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Integrated Ontology Development for Clinical Decision Support System in the Case Study of Methadone Maintenance Therapy

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ABSTRACT

Clinical Decision Support System (CDSS) is a health information system which is designed to help the physicians in decision-making process. However, it remains a challenge to successfully provide and implement CDSS in clinical practice. One of the issues is regarding the limited provisions of causal reasoning and supporting evidences for the presented outcomes or decisions in existing CDSS. These are necessary for showing the relevance and reliability of the outcomes, and helping the physicians in making proper decisions. This study has designed an ontology-based CDSS model that integrates the domain medical knowledge with causal reasoning, decision support, and supporting evidences. The CDSS model is developed for the case study of Methadone Maintenance Therapy (MMT). From the evaluation by the ontology metrics, the results show that our model is feasible and comparable to other ontology models. As a result, our CDSS model able to provide full support to the CDSS requirements particularly in the provision of causal reasoning compared to other CDSS models, and these signify the contributions of this study.

Key words : causal reasoning, clinical decision support system, ontology, supporting evidence

1. INTRODUCTION

The Clinical Decision Support System (CDSS) was introduced as one of the most effective ways in reducing medication errors and improving healthcare quality [1]. CDSS is defined as a health information system that is designed to aid the physicians in decision-making process. CDSS has been developed thirty years ago and enhanced by many techniques originated from artificial intelligence (AI), information science, and cognitive psychology [1], [2]. CDSS is promising in assisting physicians for improving decision-making process and facilitate healthcare services. Nevertheless, it remains a challenge to successfully provide and implement CDSS in clinical practice. In medicine, causality and evidence have become the main concern throughout healthcare and decision-making [3], [4]. Causality is necessary for understanding all structures of scientific reasoning and for providing a coherent and sufficient explanation for any event. However, lack of existing CDSS that provide causal reasoning and evidence for the presented outcomes or decisions [4]-[6]. These are necessary for showing the relevance and reliability of the outcomes, and helping the physicians in making proper decisions. As a result, the knowledge and clinical reasoning behind these systems are not explicable and disseminated even when they are based on strong evidence. These also may cause difficulties for the physicians to understand and assess the system's prospective performance as well as to convince them for accepting it in their clinical practice [4]-[6].

In this study, a CDSS model is developed by using the ontology-based technique. Ontology is a strong knowledge representation and communication model for intelligent agents [7]-[10]. It is important to define and maintain expressive ontology for developing a CDSS. Semantics should be considered to develop a CDSS, since in healthcare each description should have a unique and understandable meaning [7]-[10]. Besides, it can improve medical knowledge handling and reutilization as it facilitates faster knowledge access and gathering of relevant knowledge and evidence in supporting decision-making process. It also enables the system to be adaptive to clinical practice as it supports the knowledge repository to be updated and modified for incorporating new clinical cases or evidences into the system [7]-[10]. Besides, a machine learning technique (i.e. Adaptive Neuro-Fuzzy Inference System (ANFIS)) has also been used in the CDSS model for making predictions in the MMT case study (i.e. formerly presented in [11]). This paper presents the ontology-based technique that has been used for developing the CDSS model. The purpose of the CDSS model is: 1) to identify and visualize the causality in the clinical reasoning, and, 2) to integrate the concepts of domain medical knowledge with causal reasoning, decision support, and supporting evidences. These concepts are associated with each other for providing a comprehensive description or analysis of causality for the represented knowledge.

2. LITERATURE REVIEW

2.1 Clinical Decision Support System (CDSS)

Generally, CDSS can be classified into two main categories; data-driven and knowledge based CDSS [12]. The data driven CDSS are the CDSS that employ the machine learning techniques (e.g. neural network). The knowledge based CDSS are based on the logic-based techniques and they can be classified into two categories based on the form of knowledge base: rule-based and ontology-based CDSS [12]. The rule-based CDSS are composed of typical condition-action rules and associations of compiled data, which commonly in the form of IF-THEN rules (e.g. fuzzy logic).The ontology-based CDSS consist of ontology as the knowledge base, which captures the domain knowledge in terms of a semantic representation of concepts, relationships and axioms [9], [12], [13]. A logic-based knowledge reasoner is used as the reasoning engine, whereby data or information (e.g. health information, diagnostic tests) is represented in terms of instances of concepts and relations, and the output includes a set of conclusions or recommendations [9], [12], 13].

2.2 Causal Reasoning

Causality is necessary for understanding all structures of scientific reasoning and the decision making process. It is also needed for providing a comprehensive explanation for any entity or event [3], [14]. There are several causality concepts and features, as well as graphical modeling techniques.

A. Causality Concepts and Features

Causality signifies an empirical relationship or a causal action occurring between one factor and its target (or effect). There are several concepts and features of causality including causal direction, necessity and sufficiency, causal chain, and distal and proximal causes.

- Causal direction indicates the direction of an effect in a causal relationship [15]. There are two kinds of causal direction, which are positive and negative direction A positive influence direction indicates that both factors change in the same direction (e.g. an increase causes an increase effect), whereas the negative influence indicates the opposite changes (e.g. an increase causes a decrease effect).
- Causal relationships can be represented in terms of whether the causal factor is a necessary or sufficient condition for an effect to occur (14). A causal factor is considered necessary when it always precedes the effects (e.g. symptoms) and always presents when the effects occur (e.g. *Mycobacterium* is a necessary cause of tuberculosis). A cause is considered sufficient when the effects become inevitable. In other words, it is a causal factor whose presence or occurrence guarantees the occurrence of the symptoms (e.g. Down syndrome is the most common cause of mental retardation).
- Causal chain is a chain of entities linked by causal relations [14], [17]. It is a connected and ordered sequence of causal relationships between multiple factors. Causal chains typically consist of certain factor causing another, which then causes another. Visual representations of causal chains commonly use alphanumeric characters or shapes (a.k.a. nodes) for representing the factors, and are then linked by unidirectional arrows for representing the causal relationship between them. There are three types of causal chain based on different causal scenarios;
  - (i) Sequential causal chain is an ordinary conception of causal chain (i.e. non-cumulative process), which is a process that proceeds by completing the current process at every instant in time (e.g. < *accident happened* → *ambulance came* → victim *arrive at a hospital* >).
  - (ii) Ongoing causal chain can be referred as cumulative continuous process, which is a process that proceeds without completing the current process at every instant in time. For example, angiostenosis is an abnormal narrowing of a blood vessel that commonly occurs when the cholesterol plaques build up on the artery walls. These factors result in blood flow interruption and oxygen deprivation in myocardial cells. Then these causing necrosis (or death) in the heart muscle, which is also known as myocardial infarction or heart attack.
  - (iii) Concurrent causal chain is a chain, in which the causality process from cause to effect is occurring simultaneously throughout the chain. If changes occur simultaneously and without mediation, it is referred as pseudo-simultaneous causal chain (e.g. < collision → breakage >). If the simultaneous causal chain involves mediation, it is referred as state-mediated causal chain (e.g. < growing blood clot → reduction of cross section of blood vessel → reduction in oxygen supply >).
- Distal and proximal factors are another type of causal concept, which is particularly notable for the causal chain. The distal factors lie towards the beginning of causal chain (i.e. indirect causal factors), whereas the proximal factors lie towards the end of the chain (i.e. cause directly or almost directly the effect).

B. Graphical Causal Modeling

Graphic visualization is one of the basic approaches that have been employed, in order for improving the comprehension of cause-and-effect relationships [15], [18]. The graphical causal models able to illustrate the qualitative population assumptions, and the sources of bias, that are not easily noticed with other approaches [15], [18]. Causal graphs (or diagrams) are the most common visual representation of cause-and-effect relationships, which are a form of cognitive

mapping that have emerged with numerous forms and structures.

The following describe several forms of causal graphs including the directed graph, Bayesian networks (BN) and causal loop diagram (CLD) [19], [20].

- Directed graph is composed of vertices (or nodes) that represent the factors and targets, and the edges (line segment with arrowheads) that represent the causal relationships between them.
- BN is a graphical probabilistic model that represents the structure of data through a directed acyclic graph. It is composed of nodes representing the variables and directed edges representing the relations or causal dependencies between the variables. Each variable has a set of parameters that are encoded by node probability tables for defining its probabilistic relation with its parents (i.e. conditional probability), or its prior probability if the variable does not have any parents (i.e. root node).

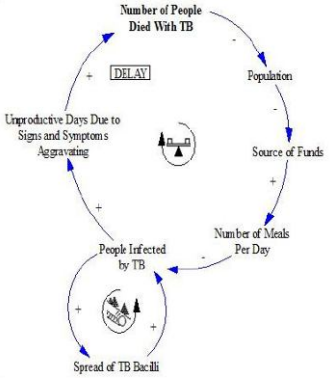

Figure 1: A CLD Model of Tuberculosis Case in Philippines [21]

- CLD is a type of causal diagram that allows the illustration of cause-effect variables in the cyclical relationship. It consists of two components:

  (i) Causal links between variables, which is represented by arrows. Each causal link is marked with polarity or causal direction (i.e. positive or negative influence direction). A causal link is marked with delay (see Figure 1) or double slashes if there is a significant delay between the cause and the effect. It is a situation where an occurrence of causal factor takes time for the effect to occur.

  (ii) Feedback loop which represents the causal relationship as a loop. There are two kinds of feedback loop which are reinforcing (or positive) loop, and balancing (or negative) loop, and they are indicated by the number of negative causal links in a loop. The positive loop contains an even or zero number of negative causal links, whereas the negative loop contains an odd number of negative causal links. The positive loop is commonly labeled at the centre of the loop either by using the letter "R" or by using an icon of snowball rolling down a hill (see Figure 1). For the negative loop, it is labeled either by using the letter "B" or by using an icon of teeter-totter. In addition, a small looping arrow is usually drawn around the feedback loop label to indicate that the label refers to the feedback loop and to show the direction of the loop's rotation.

2.3 Logic of Decision Support Requirements in CDSS

CDSS is promising in assisting physicians for improving decision-making process and facilitate healthcare services. However, it remains a challenge to successfully provide and implement CDSS in clinical practice. One of the issues in CDSS is regarding the requirement for logic of decision support (i.e. provision of recommendation, reasoning or explanation, and evidence). These features are important to assist the physicians in making the most suitable and safe decisions for patient care. The following provides the descriptions for these features including the necessity of causal reasoning and presenting evidences in CDSS.

1) Provide recommendation (or advice), rather than simply assessment (or diagnosis) [22].
   - Example: Recommends suitable drug to dispense after detecting drug interaction in a prescription.
   - Importance: Systems that provide recommendations are more helpful and practical, and thus have higher potential to be accepted and used by physicians.
2) Justification of decision support (e.g. recommendation) through provision of reasoning or explanation [22].
   - Example: Justify the recommended diabetic foot screening by mentioning the date of last exam and suggested screening frequency.
   - Importance: Allow physicians to evaluate the relevance of recommendations and consider it in their practice.
3) Provide causal reasoning or explanation for the generated outcomes (e.g. predictions, decisions or suggestions made by the system) [3]-[6].
   - Example: i) Provide explanations based on the mechanistic cause-and-effect (not simply based on inferred rules); ii) Explain the factors that cause the generated outcomes by showing the causal chain that consists of distal and proximal causal factors.
   - Importance: i) Allow the physicians to evaluate more precisely the relevance of the outcomes and facilitate them for making proper decisions particularly in complex clinical problems; ii) Physicians are more inclined to accept and acknowledge the system outcomes when the explanation is presented in the context of cause-and-effect relationship.
4) Justification of decision support through provision of evidences (e.g. sources from experts, clinical data, clinical practice guidelines (CPG), and literatures) [3]-[6].
   - Example: i) Justify the system outcomes by presenting the supported evidences such as through citations or references; ii) Justify the recommendation by presenting

the evidences (such as from CPG) that explain the significance or necessity of the recommendation.

- Importance: i) Have similar importance with the provision of causal reasoning; ii) Evidences such as CPG is based on expert's consensus and best scientific evidence that able to support the decision making process in healthcare.

3. RESEARCH DESIGN AND METHODOLOGY

Figure 2 presents the ontology development framework for this study, where an approach proposed by Uschold and Gruninger (1996) is adopted. The framework consists of four processes:

1) The ontology capture is part of the knowledge acquisition process. In this study, the ontology concepts are captured based on literature search, clinical practice guidelines, and expert's knowledge. The concepts of causal reasoning are captured through constructing the causal graphs, such as directed acyclic graphs and causal loop diagram. The features of clinical evidences and other sources of information are also identified during this process.

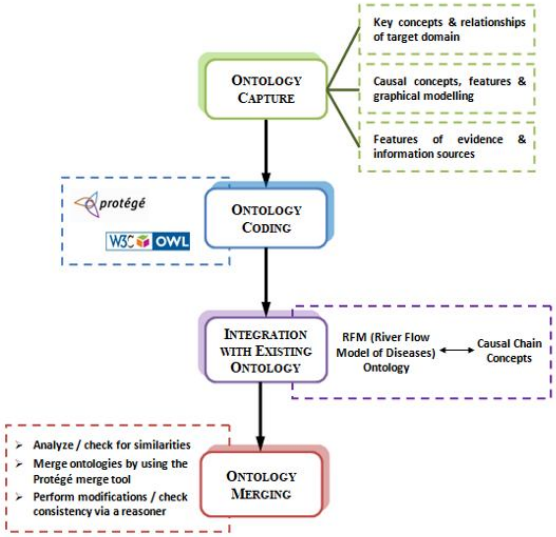

Figure 2: Ontology Development Framework

2) The ontology coding was performed using the Protégé-OWL editor and Pellet as the ontology reasoner. Protégé fully supports the latest OWL 2 Web Ontology Language and RDF specifications from the W3C. The OntoGraf plugin has been mainly used in this study for visualizing the relationships in the ontologies and organizing the structures of the ontology.

3) The integration of ontology refers to a process of reusing the existing ontology. It could be necessary to reuse the existing ontology in order to capture the previous established conceptualizations. In this study, the River Flow Model of Diseases (RFM) ontology has been adopted for capturing the concept of causal chain defined in this ontology. This integration is also shown in Figure 3 (i.e. ontology merging). RFM is an ontological theory of disease that represents the causal structure of pathology based on the analogy of rivers. RFM classes are part of YAMATO (Yet Another More Advanced Top-level Ontology), which is part of the Japan Medical Ontology Development Project for Advanced Clinical Information Systems. In this study, several of their ontology elements are adopted and modified based on the relevance and suitability of MMT case study, and for improving the ontology expressiveness and comprehensibility.

4) The ontology merging is the generation of new extended ontology from two or more sources of ontologies. Ontologies are developed at different levels of abstractions and different details (e.g. vocabularies, purposes, and points of view). Therefore, ontology merging provides a holistic view of the domain area from several knowledge sources and collectively completes each other. The merging approach for this study consists of several steps (as shown in Figure 3):

   i) Analyze the ontologies to be merged or check for similarities through analyzing their classes, properties and restrictions.

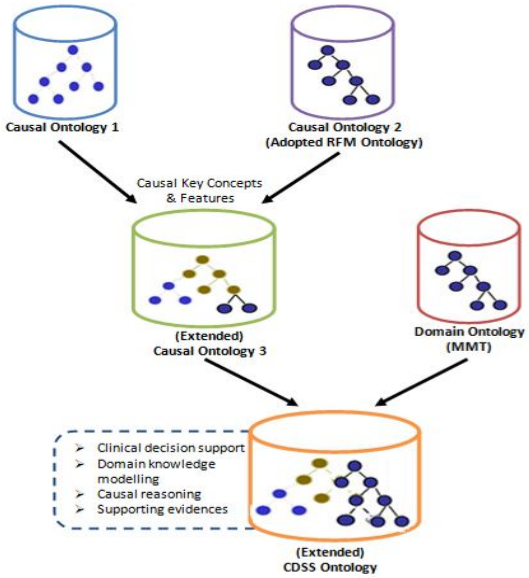

Figure 3: Structural Design of Ontology Model

   ii) Merge the ontologies by using the Protégé merge tool (i.e. merge ontologies option from refactor menu).

   iii) Check the consistency of the merged ontology via running a reasoner and/or perform modifications for removing the presented inconsistencies or similarities.

Figure 3 shows the ontology design and merging tasks involved in this study. The ontology model is initially consists of three ontologies. The Causal Ontology 1 (CO1) represents the key concepts and features of causality that have been

previously described in Section 2.3. The Causal Ontology 2 (CO2) represents the reuse of RFM ontology for modelling the causal chain concepts, whereas the third ontology is the domain ontology that models the medical knowledge for our case study (i.e. Methadone Maintenance Therapy (MMT)). The CO1 and CO2 ontologies are then merged into an extended causal ontology (i.e. Causal Ontology 3 (CO3)) in order to relate and extract the causal concepts from both ontologies. Subsequently, the CO3 ontology are then merged with the domain ontology for generating an extended ontology (i.e. CDSS Ontology) that models and integrates the domain knowledge of MMT with causal reasoning concepts, decision support, and supporting evidences.

4. DESCRIPTIONS OF ONTOLOGY-BASED CDSS MODEL FOR MMT CASE STUDY

This section describes the developed ontology-based CDSS model for the case study of Methadone Maintenance Therapy (MMT). MMT is a therapy of methadone drug substitution for drug addicts. MMT replaces hazardous drugs like heroin with methadone that have same interaction, but lower additive effects. The followings provide the brief descriptions for final extended ontology (i.e. CDSS Ontology). The resulted CDSS Ontology consists of three main classes; (i) ***Causal Reasoning***, (ii) ***Methadone Maintenance Therapy***, and (iii) ***Source*** classes (i.e. references / evidences). In this section, the ontologies are described in terms of OWL classes, properties, and instances. In order to easily recognized these terms in text, the OWL classes terms are italicized and in bold font (e.g. ***Class Name*****)**, the properties terms are solely italicized (e.g. *property name*), and the instances are underlined and italicized (e.g. *instance name*).

4.1 *Causal Reasoning* Class

The ***Causal Reasoning*** class is obtained from the merged causal ontology (i.e. Causal Ontology 3 (CO3)). This class consists of two main subclasses for representing the corresponding causality concepts and features: (1) ***Causal Concepts*** and (ii) ***Graphical Causal Modelling*** classes. Figure 4 shows the defined class hierarchy for this class. The ***Causal Concepts*** class consists of five subclasses representing the concepts of necessity and sufficiency, distal and proximal causes, causal relation (i.e. linear, cyclic), causal direction, and the causal chain concepts from RFM ontology. The ***Graphical Causal Modelling*** class represents the graphic visualization techniques in causal modeling, and consists of two subclasses representing different kind of visualization techniques. Several object properties are asserted for expressing particular relationships. Figure 5 and 6 shows the snapshots of OntoGraf or the example of object properties assertions in these classes. The rectangles with yellow circle represent the classes of the ontology, and the solid blue lines with arrowhead represent the hierarchy relationship between two classes (i.e. *has subclass*). Additionally, the dashed lines indicate the assertion of object properties between the classes or individuals. The dashed arrow with equal sign represents the equivalence class expression (i.e. *EquivalentTo*).

From Figure 5, the ***causal structure (causal chain)*** class represents the concept of causal chain (i.e. from ***Causal Chain RFM*** class). The object property *isFormedOf* is asserted for expressing the classes that are related with the concept of causal chain. In addition, *hasCausality* property is asserted between the classes that have associated causal concepts. Furthermore, from Figure 6, the object property *hasCausalRelation* is asserted for describing the corresponding types of causal relation, whereas *hasCausalInfluence* property indicates the types of causal direction involved

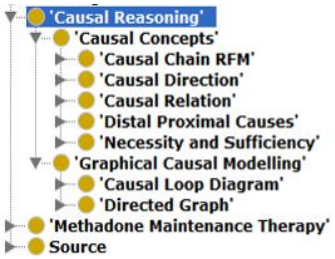

Figure 4: Class Hierarchy of ***Causal Reasoning*** Class

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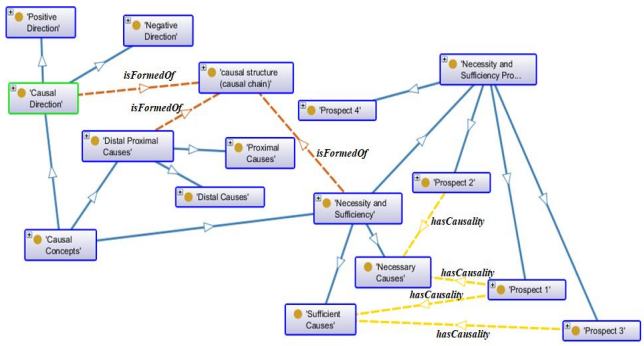

Figure 5: OntoGraf of ***Causal Concepts*** Class

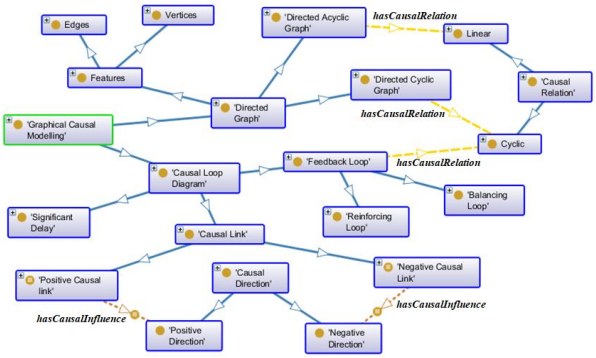

Figure 6: OntoGraf of ***Graphical Causal Modelling*** Class

4.2 *Methadone Maintenance Therapy* Class

This class models the domain knowledge of MMT with decision support and causal reasoning involved in this

therapy. The causal reasoning is discovered through exploring the three distinct phases in MMT: induction, stabilization, and maintenance phases. This involves identifying causal relationship (i.e. cause-and-effect) between clinical variables and it is based on the causality concepts and supporting evidences. Thus this class is related to the ***Causal Reasoning*** and ***Source*** classes for expressing the causality involved and evidences that support the reasoning. This class consists of three main subclasses: (i) ***Clinical Observations***, (ii) ***Dosage Adjustment***, and (iii) ***MMT Phases*** classes.

The ***Clinical Observations*** class describes the clinical attributes that being observed during MMT. This class consists of six subclasses (see Figure 7) representing different kinds of observation during the therapy. Several assertions of object and data properties are asserted for expressing particular features and relationships. For example, *isSufficientCauseFor* property denotes the sufficient causal factor (e.g. ***HIV Risk Behaviours*** *SubClassOf isSufficientCauseFor some* ***HIV***). In addition, the subclass of ***HIV Risk Behaviours*** class (i.e. ***Drug-related*** class) is related with some of the subclasses of ***Causal Reasoning*** class, as the HIV drug-related behaviours can be illustrated by a CLD model (Figure 8). The CLD model consists of two reinforcing loops that merely contain the positive causal links. The first reinforcing loop (R1) describes the causal factors or relations involved in HIV drug related behaviours.

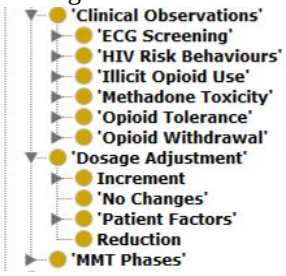

Figure 7: Class Hierarchy of ***Clinical Observations*** and ***Dosage Adjustment*** Classes

. The second reinforcing loop (R2) shows that HIV affects the occurrence of AIDS, and then in turn affects the spread of HIV infection. From Figure 8, there is a delay (i.e. double slashes (||)) involved before the HIV evolves into AIDS, since it can take many years before the infection develops into AIDS. As a result, the depicted CLD model is represented as the instances of ***Drug-related*** and ***Causal Loop Diagram*** classes (Figure 9). The following shows the Protégé / DL syntax for the asserted object properties in this class:

'Drug-related' *SubClassOf (hasCausalRelation* some ***'Cyclic'***) *and (hasDepiction* some ***'Causal Loop Diagram'***)
'Drug-related' *SubClassOf hasCausalChain* some (***'sequential causal chain'*** and ***'ongoing causal chain'***)
'Drug-related' *SubClassOf hasCausality* some (***'Distal Causes'*** and ***'Proximal Causes'***)

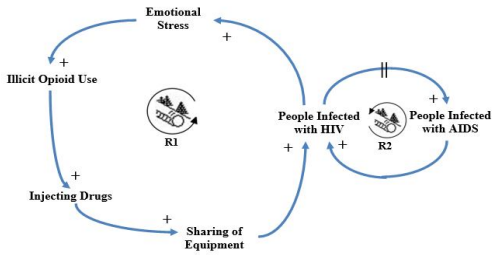

Figure 8: CLD Model of HIV Drug-related Behaviours

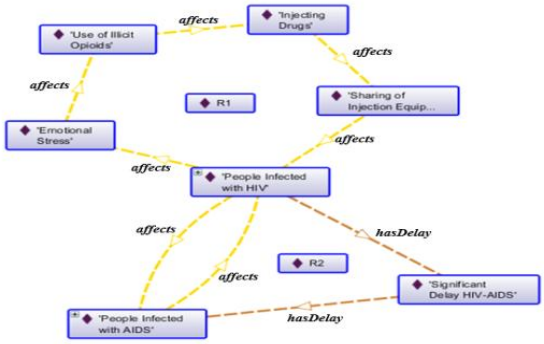

Figure 9: OntoGraf of CLD Model Instantiation

Furthermore, the ***Dosage Adjustment*** class represents the features of dosing modifications in MMT, and consists of four subclasses. The ***Increment***, ***Reduction*** and ***No Changes*** classes represent the three types of dosage adjustments in MMT, whereas the ***Patient Factors*** class describes the patient's categorization of methadone toxicity risk for the initial and increment dosing procedure.

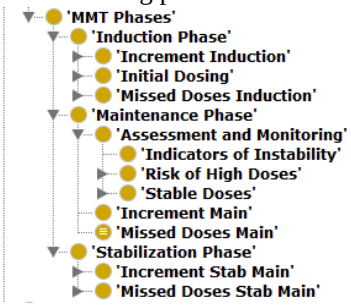

Figure 10: Class Hierarchy of ***MMT Phases*** Class

The ***MMT Phases*** class contains the description of three distinct phases in MMT and thus consists of three subclasses (see Figure 10). Each of these classes contains a description on the initial and/or increment dosing and the management of missed doses. The ***Induction Phase*** class represents the initial period of MMT in which the initial and increment of methadone dose is being prescribed. The ***Stabilization Phase*** class represents a period where the stable dose is being approached, whereas the ***Maintenance Phase*** class represents a period where the patients have achieved their stability usually on doses between 60 - 120 mg. A stable methadone dose indicates that the dose is adequate for blocking the euphoric effects of opioids (e.g. heroin) and able to inhibits the desire for seeking illicit opioids. However, some patients might respond well to a lower doses (i.e. below

60 mg), while others might require higher stable doses (i.e. above 120 mg). These can be justified based on the particular clinical conditions. From Figure 10, this class contains a subclass, which is the ***Assessment and Monitoring*** class that represents the involving evaluation and considerations during this phase. This class consists of three subclasses. The ***Indicators of Instability*** class describes the signs of patient instability (i.e. these signs indicate that the stable dose has not been achieved). The ***Risk of High Doses*** class represents the risks that associated with the patients that have high methadone doses (e.g.. risk of prolonged QTc interval and Torsades de Pointes (abnormal heart rhythm that cause sudden cardiac arrest)).

The ***Stable Doses*** class represents the achievement of stable dose, and contains three subclasses representing the stable doses categorizations (i.e. low (< 60 mg), moderate (60 – 120 mg), and high (> 120 mg)). The ***Low Stable Doses*** and ***High Stable Doses*** classes contain the descriptions for justifications of low and high stable doses. These justifications are described in terms of causal chain that consists of distal and proximal causal factors. Hence, both of these classes contain several subclasses and properties assertions that represent the respective distal and proximal causal factors of corresponding stable doses (as shown in Figure 11 to Figure 13). The causal chains are expressed in terms of instances in associated classes. The rectangles with purple diamond shape represent the instances, whereas the solid purple lines denote the instantiation relation (i.e. *has individual*). Besides, the ***High Stable Doses*** class consists of two subclasses for providing two kinds of justifications for high stable doses.

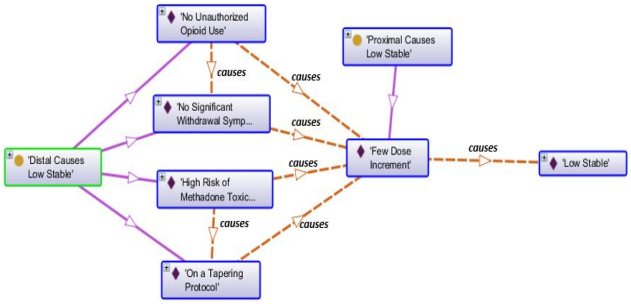

Figure 11: OntoGraf of Causal Chain Instantiation in ***Low Stable Doses*** Class (*Justification Low Stable Doses*)

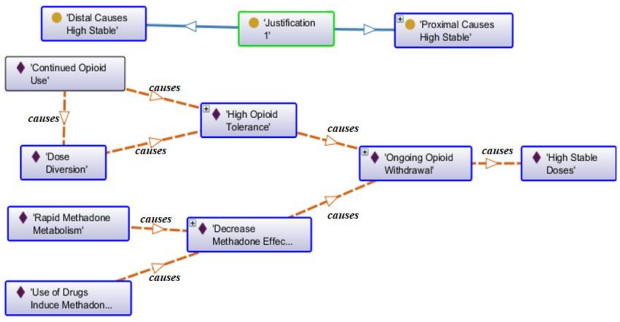

Figure 12: OntoGraf of Causal Chain Instantiation in ***Justification 1*** Class (*Justification High Stable 1*)

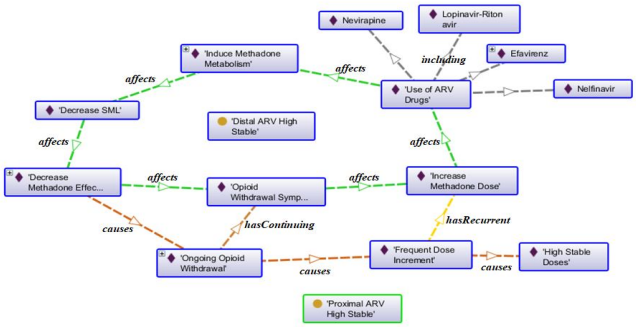

Figure 13: OntoGraf of Causal Chain Instantiation in ***Justification 2*** Class (*Justification High Stable 2*)

The ***Justification 1*** class represents the general justification that contains several causes of high stable doses. The ***Justification 2*** class represents the justification that emphasizes the relation between the use of ARV that induce methadone metabolism and high stable doses, as the case study involves the MMT patients that receive ARV (Antiretroviral) therapy. ARV is a type of therapy that is being used to treat the HIV infections.

4.3 *Source* Class

The ***Source*** class contains information about the referred experts, clinical practice guidelines (CPG), publications, and collected sample data. From Figure 14, this class contains three subclasses represent different kinds of referred sources. Several data properties and instances are asserted for describing the details of information such as *hasRefDetails* and *hasURL*. An object property *hasSource* is formed for representing the source of evidence or referred literature.

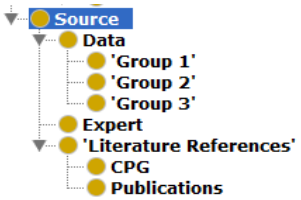

Figure 14: Class Hierarchy of ***Source*** Class

The ***Data*** class represents the data collected in MMT case study. This class consists of three subclasses representing the three groups of patient's categorization. These groups indicate the methadone toxicity risk categorization based on the factors of HIV infection status and use of ARV drugs. These subclasses contain several descriptions of causal analysis for the dataset. Figure 15 presents the analysis in terms of causal network (or Bayesian Network), which describes the analysis of patients that had achieved stable doses based on the HIV and ARV factors categorization. Furthermore, Table 1 shows the rate analysis (or probability) of stable doses achievement between the HIV and ARV factors. As a result, several properties and instances are asserted for expressing the analysis and also the justifications for the corresponding stable doses. For example;

// In instances of ***Group 1*** class
Low Risk hasLowStableRate "12.5"^^percent
Low Risk hasModStableRate "56.25"^^percent
Low Risk hasHighStableRate "31.25"^^percent
Low Stable 1 hasJustification Justification Low Stable Doses
High Stable 1 hasJustification Justification High Stable 1
// In instances of ***Low Stable Doses*** class
Low Stable hasProbInGroup1 "1.0"^^xsd:double

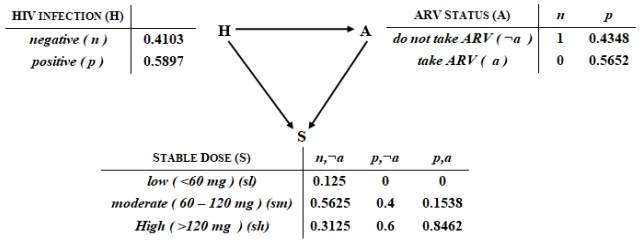

Figure 15: Causal Network of Stable Dose based on HIV & ARV

Table 1: Rate Analysis of Stable Dose between HIV & ARV Factors

	Low Doses	Moderate Doses	High Doses
(n, ¬*a*)	1	0.6	0.2273
(p, ¬*a*)	0	0.2667	0.2727
(*p, a*)	0	0.1333	0.5
Note: Italicized terms based on Figure 15			

5. EVALUATION AND DISCUSSION

For the evaluation process, several tools have been used to evaluate the developed ontologies, including the Pellet reasoner, Ontology Pitfall Scanner (OOPS), and several ontology metrics computation. Generally, ontology evaluation is the task of measuring the quality of ontology in respect to particular criteria [24]. The aim of the evaluation process is to determine i) what the ontology defines correctly, ii) what it does not define, and iii) what it defines incorrectly [25]. The ontology evaluation can be categorized in the context of two concepts which are verification and validation. Ontology verification refers to the task of evaluating if the ontology was built in the right way, while ontology validation refers to the task of evaluating if the right ontology was built [24], [25].

In this study, as regards verification, Pellet reasoner is used to evaluate the consistency of the developed ontology model. This reasoner verifies whether there are any logical contradictions in the ontology axiom. In addition, an evaluation tool known as OOPS has been used for validating the ontology model. One approach for validating the ontology is to check whether the ontology contain anomalies (or pitfalls) [25]. In OOPS, the ontologies are measured relatively to several dimensions and criteria: i) classification by dimension (structural, functional, and usability profiling dimensions); and ii) classification by evaluation criteria (consistency, completeness, and conciseness). In this study, multiple OOPS scans were performed, since the evaluation of an ontology is an ongoing and continuous process during development and engineering of ontology. Several pitfalls were detected by OOPS, including critical, important, and minor pitfalls. For each detected pitfall, its code and description are indicated in order to identify where and why the pitfall occurs. Other useful information is also needed for understanding its implications and the way to fix it. Other than that, the ontology model is also evaluated based on several ontology metrics computation for evaluating the ontology quality. This kind of metric-based (or feature-based) technique provides a quantitative perspective of ontology quality [26]. It examines through the ontology to assemble different kinds of statistics regarding the knowledge presented in the ontology. Base metrics is one of the main ontology metrics that consists of simple metrics computation such as counting of axioms, classes, properties, and individuals. The other main metrics reported in the literature includes the schema and knowledgebase metrics. The schema metrics evaluate the ontology design and its potential for rich knowledge representation. The knowledgebase metrics asses how data is represented in terms of instances of the ontology and the effective utilization of the knowledge modeled in the schema. The following describes the metrics (or computations) involved in these metrics sets.

1) Schema metrics

- Attribute richness: This metric (*AR*) is defined as the ratio of the number of attributes or properties (*att*) per class (*C*). It is assumed that the more attributes are defined, the more knowledge the ontology conveys.

$$AR = \frac{|att|}{|C|} \quad (1)$$

- Inheritance richness: This metric (*IR*) measures how well the knowledge is classified into different groups and subgroups in the ontology. It is defined as the average number of subclasses (*H*) per class (*C*).

$$IR = \frac{|H|}{|C|} \quad (2)$$

- Relationship richness: This metric (*RR*) indicates the diversity of the features of relations in the ontology. It is computed as the number of non-inheritance relationships (*P*) divided by the sum of number of inheritance (*H*) and non-inheritance relationships. Non-inheritance relationships include the object properties, equivalent classes, and disjoint classes.

$$RR = \frac{|P|}{|H| + |P|} \quad (3)$$

2) Knowledgebase metrics

- Class richness: This metric (*CR*) relates to measuring how instances are distributed across classes. It is computed as the number of non-empty classes (i.e. classes with instances) (*C`*) divided by the total number of classes defined in the schema (*C*).

$$CR = \frac{|C`|}{|C|} \quad (4)$$

- Average population: This metric (*AP*) measures the average distribution of instances (*I*) across all classes (*C*). It provides as an indication of how well is the data extraction performed to populate the knowledgebase.

$$AP = \frac{|I|}{|C|} \quad (5)$$

The obtained metrics are then compared with other OWL ontologies that are available and relevant to our study (see Table 2). There are four ontologies that have been compared; (i) TrhOnt (Telerehabilitation Ontology) [27], (ii) GENE-CDS (Genomic Clinical Decision Support Ontology) [28], (iii) OAE (Ontology of Adverse Events) [29], and (v) DAO (Drug Abuse Ontology) [30]. TrhOnt is an ontology which provides a reference model for the physiotherapy treatment, especially in the glenohumeral (i.e. shoulder) joint issues. GENE-CDS is a type of pharmacogenomics ontology that provides a decision support for the adverse drug reactions cases. Furthermore, OAE is a biomedical ontology that describes adverse events that occur after medical interventions (e.g. vaccination, surgeries). In OAE, the causality is emphasized to discover the causal relationship between the adverse events and medical interventions. In addition, DAO is an ontology that models the prescription drug abuse domain and is the result of joint manual effort of domain experts from Ohio Center of Excellence in Knowledge-enabled Computing.

From Table 2, it shows that our ontology model has a high value for these schema and knowledgebase metrics. For the attribute richness, our ontology model has a high number of properties for capturing the domain knowledge with causal reasoning concepts and evidences, and thus has higher value for this metric than the other models.

Table 2: Comparison of Ontology Metrics

Metrics	TrhOnt	GENE-CDS	OAE	DAO	Our Model
# of Classes	120	2265	4566	82	207
# of Properties	57	2	24	38	165
# of Instances	126	0.0	0.0	266	684
# of Subclasses	67	3292	6761	69	378
Attribute richness	0.475	8.8E-4	5.3E-3	0.463	0.7971
Inheritance richness	0.5583	1.4534	1.4807	0.841	1.8261
Relationship richness	0.5864	0.2387	0.0111	0.349	0.6655
Class richness	0.1917	0.0	0.0	0.415	0.9517
Average population	1.05	0.0	0.0	3.24	3.3043

Moreover, our ontology model has a high value for the inheritance richness since a high number of subclasses have been defined for integrating several concepts and knowledge. Besides, our ontology model also has richer non-inheritance relationship (i.e. relationship richness) than the other models. Higher values of this metric indicate a higher diversity of relations between classes and more expressivity in the ontology. The TrhOnt ontology also has a high value for this metric, since it integrates several knowledge sources such as from other ontological models and databases for capturing the physiotherapy domain knowledge. Furthermore, for class richness, our ontology model has higher value for this metric. This indicates that our ontology contains a richer knowledgebase, and the instances are well distributed across the classes. Subsequently, our ontology model also has higher value for average population metric since a high number of instances have been defined for representing several knowledge and concepts. The DAO ontology also has a high value for this metric as it captures the behaviors of prescription drug abusers from several web forum posts and other social media sites for the drug abuse epidemiologic research.

As a result, these indicate that our model is feasible and contains good quality as other ontology model. In addition, these also indicate that our ontology is not likely to contain the redundant classes and properties.

Besides that, in order to further evaluate the developed CDSS model, a comparison is made (i.e. Table 3) with the existing CDSS models based on the CDSS requirements for logic of decision support. Most of these CDSS models used the ontology-based technique for developing their models. As described previously, ANFIS has been used in this study for predicting the methadone stable doses [11].

Table 3: Comparison of Logic of Decision Support Requirements

	Recommendation	Reasoning	Causal Reasoning	Evidence
CDSS[1] [31]	✓	✓	-	✓
CDSS[2] [5]	-	-	-	✓
CDSS[3] [27]	✓	-	-	-
CDSS[4] [32]	-	✓	-	-
CDSS[5] [7]	✓	-	-	✓
Our Model	✓	✓	✓	✓

Besides, the ontology-based technique has also been used for developing the CDSS model that integrates the MMT domain knowledge with causal reasoning, decision support, and supporting evidences. From Table 3, it shows that our CDSS

model able to provide full support to these requirements particularly in the provision of causal explanation compared to other CDSS models. For example, Yet and his colleagues (2017) developed a CDSS for mangled extremity cases, and the CDSS model provides predictions that are useful for clinicians in trauma care [5]. However, the rationales for the generated predictions are not being concerned and explained. For instance, instead of simply showing the patient survival risks, it is more helpful and practical if the system provides causal explanations and evidences for the predicted risks for making better risk assessment. Moreover, Esposito and De Pietro (2011) developed a CDSS that classify cerebral white matter lesions for supporting the neuroradiologists in multiple sclerosis case [32]. They provide explanations for their diagnostic results by expressing it in the ontology model. Nevertheless, the given explanations are not sufficient as the explanations lack of causal mechanism, and the evidences are not presented. Furthermore, Kong (2011) developed a CDSS that predicts the risks of cardiac chest pain [31]. Although the explanation for the diagnostic result is provided and based on evidence, but the given explanation are not sufficient as it lack of causal reasoning and simply based on inferred rules. This matter is relatively similar to other studies such as in [32].

As a result, these signify the contributions of this study. The developed CDSS model shows potential for providing a good decision support The CDSS model can be further applied as an online system that provide decision support in MMT including the provisions of recommendations, causal reasoning, and supporting evidences. These can facilitate the physicians in managing and improving the MMT care services.

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