realized in p

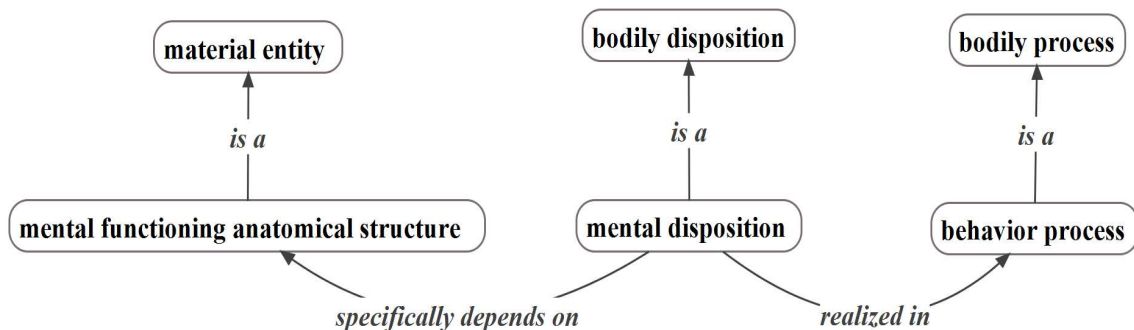


Figure 12 The Belief Structure Under BFO

Belief includes several subcategories that are categorized based on the results of the above-mentioned review into: Capability belief, behavioral consequences belief,

normative belief, and risk-related belief. Definitions of those classes and their subcategories are entered into Protégé.

Desire, memories, capability, power, skills, habit, phobia, fear and other psychological determinants are treated in the same way as belief and are analyzed individually to satisfy the BFO category. Unfortunately, due to space constraints, it is impossible to cover all psychological determinants separately. Therefore, a brief description of some of them will be provided. Desire, for example, is similar to belief, as is disposition. Action-based theory of desire (Anscombe, 2000) claims that, having a desire is comparable to having tendencies to act in or think in certain ways. For example, the patient has a desire to prevent breast cancer from spreading or recurring; this is because he or she is disposed to taking medication on time and thinking positively about the medication. Desire may not manifest. Similar to the fragility of glass, the glass may not break if the physical circumstances do not exist. A patient may have had a desire to get a second opinion four months ago; however, that desire did not manifest. The desire a person has may be stored somewhere in the person's mind most of the time, and it mostly generates thoughts, feelings, and actions. Capability is a disposition, too. The capability to read instructions related to one's medication is the disposition to read, the ability to understand, or speak the written word. Memory can also be categorized as a disposition or enduring dispositional memory in which an individual retains, as long as he or she has the capacity to remember.

Skill is also the disposition to engage in certain acts and use those skills, such as problem-solving and decision-making. Intent is a disposition where an individual has to pursue some goal in a particular circumstance. Intention can exist without undergoing or

producing any effect or change. Similar to fragility, belief, desire, and intention can be present for an indefinite period of time and not manifest or be realized until triggered by an appropriate event or elicitor.

Motive can also be categorized as a realizable entity that represents a need, desire, or drive within an individual that motivates him or her to action (adopted from Life ontology <https://bioportal.bioontology.org/>). For motive subclasses, Maslow’s hierarchy was adopted (Maslow & Lewis, 1987). It includes physiological need, safety need, motive for social belonging, motive for self-actualization, and motive for self-esteem. Each class has subclasses. For example, the need for health—(a subcategory of safety need)—motivates individuals to take their medication. Therefore, psychological determinants represented as a mental disposition under bodily disposition (adopted from Mental Functioning Ontology (Hastings et al., 2012)), are shown in Figure 13.

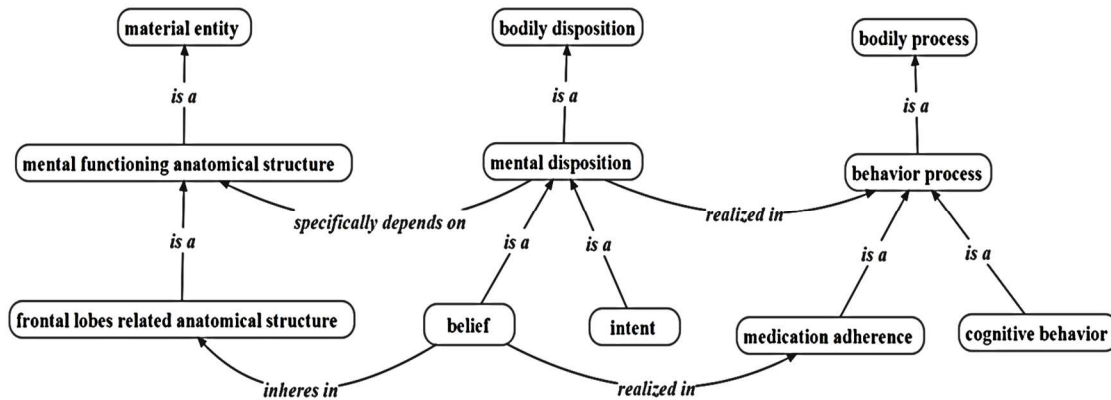


Figure 13 The Mental Disposition Structure Under BFO

III. Generic Dependent Continuant Entity

Many entities could be measured using standardized tests, such as those that measure medication adherence, determinants of medication adherence, and age. The output of measurement methods includes some information-content entities

(measurement datum) that concretized in some form of material entity, such as paper assessment questionnaires given out to the patient. Such a test can be linked by relation (e.g., measures) to the quality or process that is measured. The relation “is concretized as” is one between measurement datum (generic dependent continuant) and concretization of measurement datum (specifically dependent continuant) upon which it existentially depends. For example, when the questionnaire is printed on paper, the ink color and pattern formed by the ink splotches are qualities of the ink used on paper. This quality depends on independent continuant (i.e., ink). The quality (color of ink) exists only if the bearer exists (ink) and does not need a process to be realized. This category—the generic dependent entity—is discussed in the next sections, along with the process (Figure 14).

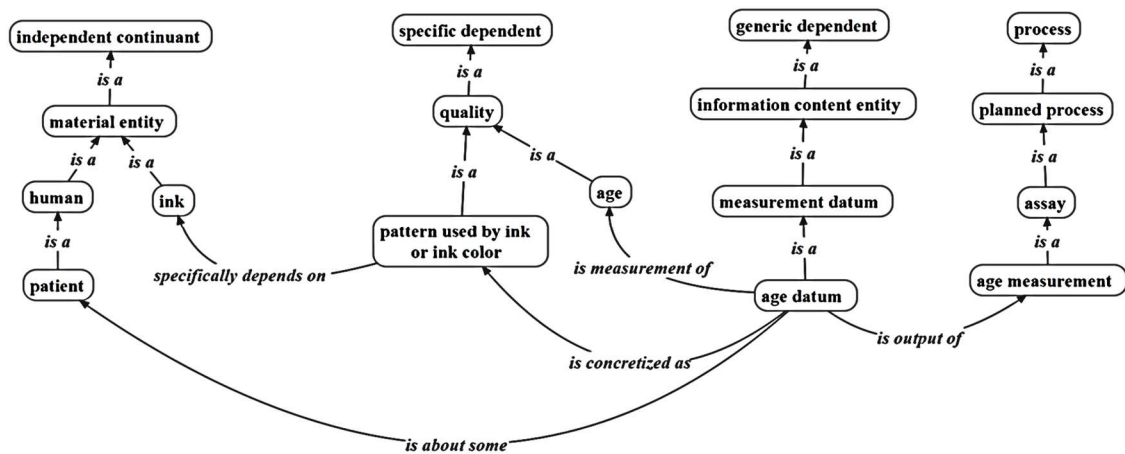


Figure 14 Measurement Under BFO

4.3.4.2 Occurrent Entity

A. Process

Several processes are included in MAB-Ontology, such as the behavior process, physiological process, mental process, and treatment process. Some will be explained in this section, while the full classes are represented in Protégé. To define medication

adherence, other entities need to be specified, such as medication recommendations (e.g., duration, dose, and time for medication administration), methods used to evaluate the patient's medication adherence, the process that is part of the medication adherence process, and the barrier to medication adherence. In the previous section, mental disposition was both represented and discussed in terms of how it can be instantiated and linked to medication adherence; other entities, however, may cause medication non-adherence. Measuring these entities will be discussed in this section.

1. Medication adherence

In general, medication adherence is a subclass of the behavior process based on Mental Functioning Ontology <http://www.ontobee.org/ontology/MFO>. The behavior process is defined as “Patterned activity of a whole organism in a manner dependent upon some combination of that organism's internal state and external conditions (Hastings et al., 2012).” Therefore, a definition given to the medication adherence behavior is, “behavior associated with the consumption or use of a chemical substance with presumed curative, preventive, or medicinal value in accordance with the provider's recommendation concerning the timing, dosage, and frequency.” Figure 15 shows this process, which means that there is a process *p* (medication adherence process), material entity *m* (patient), dose specification *d*, dose frequency specification *f*, duration specification *s*, time specification *t*, value *v* and medication adherence process

- has participant *m*, *d*, *f*, *s*, *t*
 - *d*, *f*, *s*, *t* has *v*

When a physician treats a patient, he or she follows a protocol, such as the one developed by the World Health Organization (WHO), which serves as a guideline in the

management of breast cancer according to T.N.M.—“T.N.M. Staging of tumors according to three components: primary tumor (T), regional nodes (N), and metastasis (M) (Geara et al., 2006),” or he or she uses practical experience. The protocol specifies the drug, dose, frequency, and duration for each disease stage or type. The physician may consider how the determinants impact medication taking, risk factors, demographic characteristics, types of hormone receptors, menopausal status, etc., in the treatment process. Therefore, a specification of this recommendation is important. A class named “cancer treatment regimen specification” was created that is an extension of the Ontology for Biomedical Investigating (OBI) plan specification and is defined as “a plan specification that prescribes actions whose goal is to cure and prevent a patient’s breast cancer from reoccurring. A cancer treatment regimen specification takes into account the standard protocol, determinants and risk factors, specific patient characteristics (e.g., age, weight, menopausal status, family history), as well as the patient’s preference.” This class included several classes as part of such a dose specification, frequency specification, duration specification, dietary specification, etc. Dose specification is that part of a cancer treatment specification that states the dose to be prescribed to the patient (e.g., 5 ml). Duration specification is a scalar specification that is part of a plan specification that specifies a length of time the patient should take the medication for a single dose (30 minute for infusion) and for the entire course (e.g., 30 days, 2 months, 1 year). Frequency specification is a “value specification that is part of a plan specification and specifies the frequency of the drug supply.” This includes subclass as: drug dispensing frequency specification, which is “a frequency specification that specifies the frequency of drug dispensing (e.g., 12 dispensings per year.” Drug administering frequency specification,

which is “a frequency specification that specifies how often a drug taken (i.e., 1 tablet per day, 2 tablets per day).”

The process that implements the treatment specified in the cancer treatment regimen specification is referred to as the planned treatment process. It fits under the healthcare process class from Ontology for General Medical Science (OGMS)

<http://www.ontobee.org/ontology/OGMS> and is defined as “a planned process that has_specified_input; some concretizes some cancer treatment regimen specification.”

The concretization of the planned process could be a plan in the physician’s brain or a written note that is part of the patient’s medical record. Figure 16 shows the process of treatment regimen.

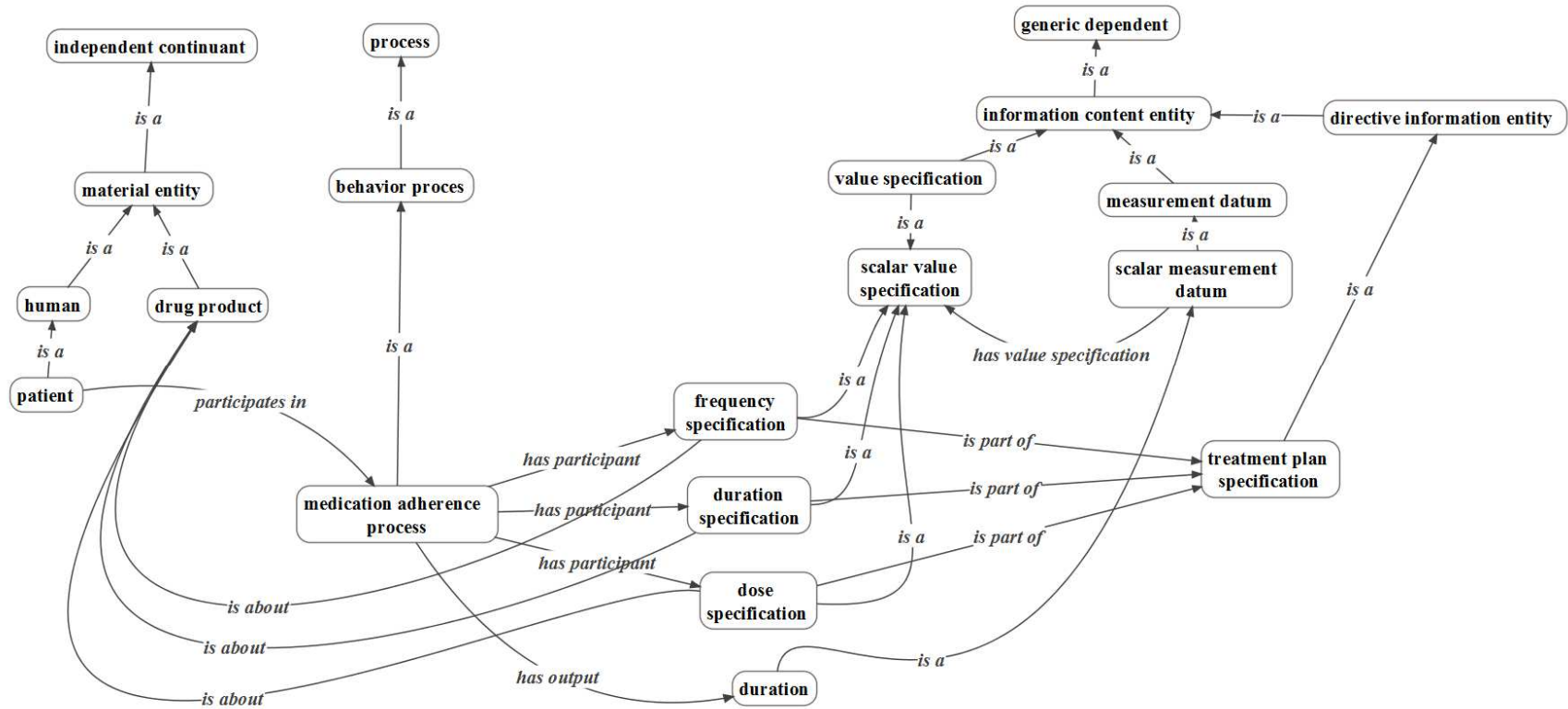


Figure 15 Medication Adherence Process

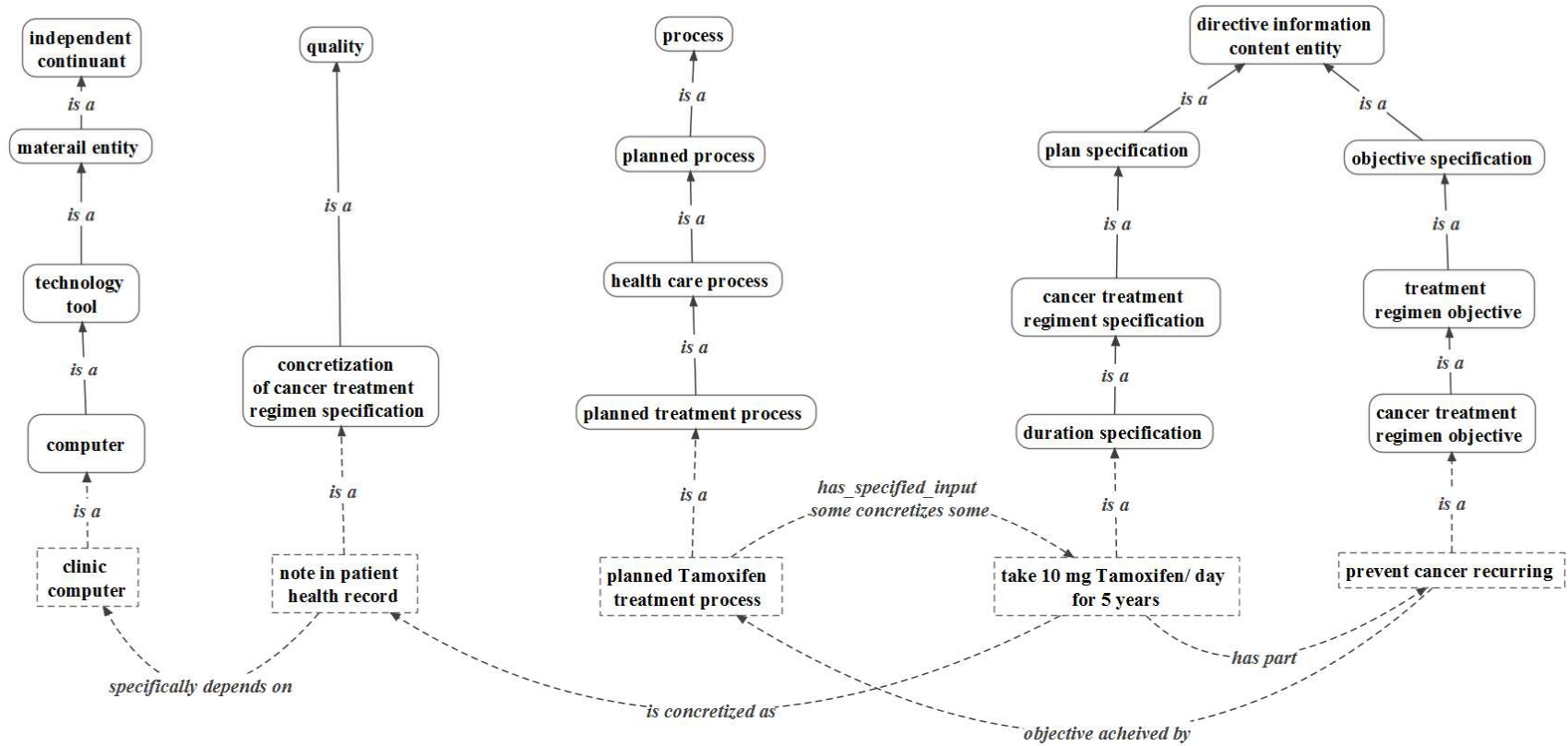


Figure 16 Treatment Process

2. Medication adherence measurement

Medication adherence rate (measurement datum) is about the quality of process (such as increased adherence, regular adherence, irregular adherence). Quality under BFO is a continuant and has no temporal parts. Therefore, it cannot inhere in occurrents, and it is not possible to make any statement on whether a medication adherence is regular by inspecting a snapshot of this process at a particular moment in time. While, under BFO quality of a continuant entity, it is possible to describe a change quality has in their bearers over time, such as changes in temperature against time (temperature chart) or changes in an individual's weight over times (as increases or decreases). When measuring continuant quality, such as the weight of patient "A," this weight is quality that inheres in an individual at a specific time. It is easy to create a chart for the weight of this patient against time. So, we can represent increasing and decreasing weight and/or regular or irregular weight for the same patient over different times. In terms of the occurrent part, however, there is no such counterpart. We cannot say process one is an instance of universal "A" at t_1 and universal "B" at t_2 . Instead, we can say that there is a process p that has two occurrent parts: "a," which is an instance of universal "A" and "b," which is an instance of universal "B." BFO assumes the process is a change, and changes cannot change; therefore, they cannot have quality-like entities that inhere in occurrents. Each process has at least one participant (continuant entity) and one duration (extent of the time interval between beginning and ending). The process can have many subprocesses in which each has some participant and duration. To this end, two classes are created, namely, dose administration process and medication adherence process. (a) The dose administration process is defined as "a process that has as participants an

organism and a drug product and that results in a specified portion of the drug product (a single dose) being located in the organism.” This means that there is a dose administration process p , dosage specification s_1 , dose administration duration specification s_2 , dose timing specification s_3 , drug product specification s_4 , and patient p , drug d , and dose administration process p

- has participant s_{1-4} , p , d
 - s_{1-4} is about d

(b) The medication adherence process is defined as a behavior process that has at least two dose administration processes. So, to define 30 days, medication adherence process is to say that “a process that has part 30 dose administration process (single dose/day of tamoxifen). If the medication is taking twice daily, then we can say that it is a process that has 60 doses taking process.” Any missing dose, therefore, is “a process that lacks part of some dose administration process.”

Dealing with the quality of the medication adherence process (e.g., regular adherence rate, irregular adherence rate) under BFO is challenging. Therefore, to represent such a quality under BFO, there were five analyzed options to choose from:

(i) Representing the process attributes as if they were attributes of the continuant participants by following the Vital Sign Ontology (VSO), which represents the process quality as a continuant quality that inherence in independent continuant entity, so the adherence rate will be one that inheres in an individual. This way could be reasonable for the simple process. However, it becomes complicated when dealing with a change in the adherence rate and in relation to the other entity (substance or process), such as a change in the duration of adherence due to a side effect of the medication. Therefore, there is a

need to capture the knowledge of the effect or change a side effect can have on medication adherence or to relate such a change back to the side effect. This requires explicit representation of process attributes. It is also necessary to record such changes in medical records to tailor interventions based on the reason for such changes.

(ii) Represent the quality of process under class quality and have process qualities as subclasses by following the phenotypic quality ontology (PATO), so that the process quality for medication adherence is defined as a quality that inheres in the medication adherence process. By using this method, medication adherence attributes, such as regular, irregular, rate, frequency, duration, accelerating, abnormality, and having an extra or missing sub-process part can be represented. And the process be connected with the rate or modifier, such as increased adherence rate, irregular adherence, or missing adherence. However, this method contradicts the BFO definition of quality. Quality is a dependent continuant that presents as a whole at one point in time and can change over time. For example, the height of an individual changes as he or she grows. If there is a process quality based on BFO, it should depend on the process as a whole and can extend over time (process duration) based on whether it cannot be wholly presented at a given time or change over time (there is no medication adherence rate at 3:30). Instead, there is a medication adherence rate for the medication adherence process that starts at 3:30 pm.

(iii) Represent the process attributes as a result of drawing a conclusion based on data by extending the “conclusion based on data” class from the ontology of biomedical investigations (OBI) to include the medication adherence rate and include its sub-category as a regular or irregular rate that can be linked to the adherence process by relation (is about). By using such a technique, the medication adherence process will

assume a normal or regular process. Any information regarding irregular data will appear under the information content entity as a finding or conclusion based on finding only and will not be represented under process as a type or quality.

(iv) Directly represent complicated medication adherence process hierarchies by creating a process profile under BFO for medication adherence in which every instance should be universal (for example, an adherence rate of 70% during a duration of 30 days of the first year, an 80% adherence rate for 6 months during the third year of the medication adherence process, etc.). Therefore, the process attributes (such as increased, decreased, missing one dose, two doses per day, one refill per period of time, so on) is represented as an instantiation relation. Creating a process profile contains classifications of the process universals instantiate each subtype of the process, however, may lead to a complex list, as for every instance, a universal should exist. For example, in terms of the process of medication adherence, there is a rate process profile that contains a cyclical process profile that contains a regular cyclical process profile. In turn, it will have a 30 doses per 30 days duration, a 60 doses per 30 day duration, etc. An irregular process profile, on the other hand, contains 29 doses per 30 days duration, 28 doses per 30 days duration, etc. Representing process quality in such a way is complicated if it compared with the continuant quality that can be represented simply. For example, the “20 mg mass of Tamoxifen” is represented by having a universal class of mass, a universal class of tablet, a universal class for measurement, and the relationship between each.

(v) Lastly, create a new class for process attributes and define it as occurrents that describe a process without committing this class to any existing entity in reality at this point. Once the definition of the process attributes has been achieved and is assigned in

an upper-level ontology, an update to the ontology will take place accordingly. So, under this type, a medication adherence process is classified into a single process and cyclic process. Adherence to medication as a cyclic process may take an entire lifetime and for tamoxifen, it takes up to 10 years. The quality of the medication adherence process represented under occurrent is a class named “process attribute” and is connected with the relation “is process attribute of.” Under this class, several attributes can be categorized, such as process duration (regular and irregular), process occurrent (missing dose), and process frequency (adherence rate). Although the last way is preferred to represent the medication adherence attribute, it contradicts the BFO/OBO-principles. Therefore, representing process attributes as if they were attributes of the continuant participants, as well as a conclusion based on data, are the ways that have been adopted to represent the medication adherence process attribute.

Medication adherence can be measured using different methods (Figure 17):

(i) Drug concentration assay is an assay that measures concentration of the active ingredient of a drug product in a specified body fluid, such as the blood and urine of an individual in order to assess whether or not the patient can take the medication regimen. The results can be represented as “contains 1.3ng/ml,” or “no drug detected.” The output of this assay is scalar measurement datum that is about body fluid (i.e., evaluant), which is part of the patient or it can be direct-linked with the patient. This scalar measurement has a specified value and measurement-unit label (ng/ml) based on the value specified. Figure 18 describes this process and provides an example. The formal definition of Drug concentration assay =Def. Medication adherence assay, is such that there exists some drug d , analyte role r_1 , evaluant role r_2 , body fluid specimen (e.g., blood or urine) b ,

measurement device v , measure function f , drug concentration assay objective g , drug concentration measurement c , and drug concentration assay

- realizes r_1, r_2, f
 - r_1 inheres in d
 - r_2 inheres in b
 - f inheres in v
- has specified input d, b, v
 - d part of b
- has specified output c
 - c is about b
- and is directed toward achieving goal g

(ii) Direct observation is a medication adherence assay in which the subject is monitored and the medication consumption recorded. The output of this assay is categorical measurement (e.g., “drug taken” or “not taken”), which is about the patient (i.e., evaluant). Figure 19 shows this process. The formal definition of direct observation=Def. Medication adherence assay which is such that there exists some patient p , drug d , human h , evaluant role r_1 , observer role r_2 , direct observation objective g , categorical measurement datum m , and medication administration observation

- has specified input p, d , and h
 - d part of p
- realizes r_1 and r_2
 - r_1 inheres in p
 - r_2 inheres in h

- has specified output m
 - m is about p
- is implemented towards achieving goal g

(iii) Dosing event recording is a medication adherence assay that uses monitoring devices, such as the Medication Event Monitoring System (MEMS) incorporated into the packaging of a prescription medication. These devices contain a microprocessor that records the time and date whenever the patient opens the cap of the medication container, assuming that the patient has taken that dose at that specific time. The output of this assay is time measurement data and count measurement datum that records time and the number of doses taken by the patient (i.e., evaluant). Figure 20 exemplifies this process. The formal definition of dosing event recording=Def. Medication adherence assay, is such that there exists some patient p, drug d, evaluant role r, monitoring device (e.g., Medication Event Monitoring System) m, monitoring device function f, number of drugs taken d, dosing event recording objective g, and the dosing event recording

- has specified input p, d, and m
- realizes r and f
 - r inherence in p
 - f inherence in m
- has specified output n
- and is directed toward achieving goal g

(iv) Pill counting is a medication adherence assay that counts the number of doses that have been taken between two scheduled appointments or clinic visits. The output of this assay is a count datum that is about some container (i.e., evaluant). Figure 21 shows this

assay. The formal definition of pill counting=Def. Medication adherence assay which is such that there exists some drug d, drug container c, evaluant role r, drug counting device k, drug counting device function f, measurement of the remaining number of drug n, pill counting objective g, and the pill counting

- has specified input d, c, and v
 - d part of c
- realizes r and f
 - r inherence in c
 - f inherence in v
- has specified output n
- and is directed toward achieving goal g

(v) Self-reported medication adherence assessment is a medication adherence assay in which an individual was asked to respond to characterize his or her medication adherence behavior. A medication adherence self-report includes questions that range from simple, single-item questions regarding missed doses, to complex multi-item assessments that incorporate reasons for non-adherence. The output of this measurement is about the patient (evaluand). This class included several subclasses:

1. Patient interview: is a self-reported medication adherence assessment in which the patient is asked to estimate his or her medication-taking behavior and whether he or she follows the prescribed regimen. Its specified output is an adherence categorical measurement datum, which is a measurement of the patient's adherence behavior and is recorded using a category "adherent" or "non-adherent," (Figure 21). The formal definition of patient interview=Def. Self-reported assay, which is such that there exists

some patient p , human h , evaluant role r_1 , interviewer role r_2 , categorical measurement datum m , self-reported objective g , and the self-reported medication adherence assessment

- has specified input p and h
- realizes r_1 and r_2
 - r_1 inherence in p
 - r_2 inherence in h
- has specified output m
- and is directed toward achieving goal g

2. Adherence assessment with questionnaire: is a self-reported medication adherence assessment that use a series of questions to gatherer information from the patient about his or her medication adherence behavior or barrier to adherence. The answers to these questions are turned into scores to assess adherence. The questionnaire can be used by an observer assessing the patient or the patient's self-reporting adherence behavior. Figure 22 shows the process with an example. The formal definition of adherence assessment with questionnaire =Def. Self-reported assay, which is such that there exists some patient p , questionnaire q , evaluant role r , scalar measurement datum m , adherence assessment with questionnaire objective g , and the self-reported medication adherence assessment

- has specified input p and q
- realizes r
 - r inherence in p
- has specified output m
- and is directed toward achieving goal g

(vi) Prescription filling and refilling assay is a medication adherence assay in which the time of the filled prescription has been assessed in order to measure the number of days in which the patient has medication on-hand (possession ratio) or the total number of days the patient is without medication (gap) in an observation period. The output of this assay is a time measurement datum (e.g., 01/01/2018) that is about evaluant (i.e., patient).

Figure 23 shows this type of assay. The formal definition of prescription filling and refilling assay =Def. Medication adherence assay which is such that there exists some patient p, pharmacist s, observer role r₁, pharmacy computer c, pharmacy record d, concretization of pharmacy record q, evaluant role r, ratio measurement datum m, prescription filling and refilling objective g, and the prescription filling and refilling assay

- has specified input p, s, and q
- realizes r
- has specified output m
- and is directed toward achieving goal g

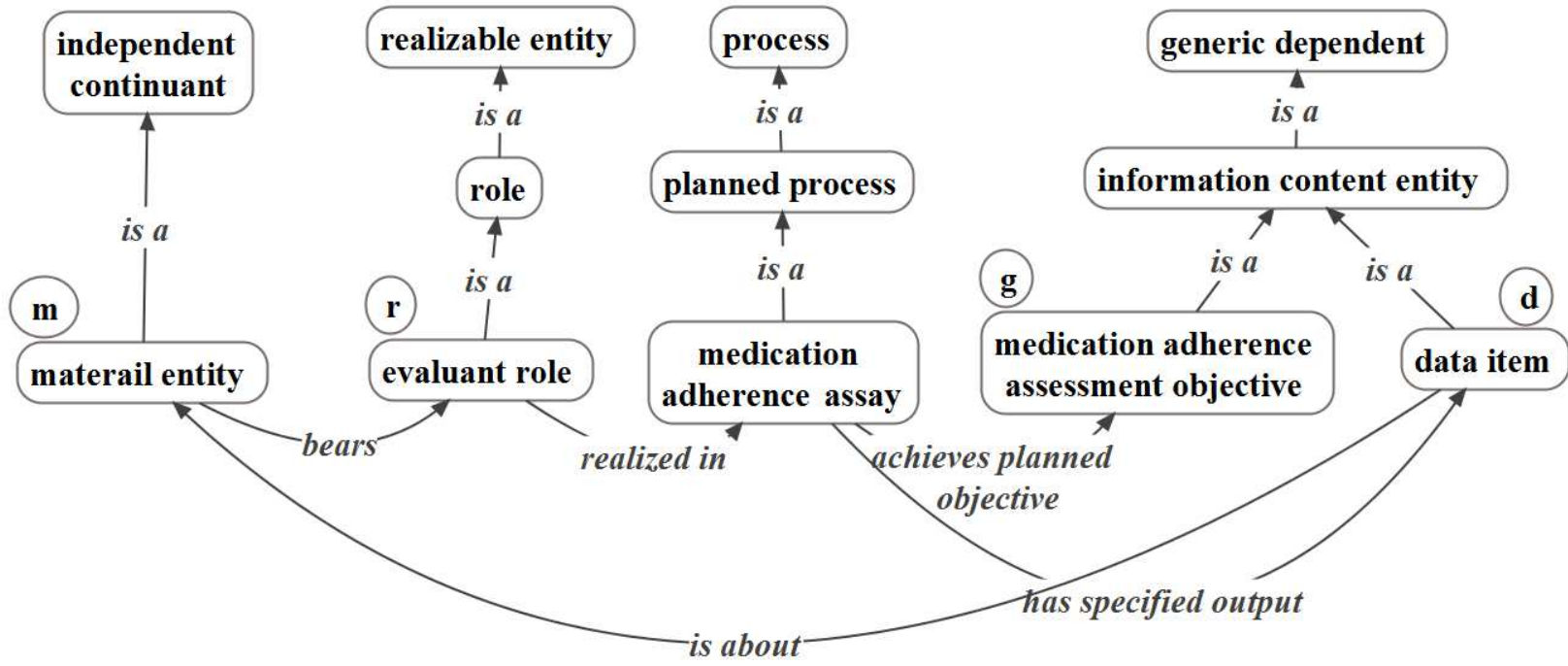


Figure 17 Medication Adherence Assay

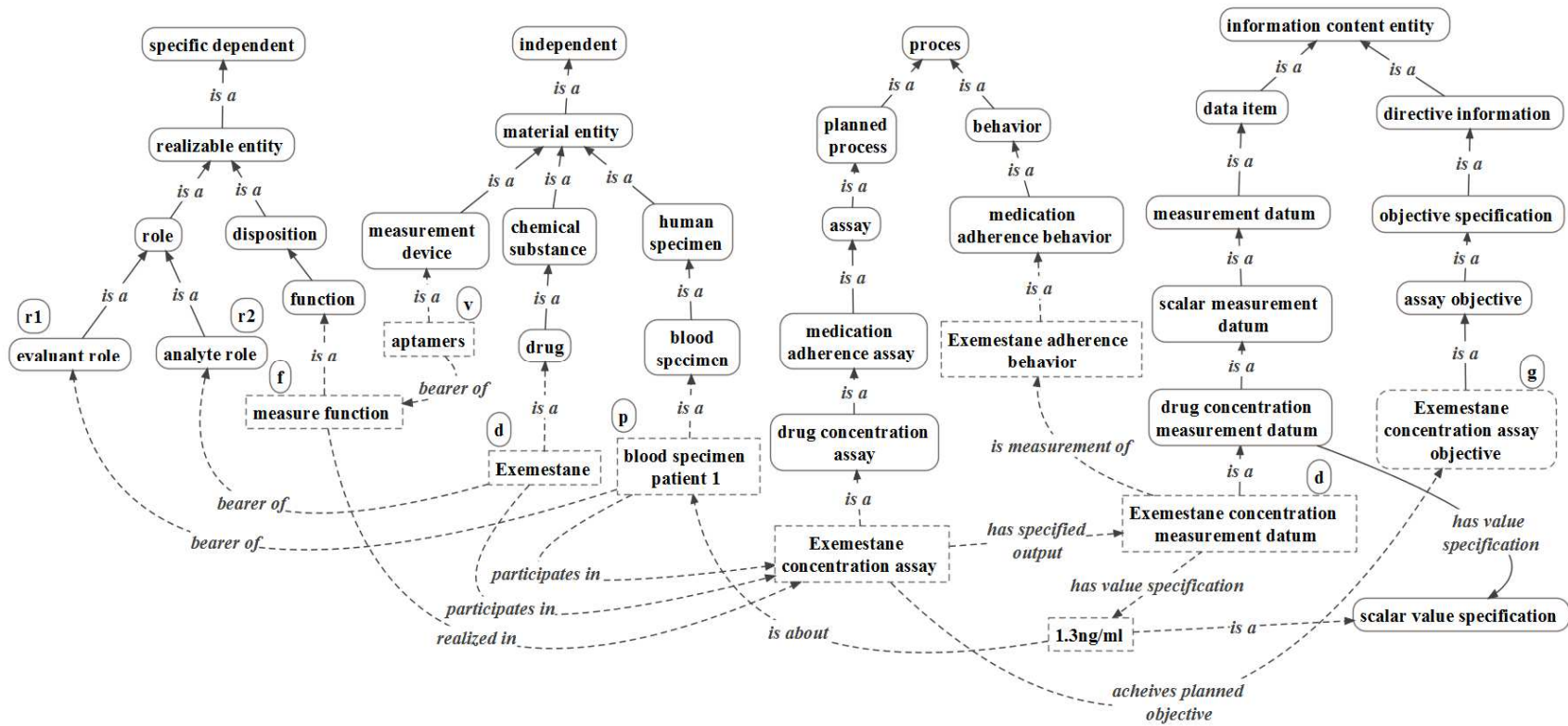


Figure 18 Drug Concentration Assay
 Note: - - - - represents instances classes.

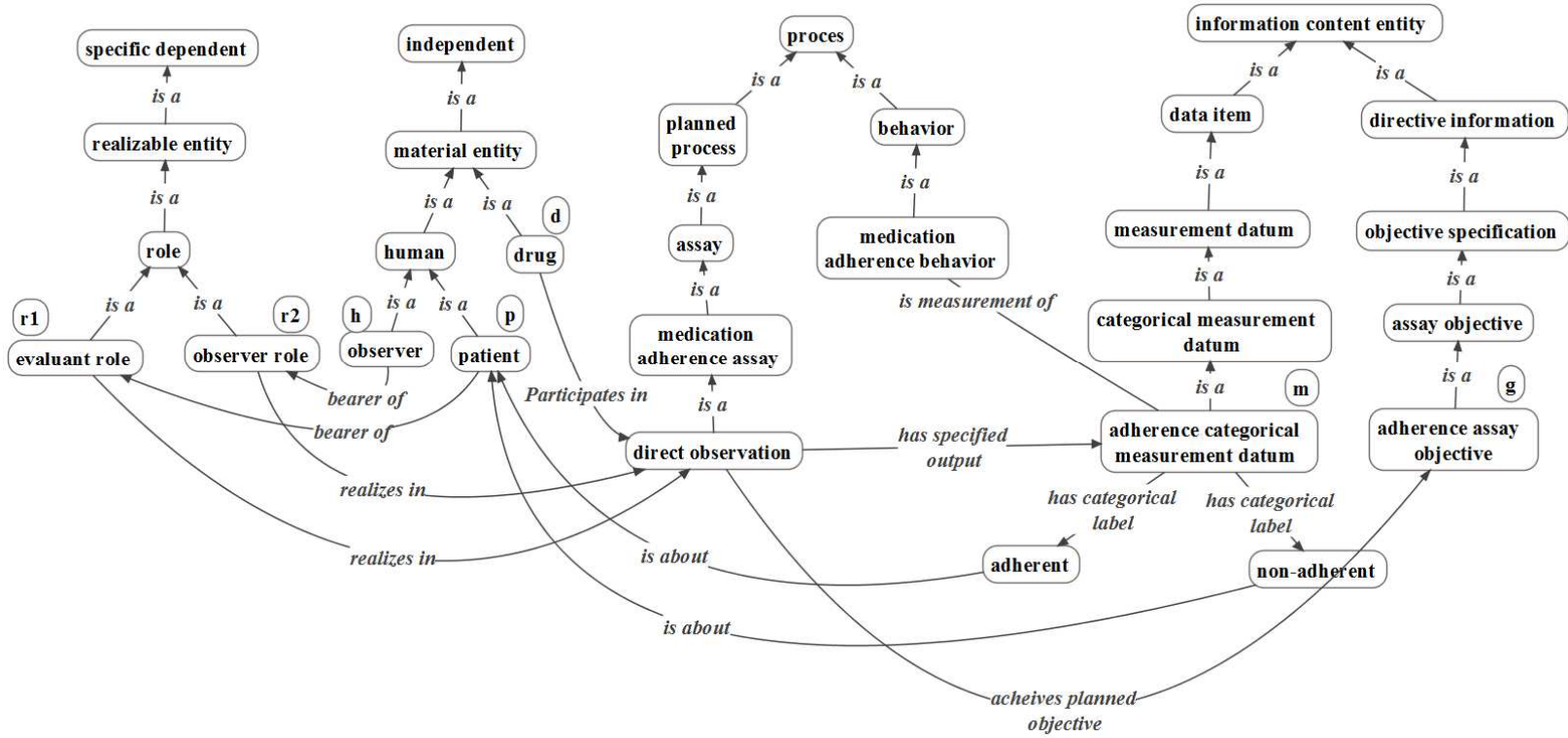


Figure 19 Direct Observation Assay

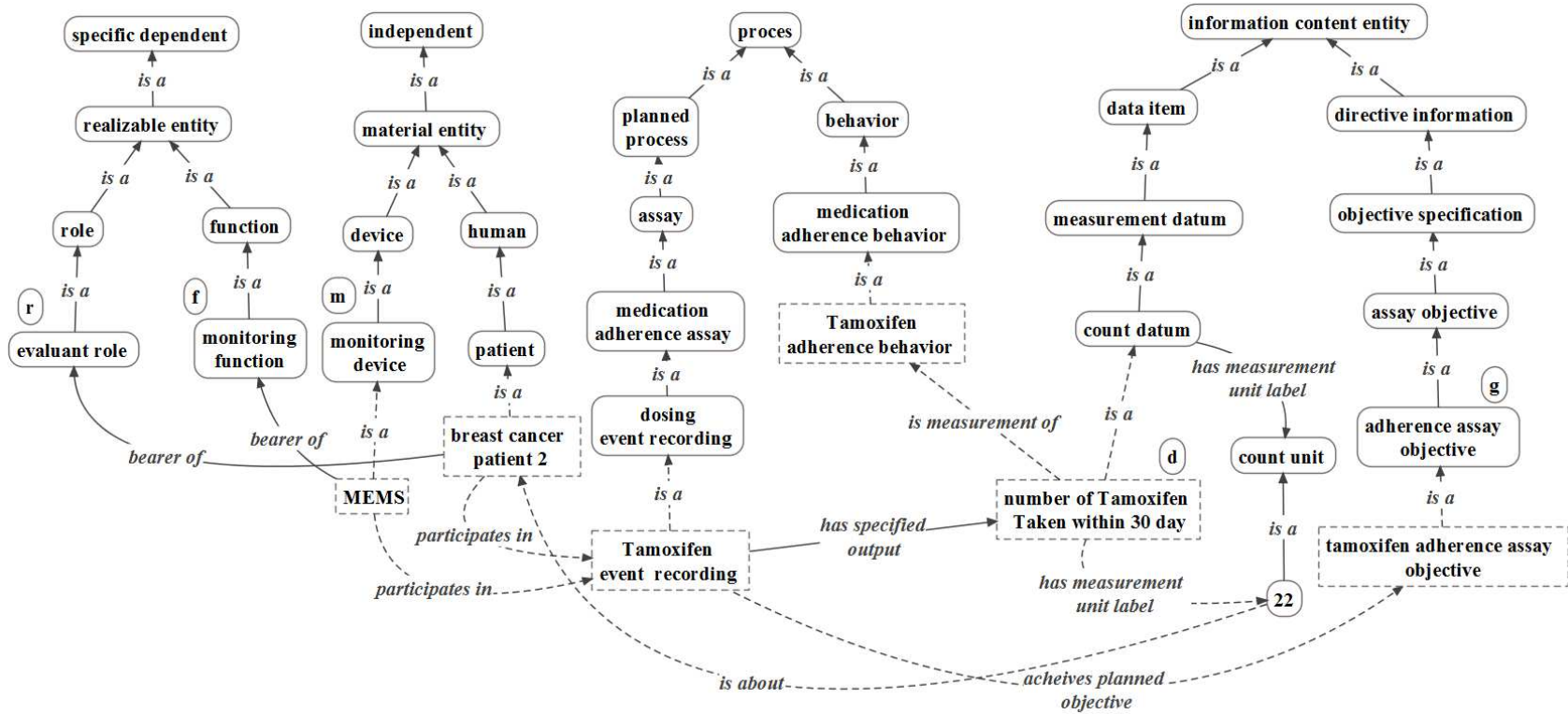


Figure 20 Dosing Event Recording
 Note: - - - - represents instances classes.

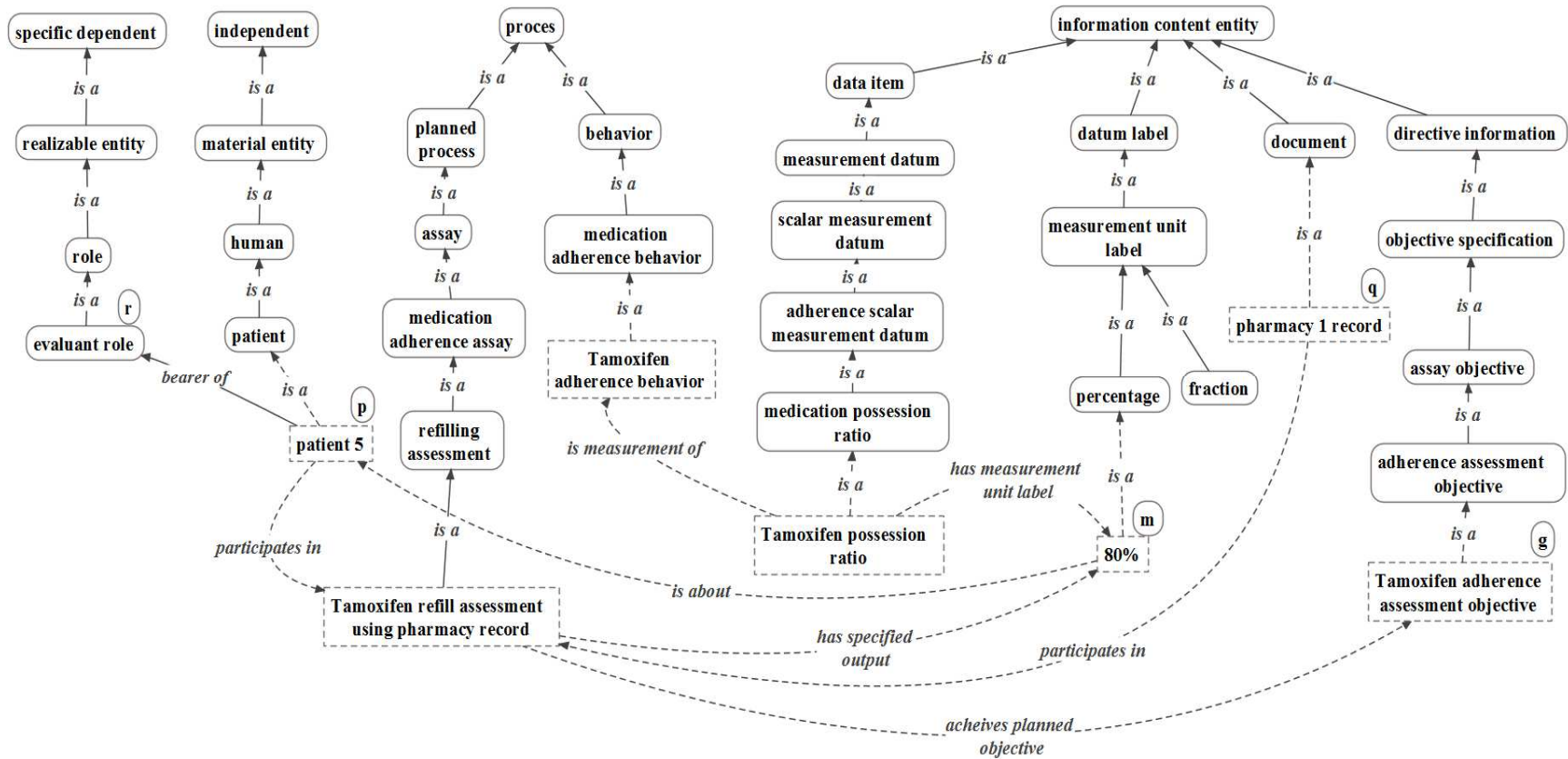


Figure 23 Prescription Refill Assessment
 Note: - - - - represents instances classes.

3. Behavioral intervention.

Adherence intervention is categorized under Ontology for Biomedical Investigation (OBI) planned process (Peters & Consortium, 2009) (Figure 24).

“Adherence behavior intervention specification” is a subclass of OBI plan specification and is defined as=Def. A plan specification that prescribes actions whose goal is to improve, prevent, or maintain the behavior process. A medication intervention specification takes into account the specific patient’s psychological determinants; duration of medication taking (i.e., long-term vs. short-term); medication-taking phases (i.e., initiation vs. continuation); mode of delivery; the behavioral theory(ies) used to explain the determinants’ effect on behavior; and the standard protocol for developing, implementing, and evaluating the type of intervention used.

“Medication adherence intervention” is the process that carries out the adherence intervention specification and is defined as=Def. A planned process that has_specified_input some concretizes some cancer treatment regimen specification.

“Behavior change technique” is defined as=Def. A planned process that is part of the medication adherence intervention and is designed based on one or more behavioral theories with a goal to influence one or more psychological determinants of behavior.

“Medication adherence intervention objective specification” is defined as =Def. An objective specification that describes the endpoint of medication adherence intervention.

“Intervention delivery process” is defined as=Def. A planned process by which the planned behavior intervention is delivered to an individual or group of individuals using either the personal or impersonal mode.

“The formal definition of planned behavior intervention” is defined as=Def. A planned process which is such that there exists some human a, technology tool t, mode of delivery role r, concretization of behavior intervention specification c, intervention delivery process d, behavior change method m, behavior intervention specification s, behavior intervention objective g and the planned behavior intervention process

- initiated by a
- has specified input some concretizes s
 - s concretized as c
- has part m, d, and
 - d realizes r
 - r inheres in t
- directed toward achieving the goal g of p

An example of medication adherence intervention designed to improve self-belief, using a mobile application (patient partner), is shown in Figure 25. The categories of intervention are adopted from the behavior change technique, while the mode of delivery is built based on the review carried out by Sawesi, Rashrash, Phalakornkule, Carpenter, & Jones (2016).

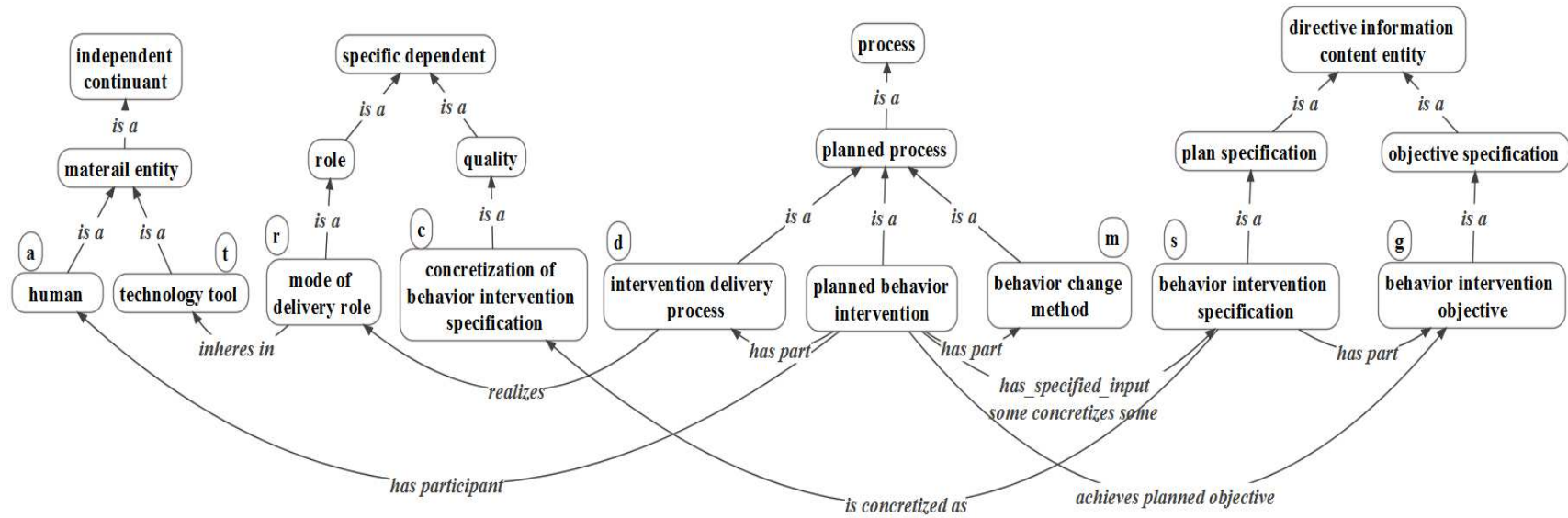


Figure 24 Behavior Change Intervention

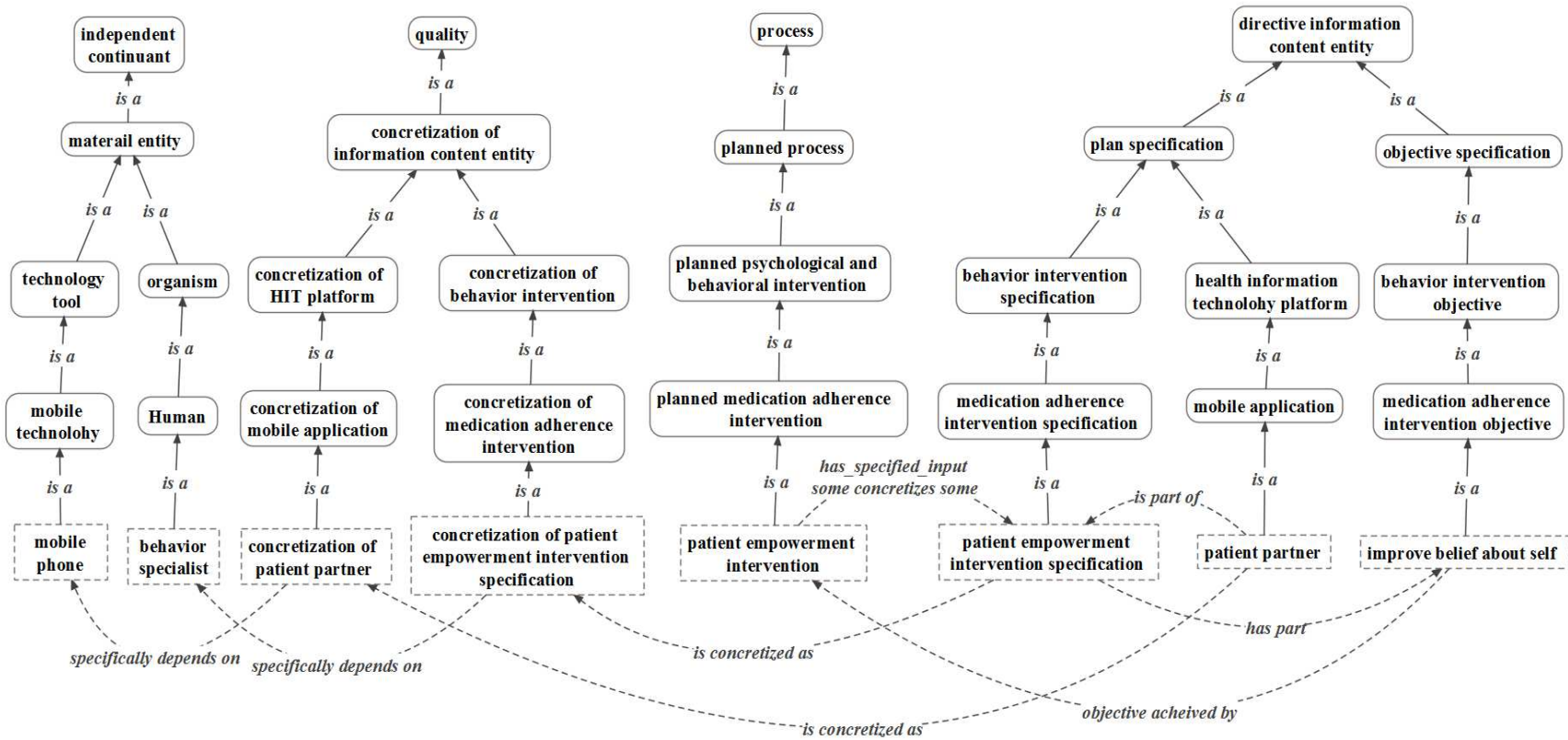


Figure 25 Medication Adherence Intervention
 Note: - - - - represents instances classes.

4. Measuring Medication Adherence Determinants

Findings about adherence determinant can be represented in two ways: (i) Expand the planned process to include class “medication adherence barrier assessment” that has a goal to assess medication adherence, so the result is a scalar measurement datum that has a measurement unit label and value. (ii) The clinical history-taking class from the Ontology of General Medical Science OGMS <http://www.ontobee.org/ontology/OGMS> has been expanded to include a new class, adherence history taking, as shown in Figure 26. The class is defined as “Clinical history taking that records the past event and circumstances that are or may be relevant to a patient’s current medication-taking state with an account of actual and perceived determinants of adherence.”

Adherence determinate finding can then be the outcome of this process. The class adherence history taking is defined as= a clinical history taking in which there exists some information entity *i* (adherence finding), some material entity (patient) *m*, and measurement datum *d* and adherence history taking

- has output *i*
 - has part *d*
- is about *m*

5. Drawing a conclusion based on data

To say that this patient did not take his or her medication because of a negative belief about the effects of the medication or because of the cost of treatment, or even the burden of a schedule, is to draw an inference based on some findings (data item) that this reason causes that behavior. Therefore, there is a need for a class that represents this implication or inference. A class was named that drawing a conclusion based on data and was adopted from Ontology of Biomedical Investigation

<http://www.ontobee.org/ontology/OBI>. Drawing a conclusion based on data is=Def. A planned process p in which new information is inferred from existing information. That means that there is a planned process, which is such that there exists some data item (measurement data) m, conclusion c (conclusion based on data). and planned process

- has participant d
- has output c

Therefore, a subclass named causal determinant of non-adherence assessment is created and defined as drawing a conclusion based on data from assays that evaluate the disposition or quality inherent in an organism and comparing it with an evaluative result or another organism's data to make conclusions about this difference. The output of this process is an information-entity-named conclusion about causal adherence determinant, which is defined as a conclusion about a determinant that expresses the result of reasoning about something being a causal determinant or a risk factor. For a variable to be a causal determinant, a correlation must exist and precedes the outcome. This determinant can change and, when changed, can cause change in risk for the outcome. Therefore, as shown in Figure 27, causal determinant of non-adherence assessment is

defined as=Def. A drawn conclusion based on data d, in which there exists some information entity (conclusion about causal adherence determinant) i, measurement data (adherence determinant measurement data) m, assay (adherence determinant assay) a, disposition d, human h and, causal determinant of non-adherence assessment

- has participant m
 - m output of a
 - m about d
 - d inheres in h
- has output i

Increasing the medication adherence rate

The medication adherence process has duration. If the goal was to measure a daily event, such as by using a medication event-monitoring system, then the duration of the process would be recorded daily (one day). Making a conclusion or inference about the patient adherence rate is based on the accumulated data that is taken daily, weekly, monthly, or yearly; it is a class-named medication-adherence-pattern assessment, which is defined as drawing a conclusion based on data in which the adherence data aggregated is evaluated based existing knowledge to generate a conclusion that patient adherence is increasing, decreasing, or no changes occur. This class has an output class-named adherence-pattern conclusion, which is an information content entity that is inferred from the adherence measurement rate. Therefore, as shown in Figure 28, the medication adherence pattern assessment=Def. A drawn conclusion based on data such that there exists some information content entity (conclusion based on adherence rate) i, measurement data (adherence rate measurement datum) m, planned process (adherence

assay) p_1 , process (adherence process) p_1 , human (patient) h and, medication adherence pattern assessment:

- has participant m
 - m output of p_1
 - m about h
 - h participates in p_1 and p_2
 - m is measurement of p_1
- has output i

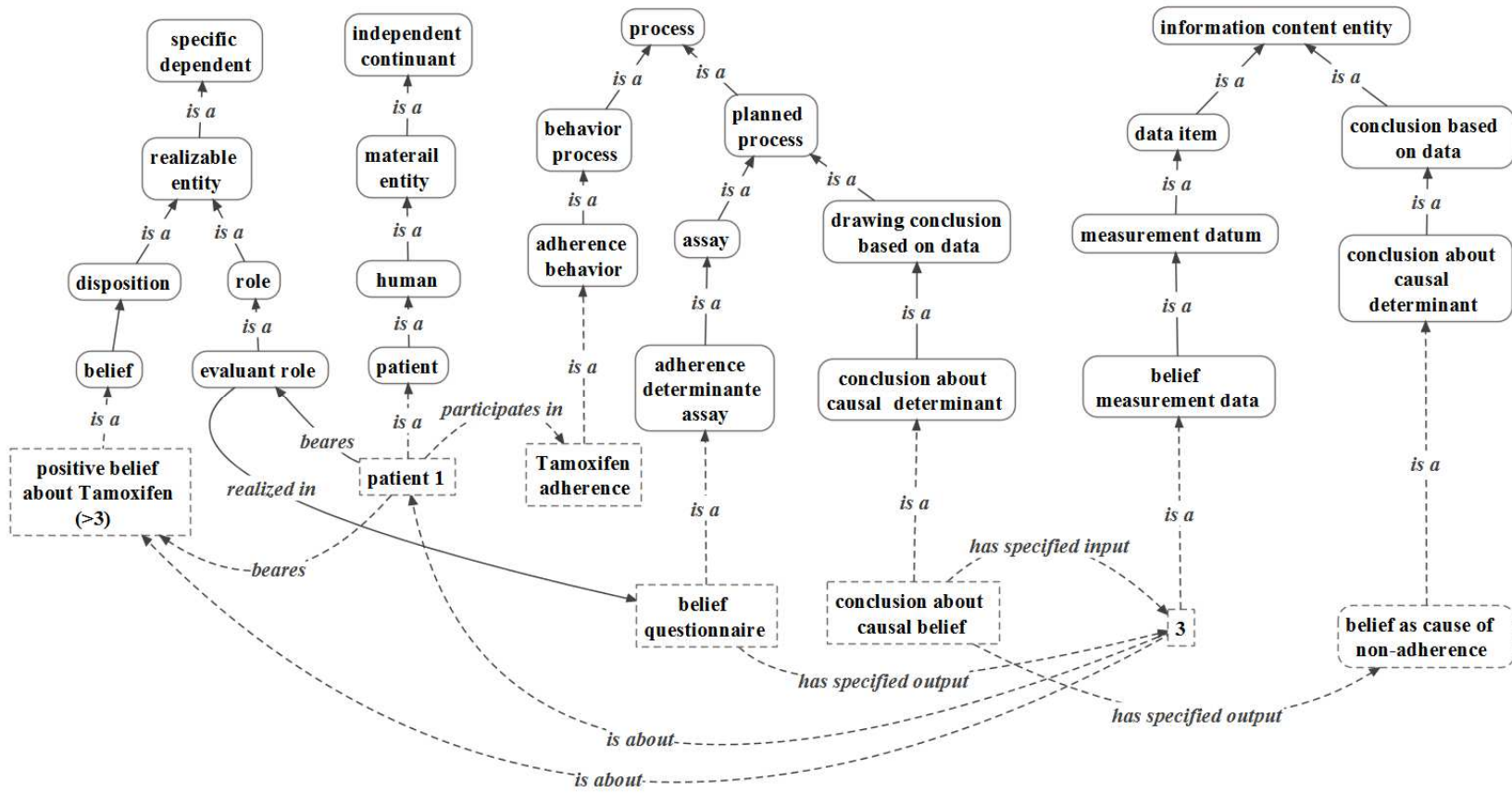


Figure 27 Conclusion Based on Data About Causal Belief

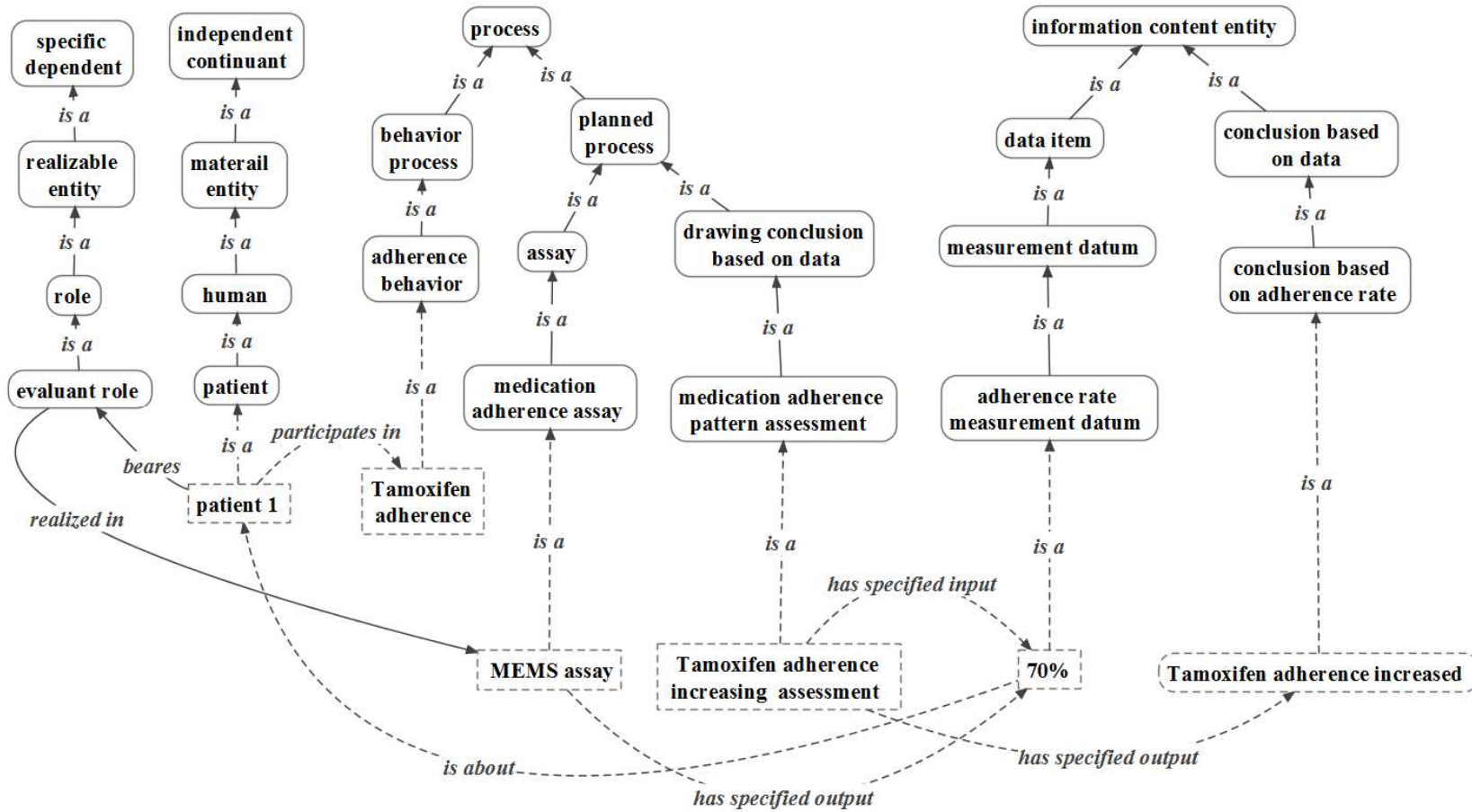


Figure 28 Conclusion Based on Data About Adherence Pattern

4.4 Model Integration

Several terms in MAB-Ontology were built based on other ontologies' categories. For instance, medication adherence assessment, drawing conclusion-based data, and behavior intervention were built by expanding the planned process class in the Ontology of Biomedical Investigation (Peters & Consortium, 2009). The mental function anatomical structure and the psychological factors were built based on the Mental Functioning Ontology (Hastings et al., 2012) and Emotion Ontology (Hastings et al., 2011). Breast cancer was built based on the Disease Ontology (Schriml et al., 2011). The breast cancer treatment regimen built based on the Drug Ontology (Hanna et al., 2013). Leverage Ontology Summary:

Seven ontologies were used for leveraging. Table 22 below, summaries the included ontologies.

Table 22 Listing of Leveraged Ontology

Source	Terms	Description	Data type
Basic Formal Ontology	35	Upper-level ontology used to support domain ontologies to enhance interoperability and connection with other biomedical ontologies.	Controlled terminology/ontology
Ontology of Biomedical Investigation	3380	A domain ontology for biomedical data annotating.	Controlled terminology/ontology
Human Disease Ontology	17632	An ontology representing human disease classifications and organized by etiology.	Controlled terminology/ontology

Ontology for General Medical Science	124	A domain ontology for representing diagnosis and treatment of disease, carcinomas, and other pathological entities.	Controlled terminology/ontology
The Drug Ontology	434663	A domain ontology used to enhance comparative effectiveness researchers studying claims data.	Controlled terminology/ontology
Mental Functioning Ontology	692	A domain ontology focused on mental functioning aspects.	Controlled terminology/ontology
Behavior Change Technique Taxonomy	114	A taxonomy-classified behavioral intervention.	Taxonomy

4.5 Model Formalization

The resulting model was built manually using Protégé to formalize the entities and relations discussed above into an OWL for computation. A term definition was given for each class and property entered in Protégé, as shown in Figure 29. The process starts by extracting BFO ontology and other upper classes borrowed from other ontologies using OntoFox, as shown in Figure 30. Then MAB-Ontology classes and the relationship used were entered into Protégé. The resulting ontology included 629 classes, 529 individuals, 51 object property, and 2 data property. Figure 31 shows the object properties and data properties included in the MAB-Ontology.

Figure 29 MAB-Ontology Viewed in Protégé

OntoFox

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Ontofox is a web-based **Ontology** tool that fetches ontology terms and axioms. Ontofox supports ontology reuse. It allows users to input terms, fetch selected properties, annotations, and certain classes of related terms from source ontologies and save the results using the RDF/XML serialization of the OWL. Ontofox follows and expands the **MIRSCIT** principle. Inspired by existing ontology modularization techniques, Ontofox also develops a new SPARQL-based ontology term extraction algorithm that extracts terms related to a given set of signature terms. In addition, Ontofox provides an option to extract the hierarchy rooted at a specified ontology term. **Note:** We have now changed the name "OntoFox" (with capital F) to "Ontofox" (with low case f) to be consistent with other Ontoanimal tools.

Notice: All the OBO ontologies have changed the term URI format from http://purl.org/obo/owl/ontology#ontology_nnnnnnn to http://purl.obolibrary.org/obo/ontology_nnnnnnn. Please make sure your input files are updated.

Ontofox is implemented using one of the following three methods, based on how data is input and whether the Ontofox web interface is used:

1. Data input using web forms:
 Examples: [Example 1](#), [example 2](#), [example 3](#), [example 4](#), [example 5](#)

(1) **Select one ontology:**
 Ontology for Biomedical Investigations (OBI) [v]
 Or enter your favorite source ontology and SPARQL endpoint: [Example](#)

(2) **Term specification:**

(a) **Include low level source term URIs:**
 (One URI per line. To include all child terms of a source term (extract the whole branch), enter "IncludeAllChildren" in the line next to the source term)
 Search a term: `conclusion textual entity` http://purl.obolibrary.org/obo/IAO_000144 [Add](#)
`http://purl.obolibrary.org/obo/IAO_000144 #conclusion textual entity`

(b) **Include top level source term URIs and target direct superclass URIs (One URI per line, optional):**
 Search a term: `conclusion based on data` http://purl.obolibrary.org/obo/OBI_0001909 [Add](#)
`http://purl.obolibrary.org/obo/OBI_0001909 #conclusion based on data`
`subClassOf`

(c) **Select a setting for retrieving intermediate source terms:**

Figure 30 Class extraction process using OntoFox



Figure 31 Object Properties and Data Properties in the MAB-Ontology

4.6 MAB-Ontology Evaluation

In order to meet the last step of the ontology construction process, evaluation methods were carried out.

4.6.1 Face Validity of Intermediate Representation

This method was carried out by experts who assessed whether the domain was represented properly by the entities and relationships established so that both the ontology's key entities and a formal description of the domain knowledge could be detected.

a. Content validity. The included information was validated against both the structure and entity validity. Structure validity ensures that entities and relations in MAB-Ontology cover the domain in a proper manner, while entity validity is intended to eliminate and add entities. An informal meeting was conducted with domain experts, Dr. JJ and Dr. JC, in which several rounds were taken. Several data items were included, based on Dr. JJ's model validation. Figure 32 shows a representation of those items in Protégé. The outcomes of the face-validity conducted with Dr. JC include: comorbidity class removed from treatment-related and assigned under disease-related. Cognitive impairment was also removed from patient-related and was added to the disease-related class. A class of treatment, based on the cancer's stage, was added under treatment plan specification. Breast cancer patients were categorized, based on their menopausal-to postmenopausal status: female breast cancer patients and premenopausal female breast cancer patients, because their breast cancer treatment is specific, were based on menopausal status. Breast cancer was also categorized, based on hormone receptors, as shown in Figure 33.

The screenshot displays the OntoGraf interface with the following components:

- Class Hierarchy (Left Panel):** A tree view showing the hierarchy of classes. The root is `'medication adherence finding'`, which is a subclass of `'adherence influencing finding'`. Other subclasses include `'demographic related finding'`, `'disease related finding'`, `'economic related finding'`, `'health care system related finding'`, `'health literacy finding'`, `'life style finding'`, `'medication adherence risk factor'`, `'psychological determinant finding'`, `'social related finding'`, and `'technology use to support adherence re'`.
- Annotations (Top Right Panel):** Shows the label `adherence influencing finding` and a definition: "A medication adherence finding that is about some quality, belief, emotion, or processe, or automatic associations, etc. that influence patint and or his participation in the medication adherence behavior. These findings are the output of self-report assessment that built based on validated criterias."
- Description (Middle Right Panel):** Shows the description for `'adherence influencing finding'`.
- Equivalent To (Bottom Right Panel):** Lists equivalent classes, including `'medication adherence finding'` with constraints: `and 'scalar score from composite inputs'`, `and ('has measurement unit label' some percent)`, `and ('is about' some ('homo sapiens' and ('has role' some 'patient role')))`, and `and ('has measurement value' some xsd:float)`.
- SubClass Of (Bottom Right Panel):** Lists subclasses, including `'breast cancer patient'` with constraints: `and ('bearer of' some (age and (('is quality measured as' some 'age measurement datum') and ('has measurement value' some xsd:float))))`.
- General class axioms (Bottom Right Panel):** Lists axioms such as `'has value specification' some 'scalar value specification'` and `is_specified_output_of some 'data transformation'`.

Figure 32 Factors Impact Medication Adherence Process

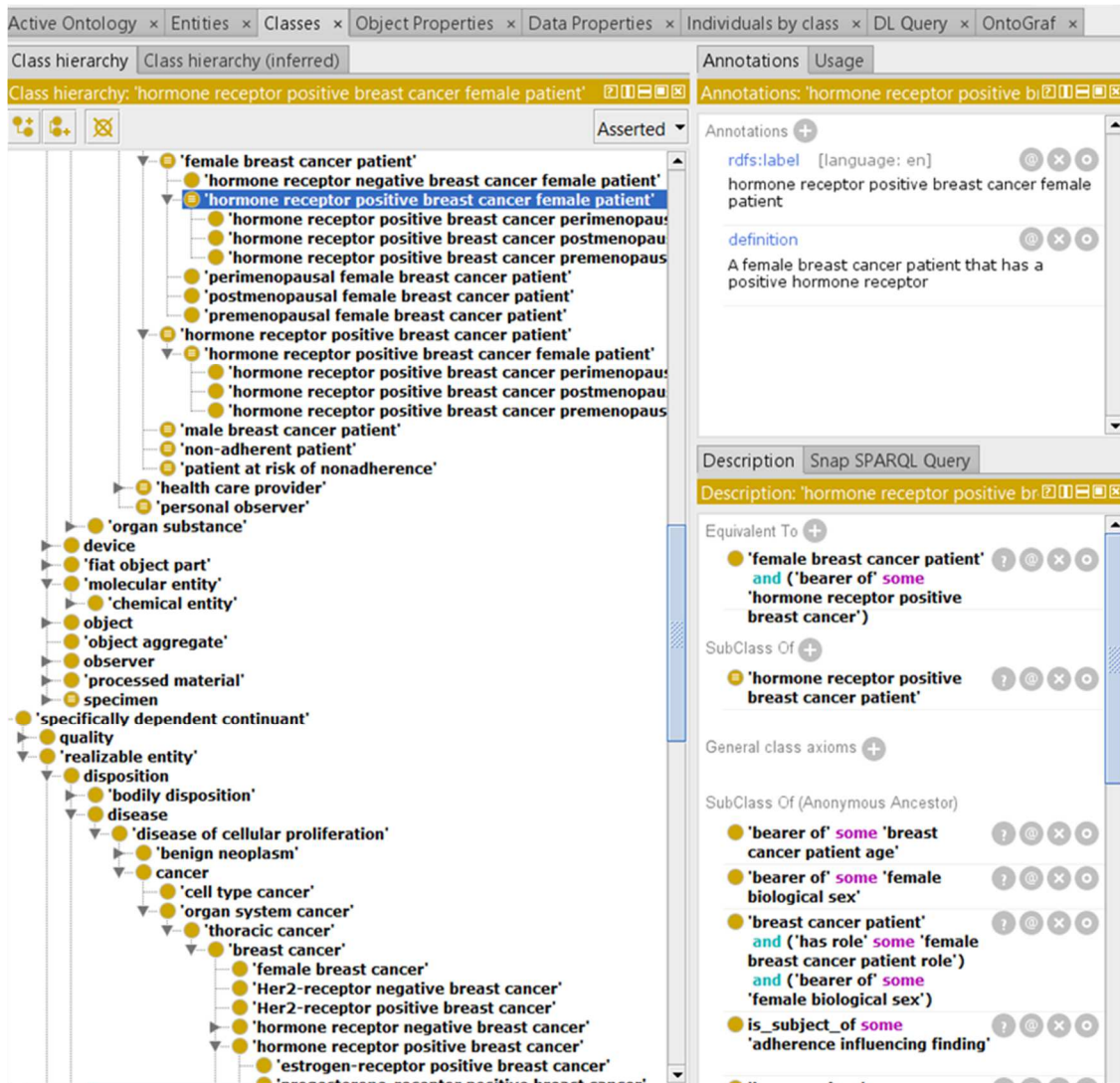


Figure 33 Breast Cancer Patient and Disease Categories

b. Structure validly. Informal face-validity performed with an expert in BFO structure to validate consistency of the entities included in the MAB-Ontology with upper-level ontology. The iterative process outcomes were: simplifying the model representation, defining the breast cancer treatment process, adding class conclusion based on data, and defining age under measurement datum. Change relations “realizes some concretizes some” into “has_specified_input some concretizes some.” Based on Dr.

WD's philosophy, plan specification is a generic-dependent entity; it cannot be realized in a planned process, only a realizable entity can be realized in a process.

4.6.2 Competency Question

The MAB-Ontology was validated against the sample list of questions, as shown below. MAB-Ontology successfully answered all the questions.

CQ1: Is it possible to search the MAB-Ontology for factors that impact medication adherence? MAB-Ontology successfully represents the 69 instances of factors that influence adherence to the endocrine therapy/regimen, as shown in Figure 34. These factors were extracted from the literature review discussed in chapter two, part one.

The screenshot shows a web interface for a DL Query. At the top, there are tabs for 'Object Properties', 'Data Properties', 'Individuals by class', 'DL Query', and 'Active ontology'. Below the tabs, there is a yellow bar with the text 'DL query:'. Underneath, there is a section titled 'Query (class expression)' with a text input field containing the query: 'adherence influencing finding'. Below the input field are two buttons: 'Execute' and 'Add to ontology'. The main section is titled 'Query results' and shows 'Instances (69 of 69)'. A list of 13 instances is displayed, each with a purple diamond icon and a question mark icon to its right. The instances are: 'Inability or difficulty accessing pharmacy', 'adherence to endocrine regimen influencing factor', 'alcohol consumption', 'asymptomatic of disease', 'awareness of technology aid', 'burdensome schedule', 'cognitive impairment', 'confused about how much medication of each kind to take', 'control over behavior belief', 'drug abuse', 'engagement in drug selection', 'fear of side effect finding', and 'forget to take medication'. To the right of the list is a 'Query for' section with several checkboxes: 'Direct superclasses', 'Superclasses', 'Equivalent classes', 'Direct subclasses', 'Subclasses', and 'Instances' (which is checked). Below this is a 'Result filters' section with a 'Name contains' input field.

Figure 34 Adherence Influencing Factors

CQ1a: Is it possible to search the MAB-Ontology for cognitive-related factors that impact medication adherence? MAB-Ontology successfully represents the 21 instances that represent the psychological factors influence adherence to endocrine therapy, as shown in Figure 35.

DL query: ⏏ ⏏ ⏏ ⏏

Query (class expression)

'psychological determinant finding' and 'is about' some ('aromatase inhibitor adherence process' or 'tamoxifen adherence process')

Execute Add to ontology

Query results

Instances (21 of 21)

- ◆ 'control over behavior belief' ?
- ◆ 'fear of side effect finding' ?
- ◆ 'forget to take medication' ?
- ◆ 'intentionally modify the dosage' ?
- ◆ 'intentionally stop medicine' ?
- ◆ 'joint pain' ?
- ◆ 'lack of community support' ?
- ◆ 'lack of family support' ?
- ◆ 'loss of sex drive' ?
- ◆ 'medication cost' ?
- ◆ 'negative consequences belief' ?
- ◆ 'night sweat' ?
- ◆ 'perceived severity finding' ?
- ◆ 'perceived susceptibility finding' ?
- ◆ 'positive consequences belief' ?
- ◆ 'remember to get refill' ?
- ◆ 'satisfaction related finding' ?
- ◆ 'self-efficacy finding' ?
- ◆ 'stigma belief' ?
- ◆ 'vaginal dryness' ?
- ◆ homelessness ?

Query for

Direct superclasses

Superclasses

Equivalent classes

Direct subclasses

Subclasses

Instances

Result filters

Name contains

Display owl:Thing
(in superclass results)

Display owl:Nothing
(in subclass results)

Figure 35 Psychological Determinants of Medication Adherence

MAB-Ontology successfully answered all competency questions from CQ1b to CQ1l in the same way as CQ1a.

CQ1m: Is it possible to search the MAB-Ontology for factors that influence medication adherence among 60 year-old patients who take tamoxifen? Yes, MAB-

Ontology successfully retrieved factors that impact patients under those categories, as shown in Figure 36.

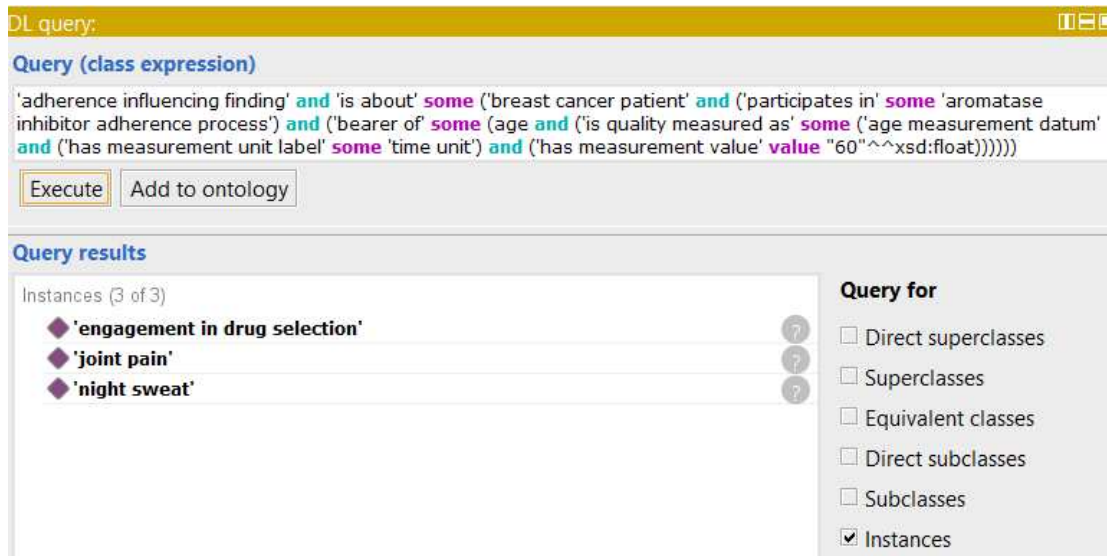


Figure 36 Determinants Influence 60 Year-old Patients Taking Tamoxifen

CQ1n: Is it possible to search the MAB-Ontology for a patient who discontinues tamoxifen due to the side effects? MAB-Ontology successfully answered this question. First, patients 1, 2, and 3 are premenopausal. That means they are taking tamoxifen as aromatase inhibitors as prescribed for postmenopausal women. Patient 1 is the only patient to discontinue his tamoxifen and mentioned side effects as a reason. Patient 2 is at risk for non-adherence, because she is fasting some days (i.e., religious reasons), as shown in Figure 37.

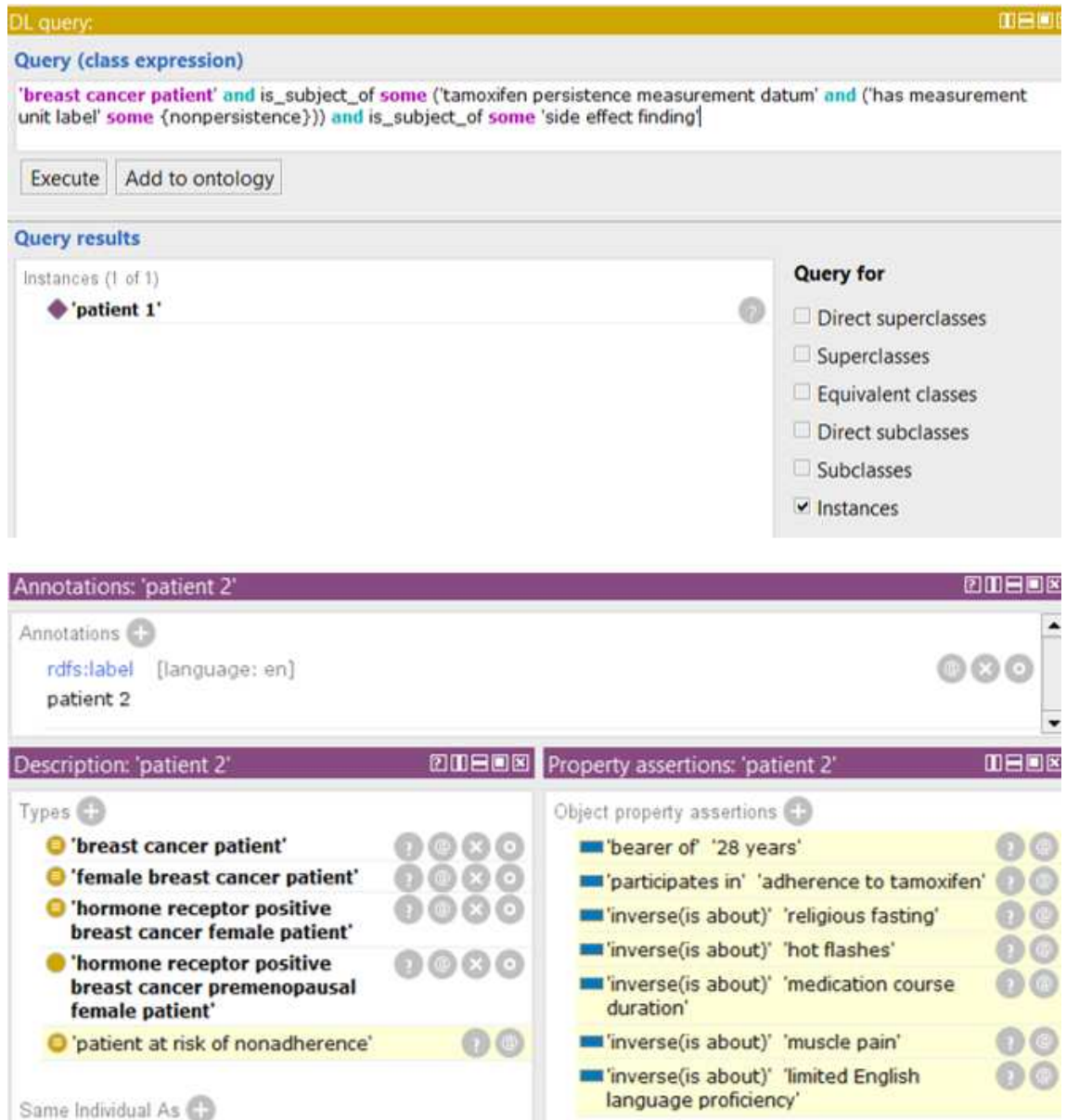


Figure 37 Patient Discontinues Tamoxifen Due to Side Effects

MAB-Ontology successfully answered all competency questions from CQ10-CQ1b in the same way as CQ1n.

CQ2: Is it possible to search the MAB-Ontology for behavioral change techniques used to change/sustain medication adherence? MAB-Ontology successfully answered this question, as shown in Figure 38.

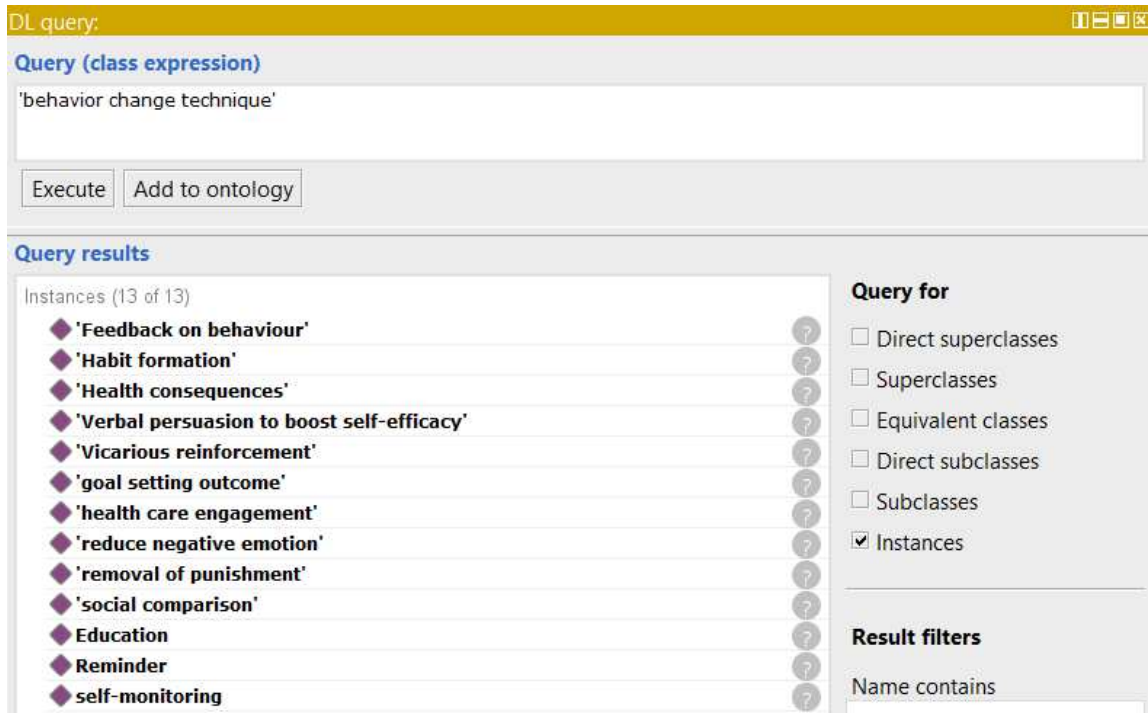


Figure 38 Behavioral Change Techniques Used to Change Medication Adherence

CQ2: Is it possible to search the MAB-Ontology for Information Technology platforms used to change/sustain medication adherence? MAB-Ontology successfully answered this question, as shown in Figure 39.

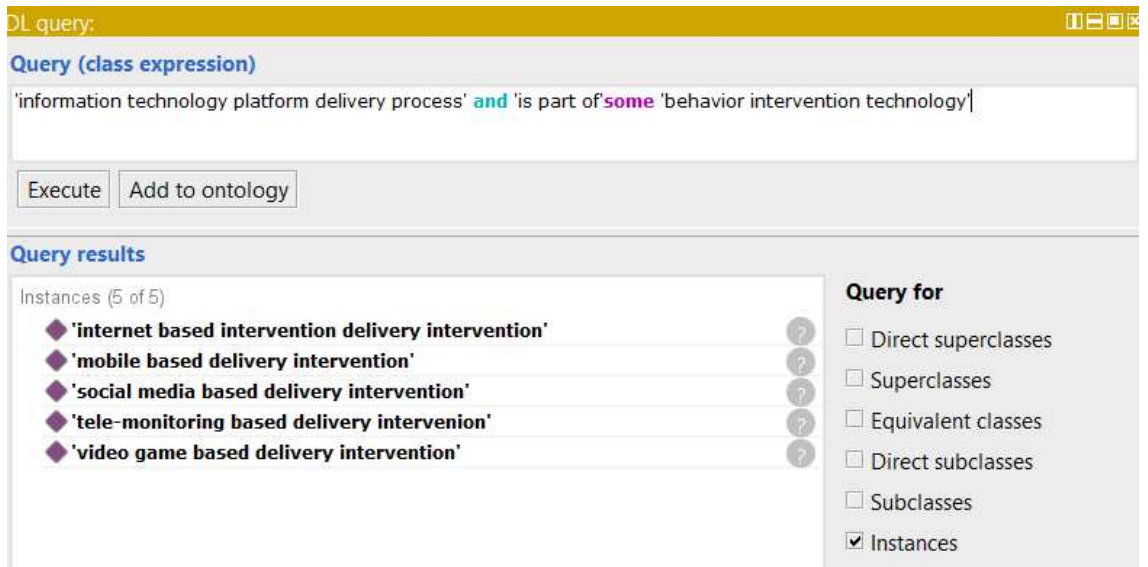


Figure 39 Information Technologies Used to Change Medication Adherence

CQ3: Is it possible to search the MAB-Ontology for methods used to measure medication adherence? MAB-Ontology successfully answered this question, as shown in Figure 40.

The screenshot shows a web interface for a DL query. At the top, a yellow bar contains the text 'DL query:'. Below this, a section titled 'Query (class expression)' contains a text input field with the query 'medication adherence assessment'. Below the input field are two buttons: 'Execute' and 'Add to ontology'. The main area is titled 'Query results' and is divided into two sections: 'Subclasses (19 of 20)' and 'Instances (5 of 5)'. The 'Subclasses' section lists 19 class expressions, each with a yellow circle icon and a question mark icon. The 'Instances' section lists 5 class expressions, each with a purple diamond icon and a question mark icon. On the right side, there are two panels: 'Query for' and 'Result filters'. The 'Query for' panel has four checkboxes: 'Direct superclasses', 'Superclasses', 'Equivalent classes', and 'Direct subclasses' (all unchecked), and two checked checkboxes: 'Subclasses' and 'Instances'. The 'Result filters' panel has a text input field for 'Name contains' and two checked checkboxes: 'Display owl:Thing (in superclass results)' and 'Display owl:Nothing (in subclass results)'.

Figure 40 Methods Used to Measure Medication Adherence

CQ3a: Is it possible to search the MAB-Ontology for direct methods used to measure medication adherence? MAB-Ontology successfully answered this question as shown in Figure 41.

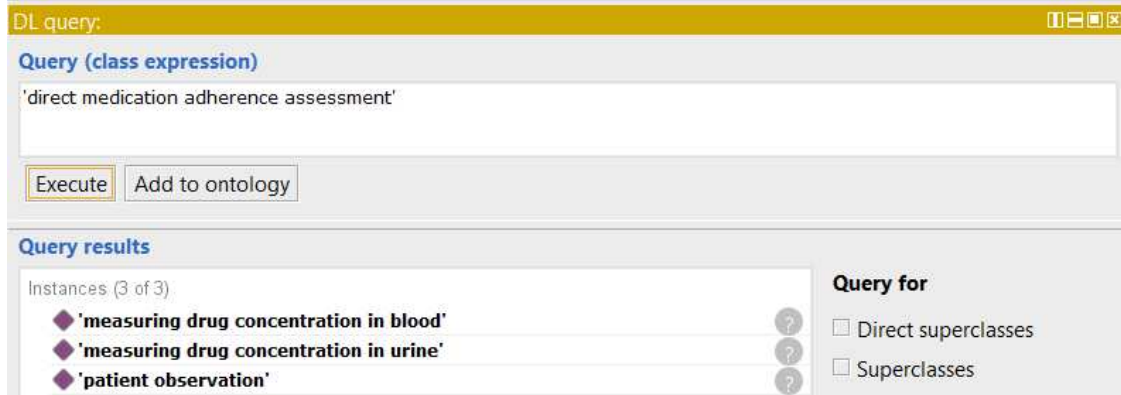


Figure 41 Direct Methods Used to Measure Medication Adherence

MAB-Ontology successfully answered all competency questions from CQ3b and CQ3c and they gave the same results as CQ3a.

CQ3d: Is it possible to search the MAB-Ontology for methods used to measure medication adherence among patient 1? MAB-Ontology successfully answered this question, as shown in Figure 42.

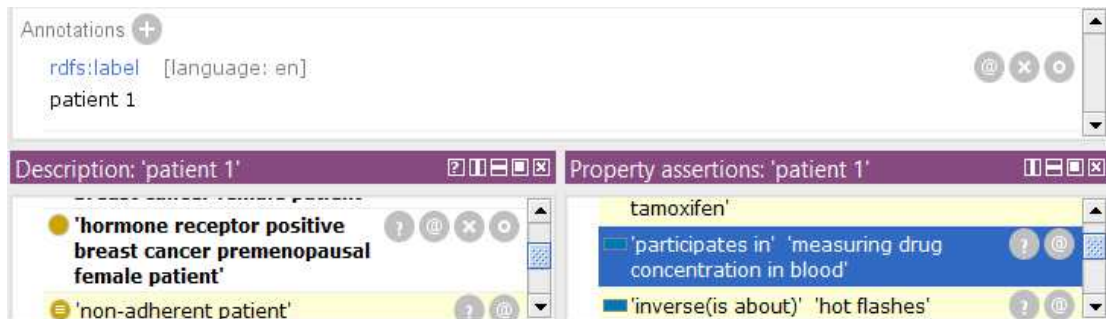


Figure 42 Methods Used to Measure Medication Adherence Among Patient 1

CQ3e: Is it possible to search the MAB-Ontology for questionnaires used to measure adherence to endocrine therapy/regimen? MAB-Ontology successfully represented 45 questionnaires used to measure adherence to the endocrine regimen (Figure 43).

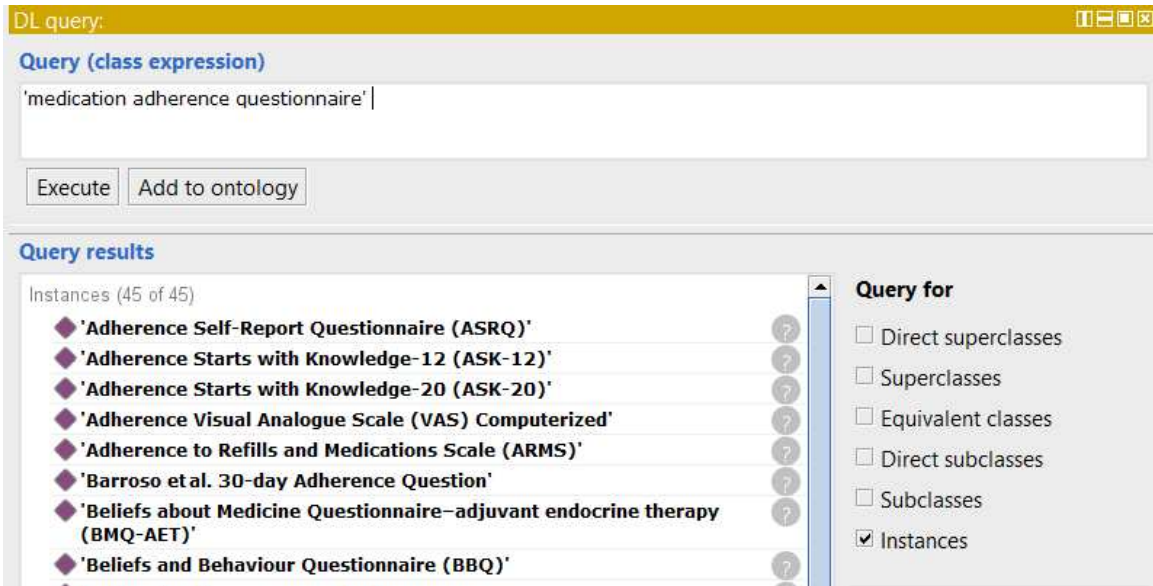


Figure 43 Questionnaires Used to Measure Adherence to Endocrine Therapy

CQ3d: Is it possible to search the MAB-Ontology for questionnaires used to measure only medication adherence behavior? MAB-Ontology successfully answered this question, as shown in Figure 44.

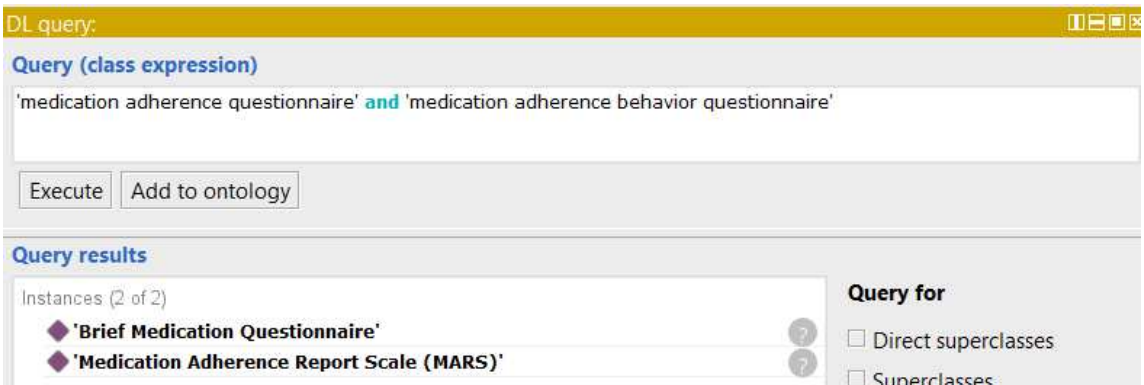


Figure 44 Questionnaires Used to Measure Only Medication Adherence Behavior

CQ3e: Is it possible to search the MAB-Ontology for questionnaires used to measure medication adherence behavior and the barriers that impact medication adherence? MAB-Ontology successfully answered this question, as shown in Figure 45.

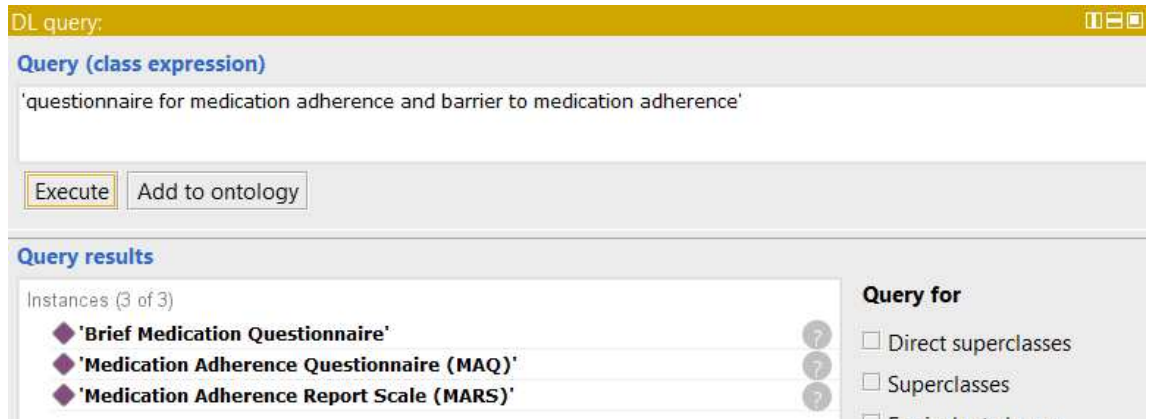


Figure 45 Questionnaires Measure Medication Adherence Behavior and Barriers

MAB-Ontology successfully answered CQ3f, CQ3g and they had the same answers as the CQ3e&d.

CQ4: Is it possible to search the MAB-Ontology for theories used as a part of a plan specification for medication adherence intervention development? MAB-Ontology successfully represented 49 medication adherence-related theories, as shown in Figure 46. Behavioral theory is part of a plan specification when designing an intervention.

Based on the review of 1,057 articles, 49 behavioral theories associated with medication adherence behavior were included in this project.

DL query: ⏏ ⏏ ⏏

Query (class expression)

'theory of behavior change' and 'is part of' some 'adherence behavior intervention specification'

Execute Add to ontology

Query results

▼ Empowerment theory	?
◆ 'Extended Parallel Process Model'	?
◆ 'Goal Framing Theory'	?
◆ 'Goal Setting Theory'	?
◆ 'Health Action Process Approach'	?
◆ 'Health Promotion Model'	?
◆ 'Health belief model'	?
◆ 'I-change model'	?
◆ 'Information-motivation-behavioural skills model'	?
◆ 'Integrated Theory of Health Behaviour Change'	?
◆ 'Lewin's 3 stage model of change'	?
◆ 'MASLOW'S HERARCHY NEED THEORY'	?
◆ 'Main Determinants of Health Model'	?
◆ 'Model of Goal Directed behavior'	?
◆ 'Operant or instrumental conditioning theory'	?
◆ 'Orem's self-care theory'	?
◆ 'Precaution Adoption Process Model'	?
◆ 'Problem solving theory'	?
◆ 'Prospect Theory'	?
◆ 'Protection motivation theory'	?
◆ 'Regulatory fit theory'	?
◆ 'Relapse prevention'	?
◆ 'Rogers' client-centred counselling'	?
◆ 'Roy Adaptation Model'	?
◆ 'Self management theory'	?
◆ 'Self-Determination Theory'	?
◆ 'Social Cognitive Theory'	?
◆ 'Social action theory'	?
◆ 'Stages of Change model'	?
◆ 'Theory acceptance Model 2'	?
◆ 'Theory acceptance Model'	?
◆ 'Theory of planned behavior'	?
◆ 'Theory of reasoned action'	?

Query for

Direct superclasses

Superclasses

Equivalent classes

Direct subclasses

Subclasses

Instances

Result filters

Name contains

Display owl:Thing
(in superclass results)

Display owl:Nothing
(in subclass results)

Figure 46 Behavioral Theories Used for Medication Adherence Intervention

CQ4a: Is it possible to search the MAB-Ontology for theoretical constructs of the theory of planned behavior? MAB-Ontology successfully answered this question, as shown in Figure 47. Each theory has its constructs as parts. Interventions may target only one construct. For example, improve self-efficacy.

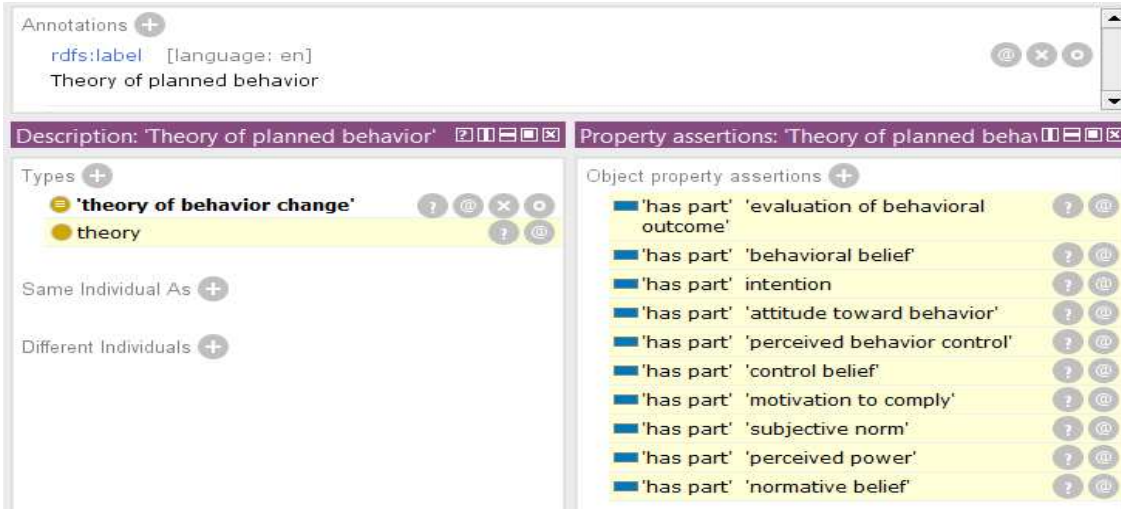


Figure 47 MAB-Ontology for Theory of Planned Behavior Constructs

CQ4b: Is it possible to search the MAB-Ontology for theories that include constructs that represent behavior capability belief? MAB-Ontology successfully answered this question (28 out of 49 theories), as shown in Figure 48.

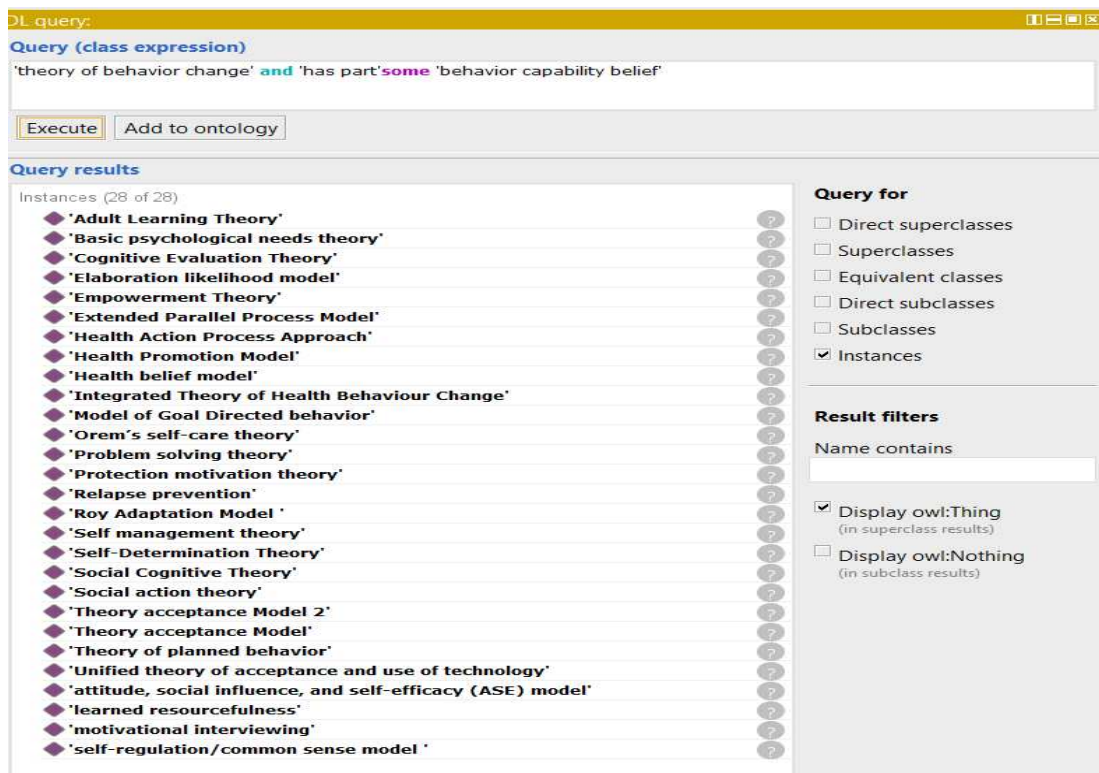


Figure 48 Theories That Include Constructs Represent Behavior Capability Belief

MAB-Ontology successfully answered the competency question CQ4c in the same way as CQ4b.

CQ5: Is it possible to search the MAB-Ontology for patients who are at risk for non-adherence? MAB-Ontology successfully answered this question, as shown in Figure 49.

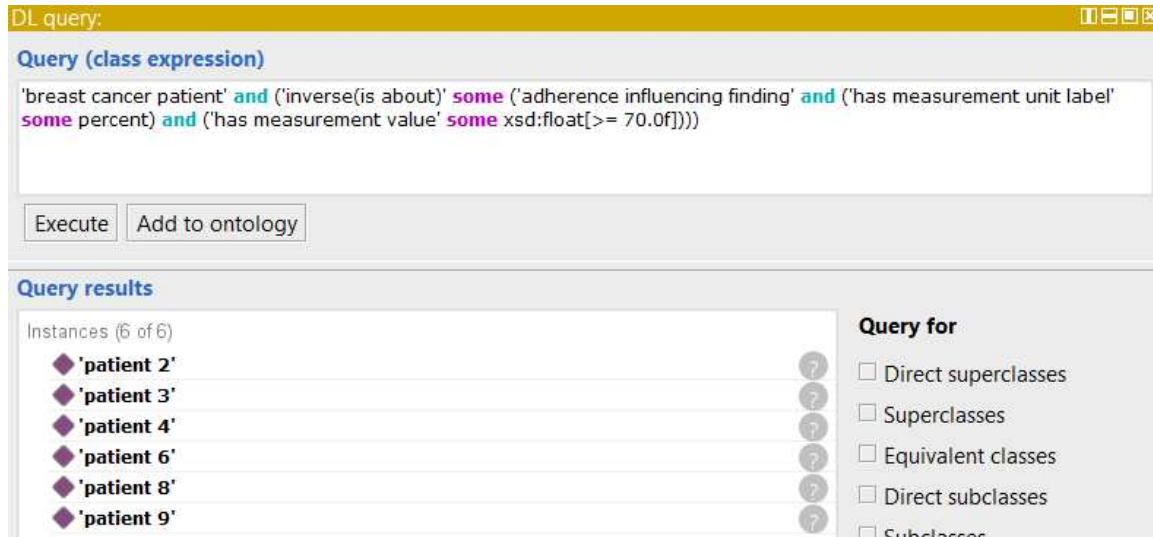


Figure 49 Patients at Risk of Non-adherence

CQ5a: Is it possible to search the MAB-Ontology for a 60 year-old breast cancer patient who is at risk for non-adherence? MAB-Ontology successfully answered this question, as shown in Figure 50.

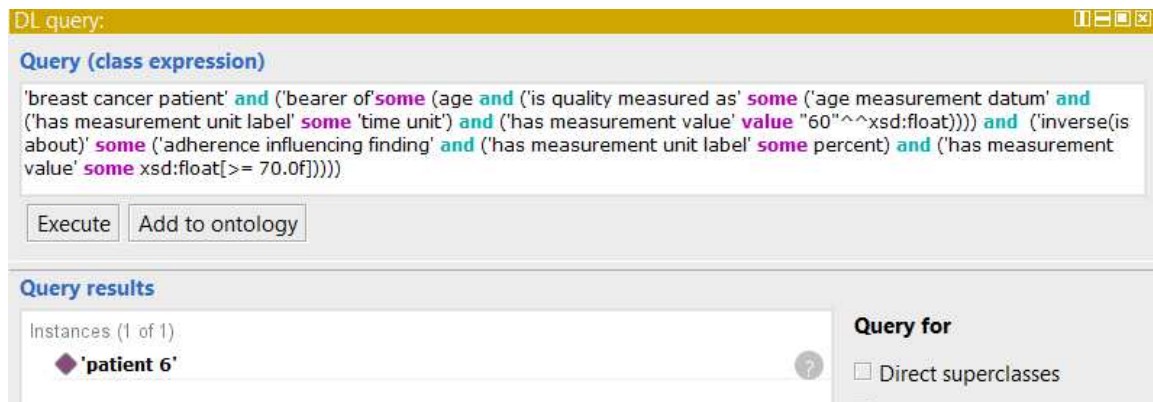


Figure 50 Sixty Year-old Breast Cancer Patient at Risk for Non-adherence

CQ6: Is it possible to search the MAB-Ontology for non-adherent patients?

MAB-Ontology successfully answered this question based on an 80% cutoff for adherence rate, as shown in Figure 51.

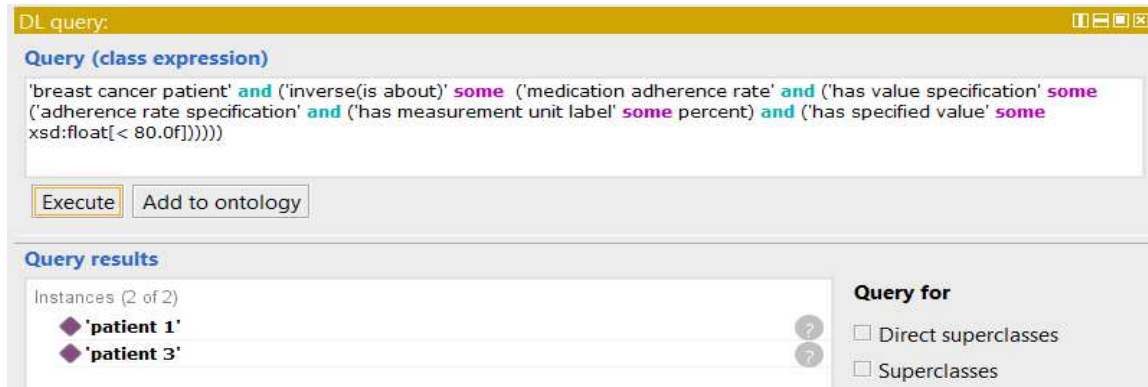


Figure 51 MAB-Ontology for Non-adherent Patients

CQ7: Is it possible to search the MAB-Ontology for medication adherence risk factors? MAB-Ontology successfully represents the 21 risk factors that influence the patient adherence process, as shown in Figure 52.

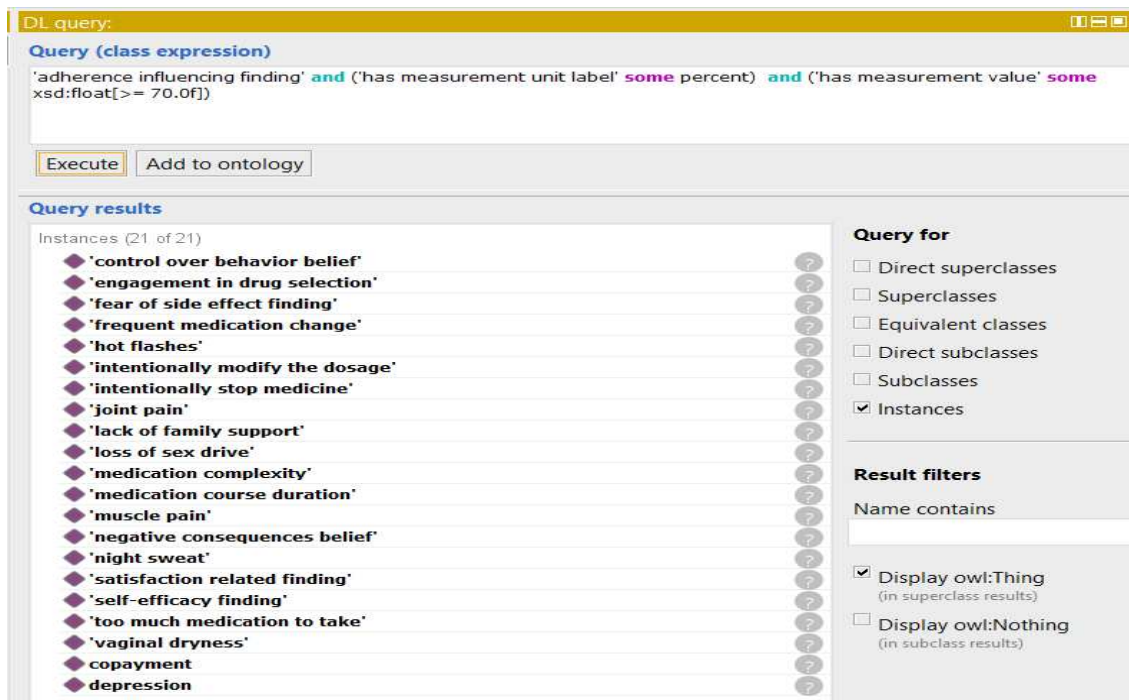


Figure 52 MAB-Ontology for Medication Adherence Risk Factors

4.6.3 Use Case Scenario

A program officer planning to design a new intervention to improve medication adherence among breast cancer patients uses information technology platforms. The data gathered by the program officer at the point of care is an indication that there is a high number of fluctuations in the adherence rate among the breast cancer population in the first three months. The program officer does not understand the reasons for this discrepancy. He wishes to identify a list of potential factors influencing the adherence rate among breast cancer patients in the first three months. He requires this knowledge in order to develop a proper intervention plan that will reduce the rate of non-adherence among this population. The answer to this question is shown in Figure 53.

The screenshot displays a query interface with the following components:

- Query (class expression):** 'adherence influencing finding' and 'is about' some ('90 days medication adherence process' and ('preceded by' some 'initial drug dispensing process'))
- Buttons:** Execute, Add to ontology
- Query results:** A list of 30 factors, each preceded by a purple diamond icon. The factors include: 'Inability or difficulty accessing pharmacy', 'alcohol consumption', 'asymptomatic of disease', 'burdensome schedule', 'cognitive impairment', 'confused about how much medication of each kind to take', 'control over behavior belief', 'drug abuse', 'engagement in drug selection', 'fear of side effect finding', 'forget to take medication', 'frequent medication change', 'hearing impairment', 'hot flashes', 'intentionally modify the dosage', 'intentionally stop medicine', 'joint pain', 'lack of community support', 'lack of family support', 'lack of insurance', 'lack of positive reinforcement from the health care provider', 'limited English language proficiency', 'limited access to health care facilities', 'long wait time', 'loss of sex drive', 'low health literacy', 'medication complexity', 'medication cost', 'medication course duration', 'medication efficacy', 'muscle pain', and 'negative consequences belief'.
- Query for:** A panel with checkboxes for: Direct superclasses, Superclasses, Equivalent classes, Direct subclasses, Subclasses, and Instances (checked).
- Result filters:** A panel with a text input field for 'Name contains' and checkboxes for: Display owl:Thing (in superclass results) (checked) and Display owl:Nothing (in subclass results).

Figure 53 Factors That Influence Adherence in the First Three Months

4.6.4 Consistency Checking

Pellet identified no inference class violations for equivalency or unsatisfiability for the MAB-Ontology, as shown in Figure 54.

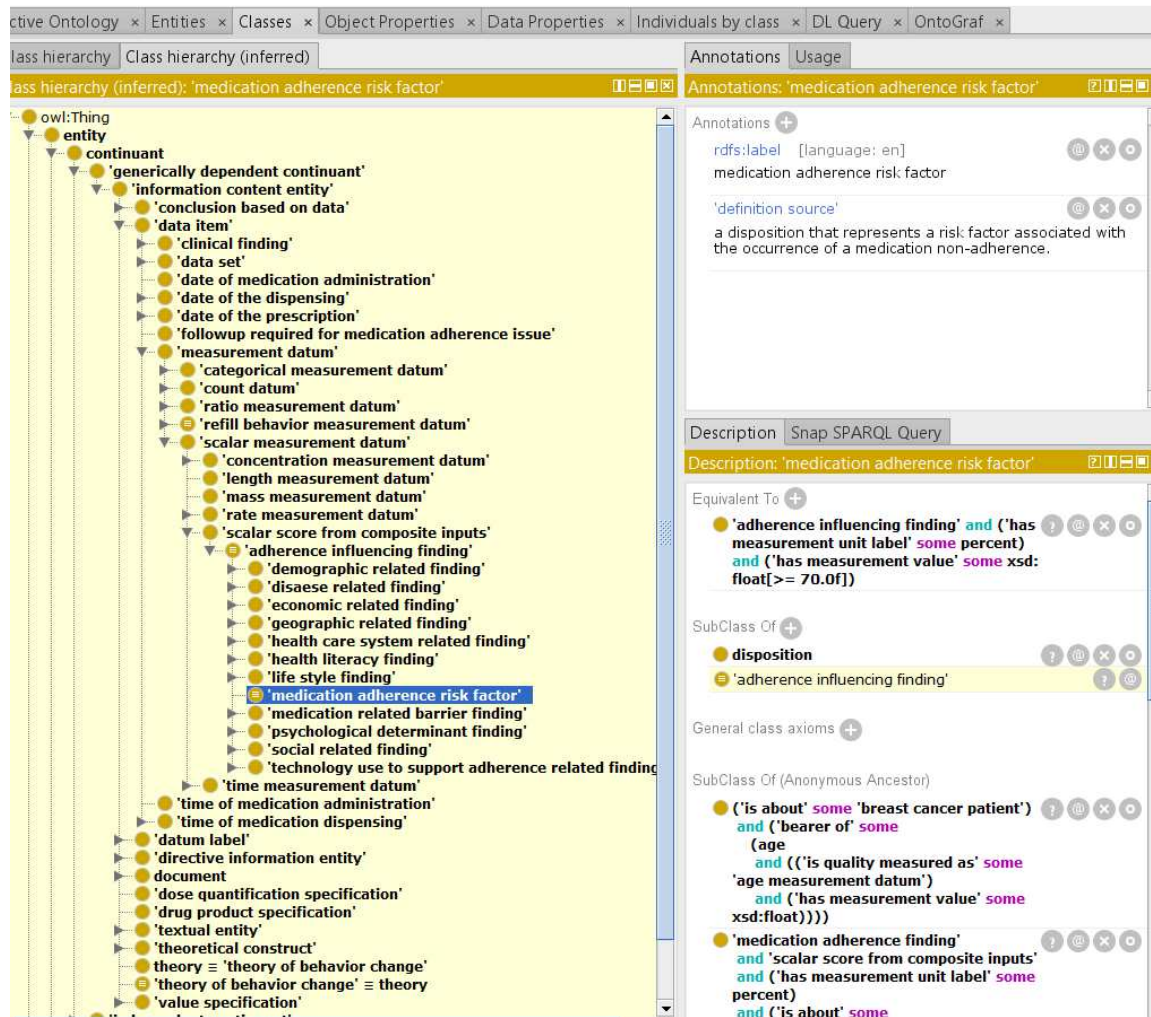


Figure 54 Consistency Checking

4.6.5 Compliance with OBO Foundry.

OBO design principles were followed in building MAB-Ontology where possible. The majority of the principles were considered throughout data collection, analysis, and evaluation. Table 23 shows the OBO principles and the rational for the adherence or non-adherence.

Table 23 Adherence to the OBO Foundry Principles.

OBO FP ID	Principle Type	Rationale	MAB-Ontology
FP 001	Open	The ontology must be open and accessible to be used without any restriction.	Protégé OWL generates automatically.
FP 002	Common format	Ontology expressed in a common shared syntax.	Protégé generates OWL, RDF, and XML.
FP 003	Identifier space	Each class and relation should have a unique URI identifier.	Protégé generates unique URIs for all entities.
FP 004	Versioning	The ontology provider has procedures for identifying distinct successive versions.	Protégé versioning.
FP 005	Clearly delineated content	The ontology has clearly-specified and clearly-delineated content.	Natural language used for terms, definitions.
FP 006	Textual definitions	Terms should be defined so that their precise meaning within the context is clear to a human reader.	Literature, other existing ontology, no two terms share a definition. An Aristotelian definition was used.
FP 007	Relations	Uses unambiguously defined relations following the pattern of Definitions in OBO Relation Ontology.	Use of OBO Relations Ontology (RO).

FP 008	Documented	Publications for users and developers.	Dissertation publication; planned article publications.
FP 009	Plurality of users	URIs used in a variety of projects.	n/a/a/t
FP 010	Commitment to collaboration	Consistency with OBO Foundry ontologies and use of relevant terms from neighboring ontologies.	Adherence to OBO principles, leveraging with other ontologies.
FP 011	Locus of authority	Maintain integrity and further development.	Author's name will be provided on ontology website.
FP 012	Naming conventions	Enhance communication, simplify, support integration, facilitate automated tools.	Consistently naming entities.
FP 016	Maintenance in light of scientific advances	Ensure the improvement of ontology over time.	Domain engagement and update schedule.

4.6.6 Compliance with METHONTOLOGY

Besides following the OBO principles in developing MAB-Ontology, METHONTOLOGY methods played an essential role in MAB-Ontology construction. The compliance to the METHONTOLOGY's steps and strategies was evaluated. Table

24 shows the basic steps the METHONTOLOGY method includes. The result indicates that all the steps were satisfied, except for the maintenance stage as it is an iterative step.

Table 24 Adherence to the METHONTOLOGY Method

METHONTOLOGY	Validation (yes-no)	Added Value
Specification	Yes	Adopted to medication adherence.
Knowledge acquisition	Yes	Classify factors based on treatment phase.
Conceptualization	Yes	Intermediate representation using VUE.
Formalization	Yes	Human language-based definition, using Aristotelian definition.
Integration	Yes	Leverage with other ontologies.
Implementation	Yes	Using Protégé.
Evaluation	Yes	Competency question, face-validity.
Documentation	Yes	Tables, text, figures, poster, and dissertation.
Maintenance	n/a	Iterative cycle.

n/a=not applicable at this phase.

4.6.7 Expandability Testing

The developed model was tested for expandability and reusability by using it in another domain. Using the MAB-Ontology to include factor-impact-technology use was one of the aims of this work at the proposal level. However, and due to the fact that they are two separate domains, a decision was made to design one domain and expand it to include the other. Technology adoption ontology (TAB-Ontology) was built using the

same approach used for MAB-Ontology. The ontology scope was to represent factors that have an impact on technology adoption, specifically mobile-based technology. The motivation behind this is featured in the first chapter. Several competency questions were developed to clarify the ontology's scope. The following are some and the list could be expanded.

Q1: Is it possible to search TAB-Ontology for a list of factors that impact technology adopting at the initiation phase?

Q2: Is it possible to search TAB-Ontology for the factor that has a negative value among people older than age 50?

Q3: Is it possible to search TAB-Ontology for the human who discontinues the technology?

Knowledge extraction was built based on the data extracted from review carried out by Sawesi, Rashrash, Phalakornkule, Carpenter, & Jones (2016). A total of 113 classes and 69 individuals were created and integrated with the MAB-Ontology using the same structure, with some modifications, as shown in Figure 58. Three classes were created under class human to define the type of technology user named: technology adopter, technology user, and technology discontinuer. Technology adoption class was represented as a subclass of the behavior process. The methods used to assess factors that impact medication adherence were expanded to include methods use to assess factor-impact technology-use. The relations used between the instances were the same as those used for MAB-Ontology instances (Relation Ontology).

Evaluation of the model was carried out in two ways: (1) Face-validity with a domain expert. An informal meeting with Dr. JJ was done to validate the ontology

structure and content validity. An adjustment was made, based on feedback. (2)

Competency Question: An evaluation based on answering the competency questions was implemented.

Q1: Is it possible to search TAB-Ontology for a list of factors that impact adopting technology? The model successfully answered this query and extracted all the factors that impacted technology adoption, as shown in Figure 55.

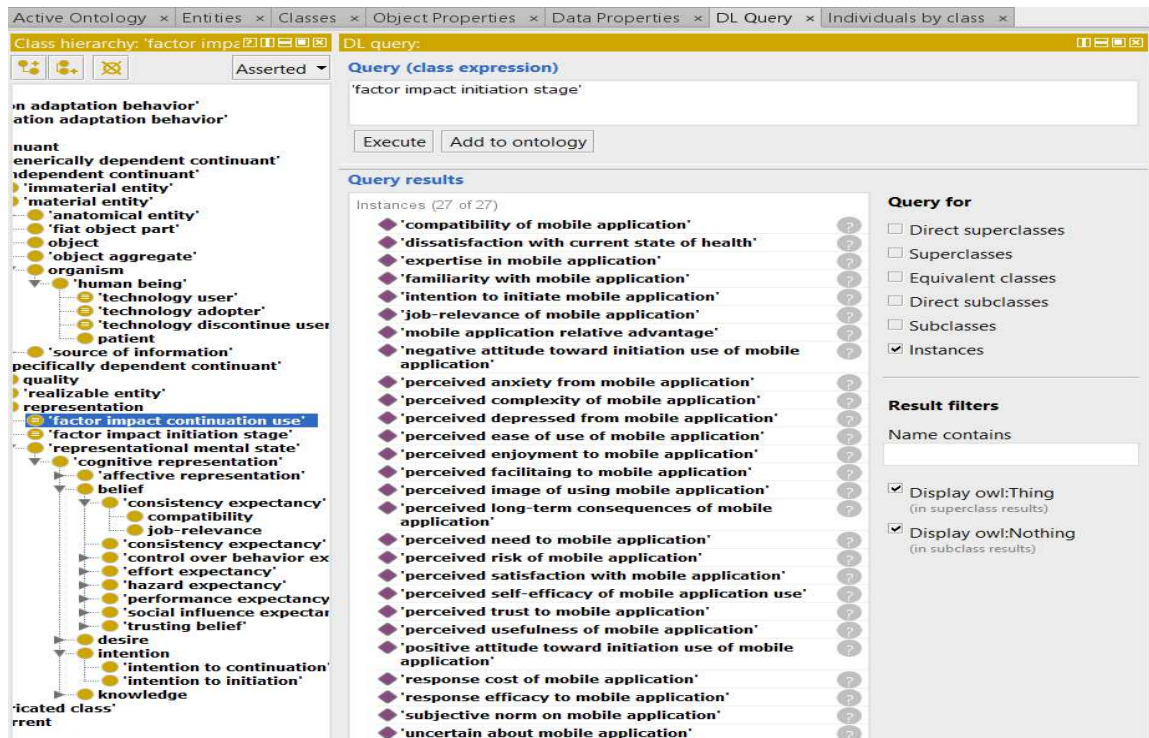


Figure 55 TAB-Ontology

Q2: Is it possible to search TAB-Ontology for the factor that has a negative value among people older than age 50? TAB-Ontology successfully answered the query and extracted the factors in question, as shown in Figure 56.

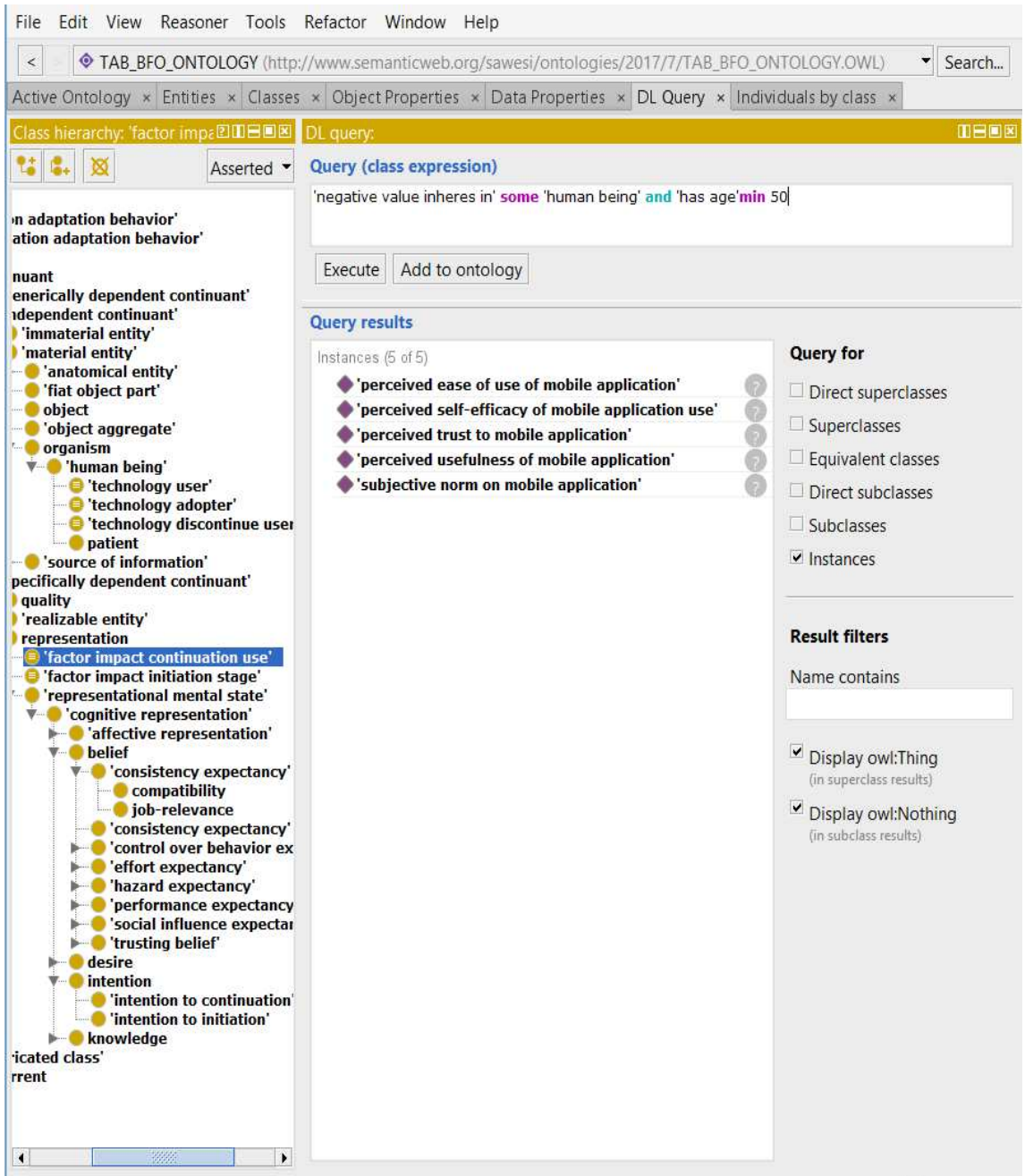


Figure 56 Factors with Negative Value

Q3: Is it possible to search TAB-Ontology for the human who discontinues the technology? TAB-Ontology successfully answered the question, as shown in Figure 57.

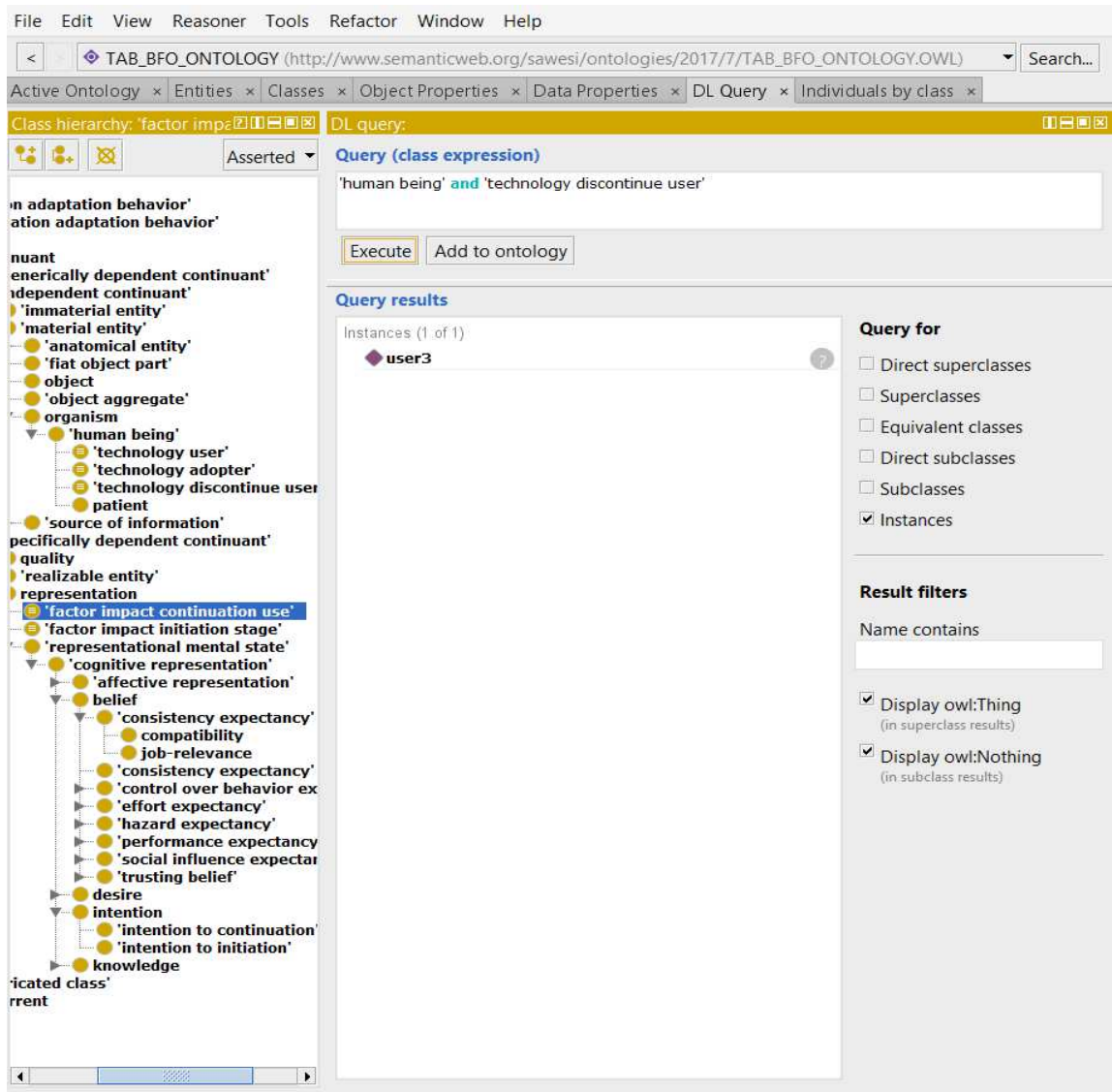


Figure 57 Technology Discontinuation

Results of the TAB-Ontology demonstrated that MAB-Ontology is expandable. TAB-Ontology classes were integrated among MAB-Ontology by adding new class categories and sub-classes in existing classes.

The reasoning for this is that it can be done using a single query, such as question number (Q1), as well as using a combination of some or all of the dimensions of the influencing factor. More complex queries could be used.

CHAPTER FIVE: CONCLUSION AND FUTURE WORK

5.1 Conclusion

Medication adherence is a complex domain. It poses difficulty for clinical research. Several technology-based interventions have been developed to maintain and enhance the medication adherence process. However, a lack of common terms to define medication adherence behavior and its determinants that impact patients who participate in this process is evident in the literature when these areas are examined. This, in turn, limits the ability to develop interventions and measure the effectiveness of these interventions. From an informatics viewpoint, data sharing is challenging, due to heterogenicity, complicity, and a lack of standardization.

To provide insight into the aforementioned challenge and support knowledge accumulation, this work has applied ontological engineering to develop an overarching framework to clarify the multiple dimensions of medication adherence domain, based on reviewing 1,304 articles. The determinants impact adherence to medication, along with technology adoption extracted from 49 theories, to represent factor-impact adherence to medication and technology use based on theory. The relationship between terms was implemented. Precise interpretation is a necessary prerequisite for automatic search, retrieval, and processing of adherence data. This approach describes the information related to adherence domain in such a way that domain users can easily obtain relevant information based on their need. MAB-Ontology focuses on three major areas: determinants that impact adherence to medication, methods used to measure adherence, and technology interventions used to enhance medication adherence. The latter is based on the theoretical constructs extracted from behavioral theories used to study, change,

and sustain medication adherence This ontology was developed using a methodology that merges the approach (METHONTOLOGY and FBO Principles), which made development of the MAB-Ontology more effective and intuitive. This approach is illustrated to provide guidance on how to develop an ontology in the medication adherence domain. The proposed approach was used to capture, organize, and define knowledge to develop a derived ontological framework to integrate dimensions of medication adherence and relationships. BFO was used to facilitate domain interoperability between MAB-Ontology and other systems. Finally, the proposed ontology framework was validated through face-validity, a series of competency questions, case scenario, and against METHONTOLOGY and OBO/BFO principles.

5.2 Impact of the Research

1. This study provides a unified method for developing a computerized-based adherence model that can be applied among various disease groups and different drug categories.
2. The METHONTOLOGY approach addressed the details of identifying the ontology domain scope, classes, and properties, along with demonstrating the usefulness of developing an ontology based on BFO principles. Building an MAB-Ontology based on BFO should facilitate the process of its expanding to support other tasks and its interoperability with other ontologies.
3. This approach has been developed to deliver explicit knowledge related to medication adherence that can be utilized in areas such as healthcare decision-making, intervention development, detection risk for non-adherence, capturing current and future findings from medication adherence-related publications, and so on.

4. An intervention developer can query and navigate through the MAB-Ontology to select adherence to medication factors among specific patients or age groups in order to build a tailored intervention. The researcher will be able to study different factors that impact technology use in order to design a technology-based intervention.

5.3 Challenges in the Development of MAB-Ontology

1. The first limitation of this work is that the MAB-Ontology was created by a single person; a collaborative approach that reflects diverse viewpoints is preferred.
2. Manual extraction of data from existing research was tedious, time-consuming, and challenging. It requires both domain and tool expertise.
3. Developing an ontology using software tools, such as Protégé for knowledge representation, was challenging and requires practice with the tool before building the model.
4. Building an ontology based on an upper-level ontology requires deep philosophical skills in order to represent the nature of terms as they exist in reality. Terms, such as belief, desire, and intention, lack clear definition in the literature. Such ambiguity of terms/definitions makes it difficult for an ontology developer to decide under which BFO category they belong.
5. There is no candidate category in a BFO ontology for process quality, as BFO has no occurrent counterpart. Ontologies aligned with BFOs need to include process quality or be attributed to represent, for instance, the increase and decrease in adherence rate and regular and irregular adherence processes. Therefore, in order to represent changes in process, either by representing them as an attribute of the material entity

or as a complicated process with no reference to these attributes, this infers that there is no mechanism of comparison of process based on their attributes.

6. Access to real-time observations and evidence-based practice data could be used to represent the domain vocabulary more precisely according to demand.

5.4 Future Work

The MOB-Ontology was developed as a proof-of-concept and to demonstrate the advantages of data sharing. The following work can be done to improve the ontology:

1. The MAB-Ontology can be expanded by considering other out-of-scope areas, such as adherence to physical exercise and considering other chronic diseases and drug categories.
2. A real use case based on this work could be used to validate the implementation of MAB-Ontology in healthcare-related areas.
3. Knowledge capturing and analysis could be done automatically. The advanced text mining method with natural language processing (NLP) could be an alternative to extracting knowledge from scientific publications and entering them into the ontology.
4. Further development of end users' interface using Semantic web technology, such as OWL API, is important.
5. MAB-Ontology can be extended to represent medication adherence based on healthcare-provider perspectives to gain a comprehensive picture that one viewpoint may not cover.

APPENDICES

Appendix 1

INDIANA UNIVERSITY INSTITUTIONAL REVIEW BOARD (IRB)

APPLICATION FOR NON-HUMAN SUBJECTS' RESEARCH (RESEARCH NOT SUBJECT TO FDA OR COMMON RULE DEFINITIONS OF HUMAN SUBJECTS RESEARCH)

Principle Investigator: MacDorman

Please type only in the gray boxes. To mark a box as checked, double-click the box, select "checked," and click "OK."

SECTION I: PROJECT TYPE

STOP! Before completing this form, refer to the IU Human Subjects Office website for additional information on determining if the activity is considered Human Subjects Research at http://researchadmin.iu.edu/HumanSubjects/hs_submissions.html. Investigators conducting research falling into the categories below do not need to submit an application to the IRB unless specifically requested by a sponsor or collaborator.

- Project meets the definition of human subjects research; however, Indiana University is not considered engaged in this research** in accordance with the Office for Human Research Protections (OHRP) Guidance on Engagement of Institutions in Human Subjects Research available at <http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html>.
- Project is NOT a systematic investigation** designed to expand the knowledge base of a scientific discipline or other scholarly field of study through the attempt to answer research question(s) and draw conclusions. Please proceed to Section II.
- IU Researcher(s)** receive de-identified information (not Health Information) from another source or institution which requires confirmation that no IU IRB Review is needed. Please proceed to Section II.
- Research Involving Data on Decedent PHI.** Please indicate that the following criteria are satisfied:
 - The use is solely for research on the identifiable health information of decedents.
 - The PHI sought is necessary for the purposes of the research; and
 - Upon request, the covered entity disclosing the data may require the investigator to provide documentation of the death of the individual(s) about whom information is being sought.
- De-Identified Health Information.** The research involves the use or disclosure of de-identified health information.
 - This project type may only be selected if the following is true: The health information excludes all of the following: (1) Name; (2) All geographic subdivisions smaller than a state, including street address, city, county, precinct, zip codes if the geographic unit of combining all the same three initial digits contains more than 20,000 people; (3) All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated in a single category of age 90 or older; (4) Telephone numbers; (5) Fax numbers; (6) Electronic mail addresses; (7) Social security numbers; (8) Medical record numbers; (9) Health plan beneficiary numbers; (10) Account numbers; (11) Certificate/license numbers; (12) Vehicle identifiers and serial numbers, including license plate numbers; (13) Device identifiers and serial numbers; (14) Web universal resource locators (URLs); (15) Internet protocol (IP) address numbers; (16) Biometric identifiers, including finger and voice prints; (17) Full face photographic images and any comparable images; and (18) Any other unique identifying number, character, or code.

- Coded Private Information or Biological Specimens.** The research involves only coded private information or specimens. To qualify for this type of review, the private information or specimens cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems. To qualify, both of the following conditions must be met:
- The private information or specimens were **not** collected specifically for this proposed research project through an interaction or intervention with living individuals. **NOTE:** If this condition is not met, then your research involves human subjects and requires a human subjects research submission. **AND**
 - The investigator(s) cannot readily ascertain the identity of the individuals to whom the private information or specimens pertain because: (mark which option(s) applies)
 - The key to decipher the code will be destroyed before the research begins.
 - The investigator(s) and the holder of the key will enter into an agreement prohibiting the release of the key to the investigator(s) under any circumstances, until the individuals are deceased.

1 IRB Form v3/31/2016

1610704702 determined IU IRB Review Not Required 7-Nov-2016

- Other. Please explain:

For additional information on research with coded private information or biological specimens, please refer to the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (October 16, 2008) at: <http://www.hhs.gov/ohrp/policy/engage08.html>.

SECTION II: PROJECT DESCRIPTION

1. Provide a brief description, in lay terms, of the purpose of the proposed project and the procedures to be used.
 - A modified Delphi Study to assess a developed model of medication adherence. A model will be validated by a dissertation committee's members. Multiple rounds may take place based on their comments.
2. Provide a list of all data points that will be collected below or attach a data collection sheet.
 - A data collection sheet will be attached.

Statement of Principle Investigator. By submitting this form, the Principle Investigator acknowledges that he/she has personally reviewed this report and agrees with the above assessment.

Nov 4, 2016

2 IRB Form v3/31/2016

1610704702 determined IU IRB

Appendix 2

Literature Source Type: Examples Before Analysis

Source Type	How is medication adherence described/ defined in the source type?	How is medication adherence measured in the source type?	How is medication adherence impacted in the source type?	How is intervention described and what contains in the source type?	What are the critical themes, concepts concerning MAB research in this source type?
(Williams et al., 2011)	Process, behavior, skip dose, non-adherence, non-persistence, discontinuation.	Direct, indirect, questionnaire, self-reporting.	Patient-related factors: patients' beliefs toward TAM and AIs, patients' knowledge about the disease, forgetfulness, smoking, age, and race or ethnicity. Therapy-related factors: therapy duration, side effects.	Plan, treatment, knowledge, interview.	Granularity of adherence factor, Intervention component, assessment methods.
(Meichenbaum et al., 1987)	Behavior, medication management,	Electronic monitoring,	Disease stage, age, patient related, and perceived interference,	Prescription simplicity,	Stage of breast cancer, adherence

	compliance, persistence, adherence, medication taking.	prescription refill records.	additional prescribed medications.	feedback and social support.	range.
(Nasseh et al., 2012)	Behavior, medication taking, persistence, adherence, skipping dose.	Medication possession ratio, objective measurement.	Age, healthcare system-related factors: patient- provider relationship. Socioeconomic factors: medication cost, work complexity, religious practices, and marital status.	Reminder, plan, intervention.	Length of study, treatment class, impact type, intervention goal.
(Nekhlyudov et al., 2011)	Behavior, medication taking, self-management, self-regulation, treatment monitoring, not taking.	Direct measurement, indirect measurement, self-reporting, and electronic monitoring,	Patient-related factors, medication-related factors, treatment-related factors, healthcare-related factors, socioeconomic-related factors.	Service delivered through technology, mobile app, internet, email,	Behavior, direct assay, indirect assay, Intervention content, duration, outcome, healthcare engagement,

		questionnaire, pill count, insurance data, possession ratio.		video game, telemonitoring, message, text, reminder, education, Motivation for health behavior change, long-standing adherence.	technology-related factor, patient related factor.
(Bodenreider et al., 2006)	process, planned process, drug management, behavior, adherence, persistence, non-persistence.	Self-reporting, and electronic monitoring, questionnaire.	Beliefs, age, side effect, medication cost, schedule burden, comorbidity, disease stage.	Structured interview, health belief model, education, feedback, monitoring	Disease stage, efficacy, impact type, stage of cancer. Long term and short term.

(Kaplan et al., 2011)	Behavior, skipped dose, missed dose, discontinuation, drug management.	Self-reported, medication monitoring system, subjective, objective.	Beliefs, knowledge, social impact, healthcare relation, communication.	Knowledge, education, session, text message.	Drug class, type of cancer estrogen receptor–positive breast cancer.
(Winstead et al., 2012)	Behavior, process, habit, initiation, continuation.	Direct measurement, indirect measurement, self-reporting, and electronic monitoring, pill count, prescription refill.	Awareness, attitude, information searching, prior Knowledge, novelty, past experience	Treatment theory, consequences actions, awareness, information searching. Knowledge, social support, emotion, motivation, reinforcement, feedback.	Behavior time, belief, emotion granularity, desire, intention, awareness, decision making, information processing, planned study, goal of study, intervention.

(Trust, 2012)	Decision making, problem recognition, stop taking.	Monitoring.	confirmation of expectation, expertise, perceived alternative, evaluation process, dissatisfaction, perceived knowledge skills, social impact, belief, reinforcement, antecedent, health consequence, self-efficacy, perceived behavioral control, emotion.	Telemonitoring, internet, monitoring, Study design, type of study, theory, constructs, stage of adherence, disease type, days covered.	Adherence rate, comorbidity, components, theoretical construct.
(Brendryen, & Kraft, 2008)	Adherence, behavior, quality of life, missed dose. Non-continue.	Subjective ratings, questionnaires, objective strategies, Biochemical measurement, dose-response curve, Pharmacy databases.	Cognitive dissonance, social learning, self-regulation, experience, social norm, behavioral belief, social rule, barrier, facilitator, external variable, modifying factor, cue to action.	Mobile, reminder, social cognitive theory.	Adopter, social interaction, severity.

(Coulter, 2008)	Multidimensional, Behavior, activity taking medication as recommended, agreed on recommendation.	Medication event monitoring systems, objective electronic measurement, Morisky scale directly observed therapy, therapeutic drug monitoring, measurement of biologic marker, electronic compilation, dosing histories, counts of returned tablets / untaken dosage forms, prescription records.	Capability, behavior, intervention, threat, intention, goal, environment, desire, attitude, self-determinant, feeling, self-care, ability, opportunity, socioeconomic, fear, engagement, maintenance, relapse.	Role-play, education, support, communication, habit maintaining, comorbidity treating as depression, motivation.	Behavior, subjective measurement, objective measurement, patient related factor, treatment-related, disease-related, healthcare system-related, socioeconomic-related, intervention component granularity.
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(Andrade et al., 2006)	Behavior, Typology.	refills, self-report patient questionnaires and diaries, assessment of patients' clinical responses and/or physiological marker or effect.		Goal setting, outcome, problem solving, action planning, review behavior goal, behavior discrepancy, commitment, monitoring, feedback, self-monitoring, social support, knowledge.	Knowledge granularity, belief granularity, social impact granularity, emotion granularity, reinforcement granularity, environment granularity, goal, component.
(Buntin et al., 2011)	Process, typology, initiation, discontinuation, implementation,		Knowledge, skills, social role, belief about capability, optimism, belief about consequences, reinforcement, intention, goal,	Education material to promote medication	Intervention content granularity, adherence typology, adherence

	persistence, management of adherence.		memory, decision process, environment, social influence, emotion, behavioral regulation.	knowledge, video to promote adherence, what do instruction if dose is missed, development of less complex medication.	measurement granularity, factors granularity.
(Culter et al., 2018)			Socio-economic factors, healthcare team and system-related factors, condition-related factors, therapy- related factors, patient-related factors, demographics, medicines.	expenditure, and satisfaction, Technology platforms, mobile application, text message, video.	adherence typology, adherence measurement granularity, factors granularity.

(Nasseh et al., 2012)	Patient compliance, attitude to health, behavior.	Direct observed therapy, medication tracking device.	motivation, coping, expectancy, usefulness, ease of use, autonomy, communication, punishment, reinforcement.	packaging methods, reminder, pill organizing, telephone support, text message reminder, internet based, low literacy and resources intervention, aged intervention.	belief, emotion granularity, desire, intention.
(Iuga, & McGuire, 2014)	Patient compliance, attitude to health, health behavior,	Direct observed therapy, medication tracking device.	Incorrect drug dose administration, omitted dose, error drug administration, over dose, under	Medication therapy management	

	behavior, pharmacology, medication management.		dose, ease of use medication.	medical device usage for medical intervention, medication knowledge, take medication at correct time, take medications as prescribed.	
(Coulter et al., 2008)	Patient compliance, attitude to health, behavior, medication taking, drug administration, medical intervention	Direct observed therapy, medication tracking device	High cost of transportation, inability or difficulty accessing a pharmacy, lack of healthcare insurance, medication cost, cultural and lay beliefs about illness and treatment, family dysfunction low income, religious	Video game, internet, social media, tele- monitoring, motivation, social impact, past adherence	Behavior, direct assay, indirect assay, Intervention content, duration, outcome, healthcare engagement, technology-related

			and healthcare team /	history, technology satisfaction.	factor, patient related factor.
(Bailey, McMullin, & Coble, 2001)	Adherence type, direct measurement, indirect measurement.	Electronic monitoring, prescription refill records.	Provider and those of the patient, weak capacity of the system to educate patients and provide follow-up, lack of knowledge of adherence and effective interventions for improving it, overworked.		Disease stage, efficacy, impact type, stage of cancer. Long term and short term.
(Bramwell et al., 2010)	Adherence type, direct measurement, indirect measurement, drug error, mode of delivery, type of	Medication possession ratio, objective measurement.	healthcare providers, lack of incentives and feedback on performance short consultations, lack of incentives and feedback on performance, inability to establish community support and self-	reward, learning, habit formation, graded task, incentive, self- reward, restructuring	Drug class, type of cancer estrogen receptor–positive breast cancer.

	intervention, management process.		management capacity.	physical environment, self-role, punishment, self-belief, persuasion, learning.	
(Ajzen, 2002)	Adherence typology, direct and indirect granularity.	Direct measurement, indirect measurement, self- reporting, and electronic monitoring, questionnaire, pill count, insurance data, possession ratio.	Goal setting, outcome, problem solving, action planning, review behavior goal, behavior discrepancy, commitment, monitoring, feedback, self- monitoring, social support, knowledge, education, consequences, social comparison, cue to action, reward, learning, habit formation, graded task,	regimens, development of combination drugs, development of patient-drug delivery systems, establishment of patient	Behavior time, belief, emotion granularity, desire, intention, awareness, decision making, information processing, planned study, goal of study, intervention.

			incentive, self-reward, restructuring physical environment, self-role, punishment, self-belief, persuasion, learning.	assistance programs, use of adherence enhancing.	
(Khan et al., 2007)	Process, behavior, skip dose, non-adherence, non-persistence, discontinuation.	Self-reporting, and electronic monitoring, questionnaire.	Education material to promote medication knowledge, video to promote adherence, instruction if dose is missed, less complex medication regimens, development of combination drugs, development of patient- drug delivery systems, assistance programs, adherence enhancing packaging, reminder, pill organizing, text message reminder.	game, internet, social media, tele-monitoring, motivation, social impact, past adherence history, technology satisfaction.	

(Winstead et al., 2012)	Behavior, medication management, compliance, persistence, adherence, medication taking.	Self-reported, medication monitoring system, subjective, objective.	requires significant behavioral changes. Socio-economic-related: low level of education, lack of family or social support network, unstable living conditions, unemployment, homeless, burdensome schedule, limited access to healthcare facilities, long distance from treatment center.	role-play, education, support, communication, habit maintaining, comorbidity treating as depression, motivation.	
(Walters, 2007)	Behavior, medication taking, persistence, adherence, skipping dose.		Substance abuse, smoking, visual impairment, hearing impairment, cognitive impairment, impaired mobility or dexterity, swallowing problems. Condition-related: chronic conditions, lack of symptoms, severity of symptoms,	Goal setting, outcome, problem solving, action planning, review behavior goal, behavior discrepancy,	

			rate of progression, severity of disease, co-morbidity; as depression, psychotic disorder, mental retardation/developmental.	commitment, monitoring, feedback, self-monitoring, social support, knowledge, education, consequences, social comparison, cue to action, reward, learning, habit formation, graded task, incentive.	
(McCowan et al., 2008)	Behavior, medication taking, self-		system-related: provider-patient relationship, poorly developed	reward, restructuring	awareness, decision making, information

	management, self-regulation, treatment monitoring, not taking.		health services with inadequate or non-existent reimbursement by health insurance plans, poor medication distribution systems, disparity between the health beliefs of the healthcare.	physical environment, self-role, punishment, self-belief, persuasion.	processing, planned study, goal of study, intervention.
(Ma et al., 2008)	process, planed process, drug management, behavior, adherence, persistence, non-persistence.		use, health status, affordability, adherence, optimism, beliefs, self-efficacy, health service use, barriers and social support, illness perceptions, income.		
(Hershman, 2010)	Behavior, skipped dose, missed dose, discontinuation, drug management.	Self-reported, medication monitoring system, subjective, objective.	Beliefs, knowledge, social impact, healthcare relation, communication.	Knowledge, education, session, text message.	Drug class, type of cancer estrogen receptor-positive breast cancer.

(Sawesi et al., 2016)	Behavior, process, habit, initiation, continuation.	Direct measurement, indirect measurement, self-reporting, and electronic monitoring, pill count, prescription refill.	Awareness, attitude, information searching, prior Knowledge, novelty, past experience.	Treatment theory, grouping and consequences actions, awareness, information searching. Knowledge, social support, emotion, motivation, belief change, reinforcement, feedback, goal, environment, self-regulation.	Behavior time, belief, emotion granularity, desire, intention, awareness, decision making, information processing, planned study, goal of study, intervention.
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(Brendryen, & Kraft, 2008)	<p>Understanding reason is medication needed and consequences of poor compliance (+/-). Understanding of instructions about medications (+/-) Understandings of side-effects (+/-) Understanding benefit of treatment (+/-) Patient beliefs.</p>	<p>Electronic monitoring, prescription refill records.</p>	<p>Disability, drug and alcoholic abuse. Therapy-related: complexity of medication, regimen; number of prescriptions, treatment required mastery of certain technique, duration of therapy.</p>	<p>Structured interview, health belief model, education, feedback, monitoring.</p>	<p>outcome, healthcare engagement, technology-related factor, patient related factor.</p>
(Van den Berg et al., 2007)	<p>Burdensome schedule, rout of administration Feeling stigmatized.</p>	<p>Ratio, objective measurement.</p>	<p>Age, patient related, and perceived interference, additional prescribed medications.</p>	<p>Simplicity, feedback and social support.</p>	<p>Intervention component, assessment methods.</p>

(Herbst et al., 2014)	Visual impairment, hearing impairment, cognitive impairment, immobility or dexterity, dysphagia.	Direct, indirect, questionnaire, self-reporting.	frequent change in medication regimen, lack of medication benefit of therapy, medications with social stigma attached to their use, actual or perceived unpleasant side effects, treatment interferes with lifestyle.	Plan, treatment, knowledge, interview.	Stage of breast cancer, adherence range.
(Tildesley et al., 2010)	Complexity of medication regimen, duration of therapy, frequent change in regimen, lack of immediate benefit of therapy, social stigma, actual or perceived unpleasant side effect.	electronic monitoring, questionnaire, pill count, insurance data, possession ratio.	treatment-related factors, healthcare-related factors, socioeconomic-related factors.	Technology platforms, text, mobile application, video game, social media, tele-monitoring, motivation, social impact, past adherence.	outcome, healthcare engagement, technology-related factor, patient related factor

Appendix 3

Glossary of Terms: Examples Included in Protégé

Terms/ Phrases	Description	Definition	Type (noun/ verb)	Definition Source
Behavior		Patterned activity of a whole organism in a manner dependent upon some combination of that organism's internal state and external conditions.	Noun	MFO http://www.ontobee.org/
Medication adherence	Medication taking behavior; behavioral response to medication, medication compliance.	Behavior associated with the consumption or use of chemical substance with presumed curative, preventive or medicinal value in accordance with the provider's recommendation concerning the timing, dosage, frequency, and duration.	Noun	Sawesi
Medication initiation	Primary adherence, adoption.	Medication adherence that is associated with the new prescription for a given course of treatment.	Noun	Sawesi

Medication continuation	Secondary adherence, medication implementation, medication execution, medication Maintenance.	Medication adherence behavior that is associated with the continuation of an existing prescription or order for a given course of treatment.	Noun	Sawesi
Medication non-initiation	Primary non-adherence, dispensation delay.	Medication adherence behavior in which the new prescription did not initiate or dispense within a defined number of days after the medication was ordered. Usually within 30-90 days.	Noun	Sawesi
Suboptimal adherence	Inadequate adherence.	Medication adherence behavior associates with incorrect dosing, incorrect time, incorrect frequency, and incorrect duration.	Noun	Sawesi
Medication discontinuation	Stop taking medication	Medication taking behavior that is	Noun	Vrijens et al., 2012

		associated with the act of stop taking the treatment for whatever reasons.		
Medication discontinuation for database analysis	Termination, end of therapy.	Failure to have a medication dispensing within a defined number of days after exhaustion of the days' supply of the previous dispensing some time 180 days used (often includes exhaustion of any stockpiled medication accumulated from previous dispensings).	Noun	Sawesi
Adequate medication continuation	Adequate adherence, Adherence, Ongoing adherence Compliance, adequate secondary adherence	Medication continuation adherence with either an overall (1) gap in days of medication possession not exceeding 20% of the days between the date of initial dispensing and the date of the end of the measurement period (gap measures) or (2) number	Noun	Raebel et al., 2013

		of days of medication possession of no less than 80% of the days between the Date of initial dispensing and Date of the end of the Measurement period		
Inadequate medication continuation	Partial adherence, poor adherence, inadequate adherence, non-compliance, inadequate secondary Adherence	Medication adherence with either an overall (1) gap in days of medication possession exceeding 20% of the days between the date of initial dispensing and the date of the end of the measurement period or (2) number of days of medication possession of less than 80% of the days between the date of initial dispensing and the date of the end of the measurement period.	Noun	Raebel et al., 2013
Cut-point		The value on an ordinal scale beyond which	Noun	Sawesi

		<p>values are regarded as abnormal adherence. The cut-points commonly Used are:</p> <p>Gap: Cmg >20%, Npmg >20%</p> <p>Possession: Mpr <80%</p> <p>Pdc <80%.</p>		
Medication persistence		<p>The duration of time from initiation to discontinuation of therapy or last dose taking. It is dichotomous (yes/no).</p>	Noun	Nekhlyudov et al., 2011
Early-stage persistence	<p>Point-of-time, persistence, early persistence, persistence</p>	<p>A new prescription was dispensed (medication initiated) and at least one Refill of that prescription was Dispensed over a time period consistent with (implying) current use of the drug.</p>	Noun	Nekhlyudov et al., 2011
Time period		<p>Time period allowed or considered between the one dispensing and the</p>	Noun	Sawesi

		following expected refill or time period Allowed after last refill in the measurement period.		
Early-stage non-persistence	Early non-persistence	Failure to have the new prescription refilled over a time period consistent with current use of the drug.	Noun	Nekhlyudov et al., 2011
Later-stage persistence	Second stage persistence, refill compliance, persistent/persistence	Two or more refills (i.e., the new prescription was Dispensed and at least 2 refills of that prescription were Dispensed) over a time period consistent with current use of the drug. The time period can Span several refills that occur over 6 months, 12 months, or longer.	Noun	Nekhlyudov et al., 2011
Later-stage Non-persistence	Second stage non-persistence, suboptimal persistence,	Failure to have two or more refills over a time period consistent with current use of The drug. Can imply		Nekhlyudov et al., 2011

	not persistent, non-persistence	either that the patient has discontinued the medication or that usage is inconsistent over time.		
Duration of treatment course	Length of therapy	The period from the start to the end of a treatment course.	Noun	Apollo_sv http://www.ontobee.org/
Adherence rate		Percentage of doses taken as prescribed from initiation of medication or start of observation until stop medication or end of observation.	Noun	Hugtenburg et al., 2013
Habituation	Habit	A condition resulting from repeating the consumption or use of a chemical substance presumed curative, preventive or medicinal value with a desire (but not compulsion) to continue taking the medication for the sense of improved well-being or prevent disease	Noun	Sawesi

		recurrence which it engenders; and no tendency to miss or skip the dose; postpone the dose; or stop dose for whatever reason without provider recommendation.		
Direction of effect	Type of effect	Determinants were classified according to their positive, negative, neutral effect on adherence.	Noun	Kardas et al., 2013
Determinant	Factor	Anything that contributes causally to a result.	Noun	https://www.merriam-webster.com/dictionary/determinant
New prescription		A prescription that include a new medication or therapy that has not been used before by the patient to treat current disease or condition.	Noun	Sawesi
Defined number of day		Number of day in which prescription presumed to be dispensed after it has	Noun	Sawesi

		been ordered. The commonly used days are 30 or 60 days.		
Intention-non-adherence		A medication adherence behavior preceded by a rational decision to deviate from treatment regimen. Or has an appraisal process as part.	Noun	Sawesi
Non-intention-non-adherence		A medication adherence behavior that is largely driven by circumstance out of an individual's control such as forgetfulness, lack of resources.	Noun	Sawesi
Management of adherence process		The process of monitoring and supporting patients' adherence to medications by healthcare systems, providers, patients, and their social networks.	Noun	Vrijens et al., 2013

Behavioral intervention		Psychological or behavior intervention is a combination of program elements, strategies, or modalities designed to influence psychological or behavioral processes or outcomes.	Noun	Eagle_i resource ontology http://www.ontobee.org
Adherence use mems		“adherent” when at least a single mems cap opening occurred on a given day.	Noun	Ayelward et al., 2014
Non-adherence use mems		When all prescribed mems cap openings were missed on any given day (e.g., patient prescribed to take morning and evening dose and didn’t open the electronic pill container.	Noun	Ayelward et al., 2014
Direct measurement of medication adherence		Determination of medication adherence by directly observe consumption process or assaying the presence of medication in body fluid.	Noun	Sawesi

Indirect measures of adherence		Determination of medication adherence by measuring related parameters other than object characteristics and convert them into measurement of the characteristics in question (medication adherence).	Noun	Sawesi
Objective measurement of adherence		Determination of medication adherence based on impartial measurement, observable phenomenon and not on personal feeling or bias.	Noun	Sawesi
Subjective measurement of adherence		Determination of medication adherence-based observer's personal judgment and on how well the drug was taken.	Noun	Sawesi
Drug concentration in blood		A measurement method that determine the concentration of drug in a blood serum sample.	Noun	Sawesi

Drug concentration in urine		A measurement method that determine the concentration of drug in a urine sample.	Noun	Sawesi
Evaluation of presence of biomarker given with drug		A measurement method that record medication adherence based on an ingestible sensor imbedded in tablet (tablet co-encapsulated) that digitally records medication ingestion by sending a signal to a patch worn by patient. The information then transfers to physician device.	Noun	Sawesi
Direct observation of patient taking medication		Determination of medication adherence by direct watching and recording patient taking medication.	Noun	Sawesi
Secondary database analysis		Is analysis of data that was collected for another primary purpose.	Noun	Sawesi

Medication possession ratio (MPR)		Ratio of the number of days for which a patient has medication on hand divided by the total number of days a patient was observed. Used for refill adherence	Noun	Raebel et al., 2013
Medication possession ratio modified (MPRM)		Ratio of the days' supply of medication dispensed during specified observation period excluding last refill, divided by number of days between first and last dispensing. Used for refill adherence.	Noun	Raebel et al., 2013
Medication refill adherence		Total days' supply divided by number of days in observation period. For refill adherence.	Noun	Raebel et al., 2013
MEDSUM		Number of daily doses dispensed in a period divided by number of Days in period.	Noun	Bryson et al., 2007

<p>Proportion of days covered (PDC)</p>		<p>Total number of days' supply dispensed during specified observation period divided by number of days (from first to end) in patient's observation period. For refill adherence and persistence.</p>	<p>Noun</p>	<p>Bryson et al., 2007</p>
<p>Continuous measure of medication acquisition (CMA)</p>		<p>Total days' supply of medication obtained throughout study period divided by number of days from first dispensing until study completion date (number of days in observation period). For refill adherence.</p>	<p>Noun</p>	<p>Raebel et al., 2013</p>
<p>Continuous, single interval measure of medication acquisition (CSA)</p>		<p>Single-interval measure of medication availability; provides an adherence value for each patient between dispensings (not Overall study period).</p>	<p>Noun</p>	<p>Raebel et al., 2013</p>

Compliance rate or compliance ratio (CR)		Sum of days' supplies minus days' supply obtained at last dispensing divided by number of days from First up to (not including) last dispensing date.	Noun	Raebel et al., 2013
Refill compliance rate (RCR)		The total days' supply was multiplied by 100 and divided by the number of days from first to last medication dispensation.	Noun	Hess et al., 2006
Refill compliance (RECOMP)		Total number of drug days that apply within an observation period plus oversupply divided by the number of days in the observation period.	Noun	Hess et al., 2006
Medication-total (MED_TOT)		Total supply of pills dispensed divided by the total number of days elapsed.	Noun	Andrade et al., 2006
Medication interval		Ratio of days' supply obtained at the beginning	Noun	Raebel et al., 2013

(MED_INT)		of a specific time interval to the days elapsed before the subsequent refill.		
Refill compliance rate (RCR)		The total days' supply was multiplied by 100 and divided by the number of days from first to last medication dispensation.	Noun	Dunbar et al., 2010
New prescription medication gap (NPMG)		Time between date provider first prescribes medication until first of the following: end of follow-up, censoring due to patient being switched to alternate therapy or medication discontinued by prescriber. For initiation, persistence and refill adherence.	Noun	Raebel et al., 2013
Continuous measure of medication gaps (CMG) Or cumulative		Number of days in which the medication was not available (gap) between each prescription fill, divided by the number of	Noun	Raebel et al., 2013

medication gap (CMG)		days between the first and last medication fill during the study period. For refill adherence.		
Continuous multiple interval measure of over supply (CMOS)		Total number of days' supply (if gap) or surplus divided by days in observation period or total days to next fill.	Noun	Lam et al., 2015
Cumulative gap ratio		Number of days in which the medication was not available (gap) between each prescription fill, divided by the number of days between the first and last medication fill during the study period.	Noun	Andrade et al., 2006
Medication out (MED_OUT or MEDOUT)		Total number of days without medications divided by the total days of observation.	Noun	Bryson et al., 2007
Days between fill adherence rate (DBR)		The total days' supply was subtracted from the number of days between	Noun	Raebel et al., 2013

		dispensations divide by the number of days between dispensations.		
Prescription	Written instruction	A document that represents verbal or written order given by an authorized person instructing a patient to obtain and use a medical device, prescription or undergo a procedure.	Noun	NCI thesaurus http://www.ontology.org
Patient	Sick person	Patient is the involved participant in the Treatment process.	Noun	
Healthcare encounter	Patient present at healthcare system	A temporally-connected healthcare process that has as participants an organization or person realizing the healthcare provider role and a person realizing the patient role. The healthcare provider and patient are realized during the healthcare encounter.		OBI http://www.ontology.org

Physical examination		A sequence of acts of observing and measuring qualities of a patient performed by a clinician; measurements may occur with and without elicitation.		OGMS http://www.ontobee.org
Clinical history taking		An interview in which a clinician elicits a clinical history from a patient or from a third party who is reporting on behalf of the patient.	Verb	OGMS http://www.ontobee.org
Prescribe		Is to issue a medical prescription or recommend with authority.	Verb	Oxford dictionary
Start new medication		Instantiate new prescription.	Verb	Sawesi
Change current medication		Substitute the current medication with another.	Verb	Sawesi
Continue current medication		Issue refill or recommend continuation.	Verb	Sawesi

Discontinue medication by physician		Advise to stop the current medication for medical reason.	Verb	Sawesi
Behavioral intervention		An intervention that use a combination of program elements or techniques, strategies, and modalities to influence psychological or behavioral processes or outcomes.	Noun	ERO http://www.ontobee.org
Breast cancer		A thoracic cancer that originates in the mammary gland.	Noun	DODI http://www.ontobee.org
Tamoxifen		An antineoplastic nonsteroidal selective estrogen receptor modulator (serum). Tamoxifen competitively inhibits the binding of estradiol to estrogen receptors, thereby preventing the receptor from binding to the estrogen-response	Noun	NCI thesaurus http://www.ontobee.org

		<p>element on dna. The result is a reduction in dna synthesis and cellular response to estrogen. In addition, tamoxifen up-regulates the production of transforming growth factor b, a factor that inhibits tumor cell growth, and down-regulates insulin-like growth factor 1, a factor that stimulates breast cancer cell growth.</p>		
Aromatase inhibitors		<p>Any compound that inhibits aromatase and reduces production of estrogenic steroid hormones.</p>	Noun	<p>Biomodels https://bioportal.bioontology.org/</p>
Breast cancer stage		<p>A staging of breast cancer for example by the American Joint Committee on Cancer, stage 7, or other coding system.</p>	Noun	<p>EFO http://www.ontobee.org</p>

Neoadjuvant endocrine therapy		Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.	Noun	Fleming et al., 2017
Hormone-receptor-positive		Cancer cell with receptors for estrogen or progesterone as it needs these hormones to grow.	Noun	Ingle et al., 2003
Needs recognition		Is an adoption stage in which an individual recognizes the difference between the desired state and the actual condition.		Http://academic.udayton.edu/johnsparks/tools/notes/conprobrec.pdf
Perceived threat		A belief that a threatening health problem is serious and has potential negative consequences for lifestyle. This belief		Http://medical-dictionary.thefreedictionary.com/health+beliefs%3a+perceived+th

		triggers awareness of the problem and stimulate individual to participates in a behavior to prevent or minimize the threat.		reat
Perceived severity		A perceived threat that refers to the individual's belief about the seriousness or severity of a disease.		https://chirr.nlm.nih.gov/perceived-susceptibility.php
Perceived susceptibility		A perceived threat that refers to the subjective belief about the risk of contracting a condition.		https://chirr.nlm.nih.gov/perceived-susceptibility.php
Needs awareness process		A process in which an individual exposed to internal or external trigger and perceived need toward technology.		
Internal stimuli		A stimulus that results from thoughts or physiological sensations that trigger a need.		https://www.b2bmarketing.net/en/resources/blog/5-steps-understanding-

				your-customers-buying-process.
External stimuli		A stimulus from an outside/environment that touches upon one of the five senses and trigger a need.		Http://rachel.golearn.us/modules/en-boundless/www-boundless.com/marketing/definition/stimuli/index.html
Perceived needs		A cognitive representation of feeling or state of strongly wanting something.		Http://dictionary.cambridge.org/dictionary/english/need
Information search		A process in which the information seeker gets involved to satisfy his need either by activating the knowledge stored in his/her memory or by acquisition of information from the environment using different sources.		
Perceived uncertainty		A subjective perception of need of information		

		<p>about object or situation.</p> <p>It is a state of lack of information.</p>		
In-memory search process		An information searching process in which an information seeker examining memory for available information.		<p>Lee, y. (2006).</p> <p>Determinants of consumers' information search patterns in online marketing communication.</p>
Prior knowledge		A knowledge that occurs in an individual's memory and it is multidimensional construct that comprised of three dimensions.		
Perceived familiarity of technology		A prior knowledge an individual knows or perceives about the attributes of the technology.		<p>Http://journals.sagepub.com.proxy.ulib.uits.iu.edu/doi/pdf/10.1177/1096348003261218</p>

Perceived past experience		A prior knowledge an individual gained from the previous usage of the		https://www.researchgate.net/profile/deborah_kerstetter/publication/223955678_prior_knowledge_credibility_and_information_search/links/53f241a70cf2bc0c40e731d5.pdf?origin=publication_list
Perceived expertise		A prior knowledge that refers to an individual ability to perform product-related tasks successfully.		Khosrowjerdi, m., & iranshahi, m. (2011)
Perceived novelty		The degree of contrast between present perception and past experience.		https://pdfs.semanticscholar.org/bdd8/00f3863b6c6902f5e174e0b40f86544f3e2d.pdf

Perceptual process		<p>An information searching process in which information seeker selects, organizes and interprets information received via his/her sense from different environmental sources when he/she has no prior knowledge and limited experience and expertise about a product (technology). The searching sources could be personal sources (e.g., Word of mouth from friends/family) and/or impersonal sources (e.g., internet/social media).</p>		
Perceptual selection		<p>A perceptual process in which a sensory data selected for more processing.</p>		

Perceptual categorization		A perceptual process in which selected sensory data mentally structured in coherent way.		
Perceptual interpretation		A perceptual process in which a meaning to the information received and categorized is assigned.		
Perceived technology attribute knowledge		A new knowledge about the product or/and its medium (e.g., application on phone) from an outside source via either acquisition or imitation.		
Perceived concrete attributes		A perceived knowledge of product that refers to the physical characteristics of a product or its medium and can be assessed base on some criteria such as color, size, or shape.		
Perceived abstract attributes		A perceived knowledge of product that refers to the pseudo-physical		

		characteristics which is intangible such as design, function, social and psychological benefits.		
Use initiation		An adoption stage occurs in response to cognitive representation (prior knowledge, perceived knowledge, beliefs, feeling and attitude).		
Evaluation process		A process in which a user evaluates his/her prior knowledge or the perceived knowledge and make belief, attitude and feeling toward the product.		
Performance expectancy	Perceived benefit; benefit expected of technology, extrinsic motivation	The degree to which an individual believes that using the system will help him or her to attain gains in job performance.		

Perceived usefulness	Job-fit; task-technology fit	The degree to which an individual believes that using a system would enhance his or her job performance.		TAM1/TAM2/I DTPB/ MODEL OF PC; TTF
Relative advantage		The degree to which an innovation is perceived as better than what already exists.		
Response efficacy		The extent people believe a recommended behavior effectively deters or alleviates possible harm. (tangible or intangible harm).		PMT
Long-term consequence	Outcome of outcome (e.g., using technology will improve adherence which will prevent cancer recurrence)	A belief about the outcomes of behavior that have a pay-off in the future.		MPCU

Concern expectancy		The degree to which an individual believes that using the system associated with some drawback.		Model of pre-implementation acceptance
Response cost		The degree to which an individual believes that using a system associated with unpleasant, unexpected consequences.		PRT Note: for after acceptance phase
Perceived risk		The degree to which an individual believes that there is an ease associated with the use of the system.		UTAUT
Effort expectancy		The degree to which an individual believes that there is an ease associated with the use of the system.		UTAUT
Perceived ease of use		The degree to which a person believes that using a particular system would be free of effort.		TAM/TAM2/ID TPB/IDT

Complexity (antonym of ease of use)		The degree to which an innovation is perceived as relatively difficult to understand and use.		IDT/MPCU
Compatibility		The degree to which an innovation is perceived as being consistent with the existing values, needs, and past experiences of potential adopters.		IDT/DTPB
Job relevance		The degree to which target system is applicable to the individual's job.		Tam2
Social influence		The degree to which an individual perceives that important others believe that he or she should use the new system.		UTAUT
Subjective norm		A social influence that refers to the person's perception that most people who are important to him think he should or not perform the behavior.		TRA/TPB/TAM 2/IDTPB

Social factors		A social influence that represents cues individual receives from a member of his/her social structure which prompt him/her to behave in certain way.		MPCU
Image		The degree to which use of an innovation is perceived to enhance one's status in one's social system.		TAM2
Perceived behavioral control		Individual belief about ability to perform a given behavior. It encompasses of self-efficacy and controllability.		TPB/IDTPB
Control over behavior	Control belief/control lability	An individual belief about the presence of factors that may facilitate or impede performance of the behavior.		TPB
Perceived facilitating	Facilitation	The degree to which an individual believes that an organizational and technical infrastructure		SCT/MPCU/ID TPB

		exists to support use of the system.		
Perceived barrier		Person's perception on the obstacles to performing a recommended action.		HBM
Self-efficacy		Individual confidence in his ability to perform a given behavior and overcome barrier. It encompasses skill and confidence that individual can effectively and consistently use.		SCT/HBM/PMT
Perceived autonomy		The degree to which an individual perceives his or her actions. As a result of his or her own free will, without external interference in a certain situation.		
Perceived voluntariness		The degree to which an individual perceives his or her self not under the influence or control of		IDT/TAM2/UT AUT

		another person when making decision.		
Attitude toward technology		A cognitive representation results from an individual's evaluation of the product or the behavior based on his/her beliefs, prior behavior, or feeling to form a favorable or unfavorable perspective.		
Affect toward technology		An affective representation that represents an individual's feelings toward behavior or product such as feeling of satisfying, joy, elation, or pleasure, or depression, disgust, displeasure, or hate associated by an individual with a particular act.		The model of pc utilization. Http://www.swdsi.org/swdsi2010/sw2010_precedings/papers/pa104.pdf

Decision making process		A process in which an individual chooses to adopt or reject the technology based on his/her cognitive representation (prior knowledge, belief, attitude and feeling).		
Intention to initiate use		Is a cognitive representation of act in which an individual perceived likelihood or “subjective probability that he or she will engage in a given behavior/adopt the technology.		
Behavior modification (initiation use)		A process by which an individual use the system as intended.		
Perceived performance experience		A knowledge that is gained from the performing a behavior.		
Use continuation		An adoption stage occurs based on prior performance experience		

		as well as belief, feeling, and attitude.		
Expectation confirmation		An evaluation process in which an individual evaluates his/her performance experience to confirm or update his prior belief, attitude.		
Perceived satisfaction		An affective representation that result from an individual assessment after having direct experience with a product or service in terms of whether that product or service has met his/her needs and expectations.		http://www.scialert.net/fulltext/?doi=jas.2014.860.872&org=11
Perceived confirmation of expectation		The degree to which an individual's initial expectation about the performance of a system is being confirmed after having an experience with the system.		

Intention to continuation		Is a cognitive representation of act in which an individual perceived likelihood or “subjective probability that he or she will continue engaging in a current behavior/ continue using the technology.”		
Intention to discontinue		Is a cognitive representation of act in which an individual perceived likelihood or “subjective probability that he or she will discontinue using the technology.”		
Technology adoption		A behavioral process that occurs in response to the cognitive representation.		

REFERENCES

- Abidi, S. R., Abidi, S. S. R., Butler, L., & Hussain, S. (2008). *Operationalizing prostate cancer clinical pathways: An ontological model to computerize, merge and execute institution-specific clinical pathways*. Paper presented at the Workshop on Knowledge Management for Health Care Procedures.
- Adachi, Y., Sato, C., Yamatsu, K., Ito, S., Adachi, K., & Yamagami, T. (2007). A randomized controlled trial on the long-term effects of a 1-month behavioral weight control program assisted by computer tailored advice. *Behaviour Research and Therapy, 45*(3), 459-470.
- Agarwal, R., Anderson, C., Zarate, J., & Ward, C. (2013). If we offer it, will they accept? Factors affecting patient use intentions of personal health records and secure messaging. *Journal of Medical Internet Research, 15*(2), e43.
- Aikens, J. E., Zivin, K., Trivedi, R., & Piette, J. D. (2014). Diabetes self-management support using mHealth and enhanced informal caregiving. *Journal of Diabetes and its Complications, 28*(2), 171-176.
- Ajzen, I. (2002). Perceived behavioral control, self-efficacy, locus of control, and the theory of planned behavior. *Journal of Applied Social Psychology, 32*(4), 665-683.
- Anagnostakis, A. G., Tzima, M., Sakellaris, G. C., Fotiadis, D. I., & Likas, A. C. (2005). Semantics-based information modeling for the health-care administration sector: The citation platform. *IEEE Transactions on Information Technology in Biomedicine, 9*(2), 239-247.
- Andrade, A. S., McGruder, H. F., Wu, A. W., Celano, S. A., Skolasky, R. L., Selnes, O. A., . . . McArthur, J. C. (2005). A programmable prompting device improves adherence to highly active antiretroviral therapy in HIV-infected subjects with memory impairment. *Clinical Infectious Diseases, 41*(6), 875-882.
- Andrade, S., Kahler, K., Frech, F., & Chan, K., Arnold (2006). Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and Drug Safety, 15*(8), 565-574; discussion 575-567. doi:10.1002/pds.1230
- Andrade, S. E., Kahler, K. H., Frech, F., & Chan, K. A. (2006). Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiology and drug safety, 15*(8), 565-574.
- Anscombe, E. (2000). *Intention* (2nd edition ed.): Cambridge, MA: Harvard University Press.
- Apperly, I. (2010). *Mindreaders: the cognitive basis of "theory of mind"*: Psychology Press.
- Aranguren, M. E. (2005). *Ontology design patterns for the formalisation of biological ontologies*. (Master Of Philosophy), University of Manchester.
- Aronson, J. K. (2007). Compliance, concordance, adherence. *British Journal of Clinical Pharmacology, 63*(4), 383-384.
- Arora, S., Peters, A. L., Burner, E., Lam, C. N., & Menchine, M. (2014). Trial to examine text message-based mHealth in emergency department patients with diabetes (TExT-MED): A randomized controlled trial. *Annals of Emergency Medicine, 63*(6), 745-754.

- Arp, R. (2010). Ontology: not just for philosophers anymore. *Practical Philos*, 10(1).
- Arp, R., Smith, B., & Spear, A. D. (2015). *Building ontologies with basic formal ontology*: Mit Press.
- Atkins, L., & Fallowfield, L. (2006). Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *European Journal of Cancer*, 42(14), 2271-2276.
- Aylward, B. S., Rausch, J. R., & Modi, A. C. (2014). An examination of 1-year adherence and persistence rates to antiepileptic medication in children with newly diagnosed epilepsy. *Journal of Pediatric Psychology*, 40(1), 66-74.
- Bailey, T. C., McMullin, S. T., & Coble, J. (2001). Using information systems technology to improve antibiotic prescribing *Critical Care Infectious Diseases Textbook* (pp. 245-252): Springer.
- Banning, M. (2012). Adherence to adjuvant therapy in post-menopausal breast cancer patients: a review. *European Journal of Cancer Care*, 21(1), 10-19.
- Bantum, E. O. C., Albright, C. L., White, K. K., Berenberg, J. L., Layi, G., Ritter, P. L., . . . Lorig, K. (2014). Surviving and thriving with cancer using a Web-based health behavior change intervention: randomized controlled trial. *Journal of Medical Internet Research*, 16(2), e45.
- Baptist, A. P., Thompson, M., Grossman, K. S., Mohammed, L., Sy, A., & Sanders, G. M. (2011). Social media, text messaging, and email—preferences of asthma patients between 12 and 40 years old. *Journal of Asthma*, 48(8), 824-830.
- Barello, S., Graffigna, G., Vegni, E., & Bosio, A. (2014). The challenges of conceptualizing patient engagement in healthcare: a lexicographic literature review. *Journal of Participatory Medicine*, 6(11), 259-267.
- Barnabei, V. M., O'Connor, J. J., Nimphius, N. M., Vierkant, R. A., & Eaker, E. D. (2008). The effects of a web-based tool on patient-provider communication and satisfaction with hormone therapy: a randomized evaluation. *Journal of Women's Health*, 17(1), 147-158.
- Beale, T., & Heard, S. (2007). *An ontology-based model of clinical information*. Paper presented at the Medinfo 2007: Proceedings of the 12th World Congress on Health (Medical) Informatics; Building Sustainable Health Systems.
- Bell, A. M., Fonda, S. J., Walker, M. S., Schmidt, V., & Vigersky, R. A. (2012). Mobile phone-based video messages for diabetes self-care support. *Journal of Diabetes Science and Technology*, 6(2), 310-319.
- Benhamou, P., Melki, V., Boizel, R., Perreal, F., Quesada, J., Bessieres-Lacombe, S., . . . Hanaire, H. (2007). One-year efficacy and safety of Web-based follow-up using cellular phone in type 1 diabetic patients under insulin pump therapy: the PumpNet study. *Diabetes & Metabolism*, 33(3), 220-226.
- Bentley, D. R., & Richardson, C. R. (2014). Comparison of Veteran experiences of low-cost, home-based diet and exercise interventions. *Journal of Rehabilitation Research and Development*, 51(1), 149-160.
- Bhosle, M. J. (2007). *Outcomes associated with adjuvant hormonal therapy: are there any differences between black and white women with primary breast cancer?* (Doctor of Philosophy), The Ohio State University.

- Bickmore, T., & Giorgino, T. (2004). *Some novel aspects of health communication from a dialogue systems perspective*. Paper presented at the AAAI Fall Symposium on Dialogue Systems for Health Communication.
- Bickmore, T. W., Schulman, D., & Sidner, C. L. (2011). A reusable framework for health counseling dialogue systems based on a behavioral medicine ontology. *Journal of Biomedical Informatics*, 44(2), 183-197.
- Bilder, R. M., Sabb, F. W., Parker, D. S., Kalar, D., Chu, W. W., Fox, J., . . . Poldrack, R. A. (2009). Cognitive ontologies for neuropsychiatric phenomics research. *Cognitive Neuropsychiatry*, 14(4-5), 419-450.
- Bingham, P. M., Lahiri, T., & Ashikaga, T. (2012). Pilot trial of spirometer games for airway clearance practice in cystic fibrosis. *Respiratory Care*, 57(8), 1278-1284.
- Blake, T. (2016). Why We Need Deep Medication Adherence Information. Retrieved from <http://www.semanticconsulting.com.au/2016/09/22/need-deep-medication-adherence-information/>
- Blobel, B. (2006). Concept representation in health informatics for enabling intelligent architectures. *Studies in Health Technology and Informatics*, 124, 285-291.
- Blobel, B. (2007). Educational challenge of health information systems' interoperability. *Methods of Information in Medicine*, 46(1), 52-56.
- Bodenreider, O., & Stevens, R. (2006). Bio-ontologies: current trends and future directions. *Briefings in Bioinformatics*, 7(3), 256-274.
- Boland, M. V., Chang, D. S., Frazier, T., Plyler, R., Jefferys, J. L., & Friedman, D. S. (2014). Automated telecommunication-based reminders and adherence with once-daily glaucoma medication dosing: the automated dosing reminder study. *JAMA Ophthalmology*, 132(7), 845-850.
- Bolbel, B., Engel, K., & Pharow, P. (2006). Semantic Interoperability: HL7 Version 3 compared to advanced architecture standards. *Methods of Information in Medicine*, 45(4), 343-353.
- Bond, G. E., Burr, R. L., Wolf, F. M., & Feldt, K. (2010). The effects of a web-based intervention on psychosocial well-being among adults aged 60 and older with diabetes a randomized trial. *The Diabetes Educator*, 36(3), 446-456.
- Borycki, E., & Kushniruk, A. (2006). *Development of a virtual self-management tool for COPD patients: towards a user needs ontology*. Paper presented at the AMIA Annual Symposium Proceedings.
- Botts, N. E., Horan, T. A., & Thoms, B. P. (2011). HealthATM: personal health cyberinfrastructure for underserved populations. *American Journal of Preventive Medicine*, 40(5), S115-S122.
- Boudreaux, E. D., Bedek, K. L., Byrne, N. J., Baumann, B. M., Lord, S. A., & Grissom, G. (2012). The Computer-Assisted Brief Intervention for Tobacco (CABIT) program: a pilot study. *Journal of Medical Internet Research*, 14(6), e163.
- Bourget, D., & Mendelovici, A. (2016). Phenomenal intentionality. In E. N. Zalta (Ed.), *Stanford Encyclopedia of Philosophy* (Spring 2017 ed.): Metaphysics Research Lab, Stanford University.
- Boyce, S., & Pahl, C. (2007). Developing domain ontologies for course content. *Educational Technology & Society*, 10(3), 275-288.

- Bramley, D., Riddell, T., Whittaker, R., Corbett, T., Lin, R.-B., Wills, M., . . . Rodgers, A. (2005). Smoking cessation using mobile phone text messaging is as effective in Maori as non-Maori. *The New Zealand Medical Journal*, *118*(1216), U1494.
- Bramwell, V., Pritchard, K., Tu, D., Tonkin, K., Vachhrajani, H., Vandenberg, T., . . . Graham, B. (2009). A randomized placebo-controlled study of tamoxifen after adjuvant chemotherapy in premenopausal women with early breast cancer (National Cancer Institute of Canada—Clinical Trials Group Trial, MA. 12). *Annals of Oncology*, mdp326.
- Bramwell, V., Pritchard, K., Tu, D., Tonkin, K., Vachhrajani, H., Vandenberg, T., . . . Shepherd, L. (2009). A randomized placebo-controlled study of tamoxifen after adjuvant chemotherapy in premenopausal women with early breast cancer (National Cancer Institute of Canada--Clinical Trials Group Trial, MA.12). *Annals of Oncology*, *21*(2), 283-290. doi:10.1093/annonc/mdp326
- Brendryen, H., & Kraft, P. (2008). Happy Ending: a randomized controlled trial of a digital multi-media smoking cessation intervention. *Addiction*, *103*(3), 478-484.
- Brown, J., Sorrell, J. H., McClaren, J., & Creswell, J. W. (2006). Waiting for a liver transplant. *Qualitative Health Research*, *16*(1), 119-136.
- Bryson, C. L., Au, D. H., Young, B., McDonell, M. B., & Fihn, S. D. (2007). A refill adherence algorithm for multiple short intervals to estimate refill compliance (ReComp). *Medical Care*, *45*(6), 497-504.
- Bug, W. J., Ascoli, G. A., Grethe, J. S., Gupta, A., Fennema-Notestine, C., Laird, A. R., . . . Turner, J. A. (2008). The NIFSTD and BIRNLex vocabularies: building comprehensive ontologies for neuroscience. *Neuroinformatics*, *6*(3), 175-194.
- Buhrman, M., Fältenhag, S., Ström, L., & Andersson, G. (2004). Controlled trial of Internet-based treatment with telephone support for chronic back pain. *Pain*, *111*(3), 368-377.
- Buhrman, M., Skoglund, A., Husell, J., Bergström, K., Gordh, T., Hursti, T., . . . Andersson, G. (2013). Guided internet-delivered acceptance and commitment therapy for chronic pain patients: a randomized controlled trial. *Behaviour Research and Therapy*, *51*(6), 307-315.
- Buntin, M. B., Burke, M. F., Hoaglin, M. C., & Blumenthal, D. (2011). The benefits of health information technology: a review of the recent literature shows predominantly positive results. *Health Affairs*, *30*(3), 464-471.
- Call, J., & Tomasello, M. (1999). A nonverbal false belief task: The performance of children and great apes. *Child Development*, *70*(2), 381-395.
- Camp, E. (2007). Thinking with maps. *Philosophical Perspectives*, *21*(1), 145-182.
- Campbell, R., Pound, P., Pope, C., Britten, N., Pill, R., Morgan, M., & Donovan, J. (2003). Evaluating meta-ethnography: a synthesis of qualitative research on lay experiences of diabetes and diabetes care. *Social Science & Medicine*, *56*(4), 671-684.
- Capozzi, D., & Lanzola, G. (2009). *An Advanced Platform for Managing Complications of Chronic Diseases* (Vol. 5651). Berlin, Heidelberg: Springer.
- Ceusters, W., Smith, B., & Goldberg, L. (2005). A terminological and ontological analysis of the NCI Thesaurus. *Methods of Information in Medicine*, *44*(4), 498-507.

- Chakrabarti, S. (2014). What's in a name? Compliance, adherence and concordance in chronic psychiatric disorders. *World Journal of Psychiatry, 4*(2), 30-36.
- Champion, V. L., Skinner, C. S., & Foster, J. L. (2000). The effects of standard care counseling or telephone/in-person counseling on beliefs, knowledge, and behavior related to mammography screening. *Oncology Nursing Forum, 27*(10), 1565-1571.
- Chan, D. S., Callahan, C. W., Sheets, S. J., Moreno, C. N., & Malone, F. J. (2003). An Internet-based store-and-forward video home telehealth system for improving asthma outcomes in children. *American Journal of Health System Pharmacy, 60*(19), 1976-1981.
- Chandrasegaran, S. K., Ramani, K., Sriram, R. D., Horváth, I., Bernard, A., Harik, R. F., & Gao, W. (2013). The evolution, challenges, and future of knowledge representation in product design systems. *Computer-Aided Design, 45*(2), 204-228.
- Chen, Z.-w., Fang, L.-z., Chen, L.-y., & Dai, H.-l. (2008). Comparison of an SMS text messaging and phone reminder to improve attendance at a health promotion center: a randomized controlled trial. *Journal of Zhejiang University Science B, 9*(1), 34-38.
- Chiarugi, F., Colantonio, S., Emmanouilidou, D., Moroni, D., Perticone, F., Sciacqua, A., & O., S. (2008). ECG and Echocardiography Processing for Decision Support in Heart Failure. *Computers in Cardiology, 35*, 649-652.
- Chlebowski, R. T., & Geller, M. L. (2007). Adherence to endocrine therapy for breast cancer. *Oncology, 71*(1-2), 1-9.
- Cho, J.-H., Chang, S.-A., Kwon, H.-S., Choi, Y.-H., Ko, S.-H., Moon, S.-D., . . . Kim, H.-S. (2006). Long-term effect of the Internet-based glucose monitoring system on HbA1c reduction and glucose stability. *Diabetes Care, 29*(12), 2625-2631.
- Christensen, A., Christrup, L. L., Fabricius, P. E., Chrostowska, M., Wronka, M., Narkiewicz, K., & Hansen, E. H. (2010). The impact of an electronic monitoring and reminder device on patient compliance with antihypertensive therapy: a randomized controlled trial. *Journal of Hypertension, 28*(1), 194-200.
- Christensen, H., Griffiths, K. M., & Jorm, A. F. (2004). Delivering interventions for depression by using the internet: randomised controlled trial. *BMJ, 328*(7434), 265.
- Christophe, F., Bernard, A., & Coatanéa, É. (2010). RFBS: A model for knowledge representation of conceptual design. *CIRP Annals, 59*(1), 155-158.
- Cimino, J. J. (1998). Desiderata for controlled medical vocabularies in the twenty-first century. *Methods of Information in Medicine, 37*(4-5), 394-403.
- Cimino, J. J., Hayamizu, T. F., Bodenreider, O., Davis, B., Stafford, G. A., & Ringwald, M. (2009). The caBIG terminology review process. *Journal of Biomedical Informatics, 42*(3), 571-580.
- Claborn, K. R., Leffingwell, T. R., Miller, M. B., Meier, E., & Stephens, J. R. (2014). Pilot study examining the efficacy of an electronic intervention to promote HIV medication adherence. *AIDS Care, 26*(3), 404-409.
- Colantonio, S., Conforti, D., Martinelli, M., Moroni, D., Perticone, F., Salvetti, O., & Sciacqua, A. (2008). *An intelligent and integrated platform for supporting the*

- management of chronic heart failure patients*. Paper presented at the Computers in Cardiology, Bologna, Italy.
- Cole, C. L., Kanter, A. S., Cummins, M., Vostinar, S., & Naeymi-Rad, F. (2004). Using a terminology server and consumer search phrases to help patients find physicians with particular expertise. *Studies in Health Technology and Informatics*, 107(Pt 1), 492-496.
- Copi, I. M., Cohen, C., & Flage, D. E. (2007). *Essentials of logic* (2nd ed.). New Jersey, United States of America: Pearson/Prentice Hall.
- Corcho, O., Fernández-López, M., & Gómez-Pérez, A. (2003). Methodologies, tools and languages for building ontologies. Where is their meeting point? *Data & Knowledge Engineering*, 46(1), 41-64.
- Coulter, A., Parsons, S., & Askham, J. (2008). *Where are the patients in decision-making about their own care*. Copenhagen, Denmark: WHO Regional Office for Europe.
- Coyle, D., Doherty, G., & Sharry, J. (2009). An evaluation of a solution focused computer game in adolescent interventions. *Clinical Child Psychology and Psychiatry*, 14(3), 345-360.
- Cramer, J. A., Roy, A., Burrell, A., Fairchild, C. J., Fuldeore, M. J., Ollendorf, D. A., & Wong, P. K. (2008). Medication compliance and persistence: terminology and definitions. *Value in Health*, 11(1), 44-47.
- Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., & Garcia-Cardenas, V. (2018). Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*, 8(1), e016982.
- Danaher, B. G., Boles, S. M., Akers, L., Gordon, J. S., & Severson, H. H. (2006). Defining participant exposure measures in Web-based health behavior change programs. *Journal of Medical Internet Research*, 8(3), e15.
- Dang, J., Hedayati, A., Hampel, K., & Toklu, C. (2008). An ontological knowledge framework for adaptive medical workflow. *Journal of Biomedical Informatics*, 41(5), 829-836.
- Dao, T.-T., Marin, F., & Tho, M. C. H. B. (2007). *Ontology of the musculo-skeletal system of the lower limbs*. Paper presented at the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Lyon, France.
- Davids, E. L., & Roman, N. V. (2014). A systematic review of the relationship between parenting styles and children's physical activity. *African Journal for Physical Health Education, Recreation and Dance*, 20(2), 228-246.
- Davidson, D. (1989). *The myth of the subjective*. United States: Oxford University Press Inc.
- Davis, R., Shrobe, H., & Szolovits, P. (1993). What is a knowledge representation? *AI Magazine*, 14(1), 17.
- De Geest, S., & Sabaté, E. (2003). Adherence to long-term therapies: evidence for action. *European Journal of Cardiovascular Nursing*, 2(4), 323-323.
- De Jong, C. C., Ros, W. J., & Schrijvers, G. (2014). The effects on health behavior and health outcomes of Internet-based asynchronous communication between health providers and patients with a chronic condition: a systematic review. *Journal of Medical Internet Research*, 16(1), e19.
- De Villiers, J. (2007). The interface of language and theory of mind. *Lingua*, 117(11), 1858-1878.

- Demissie, S., Silliman, R. A., & Lash, T. L. (2001). Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. *Journal of Clinical Oncology*, *19*(2), 322-328.
- Dezentjé, V. O., Van Blijderveen, N. J., Gelderblom, H., Putter, H., Van Herk-Sukel, M. P., Casparie, M. K., . . . Guchelaar, H.-J. (2010). Effect of concomitant CYP2D6 inhibitor use and tamoxifen adherence on breast cancer recurrence in early-stage breast cancer. *Journal of Clinical Oncology*, *28*(14), 2423-2429.
- DiClemente, R. J., Crosby, R. A., & Kegler, M. (2009). *Emerging theories in health promotion practice and research: Strategies for improving public health* (2nd ed.). San Francisco: Jossey-Bass.
- Doan, S., Kawazoe, A., Conway, M., & Collier, N. (2009). Towards role-based filtering of disease outbreak reports. *Journal of Biomedical Informatics*, *42*(5), 773-780.
- Doggrell, S. A. (2011). Adherence to oral endocrine treatments in women with breast cancer: can it be improved? *Breast Cancer Research and Treatment*, *129*(2), 299-308.
- Downer, S. R., Meara, J. G., & Da Costa, A. C. (2005). Use of SMS text messaging to improve outpatient attendance. *Medical Journal of Australia*, *183*(7), 366-368.
- Doyle, T. J., Ma, H., Groseclose, S. L., & Hopkins, R. S. (2005). PHSkb: A knowledgebase to support notifiable disease surveillance. *BMC Medical Informatics and Decision Making*, *5*(1), 27.
- Dretske, F. I. (1980). The intentionality of cognitive states. *Midwest Studies in Philosophy*, *5*(1), 281-294.
- Dunbar-Jacob, J., Houze, M. P., Kramer, C., Luyster, F., & McCall, M. (2010). Adherence to medical advice: Processes and measurement. In A. Steptoe (Ed.), *Handbook of Behavioral Medicine* (pp. 83-95). New York, NY: Springer.
- El-Gayar, O., Timsina, P., Nawar, N., & Eid, W. (2013). A systematic review of IT for diabetes self-management: are we there yet? *International Journal of Medical Informatics*, *82*(8), 637-652.
- Elkin, P. L., Brown, S. H., Bauer, B. A., Husser, C. S., Carruth, W., Bergstrom, L. R., & Wahner-Roedler, D. L. (2005). A controlled trial of automated classification of negation from clinical notes. *BMC Medical Informatics and Decision Making*, *5*(1), 13.
- Ellis, S. E., Speroff, T., Dittus, R. S., Brown, A., Pichert, J. W., & Elasy, T. A. (2004). Diabetes patient education: a meta-analysis and meta-regression. *Patient Education and Counseling*, *52*(1), 97-105.
- Espie, C. A., Kyle, S. D., Williams, C., Ong, J. C., Douglas, N. J., Hames, P., & Brown, J. (2012). A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep*, *35*(6), 769-781.
- Fabrega, Jr, H. (2000). The feeling of what happens: Body and emotion in the making of consciousness. *Psychiatric Services*, *51*(12), 1579-1579.
- Fabrigar, L. R., Petty, R. E., Smith, S. M., & Crites Jr, S. L. (2006). Understanding knowledge effects on attitude-behavior consistency: The role of relevance, complexity, and amount of knowledge. *Journal of Personality and Social Psychology*, *90*(4), 556-577.

- Farion, K., Michalowski, W., Wilk, S., O'sullivan, D., Rubin, S., & Weiss, D. (2009). Clinical decision support system for point of care use--ontology-driven design and software implementation. *Methods of Information in Medicine*, 48(4), 381-390.
- Farmer, T., Brook, G., McSorley, J., Murphy, S., & Mohamed, A. (2014). Using short message service text reminders to reduce 'did not attend' rates in sexual health and HIV appointment clinics. *International Journal of STD & AIDS*, 25(4), 289-293.
- Feldman, P. H., Murtaugh, C. M., Pezzin, L. E., McDonald, M. V., & Peng, T. R. (2005). Just-in-time evidence-based e-mail "reminders" in home health care: Impact on patient outcomes. *Health Services Research*, 40(3), 865-886.
- Fenton, S., Giannangelo, K., Kallem, C., & Scichilone, R. (2007). Data standards, data quality, and interoperability. *Journal of AHIMA*, 78(2), 65-68.
- Fernández-López, M., & Asuncion, G.-P. (2002). Overview of methodologies for building ontologies. *The Knowledge Engineering Review*, 17(2), 129-156
- Fernández-López, M., Gómez-Pérez, A., & Juristo, N. (1997). *Methontology: from ontological art towards ontological engineering*. USA: Stanford.
- Fernandez, J., Martinez-Selles, M., Correa, C., Arredondo, M., Nicolosi, G., Koumpouros, Y., & Martinelli, E. (2004). *Self-maintained collaborative and multidisciplinary system for knowledge management in cardiology*. Paper presented at the Computers in Cardiology, 2004, Chicago, IL, USA.
- Fink, A. K., Gurwitz, J., Rakowski, W., Guadagnoli, E., & Silliman, R. A. (2004). Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor—positive breast cancer. *Journal of Clinical Oncology*, 22(16), 3309-3315.
- Fisher, J., & Clayton, M. (2012). Who gives a tweet: assessing patients' interest in the use of social media for health care. *Worldviews on Evidence-Based Nursing*, 9(2), 100-108.
- Fleming, C. A., McCarthy, K., Ryan, C., McCarthy, A., O'Reilly, S., O'Mahony, D., . . . Corrigan, M. A. (2017). Evaluation of discordance in primary tumor and lymph node response after neoadjuvant therapy in breast cancer. *Clinical Breast Cancer*, 18(2), e255-e261.
- Fonda, S. J., McMahan, G. T., Gomes, H. E., Hickson, S., & Conlin, P. R. (2009). Changes in diabetes distress related to participation in an internet-based diabetes care management program and glycemic control. *Journal of Diabetes Science and Technology*, 3(1), 117-124.
- Francesconi, E., Montemagni, S., Peters, W., & Tiscornia, D. (2010). Integrating a bottom-up and top-down methodology for building semantic resources for the multilingual legal domain *Semantic Processing of Legal Texts* (pp. 95-121): Springer.
- Franklin, V., Greene, A., Waller, A., Greene, S., & Pagliari, C. (2008). Patients' engagement with "Sweet Talk"—a text messaging support system for young people with diabetes. *Journal of Medical Internet Research*, 10(2), e20.
- Franklin, V. L., Waller, A., Pagliari, C., & Greene, S. A. (2006). A randomized controlled trial of Sweet Talk, a text-messaging system to support young people with diabetes. *Diabetic Medicine*, 23(12), 1332-1338.
- Free, C., Phillips, G., Galli, L., Watson, L., Felix, L., Edwards, P., . . . Haines, A. (2013). The effectiveness of mobile-health technology-based health behaviour change or

- disease management interventions for health care consumers: a systematic review. *PLoS Medicine*, 10(1), e1001362.
- Friedl, R., Klas, W., Westermann, U., Rose, T., Tremper, J., Stracke, S., . . . Preisack, M. (2003). The CardioOP-Data Clas (CDC). Development and application of a thesaurus for content management and multi-user teleteaching in cardiac surgery. *Methods of Information in Medicine*, 42(1), 68-78.
- Furber, G. V., Crago, A. E., Meehan, K., Sheppard, T. D., Hooper, K., Abbot, D. T., . . . Skene, C. (2011). How adolescents use SMS (short message service) to micro-coordinate contact with youth mental health outreach services. *Journal of Adolescent Health*, 48(1), 113-115.
- Gabriele, J. M., Carpenter, B. D., Tate, D. F., & Fisher, E. B. (2011). Directive and nondirective e-coach support for weight loss in overweight adults. *Annals of Behavioral Medicine*, 41(2), 252-263.
- Galiano-Castillo, N., Ariza-García, A., Cantarero-Villanueva, I., Fernández-Lao, C., Sánchez-Salado, C., & Arroyo-Morales, M. (2014). Agreement between telerehabilitation involving caregivers and face-to-face clinical assessment of lymphedema in breast cancer survivors. *Supportive Care in Cancer*, 22(1), 253-258.
- Garde, S., Knaup, P., Hovenga, E., & Heard, S. (2007). Domain knowledge governance for openEHR archetypes. *Methods of Information in Medicine*, 46, 332-343.
- Geara, F., Abbas, J., Bikhazi, K., Salem, Z., Nagi El Saghir, M., & Tawil, A. (2006). *Guidelines for the management of breast cancer*. Retrieved from Beirut:
- Gelder, T. (1990). Compositionality: a connectionist variation on a classical theme. *Cognitive Science*, 14(3), 355-384.
- Ginsburg, O. M., Chowdhury, M., Wu, W., Chowdhury, M. T. I., Pal, B. C., Hasan, R., . . . Al-Mansur, R. (2014). An mHealth model to increase clinic attendance for breast symptoms in rural Bangladesh: can bridging the digital divide help close the cancer divide? *The Oncologist*, 19(2), 177-185.
- Glanz, K., & Bishop, D. B. (2010). The role of behavioral science theory in development and implementation of public health interventions. *Annual Review of Public Health*, 31, 399-418.
- Glasgow, R., Christiansen, S. M., Kurz, D., King, D. K., Woolley, T., Faber, A. J., . . . Dickman, J. (2011). Engagement in a diabetes self-management website: usage patterns and generalizability of program use. *Journal of Medical Internet Research*, 13(1), e9.
- Glasgow, R. E., Kurz, D., King, D., Dickman, J. M., Faber, A. J., Halterman, E., . . . Estabrooks, P. A. (2012). Twelve-month outcomes of an Internet-based diabetes self-management support program. *Patient Education and Counseling*, 87(1), 81-92.
- Glynn, S. M., Randolph, E. T., Garrick, T., & Lui, A. (2010). A proof of concept trial of an online psychoeducational program for relatives of both veterans and civilians living with schizophrenia. *Psychiatric Rehabilitation Journal*, 33(4), 278-287.
- Gold, J., Lim, M. S., Hellard, M. E., Hocking, J. S., & Keogh, L. (2010). What's in a message? Delivering sexual health promotion to young people in Australia via text messaging. *BMC Public Health*, 10(1), 792.

- Gómez-Pérez, A., Fernández-López, M., & Corcho, O. (2006). *Ontological Engineering: with examples from the areas of Knowledge Management, e-Commerce and the Semantic Web* (1st ed.). Berlin, Heidelberg: Springer Science & Business Media.
- Gómez-Pérez, A., Fernández, M., & Vicente, A. d. (1996). *Towards a method to conceptualize domain ontologies*. Paper presented at the 12th European Conference on Artificial Intelligence, Budapest, Rumania.
- Goossen, W., Goossen-Baremans, A., & Van Der Zel, M. (2010). Detailed clinical models: a review. *Healthcare Informatics Research*, 16(4), 201-214.
- Gotay, C., & Dunn, J. (2011). Adherence to long-term adjuvant hormonal therapy for breast cancer. *Expert Review of Pharmacoeconomics & Outcomes Research*, 11(6), 709-715.
- Granhölm, E., Ben-Zeev, D., Link, P. C., Bradshaw, K. R., & Holden, J. L. (2011). Mobile Assessment and Treatment for Schizophrenia (MATS): a pilot trial of an interactive text-messaging intervention for medication adherence, socialization, and auditory hallucinations. *Schizophrenia Bulletin*, 38(3), 414-425.
- Gray, J. E., Safran, C., Davis, R. B., Pompilio-Weitzner, G., Stewart, J. E., Zaccagnini, L., & Pursley, D. (2000). Baby CareLink: using the internet and telemedicine to improve care for high-risk infants. *Pediatrics*, 106(6), 1318-1324.
- Green, B. B., Cook, A. J., Ralston, J. D., Fishman, P. A., Catz, S. L., Carlson, J., . . . Thompson, R. S. (2008). Effectiveness of home blood pressure monitoring, web communication, and pharmacist care on hypertension control: a randomized controlled trial. *JAMA*, 299(24), 2857-2867.
- Greene, J. A., Choudhry, N. K., Kilabuk, E., & Shrank, W. H. (2011). Online social networking by patients with diabetes: a qualitative evaluation of communication with Facebook. *Journal of General Internal Medicine*, 26(3), 287-292.
- Greysen, S. R., Khanna, R. R., Jacolbia, R., Lee, H. M., & Auerbach, A. D. (2014). Tablet computers for hospitalized patients: a pilot study to improve inpatient engagement. *Journal of Hospital Medicine*, 9(6), 396-399.
- Gruber, T. R. (1995). Toward principles for the design of ontologies used for knowledge sharing? *International Journal of Human-Computer Studies*, 43(5), 907-928.
- Grunfeld, E. A., Hunter, M. S., Sikka, P., & Mittal, S. (2005). Adherence beliefs among breast cancer patients taking tamoxifen. *Patient Education and Counseling*, 59(1), 97-102.
- Grüninger, M., & Fox, M. S. (1995). The role of competency questions in enterprise engineering. In A. Rolstadås (Ed.), *Benchmarking—Theory and Practice* (pp. 22-31). Boston, MA: Springer.
- Gustafson, D. H., Hawkins, R., Pingree, S., McTavish, F., Arora, N. K., Mendenhall, J., . . . Stewart, J. (2001). Effect of computer support on younger women with breast cancer. *Journal of General Internal Medicine*, 16(7), 435-445.
- Gustafson, D. H., McTavish, F. M., Stengle, W., Ballard, D., Hawkins, R., Shaw, B. R., . . . Chen, W. C. (2005). Use and impact of eHealth system by low-income women with breast cancer. *Journal of Health Communication*, 10(S1), 195-218.
- Güth, U., Huang, D., Schötzau, A., Zanetti-Dällenbach, R., Holzgreve, W., Bitzer, J., & Wight, E. (2008). Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer. *British Journal of Cancer*, 99(3), 428-433.

- Gutierrez, N., Kindratt, T. B., Pagels, P., Foster, B., & Gimpel, N. E. (2014). Health literacy, health information seeking behaviors and internet use among patients attending a private and public clinic in the same geographic area. *Journal of Community Health, 39*(1), 83-89.
- Habibović, M., Cuijpers, P., Alings, M., van der Voort, P., Theuns, D., Bouwels, L., . . . Pedersen, S. (2014). Attrition and adherence in a WEB-Based Distress Management Program for Implantable Cardioverter defibrillator Patients (WEBCARE): randomized controlled trial. *Journal of Medical Internet Research, 16*(2), e52.
- Hadji, P. (2010). Improving compliance and persistence to adjuvant tamoxifen and aromatase inhibitor therapy. *Critical Reviews in Oncology/Hematology, 73*(2), 156-166.
- Haider, B., Schmidt, R., Schweiger, C., Forstner, T., Labek, A., & Lampl, C. (2014). Medication adherence in patients with dementia: an Austrian cohort study. *Alzheimer Disease & Associated Disorders, 28*(2), 128-133.
- Hamine, S., Gerth-Guyette, E., Faulx, D., Green, B. B., & Ginsburg, A. S. (2015). Impact of mHealth chronic disease management on treatment adherence and patient outcomes: a systematic review. *Journal of Medical Internet Research, 17*(2), e52.
- Hanna, J., Joseph, E., Brochhausen, M., & Hogan, W. R. (2013). Building a drug ontology based on RxNorm and other sources. *Journal of Biomedical Semantics, 4*(1), 44.
- Harman, G. (1973). *Thought*: Princeton University Press
- Harris, L. T., Lehavot, K., Huh, D., Yard, S., Andrasik, M. P., Dunbar, P. J., & Simoni, J. M. (2010). Two-way text messaging for health behavior change among human immunodeficiency virus–positive individuals. *Telemedicine and E Health, 16*(10), 1024-1029.
- Harris, M. A., Clark, J., Ireland, A., Lomax, J., Ashburner, M., Foulger, R., . . . White, R. (2004). The Gene Ontology (GO) database and informatics resource. *Nucleic Acids Res, 32*(Database issue), D258-261. doi:10.1093/nar/gkh036
- Harris, S., Sheth, S. A., & Cohen, M. S. (2008). Functional neuroimaging of belief, disbelief, and uncertainty. *Annals of Neurology, 63*(2), 141-147.
- Haschler, I., Skonetzki, S., Gausepohl, H., Linderkamp, O., & Wetter, T. (2004). Evolution of the HELEN representation for managing clinical practice guidelines. *Methods. Inf. Med, 43*(4), 413-426.
- Hasin, D. S., Aharonovich, E., & Greenstein, E. (2014). HealthCall for the smartphone: technology enhancement of brief intervention in HIV alcohol dependent patients. *Addiction Science & Clinical Practice, 9*(1), 5.
- Hastings, J., Ceusters, W., Smith, B., & Mulligan, K. (2011). *Dispositions and processes in the emotion ontology*. Paper presented at the International Conference on Biomedical Ontology, Buffalo, NY, USA.
- Hastings, J., Smith, B., Ceusters, W., Jensen, M., & Mulligan, K. (2012). The mental functioning ontology.
- Hastings, J., Smith, B., Ceusters, W., Jensen, M., & Mulligan, K. (2012). *Representing mental functioning: Ontologies for mental health and disease*. Paper presented at the ICBO 2012: 3rd International Conference on Biomedical Ontology.

- Heisler, M., Choi, H., Palmisano, G., Mase, R., Richardson, C., Fagerlin, A., . . . An, L. C. (2014). Comparison of community health worker-led diabetes medication decision-making support for low-income Latino and African American adults with diabetes using e-health tools versus print materials: a randomized, controlled trial. *Annals of Internal Medicine*, *161*(Supplement 10), S13-S22.
- Helander, E., Kaipainen, K., Korhonen, I., & Wansink, B. (2014). Factors related to sustained use of a free mobile app for dietary self-monitoring with photography and peer feedback: retrospective cohort study. *Journal of Medical Internet Research*, *16*(4), e109.
- Henry, N. L., Skaar, T. C., Dantzer, J., Li, L., Kidwell, K., Gersch, C., . . . Oesterreich, S. (2013). Genetic associations with toxicity-related discontinuation of aromatase inhibitor therapy for breast cancer. *Breast Cancer Research and Treatment*, *138*(3), 807-816.
- Herbst, N., Voderholzer, U., Thiel, N., Schaub, R., Knaevelsrud, C., Stracke, S., . . . Külz, A. K. (2014). No talking, just writing! efficacy of an internet-based cognitive behavioral therapy with exposure and response prevention in obsessive compulsive disorder. *Psychotherapy and Psychosomatics*, *83*(3), 165-175.
- Hershman, D. L., Kushi, L. H., Shao, T., Buono, D., Kershenbaum, A., Tsai, W.-Y., . . . Neugut, A. I. (2010). Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *Journal of Clinical Oncology*, *28*(27), 4120-4128.
- Hess, L. M., Raebel, M. A., Conner, D. A., & Malone, D. C. (2006). Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Annals of Pharmacotherapy*, *40*(7-8), 1280-1288.
- Heyworth, L., Paquin, A. M., Clark, J., Kamenker, V., Stewart, M., Martin, T., & Simon, S. R. (2014). Engaging patients in medication reconciliation via a patient portal following hospital discharge. *Journal of the American Medical Informatics Association*, *21*(e1), e157-e162.
- Hoehndorf, R., Dumontier, M., & Gkoutos, G. V. (2012). Evaluation of research in biomedical ontologies. *Briefings in Bioinformatics*, *14*(6), 696-712.
- Hofer, B. K. (2004). Epistemological understanding as a metacognitive process: thinking aloud during online searching. *Educational Psychologist*, *39*(1), 43-55.
- Horridge, M., & Bechhofer, S. (2011). The owl api: a java api for owl ontologies. *Semantic Web*, *2*(1), 11-21.
- Horridge, M., Knublauch, H., Rector, A., Stevens, R., & Wroe, C. (2004). A practical guide to building owl ontologies using protégé 4 and co-ode tools edition 1. 2. *The University of Manchester*, *107*, e4.
- Houston, T. K., Cooper, L. A., & Ford, D. E. (2002). Internet support groups for depression: a 1-year prospective cohort study. *American Journal of Psychiatry*, *159*(12), 2062-2068.
- Howland, J. L., Wright, T. C., Boughan, R. A., & Roberts, B. C. (2009). How scholarly is google scholar? a comparison to library databases. *College & Research Libraries*, *70*(3), 227-234.

- Hugtenburg, J. G., Timmers, L., Elders, P., Vervloet, M., & van Dijk, L. (2013a). Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. *Patient Prefer Adherence*, 7, 675-682.
- Hugtenburg, J. G., Timmers, L., Elders, P. J., Vervloet, M., & van Dijk, L. (2013b). Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. *Patient preference and adherence*, 7, 675.
- Huiart, L., Dell'Aniello, S., & Suissa, S. (2011). Use of tamoxifen and aromatase inhibitors in a large population-based cohort of women with breast cancer. *British Journal of Cancer*, 104(10), 1558-1563.
- Hume, D. (2003). *A treatise of human nature*: Courier Corporation.
- Hunter, C. M., Peterson, A. L., Alvarez, L. M., Poston, W. C., Brundige, A. R., Haddock, C. K., . . . Foreyt, J. P. (2008). Weight management using the internet: a randomized controlled trial. *American Journal of Preventive Medicine*, 34(2), 119-126.
- Hurling, R., Catt, M., De Boni, M., Fairley, B., Hurst, T., Murray, P., . . . Sodhi, J. (2007). Using internet and mobile phone technology to deliver an automated physical activity program: randomized controlled trial. *Journal of Medical Internet Research*, 9(2), e7.
- I. Hasler, S. S., Gausepohl HJ, Linderkamp O, Wetter T. (2004). Evolution of the HELEN Representation for Managing Clinical PRactice Guidelines. *Clinical journal of oncology nursing*.
- Idriss, S. Z., Kvedar, J. C., & Watson, A. J. (2009). The role of online support communities: benefits of expanded social networks to patients with psoriasis. *Archives of Dermatology*, 145(1), 46-51.
- Ingle, J. N., & Suman, V. J. (2003). Aromatase inhibitors versus tamoxifen for management of postmenopausal breast cancer in the advanced disease and neoadjuvant settings. *The Journal of Steroid Biochemistry and Molecular Biology*, 86(3-5), 313-319.
- Iqbal, R., Murad, M. A. A., Mustapha, A., & Sharef, N. M. (2013). An analysis of ontology engineering methodologies: a literature review. *Research Journal of Applied Sciences, Engineering and Technology*, 6(16), 2993-3000.
- Iqbal, R., Mustapha, A., & Mohd. Yusoff, Z. (2013). An experience of developing Quran ontology with contextual information support. *Multicultural Education & Technology Journal*, 7(4), 333-343.
- Irvine, A. B., Gelatt, V. A., Seeley, J. R., Macfarlane, P., & Gau, J. M. (2013). Web-based intervention to promote physical activity by sedentary older adults: randomized controlled trial. *Journal of Medical Internet Research*, 15(2), e19.
- Islam, R., Brandeau, M., & Das, A. (2006). *A knowledge representation of local pandemic influenza planning models*. Paper presented at the AMIA. Annual Symposium proceedings.
- Iuga, A. O., & McGuire, M. J. (2014). Adherence and health care costs. *Risk Management and Healthcare Policy*, 7, 35.
- Iverson, S. A., Howard, K. B., & Penney, B. K. (2008). Impact of internet use on health-related behaviors and the patient-physician relationship: a survey-based study and review. *The Journal of the American Osteopathic Association*, 108(12), 699-711.

- James, W. (1904). Does consciousness' exist? *The Journal of Philosophy, Psychology and Scientific Methods*, 1(18), 477-491.
- Jelsma, D., Geuze, R. H., Mombarg, R., & Smits-Engelsman, B. C. (2014). The impact of Wii Fit intervention on dynamic balance control in children with probable developmental coordination disorder and balance problems. *Human Movement Science*, 33, 404-418.
- Johnson, F., & Wardle, J. (2011). The association between weight loss and engagement with a web-based food and exercise diary in a commercial weight loss programme: a retrospective analysis. *International Journal of Behavioral Nutrition and Physical Activity*, 8(1), 83.
- Johnston, J. D., Massey, A. P., & DeVaneaux, C. A. (2012). Innovation in weight loss programs: a 3-dimensional virtual-world approach. *Journal of Medical Internet Research*, 14(5), e120.
- Johnston, S. R., & Dowsett, M. (2003). Aromatase inhibitors for breast cancer: lessons from the laboratory. *Nature Reviews Cancer*, 3(11), 821-831.
- Jones, D., Bench-Capon, T., & Visser, P. (1998). *Methodologies for ontology development*. Paper presented at the IT and KNOWS Conference of the 15th IFIP World Computer Congress, Budapest.
- Jovic, A., Prcela, M., & Gamberger, D. (2007). *Ontologies in medical knowledge representation*. Paper presented at the 29th International Conference on Information Technology Interfaces, Cavtat, Croatia.
- Kadokia, K. C., Kidwell, K. M., Seewald, N. J., Snyder, C. F., Flockhart, D. A., Carpenter, J. S., . . . Stearns, V. (2016). Crossover from one aromatase inhibitor (AI) to another in the exemestane and letrozole pharmacogenetics (ELPh) trial. *Journal of Clinical Oncology*, 34(Supplement 3), 158-158.
- Kadokia, K. C., Snyder, C. F., Kidwell, K. M., Seewald, N. J., Flockhart, D. A., Skaar, T. C., . . . Carpenter, J. S. (2016). Patient-reported outcomes and early discontinuation in aromatase inhibitor-treated postmenopausal women with early stage breast cancer. *The Oncologist*, 21(5), 539-546.
- Kahn, K. L., Schneider, E. C., Malin, J. L., Adams, J. L., & Epstein, A. M. (2007). Patient centered experiences in breast cancer: predicting long-term adherence to tamoxifen use. *Medical Care*, 45(5), 431-439.
- Kaplan, K., Salzer, M. S., Solomon, P., Brusilovskiy, E., & Cousounis, P. (2011). Internet peer support for individuals with psychiatric disabilities: a randomized controlled trial. *Social Science & Medicine*, 72(1), 54-62.
- Kardas, P., Lewek, P., & Matyjaszczyk, M. (2013). Determinants of patient adherence: a review of systematic reviews. *Frontiers in Pharmacology*, 4, 91.
- Kato, P. M., Cole, S. W., Bradlyn, A. S., & Pollock, B. H. (2008). A video game improves behavioral outcomes in adolescents and young adults with cancer: a randomized trial. *Pediatrics*, 122(2), e305-e317.
- Kaufman, G., & Birks, Y. (2009). Strategies to improve patients' adherence to medication. *Nursing Standard*, 23(49), 51.
- Kay-Lambkin, F., Baker, A., Lewin, T., & Carr, V. (2011). Acceptability of a clinician-assisted computerized psychological intervention for comorbid mental health and substance use problems: treatment adherence data from a randomized controlled trial. *Journal of Medical Internet Research*, 13(1), e11.

- Kazakov, Y., Krötzsch, M., & Simancik, F. (2014). The incredible ELK: from polynomial procedures to efficient reasoning with EL ontologies *Journal of Automated Reasoning*, 53(1), 1-61.
- Kazantzis, N. E., Reinecke, M. A., & Freeman, A. E. (2010). *Cognitive and behavioral theories in clinical practice*. New York, NY, US: Guilford Press.
- Kennedy, C. M., Powell, J., Payne, T. H., Ainsworth, J., Boyd, A., & Buchan, I. (2012). Active assistance technology for health-related behavior change: an interdisciplinary review. *Journal of Medical Internet Research*, 14(3), e80.
- Kerr, J., Patrick, K., Norman, G., Stein, M. B., Calfas, K., Zabinski, M., & Robinson, A. (2008). Randomized control trial of a behavioral intervention for overweight women: impact on depressive symptoms. *Depression and Anxiety*, 25(7), 555-558.
- Keyserling, T. C., Sheridan, S. L., Draeger, L. B., Finkelstein, E. A., Gizlice, Z., Kruger, E., . . . Evenson, K. R. (2014). A comparison of live counseling with a web-based lifestyle and medication intervention to reduce coronary heart disease risk: a randomized clinical trial. *JAMA Internal Medicine*, 174(7), 1144-1157.
- Kim, C.-J., & Kang, D.-H. (2006). Utility of a web-based intervention for individuals with type 2 diabetes: the impact on physical activity levels and glycemic control. *Computers Informatics Nursing*, 24(6), 337-345.
- Kim, H.-S., & Song, M.-S. (2008). Technological intervention for obese patients with type 2 diabetes. *Applied Nursing Research*, 21(2), 84-89.
- Kim, H. S., & Jeong, H. S. (2007). A nurse short message service by cellular phone in type-2 diabetic patients for six months. *Journal of Clinical Nursing*, 16(6), 1082-1087.
- Kim, S.-I., & Kim, H.-S. (2008). Effectiveness of mobile and internet intervention in patients with obese type 2 diabetes. *International Journal of Medical Informatics*, 77(6), 399-404.
- King, S. N., Davis, L., Lehman, J. J., & Ruddy, B. H. (2012). A model for treating voice disorders in school-age children within a video gaming environment. *Journal of Voice*, 26(5), 656-663.
- Kinney, A. Y., Boonyasiriwat, W., Walters, S. T., Pappas, L. M., Stroup, A. M., Schwartz, M. D., . . . Boucher, K. M. (2014). Telehealth personalized cancer risk communication to motivate colonoscopy in relatives of patients with colorectal cancer: the family CARE randomized controlled trial. *Journal of Clinical Oncology*, 32(7), 654-662.
- Kirk, M. C., & Hudis, C. A. (2008). Insight into barriers against optimal adherence to oral hormonal therapy in women with breast cancer. *Clinical Breast Cancer*, 8(2), 155-161.
- Kiselev, A. R., Gridnev, V. I., Shvartz, V. A., Posnenkova, O. M., & Dovgalevsky, P. Y. (2012). Active ambulatory care management supported by short message services and mobile phone technology in patients with arterial hypertension. *Journal of the American Society of Hypertension*, 6(5), 346-355.
- Kornman, K. P., Shrewsbury, V. A., Chou, A. C., Nguyen, B., Lee, A., O'Connor, J., . . . Shah, S. (2010). Electronic therapeutic contact for adolescent weight management: the Loozit study. *Telemedicine and E Health*, 16(6), 678-685.

- Krishna, S., Francisco, B. D., Balas, E. A., König, P., Graff, G. R., & Madsen, R. W. (2003). Internet-enabled interactive multimedia asthma education program: a randomized trial. *Pediatrics*, *111*(3), 503-510.
- Kristin, A. Z., TAVIS, S. C., MICHAEL, S., PSYD, K., RUFF, M., STEVEN FLOWERS, M., & LINDA, E. C. (2014). A Randomized Wait-List Controlled Trial of Feasibility and Efficacy of an Online MindfulnessYBased Cancer Recovery Program: The eTherapy for Cancer AppLying Mindfulness Trial. *Psychosomatic Medicine*, *76*, 00Y00.
- Kulkarni, A., Wright, E., & Kingdom, J. (2014). Web-based education and attitude to delivery by caesarean section in nulliparous women. *Journal of Obstetrics and Gynaecology Canada*, *36*(9), 768-775.
- Kwon, H.-S., Cho, J.-H., Kim, H.-S., Song, B.-R., Ko, S.-H., Lee, J.-M., . . . Cha, B.-Y. (2004). Establishment of blood glucose monitoring system using the internet. *Diabetes Care*, *27*(2), 478-483.
- Ahmadian, R. C., & Keizer, N. (2009). Facilitating Pre-Operative Assessment Guidelines Representation using SNOMED CT. *Journal of biomedical informatics*, *2010*(43), 883-890.
- Lam, W. Y., & Fresco, P. (2015). Medication adherence measures: an overview. *BioMed Research International*, *2015*, 1-12. doi:10.1155/2015/217047
- Lancioni, G. E., Singh, N. N., O'Reilly, M. F., Sigafos, J., Ferlisi, G., Ferrarese, G., . . . Oliva, D. (2012). Technology-aided programs for assisting communication and leisure engagement of persons with amyotrophic lateral sclerosis: two single-case studies. *Research in Developmental Disabilities*, *33*(5), 1605-1614.
- Lash, T. L., Fox, M. P., Westrup, J. L., Fink, A. K., & Silliman, R. A. (2006). Adherence to tamoxifen over the five-year course. *Breast Cancer Research and Treatment*, *99*(2), 215-220.
- Lee, C., Gray, S. W., & Lewis, N. (2010). Internet use leads cancer patients to be active health care consumers. *Patient Education and Counseling*, *81*, S63-S69.
- Lee, T., Yeh, Y., Liu, C., & Chen, P. (2007). Development and evaluation of a patient-oriented education system for diabetes management. *International Journal of Medical Informatics*, *76*(9), 655-663.
- Lenert, L., Norman, G. J., Mailhot, M., & Patrick, K. (2005). A framework for modeling health behavior protocols and their linkage to behavioral theory. *Journal of Biomedical Informatics*, *38*(4), 270-280.
- Lester, R. T., Ritvo, P., Mills, E. J., Kariri, A., Karanja, S., Chung, M. H., . . . Najafzadeh, M. (2010). Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. *The Lancet*, *376*(9755), 1838-1845.
- Leventhal, H., & Cameron, L. (1987). Behavioral theories and the problem of compliance. *Patient Education and Counseling*, *10*(2), 117-138.
- Lewis, N., Gray, S. W., Freres, D. R., & Hornik, R. C. (2009). Examining cross-source engagement with cancer-related information and its impact on doctor-patient relations. *Health Communication*, *24*(8), 723-734.
- Liew, S., Tong, S. F., Lee, V. K. M., Ng, C. J., Leong, K. C., & Teng, C. L. (2009). Text messaging reminders to reduce non-attendance in chronic disease follow-up: a clinical trial. *The British Journal of General Practice*, *59*(569), 916-920.

- Lin, J. H., Zhang, S. M., & Manson, J. E. (2011). Predicting adherence to tamoxifen for breast cancer adjuvant therapy and prevention. *Cancer Prevention Research, 4*(9), 1360-1365.
- Lorig, K. R., Ritter, P. L., Laurent, D. D., & Plant, K. (2006). Internet-based chronic disease self-management: a randomized trial. *Medical Care, 44*(11), 964-971.
- Lusignan, S. (2003). What is primary care informatics? *Journal of the American Medical Informatics Association, 10*(4), 304-309.
- Ma, A. M. T., Barone, J., Wallis, A. E., Wu, N. J., Garcia, L. B., Estabrook, A., . . . Tartter, P. I. (2008). Noncompliance with adjuvant radiation, chemotherapy, or hormonal therapy in breast cancer patients. *The American Journal of Surgery, 196*(4), 500-504.
- Magnezi, R., Bergman, Y. S., & Grosberg, D. (2014). Online activity and participation in treatment affects the perceived efficacy of social health networks among patients with chronic illness. *Journal of Medical Internet Research, 16*(1), e12.
- Mair, F. S., Hiscock, J., & Beaton, S. C. (2008). Understanding factors that inhibit or promote the utilization of telecare in chronic lung disease. *Chronic Illness, 4*(2), 110-117.
- Martyn, H., & Gallant, L. M. (2012). Over 50 and wired: web-based stakeholder communication. *First Monday, 17*(6).
- Maslow, A., & Lewis, K. J. (1987). Maslow's hierarchy of needs. *Salenger Incorporated, 14*, 987.
- Maurice, A., Howell, A., Evans, D. G., O'Neil, A. C., & Scobie, S. (2006). Predicting compliance in a breast cancer prevention trial. *The Breast Journal, 12*(5), 446-450.
- McCann, L., Maguire, R., Miller, M., & Kearney, N. (2009). Patients' perceptions and experiences of using a mobile phone-based advanced symptom management system (ASyMS©) to monitor and manage chemotherapy related toxicity. *European Journal of Cancer Care, 18*(2), 156-164.
- McCarrier, K. P., Ralston, J. D., Hirsch, I. B., Lewis, G., Martin, D. P., Zimmerman, F. J., & Goldberg, H. I. (2009). Web-based collaborative care for type 1 diabetes: a pilot randomized trial. *Diabetes Technology & Therapeutics, 11*(4), 211-217.
- McCowan, C., Shearer, J., Donnan, P., Dewar, J., Crilly, M., Thompson, A., & Fahey, T. (2008). Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *British Journal of Cancer, 99*(11), 1763-1768.
- McGrath, P. (2002). Creating a language for 'spiritual pain' through research: a beginning. *Supportive Care in Cancer, 10*(8), 637-646.
- McInnes, D. K., Petrakis, B. A., Gifford, A. L., Rao, S. R., Houston, T. K., Asch, S. M., & O'Toole, T. P. (2014). Retaining homeless veterans in outpatient care: a pilot study of mobile phone text message appointment reminders. *American Journal of Public Health, 104*(S4), S588-S594.
- McInnes, D. K., Solomon, J. L., Shimada, S. L., Petrakis, B. A., Bokhour, B. G., Asch, S. M., . . . Gifford, A. L. (2013). Development and evaluation of an internet and personal health record training program for low-income patients with HIV or hepatitis C. *Medical Care, 51*, S62-S66.

- McKay, H., Danaher, B., Seeley, J., Lichtenstein, E., & Gau, J. (2008). Comparing two web-based smoking cessation programs: randomized controlled trial. *Journal of Medical Internet Research*, *10*(5), e40.
- McKay, H. G., Glasgow, R. E., Feil, E. G., Boles, S. M., & Barrera Jr, M. (2002). Internet-based diabetes self-management and support: initial outcomes from the diabetes network project. *Rehabilitation Psychology*, *47*(1), 31.
- McKay, H. G., King, D., Eakin, E. G., Seeley, J. R., & Glasgow, R. E. (2001). The diabetes network internet-based physical activity intervention. *Diabetes Care*, *24*(8), 1328-1334.
- McMahon, G. T., Gomes, H. E., Hohne, S. H., Hu, T. M.-J., Levine, B. A., & Conlin, P. R. (2005). Web-based care management in patients with poorly controlled diabetes. *Diabetes Care*, *28*(7), 1624-1629.
- Meghani, S. H., & Houldin, A. D. (2007). *The meanings of and attitudes about cancer pain among African Americans*. Paper presented at the Oncology Nursing Forum.
- Meglic, M., Furlan, M., Kuzmanic, M., Kozel, D., Baraga, D., Kuhar, I., . . . Dernovsek, M. Z. (2010). Feasibility of an eHealth service to support collaborative depression care: results of a pilot study. *Journal of Medical Internet Research*, *12*(5), e63.
- Meichenbaum, D., & Turk, D. C. (1987). *Facilitating treatment adherence: A practitioner's guidebook*: Plenum Press.
- Meigs, J. B., Cagliero, E., Dubey, A., Murphy-Sheehy, P., Gildesgame, C., Chueh, H., . . . Nathan, D. M. (2003). A controlled trial of web-based diabetes disease management. *Diabetes Care*, *26*(3), 750-757.
- Meiland, F., Hattink, B., Overmars-Marx, T., De Boer, M., Jedlitschka, A., Ebben, P., . . . Karkowski, I. (2014). Participation of end users in the design of assistive technology for people with mild to severe cognitive problems; the European Rosetta project. *International Psychogeriatrics*, *26*(05), 769-779.
- Mendonça, F., Coelho, K., de Andrade, A. Q., & Almeida, M. B. (2012). *Knowledge Acquisition in the construction of ontologies: a case study in the domain of hematology*. Paper presented at the International Conference on Biomedical Ontology, Graz, Austria.
- Michie, S., Richardson, M., Johnston, M., Abraham, C., Francis, J., Hardeman, W., . . . Wood, C. E. (2013). The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of Behavioral Medicine*, *46*(1), 81-95.
- Michie, S., West, R., Campbell, R., Brown, J., & Gainforth, H. (2014). *ABC of behaviour change theories*: Silverback Publishing.
- Munro, S., Lewin, S., Swart, T., & Volmink, J. (2007). A review of health behaviour theories: how useful are these for developing interventions to promote long-term medication adherence for TB and HIV/AIDS? *BMC Public Health*, *7*(1), 104.
- Munro, S. A., Lewin, S., Smith, H. J., Engel, M. E., Fretheim, A., & Volmink, J. (2007). Patient adherence to tuberculosis treatment: a systematic review of qualitative research. *PLoS Medicine*, *4*(7), e238.
- Murthy, V., Bharia, G., & Sarin, R. (2002). Tamoxifen non-compliance: does it matter? *The Lancet Oncology*, *3*(11), 654.

- Musen, M. (2008). AMIA 2008 tutorial T26: ontologies in biomedicine. *Washington, DC, November, 9*.
- Musen, M. (1999). Scalable software architectures for decision support. *Methods of Information in Medicine, 38*(4-5), 229-238.
- Musen, M., Noy, N. F., Shah, N. H., Whetzel, P. L., Chute, C. G., Story, M.-A., & Smith, B. (2012). The national center for biomedical ontology. *Journal of the American Medical Informatics Association, 19*(2), 190-195.
- Napolitano, M. A., Fotheringham, M., Tate, D., Sciamanna, C., Leslie, E., Owen, N., . . . Marcus, B. (2003). Evaluation of an internet-based physical activity intervention: a preliminary investigation. *Annals of Behavioral Medicine, 25*(2), 92-99.
- Nasseh, K., Frazee, S. G., Visaria, J., Vlahiotis, A., & Tian, Y. (2012). Cost of medication nonadherence associated with diabetes, hypertension, and dyslipidemia. *American Journal of Pharmacy Benefits 4*(2), e41-e47.
- Nekhlyudov, L., Li, L., Ross-Degnan, D., & Wagner, A. K. (2011). Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence among insured women with early-stage breast cancer. *Breast Cancer Research and Treatment, 130*(2), 681-689.
- Neugut, A. I., Subar, M., Wilde, E. T., Stratton, S., Brouse, C. H., Hillyer, G. C., . . . Hershman, D. L. (2011). Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. *Journal of Clinical Oncology, 29*(18), 2534-2542.
- Nguyen, H. Q., Donesky-Cuenco, D., Wolpin, S., Reinke, L. F., Benditt, J. O., Paul, S. M., & Carrieri-Kohlman, V. (2008). Randomized controlled trial of an internet-based versus face-to-face dyspnea self-management program for patients with chronic obstructive pulmonary disease: pilot study. *Journal of Medical Internet Research, 10*(2), e9.
- Nordgreen, T., Standal, B., Mannes, H., Haug, T., Sivertsen, B., Carlbring, P., . . . Havik, O. (2010). Guided self-help via internet for panic disorder: dissemination across countries. *Computers in Human Behavior, 26*(4), 592-596.
- Norman, G. J., Zabinski, M. F., Adams, M. A., Rosenberg, D. E., Yaroch, A. L., & Atienza, A. A. (2007). A review of eHealth interventions for physical activity and dietary behavior change. *American Journal of Preventive Medicine, 33*(4), 336-345. e316.
- Noy, N. F., & McGuinness, D. L. (2001). Ontology development 101: A guide to creating your first ontology. Stanford, CA: Stanford knowledge systems laboratory technical report KSL-01-05 and Stanford medical informatics technical report SMI-2001-0880.
- Noy, N. F., Shah, N. H., Whetzel, P. L., Dai, B., Dorf, M., Griffith, N., . . . Chute, C. G. (2009). BioPortal: ontologies and integrated data resources at the click of a mouse. *Nucleic Acids Research, 37*(suppl 2), W170-W173.
- Ogundele, O. A., Moodley, D., Seebregts, C. J., & Pillay, A. W. (2015). *An ontology for tuberculosis treatment adherence behaviour*. Paper presented at the Annual Research Conference on South African Institute of Computer Scientists and Information Technologists, South African.

- Oguntola, A., Adeoti, M., & Akanbi, O. (2011). Non-adherence to the use of tamoxifen in the first year by the breast cancer patients in an African population. *East and Central African Journal of Surgery*, 16(1).
- Oh, E., Jorm, A. F., & Wright, A. (2009). Perceived helpfulness of websites for mental health information. *Social Psychiatry and Psychiatric Epidemiology*, 44(4), 293.
- Op't Eynde, P., De Corte, E., & Verschaffel, L. (2002). Framing students' mathematics-related beliefs *Beliefs: A Hidden Variable in Mathematics Education?* (pp. 13-37): Springer.
- Or, C. K., & Karsh, B.-T. (2009). A systematic review of patient acceptance of consumer health information technology. *Journal of the American Medical Informatics Association*, 16(4), 550-560.
- Organization, W. H. (2014). Adherence to long-term therapies: evidence for action. Geneva: WHO; 2003.
- Ornstein, R. E. (1972). *The psychology of consciousness* (2nd ed.): Penguin Books.
- Osborn, C. Y., Mayberry, L. S., Wallston, K. A., Johnson, K. B., & Elasy, T. A. (2013). Understanding patient portal use: implications for medication management. *Journal of Medical Internet Research*, 15(7), e133.
- Österholm, M. (2010). *The ontology of beliefs from a cognitive perspective*. Paper presented at the Ongoing research on beliefs in mathematics education, Genoa, Italy.
- Ostojic, V., Cvorisec, B., Ostojic, S. B., Reznikoff, D., Stipic-Markovic, A., & Tudjman, Z. (2005). Improving asthma control through telemedicine: a study of short-message service. *Telemedicine Journal & E-Health*, 11(1), 28-35.
- Owusu, C., Buist, D. S., Field, T. S., Lash, T. L., Thwin, S. S., Geiger, A. M., . . . Yood, M. U. (2008). Predictors of tamoxifen discontinuation among older women with estrogen receptor-positive breast cancer. *Journal of Clinical Oncology*, 26(4), 549-555.
- Pandolfi, E., Gonfiantini, M. V., Gesualdo, F., Romano, M., Carloni, E., Mastroiacovo, P., & Tozzi, A. E. (2014). A cohort study of a tailored web intervention for preconception care. *BMC Medical Informatics and Decision Making*, 14(1), 33.
- Pappa, D., Telonis, P., & Stergioulas, L. K. (2006). Management of medicines information for patient safety. *Journal of Telemedicine and Telecare*, 12(supplement 1), 34-36.
- Parekh, A. K. (2011). Winning their trust. *New England Journal of Medicine*, 364(24), e51.
- Park, M.-J., & Kim, H.-S. (2012). Evaluation of mobile phone and Internet intervention on waist circumference and blood pressure in post-menopausal women with abdominal obesity. *International Journal of Medical Informatics*, 81(6), 388-394.
- Park, M.-J., Kim, H.-S., & Kim, K.-S. (2009). Cellular phone and Internet-based individual intervention on blood pressure and obesity in obese patients with hypertension. *International Journal of Medical Informatics*, 78(10), 704-710.
- Parr, J. M., Kavanagh, D. J., YOUNG, R., & Mitchell, G. (2011). Acceptability of cognitive-behaviour therapy via the Internet for cessation of benzodiazepine use. *Drug and Alcohol Review*, 30(3), 306-314.

- Partridge, A. H., LaFountain, A., Mayer, E., Taylor, B. S., Winer, E., & Asnis-Alibozek, A. (2008). Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *Journal of Clinical Oncology*, *26*(4), 556-562.
- Partridge, A. H., Wang, P. S., Winer, E. P., & Avorn, J. (2003). Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *Journal of Clinical Oncology*, *21*(4), 602-606.
- Patrick, K., Marshall, S., Davila, E., Kolodziejczyk, J., Fowler, J., Calfas, K., . . . Gupta, A. (2014). Design and implementation of a randomized controlled social and mobile weight loss trial for young adults (project SMART). *Contemporary Clinical Trials*, *37*(1), 10-18.
- Patrick, K., Raab, F., Adams, M., Dillon, L., Zabinski, M., Rock, C., . . . Norman, G. (2009). A text message-based intervention for weight loss: randomized controlled trial. *Journal of Medical Internet Research*, *11*(1), e1.
- Pattuelli, M. C. (2011). Modeling a domain ontology for cultural heritage resources: a user-centered approach. *Journal of the Association for Information Science and Technology*, *62*(2), 314-342.
- Pellegrin, L., Bonnardel, N., Antonini, F., Albanese, J., Martin, C., & Chaudet, H. (2007). Event oriented representation for collaborative activities (EORCA)-a method for describing medical activities in severely-injured patient management. *Methods of Information in Medicine*, *46*(5), 506-515.
- Pellegrini, I., Sarradon-Eck, A., Soussan, P. B., Lacour, A.-C., Largillier, R., Tallet, A., . . . Julian-Reynier, C. (2010). Women's perceptions and experience of adjuvant tamoxifen therapy account for their adherence: breast cancer patients' point of view. *Psychooncology*, *19*(5), 472-479.
- Perugini, M., & Bagozzi, R. P. (2004). The distinction between desires and intentions. *European Journal of Social Psychology*, *34*(1), 69-84.
- Peters, B., & Consortium, O. (2009). Ontology for biomedical investigations. *PLoS ONE*, *11*(4).
- Petersen, R., Sill, S., Lu, C., Young, J., & Edington, D. W. (2008). Effectiveness of employee internet-based weight management program. *Journal of Occupational and Environmental Medicine*, *50*(2), 163-171.
- Phillips, J. H., Wigger, C., Beissbarth, J., McCallum, G. B., Leach, A., & Morris, P. S. (2014). Can mobile phone multimedia messages and text messages improve clinic attendance for Aboriginal children with chronic otitis media? a randomised controlled trial. *Journal of Paediatrics and Child Health*, *50*(5), 362-367.
- Plotnikoff, R. C., McCargar, L. J., Wilson, P. M., & Loucaides, C. A. (2005). Efficacy of an E-mail intervention for the promotion of physical activity and nutrition behavior in the workplace context. *American Journal of Health Promotion*, *19*(6), 422-429.
- Poldrack, R. A. (2010). Mapping mental function to brain structure: how can cognitive neuroimaging succeed? *Perspectives on Psychological Science*, *5*(6), 753-761.
- Price, M., & Gros, D. F. (2014). Examination of prior experience with telehealth and comfort with telehealth technology as a moderator of treatment response for PTSD and depression in veterans. *The International Journal of Psychiatry in Medicine*, *48*(1), 57-67.

- Prieto Ferrero, C., Lloret, E., & Palomar, M. (2014). Towards the Design of a Textile Chemical Ontology. *International Journal of Advanced Computer Science and Applications* 4(1), 35-41.
- Qiang, C. Z., Yamamichi, M., Hausman, V., Altman, D., & Unit, I. (2011). *Mobile applications for the health sector*. Retrieved from Washington, DC: World Bank:
- Quilty-Dunn, J., & Mandelbaum, E. (2017). Against dispositionalism: belief in cognitive science. *Philosophical Studies*, 175(9), 2353–2372.
- Quinn, C. C., Clough, S. S., Minor, J. M., Lender, D., Okafor, M. C., & Gruber-Baldini, A. (2008). WellDoc™ mobile diabetes management randomized controlled trial: change in clinical and behavioral outcomes and patient and physician satisfaction. *Diabetes Technology & Therapeutics*, 10(3), 160-168.
- Raebel, M. A., Schmittdiel, J., Karter, A. J., Konieczny, J. L., & Steiner, J. F. (2013). Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Medical Care*, 51(8 0 3), S11.
- Ralston, J. D., Hirsch, I. B., Hoath, J., Mullen, M., Cheadle, A., & Goldberg, H. I. (2009). Web-based collaborative care for type 2 diabetes a pilot randomized trial. *Diabetes Care*, 32(2), 234-239.
- Ramaekers, B. L., Janssen-Boyne, J. J., Gorgels, A. P., & Vrijhoef, H. J. (2009). Adherence among telemonitored patients with heart failure to pharmacological and nonpharmacological recommendations. *Telemedicine and E Health*, 15(6), 517-524.
- Rami, B., Popow, C., Horn, W., Waldhoer, T., & Schober, E. (2006). Telemedical support to improve glycemic control in adolescents with type 1 diabetes mellitus. *European Journal of Pediatrics*, 165(10), 701-705.
- Read, E. (2014). Feasibility of the Diabetes and Technology for Increased Activity (DaTA) Study: a pilot intervention in high-risk rural adults. *Journal of Physical Activity and Health*, 11(1), 118-126.
- Reback, C. J., Grant, D. L., Fletcher, J. B., Branson, C. M., Shoptaw, S., Bowers, J. R., . . . Mansergh, G. (2012). Text messaging reduces HIV risk behaviors among methamphetamine-using men who have sex with men. *AIDS and Behavior*, 16(7), 1993-2002.
- Richardson, A., Graham, A. L., Cobb, N., Xiao, H., Mushro, A., Abrams, D., & Vallone, D. (2013). Engagement promotes abstinence in a web-based cessation intervention: cohort study. *Journal of Medical Internet Research*, 15(1), e14.
- Riley, W. T., Rivera, D. E., Atienza, A. A., Nilsen, W., Allison, S. M., & Mermelstein, R. (2011). Health behavior models in the age of mobile interventions: are our theories up to the task? *Translational Behavioral Medicine*, 1(1), 53-71.
- Rodgers, A., Corbett, T., Bramley, D., Riddell, T., Wills, M., Lin, R.-B., & Jones, M. (2005). Do u smoke after txt? Results of a randomised trial of smoking cessation using mobile phone text messaging. *Tobacco Control*, 14(4), 255-261.
- Rooke, S. E., Gates, P. J., Norberg, M. M., & Copeland, J. (2014). Applying technology to the treatment of cannabis use disorder: comparing telephone versus Internet delivery using data from two completed trials. *Journal of Substance Abuse Treatment*, 46(1), 78-84.

- Ross, S. E., Moore, L. A., Earnest, M. A., Wittevrongel, L., & Lin, C.-T. (2004). Providing a web-based online medical record with electronic communication capabilities to patients with congestive heart failure: randomized trial. *Journal of Medical Internet Research*, 6(2), e12.
- Rothman, A. J. (2004). "Is there nothing more practical than a good theory?": Why innovations and advances in health behavior change will arise if interventions are used to test and refine theory. *International Journal of Behavioral Nutrition and Physical Activity*, 1(1), 11.
- Rotondi, A. J., Anderson, C. M., Haas, G. L., Eack, S. M., Spring, M. B., Ganguli, R., . . . Rosenstock, J. (2010). Web-based psychoeducational intervention for persons with schizophrenia and their supporters: one-year outcomes. *Psychiatric Services*, 61(11), 1099-1105.
- Roy, H., & Gillett, T. (2008). E-mail: a new technique for forming a therapeutic alliance with high-risk young people failing to engage with mental health services? A case study. *Clinical Child Psychology and Psychiatry*, 13(1), 95-103.
- S. Meghani, A. H. (2007). The Meanings of and Attitudes about Cancer Pain Among African Americans. *Oncology Nursing Forum*, 34(6), 1179-1186.
- Sabaté, E. (2003). *Adherence to long-term therapies: evidence for action*: World Health Organization.
- Salem, A.-B. M., & Alfonse, M. (2008). Ontology versus semantic networks for medical knowledge representation. *Recent Advances In Computer Engineering*, 769-774.
- Samarth, A., & Grant, E. (2009). *Using Health Information Technology to Determine Medication Adherence*. AHRQ Publication No. 10-0010-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2009: (AHRQ National Resource Center for Health Information Technology under Contract No. 290-04-0016).
- Sang, L. H. (2009). *Knowledge representation and ontologies for lipids and lipidomics*. (Master of Science), National University of Singapore.
- Santschi, V., Wuerzner, G., Schneider, M.-P., Bugnon, O., & Burnier, M. (2007). Clinical evaluation of IDAS II, a new electronic device enabling drug adherence monitoring. *European Journal of Clinical Pharmacology*, 63(12), 1179-1184.
- Sawesi, S., Carpenter, J. S., & Jones, J. (2014). Reasons for nonadherence to tamoxifen and aromatase inhibitors for the treatment of breast cancer: a literature review. *Clinical Journal of Oncology Nursing*, 18(3), E50-57. doi:10.1188/14.CJON.E50-E57
- Sawesi, S., Rashrash, M., Phalakornkule, K., Carpenter, J. S., & Jones, J. F. (2016). The Impact of information technology on patient engagement and health behavior change: a systematic review of the literature. *JMIR Medical Informatics*, 4(1), e1.
- Scherr, D., Kastner, P., Kollmann, A., Hallas, A., Auer, J., Krappinger, H., . . . Jakl, G. (2009). Effect of home-based telemonitoring using mobile phone technology on the outcome of heart failure patients after an episode of acute decompensation: randomized controlled trial. *Journal of Medical Internet Research*, 11(3), e34.
- Schiffer, S. (2006). A problem for a direct-reference theory of belief reports. *Noûs*, 40(2), 361-368.
- Schmitt, F. F. (2006). *Knowledge and belief*: Routledge.

- Schnall, R., Wantland, D., Velez, O., Cato, K., & Jia, H. (2014). Feasibility testing of a web-based symptom self-management system for persons living with HIV. *Journal of the Association of Nurses in AIDS Care, 25*(4), 364-371.
- Schriml, L. (2016). Human Disease Ontology.
- Schriml, L. M., Arze, C., Nadendla, S., Chang, Y.-W. W., Mazaitis, M., Felix, V., . . . Kibbe, W. A. (2011). Disease ontology: a backbone for disease semantic integration. *Nucleic Acids Research, 40*(D1), D940-D946.
- Schurz, M., Aichhorn, M., Martin, A., & Perner, J. (2013). Common brain areas engaged in false belief reasoning and visual perspective taking: a meta-analysis of functional brain imaging studies. *Frontiers in Human Neuroscience, 7*, 712.
- Schweier, R., Romppel, M., Richter, C., Hoberg, E., Hahmann, H., Scherwinski, I., . . . Grande, G. (2014). A web-based peer-modeling intervention aimed at lifestyle changes in patients with coronary heart disease and chronic back pain: sequential controlled trial. *Journal of Medical Internet Research, 16*(7), e177.
- Sciamanna, C. N., Nicholson, R. A., Lofland, J. H., Manocchia, M., Mui, S., & Hartman, C. W. (2006). Effects of a website designed to improve the management of migraines. *Headache: The Journal of Head and Face Pain, 46*(1), 92-100.
- Searle, J. R. (1979). What is an intentional state? *Mind, 88*(349), 74-92.
- Sedjo, R. L., & Devine, S. (2011). Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. *Breast Cancer Research and Treatment, 125*(1), 191-200.
- Shaban-Nejad, A., Lavigne, M., Okhmatovskaia, A., & Buckeridge, D. L. (2016). PopHR: a knowledge-based platform to support integration, analysis, and visualization of population health data. *Annals of the New York Academy of Sciences, 1387*(1), 44-53.
- Shah, N. D., Dunlay, S. M., Ting, H. H., Montori, V. M., Thomas, R. J., Wagie, A. E., & Roger, V. L. (2009). Long-term medication adherence after myocardial infarction: experience of a community. *The American Journal of Medicine, 122*(10), e7- e13.
- Shaw, L. H., & Gant, L. M. (2002). In defense of the Internet: the relationship between Internet communication and depression, loneliness, self-esteem, and perceived social support. *Cyberpsychology & Behavior, 5*(2), 157-171.
- Shrier, L. A., Rhoads, A., Burke, P., Walls, C., & Blood, E. A. (2014). Real-time, contextual intervention using mobile technology to reduce marijuana use among youth: a pilot study. *Addictive Behaviors, 39*(1), 173-180.
- Simon, G. E., Ludman, E. J., Goodale, L. C., Dykstra, D. M., Stone, E., Cutsogeorge, D., . . . Pabiniak, C. (2011). An online recovery plan program: can peer coaching increase participation? *Psychiatric Services, 62*(6), 666-669.
- Sims, H., Sanghara, H., Hayes, D., Wandiembe, S., Finch, M., Jakobsen, H., . . . Kravariti, E. (2012). Text message reminders of appointments: a pilot intervention at four community mental health clinics in London. *Psychiatric Services, 63*(2), 161-168.
- Smith, B. (2003). *Blackwell guide to the philosophy of computing and information*: Wiley-Blackwell.
- Smith, B., Almeida, M., Bona, J., Brochhausen, M., Ceusters, W., Courtot, M., . . . Hastings, J. (2012). Basic Formal Ontology 2.0 Draft Specification and User's Guide: July.

- Smith, B., Ashburner, M., Rosse, C., Bard, J., Bug, W., Ceusters, W., . . . Mungall, C. J. (2007). The OBO foundry: coordinated evolution of ontologies to support biomedical data integration. *Nature Biotechnology*, *25*(11), 1251-1255.
- Smith, K. E., Levine, B. A., Clement, S. C., Hu, M.-J., Alaoui, A., & Mun, S. K. (2004). Impact of MyCareTeam™ for poorly controlled diabetes mellitus. *Diabetes Technology & Therapeutics*, *6*(6), 828-835.
- Sobrado, F., Juan, P., Iker, U. L., Juan, J. G., & Diego, L. d. I. (2004). *Towards a clinical practice guideline implementation for asthma treatment*. Paper presented at the Current Topics in Artificial Intelligence Berlin Heidelberg.
- Song, H., May, A., Vaidhyanathan, V., Cramer, E. M., Owais, R. W., & McRoy, S. (2013). A two-way text-messaging system answering health questions for low-income pregnant women. *Patient Education and Counseling*, *92*(2), 182-187.
- Španiel, F., Vohlídka, P., Hrdlička, J., Kožený, J., Novák, T., Motlová, L., . . . Höschl, C. (2008). ITAREPS: information technology aided relapse prevention programme in schizophrenia. *Schizophrenia Research*, *98*(1), 312-317.
- Stacy, J. N., Schwartz, S. M., Ershoff, D., & Shreve, M. S. (2009). Incorporating tailored interactive patient solutions using interactive voice response technology to improve statin adherence: results of a randomized clinical trial in a managed care setting. *Population Health Management*, *12*(5), 241-254.
- Steele, R., Mummery, K. W., & Dwyer, T. (2007). Development and process evaluation of an Internet-based physical activity behaviour change program. *Patient Education and Counseling*, *67*(1), 127-136.
- Steinberg, D. M., Levine, E. L., Lane, I., Askew, S., Foley, P. B., Puleo, E., & Bennett, G. G. (2014). Adherence to self-monitoring via interactive voice response technology in an eHealth intervention targeting weight gain prevention among Black women: randomized controlled trial. *Journal of Medical Internet Research*, *16*(4), e114.
- Sterns, A., Hughes, J., Masstandrea, N., & Smith, J. (2014). Medication event monitoring system: Google Patents.
- Stockwell, M. S., Kharbanda, E. O., Martinez, R. A., Vargas, C. Y., Vawdrey, D. K., & Camargo, S. (2012). Effect of a text messaging intervention on influenza vaccination in an urban, low-income pediatric and adolescent population: a randomized controlled trial. *JAMA*, *307*(16), 1702-1708.
- Strecher, V., McClure, J., Alexander, G., Chakraborty, B., Nair, V., Konkel, J., . . . Wiese, C. (2008). The role of engagement in a tailored web-based smoking cessation program: randomized controlled trial. *Journal of Medical Internet Research*, *10*(5), e36.
- Sugawara, Y., Narimatsu, H., Hozawa, A., Shao, L., Otani, K., & Fukao, A. (2012). Cancer patients on Twitter: a novel patient community on social media. *BMC Research Notes*, *5*(1), 699.
- Sundiātu, D., Shonu, G., Thomas, P., & Angela, S. (2012). Changing patient behavior: the next frontier in healthcare value. *Health Int*, *12*, 65-73.
- Sutcliffe, P., Martin, S., Sturt, J., Powell, J., Griffiths, F., Adams, A., & Dale, J. (2011). Systematic review of communication technologies to promote access and engagement of young people with diabetes into healthcare. *BMC Endocrine Disorders*, *11*(1), 1.

- Symons, D. K., Peterson, C. C., Slaughter, V., Roche, J., & Doyle, E. (2005). Theory of mind and mental state discourse during book reading and story-telling tasks. *British Journal of Developmental Psychology*, *23*(1), 81-102.
- Tasker, A. P., Gibson, L., Franklin, V., Gregor, P., & Greene, S. (2007). What is the frequency of symptomatic mild hypoglycemia in type 1 diabetes in the young?: assessment by novel mobile phone technology and computer-based interviewing. *Pediatric Diabetes*, *8*(1), 15-20.
- Tate, D. F., Jackvony, E. H., & Wing, R. R. (2006). A randomized trial comparing human e-mail counseling, computer-automated tailored counseling, and no counseling in an Internet weight loss program. *Archives of Internal Medicine*, *166*(15), 1620-1625.
- Tenenbaum, J. D., Whetzel, P. L., Anderson, K., Borromeo, C. D., Dinov, I. D., Gabriel, D., . . . Noy, N. (2011). The Biomedical Resource Ontology (BRO) to enable resource discovery in clinical and translational research. *Journal of biomedical informatics*, *44*(1), 137-145.
- Ter Huurne, E. D., Postel, M. G., de Haan, H. A., Drossaert, C. H., & DeJong, C. A. (2013). Web-based treatment program using intensive therapeutic contact for patients with eating disorders: before-after study. *Journal of Medical Internet Research*, *15*(2), e12.
- Thackeray, R., Crookston, B. T., & West, J. H. (2013). Correlates of health-related social media use among adults. *Journal of Medical Internet Research*, *15*(1), e21.
- Thirumurthy, H., & Lester, R. T. (2012). M-health for health behaviour change in resource-limited settings: applications to HIV care and beyond. *Bulletin of the World Health Organization*, *90*(5), 390-392.
- Tildesley, H. D., Mazanderani, A. B., & Ross, S. A. (2010). Effect of Internet therapeutic intervention on A1C levels in patients with type 2 diabetes treated with insulin. *Diabetes Care*, *33*(8), 1738-1740.
- Tran, B. X., & Houston, S. (2012). Mobile phone-based antiretroviral adherence support in Vietnam: feasibility, patient's preference, and willingness-to-pay. *AIDS and Behavior*, *16*(7), 1988-1992.
- Trautmann, E., & Kröner-Herwig, B. (2008). Internet-based self-help training for children and adolescents with recurrent headache: a pilot study. *Behavioural and Cognitive Psychotherapy*, *36*(02), 241-245.
- Trust, M. (2002). *Critical Appraisal Skills Programme (CASP): making sense of evidence*. London (UK): Oxford.
- Tudorache, T., Falconer, S., Noy, N. F., Nyulas, C., Üstün, T. B., Storey, M.-A., & Musen, M. A. (2010). *Ontology development for the masses: creating ICD-11 in WebProtégé*. Paper presented at the International Conference on Knowledge Engineering and Knowledge Management.
- Turchin, A., Wheeler, H. I., Labreche, M., Chu, J. T., Pendergrass, M. L., & Einbinder, J. S. (2008). *Identification of documented medication non-adherence in physician notes*. Paper presented at the AMIA.
- Turner-McGrievy, G. M., & Tate, D. F. (2014). Are we sure that Mobile Health is really mobile? An examination of mobile device use during two remotely-delivered weight loss interventions. *International Journal of Medical Informatics*, *83*(5), 313-319.

- Urowitz, S., Wiljer, D., Dupak, K., Kuehner, Z., Leonard, K., Lovrics, E., . . . Cafazzo, J. (2012). Improving diabetes management with a patient portal: qualitative study of a diabetes self-management portal. *Journal of Medical Internet Research*, *14*(6), e158.
- Van den Berg, M., Ronday, H., Peeters, A., Voogt-van Der Harst, E., Munneke, M., Breedveld, F., & Vlieland, T. V. (2007). Engagement and satisfaction with an Internet-based physical activity intervention in patients with rheumatoid arthritis. *Rheumatology*, *46*(3), 545-552.
- Van der Vaart, R., Drossaert, C. H., Taal, E., Drossaers-Bakker, K. W., Vonkeman, H. E., & van de Laar, M. A. (2014). Impact of patient-accessible electronic medical records in rheumatology: use, satisfaction and effects on empowerment among patients. *BMC Musculoskeletal Disorders*, *15*(1), 102.
- Van Herk-Sukel, M. P., van de Poll-Franse, L. V., Voogd, A. C., Nieuwenhuijzen, G. A., Coebergh, J. W. W., & Herings, R. M. (2010). Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: a population-based analysis. *Breast Cancer Research and Treatment*, *122*(3), 843-851.
- Verma, S., Madarnas, Y., Sehdev, S., Martin, G., & Bajcar, J. (2011). Patient adherence to aromatase inhibitor treatment in the adjuvant setting. *Current Oncology*, *18*, 3-9.
- Vilella, A., Bayas, J.-M., Diaz, M.-T., Guinovart, C., Diez, C., Simó, D., . . . Cerezo, J. (2004). The role of mobile phones in improving vaccination rates in travelers. *Preventive Medicine*, *38*(4), 503-509.
- Villegas, N., Santisteban, D., Cianelli, R., Ferrer, L., Ambrosia, T., Peragallo, N., & Lara, L. (2014). The development, feasibility and acceptability of an Internet-based STI-HIV prevention intervention for young Chilean women. *International Nursing Review*, *61*(1), 55-63.
- Viswanathan, M., Golin, C. E., Jones, C. D., Ashok, M., Blalock, S. J., Wines, R. C., . . . Lohr, K. N. (2012). Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Annals of Internal Medicine*, *157*(11), 785-795.
- Vollmer, W. M., Feldstein, A., Smith, D., Dubanoski, J., Waterbury, A., Schneider, J., . . . Rand, C. (2011). Use of health information technology to improve medication adherence. *The American Journal of Managed Care*, *17*(12 0 0), SP79.
- Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppard, T., . . . Lewek, P. (2012). A new taxonomy for describing and defining adherence to medications. *British Journal of Clinical Pharmacology*, *73*(5), 691-705.
- Vrijens, B., De Geest, S., Hughes, D. A., Przemyslaw, K., Demonceau, J., Ruppard, T., . . . Urquhart, J. (2012). A new taxonomy for describing and defining adherence to medications. *British Journal of Clinical Pharmacology*, *73*(5), 691-705. doi:10.1111/j.1365-2125.2012.04167.x
- Wakefield, B. J., Ward, M. M., Holman, J. E., Ray, A., Scherubel, M., Burns, T. L., . . . Rosenthal, G. E. (2008). Evaluation of home telehealth following hospitalization for heart failure: a randomized trial. *Telemedicine and E Health*, *14*(8), 753-761.
- Walker, J., Leveille, S. G., Ngo, L., Vodicka, E., Darer, J. D., Dhanireddy, S., . . . Oster, N. (2011). Inviting patients to read their doctors' notes: patients and doctors look

- ahead patient and physician surveys. *Annals of Internal Medicine*, 155(12), 811-819.
- Walters, W. H. (2007). Google scholar coverage of a multidisciplinary field. *Information Processing & Management*, 43(4), 1121-1132.
- Wantland, D. J., Portillo, C. J., Holzemer, W. L., Slaughter, R., & McGhee, E. M. (2004). The effectiveness of web-based vs. non-web-based interventions: a meta-analysis of behavioral change outcomes. *Journal of Medical Internet Research*, 6(4), e40.
- Ware, L., Hurling, R., Bataveljic, O., Fairley, B., Hurst, L., Murray, P., . . . Cobain, M. (2008). Rates and determinants of uptake and use of an internet physical activity and weight management program in office and manufacturing work sites in England: cohort study. *Journal of Medical Internet Research*, 10(4), e56.
- Waterhouse, D. M., Calzone, K. A., Mele, C., & Brenner, D. E. (1993). Adherence to oral tamoxifen: a comparison of patient self-report, pill counts, and microelectronic monitoring. *Journal of Clinical Oncology*, 11(6), 1189-1197.
- Webb, T., Joseph, J., Yardley, L., & Michie, S. (2010). Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *Journal of Medical Internet Research*, 12(1), e4.
- Weinstock, R. S., Brooks, G., Palmas, W., Morin, P. C., Teresi, J. A., Eimicke, J. P., . . . Shea, S. (2010). Lessened decline in physical activity and impairment of older adults with diabetes with telemedicine and pedometer use: results from the IDEATel study. *Age and Ageing*, 40(1), 98-105.
- Weppner, W. G., Ralston, J. D., Koepsell, T. D., Grothaus, L. C., Reid, R. J., Jordan, L., & Larson, E. B. (2010). Use of a shared medical record with secure messaging by older patients with diabetes. *Diabetes Care*, 33(11), 2314-2319.
- Williams, A. B., Mertz, K., & Wilkins, T. L. (2014). Issue Brief: Medication Adherence and Health IT. *Washington, DC: Office of the National Coordinator for Health Information Technology, Department of Health and Human Services*.
- Williamson, D. A., Walden, H. M., White, M. A., York-Crowe, E., Newton, R. L., Alfonso, A., . . . Ryan, D. (2006). Two-year Internet-based randomized controlled trial for weight loss in African-American girls. *Obesity*, 14(7), 1231-1243.
- Winbush, G. B., McDougle, L., Labranche, L., Khan, S., & Tolliver, S. (2013). Health empowerment technologies (HET): building a web-based tool to empower older African American patient-doctor relationships. *Journal of Health Care for the Poor and Underserved*, 24(4), 106-117.
- Winstead-Derlega, C., Rafaly, M., Delgado, S., Freeman, J., Cutitta, K., Miles, T., . . . Dillingham, R. (2012). A pilot study of delivering peer health messages in an HIV clinic via mobile media. *Telemedicine and E Health*, 18(6), 464-469.
- Winzelberg, A. J., Eppstein, D., Eldredge, K. L., Wilfley, D., Dasmahapatra, R., Dev, P., & Taylor, C. B. (2000). Effectiveness of an Internet-based program for reducing risk factors for eating disorders. *Journal of Consulting and Clinical Psychology*, 68(2), 346-350.
- Womble, L. G., Wadden, T. A., McGuckin, B. G., Sargent, S. L., Rothman, R. A., & Krauthamer-Ewing, E. S. (2004). A randomized controlled trial of a commercial internet weight loss program. *Obesity Research*, 12(6), 1011-1018.

- Xiang, Z., Courtot, M., Brinkman, R. R., Ruttenberg, A., & He, Y. (2010). OntoFox: web-based support for ontology reuse. *BMC Research Notes*, 3(1), 175.
- Yoon, K.-H., & Kim, H.-S. (2008). A short message service by cellular phone in type 2 diabetic patients for 12 months. *Diabetes Research and Clinical Practice*, 79(2), 256-261.
- Zhang, S., & Bodenreider, O. (2007). Lessons learned from cross-validating alignments between large anatomical ontologies. *Studies in Health Technology and Informatics*, 129(Pt 1), 822.
- Ziller, V., Kalder, M., Albert, U.-S., Holzhauser, W., Ziller, M., Wagner, U., & Hadji, P. (2009). Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Annals of Oncology*, 20(3), 431-436.

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Education

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Indiana University, Indianapolis, IN

Master of Pharmacy (MPharm) Aug 2000 - May 2003

Department of Pharmacy Practice, College of Pharmacy,
University Science Malaysia, USM. Penang, Malaysia.

Bachelor of Pharmacy (B. Pharm) Sep 1989 - May 1995

Department of Pharmacology and clinical pharmacy,
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Certification

Center for the Integration of Research, Teaching,
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Academic Experience

Adjunct Faculty/ Associate Faculty, Indiana University

INFO B430 Introduction to Health Informatics Fall 2016- Fall 2018

INFO B442 Clinical Decision Support Systems Spring 2017-Spring 2018

HIM M425 Quantitative Analysis of Health Information Fall 2018

Publications

1. Sawesi, S., Carpenter, J.S., & Jones, J. (2014). "Reasons for nonadherence to tamoxifen and aromatase inhibitors for the treatment of breast cancer: a literature review." *Clinical journal of oncology nursing* 18(3), E50.
2. Sawesi, S., Rashrash, M., Phalakornkule, K., Carpenter, J.S., & Jones, J.F. (2016). The Impact of Information Technology on Patient Engagement and Health Behavior Change: A Systematic Review of the Literature. *JMIR Medical Informatics*, 4(1), e1.

Conference, Presentations, and Posters

1. Sawesi, S., Carpenter, J.S., & Jones, J. (2014). Reasons for nonadherence to tamoxifen and aromatase inhibitors for the treatment of breast cancer: a review of the literature. Poster presented 2012 at the Oncology Nursing Society Connections: Advancing Care Through Science Abstracts. In *Oncology Nursing Forum* (Vol. 39, No. 6, p. E519).
2. Sawesi, S., Carpenter, J.S., & Jones, J. (2014). Behavioral change through patient engagement using information technology: A review of the literature. Poster presented 2014 at IU Simon Cancer Center Cancer Research Day.
3. Meta-analysis: Impact of Health Information Technology on Patient Engagement and Health Behavior Change. *Suhila A. Sawesi, Kanitha Phalakornkule, Josette F. Jones. AMIA 2015 annual symposium.*
4. Meta-Analysis of Ontology Applications in Healthcare. *Kanitha Phalakornkule, Suhila A. Sawesi, Josette F. Jones. AMIA 2015 annual symposium.*

5. A presentation to a group of researchers in consumer engagement in health care, particularly around technologies that promote healthy living and aging (online presentation) 06/24/2016.
6. Sawesi, S., Jones, J., and Duncan, W., “ICBO_2018_57: An Ontology For Formal Representation Of Medication Adherence-Related Knowledge: Case Study In Breast Cancer,” in *International Conference on Biomedical Ontology (ICBO 2018)*, 2018.

Peer Reviewer

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|--------------------------------|--------------|
| 1. Journal of Oncology Nursing | 2014-Present |
| 2. JMIR Medical Informatics | 2014-Present |
| 3. AMIA | 2016-Present |

Reviewer of paper:

- Lodhia, V., Karanja, S., Lees, S., & Bastawrous, A. (2016). Acceptability, usability, and views on deployment of peek, a mobile phone mHealth Intervention for eye care in Kenya: qualitative study. *JMIR mHealth and uHealth*, 4(2).
- McLean, G., Murray, E., Band, R., Saunderson, K., Hanlon, P., Little, P., ... & Mair, F. S. (2015). Digital interventions to promote self-management in adults with hypertension: protocol for systematic review and meta-analysis. *JMIR Research Protocols*, 4(4).
- Kazi, A.M., Carmichael, J.L., Hapanna, G.W., Wangoo, P.G., Karanja, S., Wanyama, D., ... & Kinagwi, K. (2017). Assessing mobile phone access and perceptions for texting-based mHealth interventions among expectant mothers and child caregivers in remote regions of northern Kenya: A survey-based descriptive study. *JMIR Public Health and Surveillance*, 3(1).

- Reviewer for AMIA 2016, 2017, 2018 Annual Symposium

AWARDS

- Ph.D. Scholarship from Libyan Ministry of Higher Education 2009-2015
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- Publication Fund from IUPUI 2016
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