

1 Article

2 **Guideline-enabled data driven clinical knowledge** 3 **model for the treatment of oral cavity cancer acquired** 4 **through a refined knowledge acquisition method**

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18

19 **Abstract:** Validation and verification are the critical requirements in the knowledge acquisition
20 method for the clinical decision support system (CDSS). After acquiring the medical knowledge
21 from diverse sources, the rigorous validation and formal verification process are required before
22 creating the final knowledge model. Previously, we have proposed a hybrid knowledge acquisition
23 method for acquiring medical knowledge from clinical practice guidelines (CPGs) and patient data
24 in the Smart CDSS for treatment of oral cavity cancer. The final knowledge model was created by
25 combining knowledge models obtained from CPGs and patient data after passing through a
26 rigorous validation process. However, detailed analysis shows that due to lack of formal verification
27 process, it involves various inconsistencies in knowledge relevant to the formalism of knowledge,
28 conformance to CPGs, quality of knowledge, and complexities of knowledge acquisition artifacts.
29 Therefore, it is required to enhance a hybrid knowledge acquisition method that thwarts the
30 inconsistencies using formal verification. This paper presents the verification process using the Z
31 formal method and its outcome as an enhanced acquisition method – known as the refined
32 knowledge acquisition (ReKA) method. The ReKA method adopted verification method and
33 explored the mechanism of theorem proving using the Z notation. It enables to identify
34 inconsistencies in the validation process used for hybrid knowledge acquisition. Additionally, it
35 refines the hybrid knowledge acquisition method by discovering the missing steps in the current
36 validation process at the acquisition stage. Consequently, ReKA adds a set of nine additional criteria
37 to be used to have a final valid refined clinical knowledge model. The criteria ensure the validity of
38 final knowledge model concerning formalism of knowledge, conformance to GPGs, quality of the
39 knowledge, usage of stringent conditions and treatment plans, and inconsistencies possibly
40 resulting from the complexities. Evaluation, using four medical knowledge acquisition scenarios,
41 shows that newly added knowledge in CDSS due to the addition of criteria by ReKA method always
42 produces a valid knowledge model. The final knowledge model was also evaluated with 1229 oral
43 cavity patient cases, which outperformed with an accuracy of 72.57% compared to a similar
44 approach with an accuracy of 69.7%. Furthermore, ReKA method identified a set of decision paths
45 (about 47.8%) in the existing approach, which results in a final knowledge model with low quality,
46 non-conformed from standard CPGs. In conclusion, ReKA is formally proved method which always

47 yields valid knowledge model having high quality, supporting local practices, and influenced from
48 standard guidelines.

49 **Keywords:** Knowledge acquisition; Clinical practice guidelines; Data driven knowledge acquisition;
50 Cancer treatment plan; Clinical decision support system; Formal verification;
51

52 1. Introduction

53 Trust in the knowledge base is a crucial factor in the adoption of clinical decision support
54 systems (CDSS) used for medical diagnosis and treatment plan [1]. It mainly depends on the
55 reliability of the knowledge source and the consistency of the knowledge acquisition method [2].
56 There are diverse sources of clinical knowledge, such as patient data, clinical practice guidelines
57 (CPGs), clinical trials, systematic reviews, and even social media. Various knowledge acquisition
58 approaches have been proposed to acquire clinical knowledge from these sources. For example, using
59 machine learning and ontological approaches, knowledge models from patient data are created [3–
60 5], and different cognitive approaches are used to develop knowledge models from CPGs and other
61 medical resources [6–9]. Depending on the requirements, these knowledge models may need to be
62 transformed into different model formats. For example, the knowledge model from CPGs can be
63 converted into computer-interpretable guidelines (CIGs) so that it could be directly plugged into
64 CDSS for inferencing. Furthermore, sometimes it is required that the knowledge acquisition methods
65 transform two different knowledge models (sharing the same domain problem possibly with
66 different sources) into a unified knowledge model. It is critical in knowledge engineering disciplines
67 that each transformation, provided by the designed knowledge acquisition method, shall ensure the
68 two basic requirements:

- 69 1. The *transformed knowledge model* is the *valid* representation of the source *knowledge model(s)*.
- 70 2. The *transformation process* is *consistent* enough to produce always the *valid knowledge model*.

71
72 Figure 1 shows the knowledge transformation with a set of knowledge acquisition methods in
73 general. The two basic requirements, for each transformation, is depicted as necessary questions to
74 be answered, at each knowledge acquisition method of transformation. Question 1 reflects the first
75 requirement mentioned above, and the answer is to provide a *validation mechanism* in the knowledge
76 acquisition method. Question 2 represents the second requirement of the knowledge acquisition
77 method, which necessitates the *verification mechanism* in the knowledge acquisition method. In a
78 nutshell, *validation*, and *verification* are the critical requirements in the CDSS development process to
79 ensure that the knowledge model is valid, and the entire knowledge acquisition method is consistent.

80 In terms of verification, most of the existing approaches [8,10,11] emphasize the principles of
81 knowledge engineering. However, none of them have focused on the alignment of the verification
82 process to the development processes of CDSS. On the other hand, formal methods are widely used
83 in software engineering disciplines such as verification of program [12], formal modeling for
84 scenario-based requirement specification [13], formal verification of secured online registration
85 protocols [14], and formal verification of web services on cloud infrastructure [15]. Additionally,
86 some attempts were made to use the formal method (Z notation) to express the knowledge base
87 structure and reasoning mechanism in the form of software architectural style. For example, Gamble
88 et al. [16] applied Z notation to formally model the knowledge-base to get the clear distinction of
89 reusability of knowledge, enhanced understandability, and flexibility of specification in comparison
90 to traditional knowledge specification approaches.

91 This paper introduces the formal verification process, using Z notation, for our earlier
92 proposed hybrid knowledge acquisition method of Smart CDSS [17] – which is intended to produce
93 guideline-enabled data-driven knowledge model. In hybrid knowledge acquisition, we equipped the
94 method with the sophisticated validation process. Although, at that time, the knowledge model
95 created for oral cavity cancer was validated based on the well-established validation criteria and test-
96 based validation process. However, the knowledge acquisition method was not formally verified for

97 internal consistencies. The adaptation of the formal verification process gives an enhanced knowledge
98 acquisition method – which is known as a refined knowledge acquisition (ReKA) method. In ReKA,
99 we are using Z notation. The selection of Z notation was mainly based on its key features such as *data*
100 *rich formalism, ease in knowledge modeling, and support of tools*. It is important to mention here, that the
101 artifacts of the proposed verification process (using z notation) align to the content of a development
102 framework that was indigenously used for the development of Smart CDSS in the cancer domain.
103 The development framework for Smart CDSS is based on RUP [18,19] and ISO RM-ODP processes
104 [20,21]. To the best of our knowledge, the existing approaches had neither explored the use of Z
105 notations for the verification of knowledge acquisition nor used the formal methods as a method
106 content in a CDSS development framework.

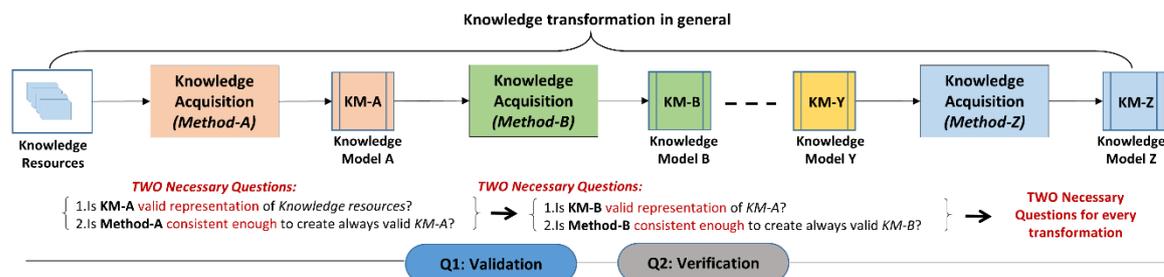
107 Before the ReKA method, the validity of the knowledge model relied on domain experts. They
108 were free to refine the decision paths in the final knowledge model. This freedom in refinement leads
109 toward a set of inconsistencies which were ignored by the previous method. Examples of some
110 possible inconsistencies in terms of clinical context of oral cavity cancer that could be introduced into
111 knowledge model; i) domain expert may add inappropriate follow-up treatments to knowledge
112 models – such as treatment surgery followed by radiotherapy for palliative patients (deviation from
113 CPGs which suggest follow-up without further treatment) and ii) domain expert may add or refine
114 the rule of evaluating next treatment plan for a variable or patient condition that is not readily
115 available or not in use in existing clinical practices – such as evaluating the palliative patient for
116 radiotherapy based on histopathological risk factor perineural invasion (PNI). In the scope of the
117 current study, this refinement produces inconsistency of introducing non-recordable risk factor
118 (outbound refinement as PNI does not exist in the healthcare system).

119 The detailed evaluation shows that the introduction of formal verification has significantly
120 contributed to revealing hidden inconsistencies in earlier proposed hybrid knowledge acquisition
121 method. In the presence of these inconsistencies, the knowledge model evolution is not always
122 guaranteed to be valid. The ReKA method, as a result of the verification, can identify the main cause
123 of the inconsistencies and guaranteed always producing the valid final knowledge model.

124 This paper addresses following research questions: a) Does introduction of formal verification
125 using Z notation is able to identify the inconsistencies in the developed knowledge acquisition
126 method with respect to standard knowledge resources such as CPG?; b) Does formal verification
127 ensures that knowledge acquisition methods will always maintain the quality of the knowledge?; c)
128 Does propose formal verification is able to prevent inconsistencies occurred due to complexity and
129 freestyle usage of refinement in the knowledge?; d) Is the knowledge model created using ReKA
130 comparable with existing hybrid knowledge models in terms of validity, quality, and integration with
131 workflows?

132 The main contribution of this work is as follow:

- 133 ● The proofs of the theorem using Z notations provides a comprehensive explanation for
134 checking the consistency of the knowledge acquisition method. These proofs enable
135 detection of hidden inconsistency in the acquisition method (hybrid knowledge acquisition)
136 and provide with an additional set of nine criteria to ensure that the enhanced method
137 (ReKA) always produces a valid knowledge model.
- 138 ● The formal verification activities are streamlined into a concrete set of processes which align
139 to various artifacts of Z notation.
- 140 ● Various aspects of Z notation exploited for the knowledge modeling and associated
141 processes are expressed as the inferenceable mathematical models.
- 142 ● The ReKA method is formally proved approach which always produces valid knowledge,
143 reflects the CPGs as global evidence and encourage the recommendations well supported
144 by local evidence. At the same time, it is revealed that the model created using ReKA is
145 outperformed compared to the similar approaches available.



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147
148
Figure 1: Knowledge acquisition process

149 **2. Overview of knowledge acquisition for Smart CDSS**

150 In our earlier work, we proposed a novel *hybrid knowledge acquisition* method for Smart CDSS
151 [17]. The acquisition method was accompanied by the proper validation process to ensure the validity
152 of the final knowledge model. In this paper, we are introducing a formal verification for the hybrid
153 knowledge acquisition method, which results in an enhanced method - ReKA. Before going into
154 details of formal verification, it is worthwhile to introduce the knowledge models and validation
155 processes briefly of the hybrid knowledge acquisition method. We encourage the readers to read [17]
156 for detailed descriptions of the models and validation processes used in the hybrid knowledge
157 acquisition method.

158
159 **2.1. Hybrid knowledge acquisition approach for Guideline enabled data-driven knowledge model**

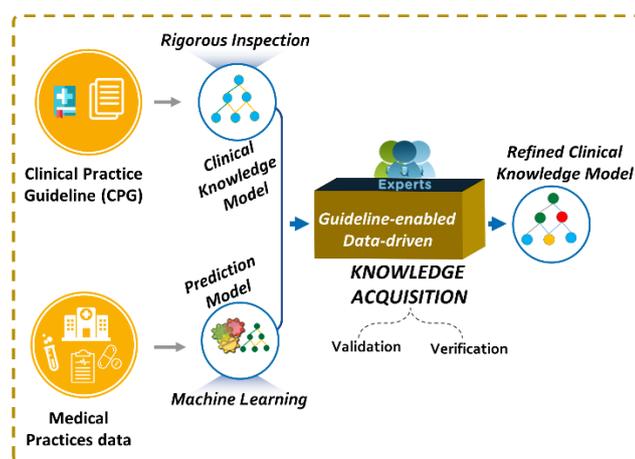
160 In the clinical domain, patient data and CPGs are the most common sources of knowledge for
161 CDSS. Most of the existing knowledge acquisition methods use both sources of knowledge
162 independently. From patient data, the knowledge models are created using machine learning, while
163 from CPGs, various cognitive methods of knowledge acquisitions apply to the knowledge models.
164 Both methods have potential pros; however, there exist some limitations for each of them. The
165 knowledge acquisition method which combines both approaches can overcome somehow those
166 limitations. The key limitations of data-driven knowledge acquisition methods using machine
167 learning are as follows:

- 168 ● The quality of the knowledge model depends on the quality of the patient dataset. So the
169 performance of the model (such as accuracy) may vary for the same domain with different
170 datasets.
- 171 ● The model validation relies on the statistical validation process (e.g., 10-fold cross-
172 validation). In this case, the validation purely depends on data; and the domain experts are
173 unable to assert any additional criteria to apply constraints on the final knowledge model.
- 174 ● The final knowledge model supports only local evidence as it derives from patient data. The
175 recommendation becomes trustworthy for another organization if standard evidence from
176 CPGs and other published studies also associate with the knowledge model.

177
178 The use of CPGs as a knowledge source somehow resolves the inherent problems with the data-
179 driven approach. CPGs covers population-based knowledge supported by standard clinical evidence
180 gathered from different clinical studies. Although it covers-up some cons of the data-driven
181 approach, however, the knowledge models derived from CPGs also come with limitations:

- 182 ● CPGs are generic, and the model representing CPGs may not be able to integrate into health-
183 care work-flows directly.
 - 184 ● The knowledge model strictly following CPGs discourages local practices. In most cases, it
185 is possible that local practices may not fully conform and contradict to CPGs, but may have
186 a huge impact on patient care at that particular jurisdiction.
- 187

188 Very few studies include CPGs and patient data as a combined source for hybrid knowledge
 189 modeling. For example, Toussi et al. [22] used a model derived from patient data to complete the
 190 missing decisions in the CPGs. However, the primary motivation of *hybrid knowledge acquisition*
 191 method is to combine the data-driven knowledge acquisition method and CPGs based knowledge
 192 acquisition method to dilute their cons and take advantages of their pros in terms of the refined
 193 knowledge model. This knowledge acquisition method is adopted under the umbrella of the three-
 194 phase iteration process model of creating an executable knowledge model for Smart CDSS [17] in the
 195 cancer domain. The first two phases of the process model dedicated to knowledge acquisition, which
 196 covers knowledge model creations from CPGs and patient data and the validation process. The third
 197 phase concentrates on the executable knowledge model and the development of associated toolset
 198 [23]. Figure 2 depicts the abstract representation of hybrid knowledge acquisition method, and the
 199 next section provides a brief description of the core knowledge models and validation process of this
 200 approach.



201
 202 **Figure 2: Hybrid knowledge acquisition method**

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203

204 2.2. Knowledge models and validation mechanism

205 Hybrid knowledge acquisition method includes a set of tasks encompassing two phases of the
 206 iterative three-phase model [17]. In this section, we briefly describe this method of explaining the
 207 knowledge models and the process associated with the validation of the models (see Figure 2). The
 208 outcome of this method is the final knowledge model - known as a refined clinical knowledge model
 209 (R-CKM), which is obtained after the rigorous validation process. It consumes the knowledge models
 210 created from CPGs - known as a clinical knowledge model (CKM) and prediction model (PM) created
 211 from patient data.

212

213 **Prediction Model:** A PM is a decision tree obtained from patient data using decision tree algorithms.
 214 The decision tree algorithm used for this study was CHAID [24], which was selected based on
 215 rigorous selection criteria. PM creation involves the formal machine learning method - CHAID and
 216 reflects the local practices from patient data. As a decision tree formalism of the machine learning
 217 paradigm - it includes the root node and grows in a top-down fashion. The nodes represent
 218 conditions and leaf nodes as conclusions. The conclusion always lies at the leaf node where the branch
 219 selection at each condition uses proper statistical evaluation processes to proceed for the appropriate
 220 decision path. Finally, performance (such as accuracy) for each decision path evaluates from patient
 221 data, and its overall performance represents as mean accuracy of all the decision paths in PM.

222

223 **Clinical Knowledge Model:** A CKM is a formal decision tree created from CPGs after a rigorous
224 inspection process by a team of physicians. It follows decision tree formalism started with a root
225 node. The tree grows in a top-down fashion from the root node by adding subsequent nodes to make
226 a decision path. The nodes represent a decision node and a conclusion node. Decision node represents
227 condition(s) (such as patient symptoms) to select the next branch of the tree among decision paths.
228 Conclusion node reflects the recommendations (such as treatment plan). In CKM, the conclusion
229 node can also play a role of condition node for the next follow-up conclusion. For example, an initial
230 treatment plan for cancer patient may be surgery, and after follow-up, the secondary treatment plan
231 can be radiotherapy only if surgery already is done. In this context, unlike the decision tree formalism
232 of PM, the conclusion node may appear as an intermediate node in the CKM decision tree. Moreover,
233 the branch selection of the CKM decision tree does not follow any probabilistic evaluation of the
234 condition. Because CKM is a reference model of CPGs, so its performance evaluation against local
235 patient data is not required.

236

237 **Refined Clinical Knowledge Model:** A R-CKM obtained after a rigorous validation process by
238 combining PM and CKM. It follows the same formalism as of CKM. However, it also reflects some of
239 the properties of PM to encourage decision making from local practices. Unlike CKM, all decision
240 paths in R-CKM evaluated from local patient data, and it also requires evidence for decision paths
241 which are refined but have no direct conformance to the CKM (i.e., guidelines).

242

243 **Validation Process:** A validation process is the core of the hybrid knowledge acquisition method
244 which unifies two different models to a single refined knowledge model. Figure 3 depicts detailed
245 steps of the process. It consumes PM and CKM as an input model and produces R-CKM as an output
246 model. Each decision path in PM is selected and added to the decision path of R-CKM after passing
247 conformance criteria based on CKM. The PM decision path may be refined by domain expert if
248 required. The activities for the validation process briefly summarized in three steps:

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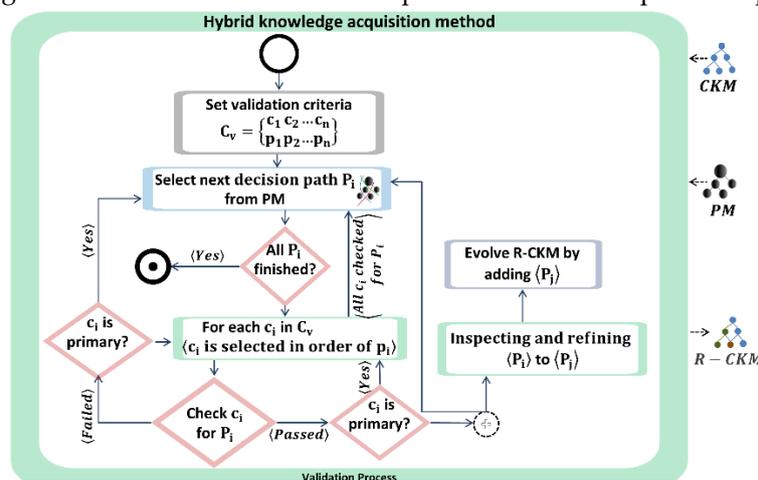
250 1. *Setting validation criteria:* Domain experts define criteria based on CKM (guidelines) and other
251 evidence to be fulfilled by decision path in PM. At the same time, each criterion is classified as
252 primary (compulsory) or non-primary (optional with an alternate), and the order of checking
253 specifies by priority. In the case of an oral cavity cancer treatment plan, domain experts decided
254 two primary and two non-primary criteria. i) The minimum performance limit *must* be satisfied
255 by each selected decision path in PM (e.g., accuracy greater than 50% in this study); ii) the
256 selected decision path in PM *must not* conflict with the CKM (guidelines); iii) the decision path
257 in PM *should* conform to any decision path in CKM, and iv) *if* criterion iii) is not fulfilled, then
258 the decision path in PM *must* be associated with an evidence which proves its necessity and
259 effectiveness of inclusion into R-CKM.

260

261 2. *PM validation against criteria:* During this step, each decision path is selected and evaluated
262 against the well-established criteria. The decision path of PM becomes part of R-CKM if it fulfills
263 the criteria.

264

- 265 3. *Inspection and refinement of selected PM decision path*: The selected decision path can become
 266 directly part of R-CKM. However, the domain expert may want to refine it further to reflect the
 267 most concrete concepts used in the healthcare workflows. Moreover, the refinement process also
 268 allows adding further choices of the treatment plan in the decision path if required.



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 270
 271
 272 **Figure 3: Validation Process [17]**

273 The hybrid knowledge acquisition method was used in the creation of the knowledge model for
 274 Smart CDSS in oral cavity cancer [17,23] with proper validation mechanism. However, it was not
 275 formally verified even after using as a core method of knowledge acquisition for Smart CDSS. In the
 276 validation process at the refinement step, the process provides the freedom to domain expert for
 277 adding further treatment plans as a condition to the selected decision path. It leads toward
 278 inconsistency and cannot guarantee the validity of R-CKM at all time. In order to cope with this issue,
 279 the content of this work introduces the verification process using formal Z notations. After applying
 280 the Z formalism, the outcome concludes with the detection of inconsistencies in the step of refinement
 281 of the validation process. It explicitly enlisted *nine additional criteria* that must be in place after
 282 refinements are made to the decision path in R-CKM. The existing knowledge acquisition method is
 283 enhanced as ReKA method to accommodate the newly discovered criteria.

284 3. Preliminaries and key motivation of using formal method for knowledge acquisition

285 3.1. Preliminaries

286 There are several ways to represent objects in the Z notation. Declaration, abbreviation, and
 287 axiomatic definitions are simple ways to represent objects in Z notation. "Schema" and "free" types
 288 are special ways to represent complex objects in Z notation. All of these types obey mathematical
 289 laws and have rules for reasoning with the information that they contain. At this point, the
 290 introduction and use of these concepts are important; however, in this paper, we skip the detailed
 291 description of the concepts used in Z notation. So, the important concepts introduced with brief
 292 details and all other concepts used in this paper provided in Figure 4. Readers may consult reference
 293 materials [25,26] and other research works that have used Z notation extensively [27–29].
 294

295 *Declaration*: This is the simplest way to define an object. When an object is a set of some basic
 296 type, brackets use to enclose the name of an object. If there are more than one objects, comma uses
 297 for separation between them. For example, type definition (1) in Figure 5 represents multiple object

298 declarations. *ConditionAttribute* and *ConditionValue* are the set of concepts and the corresponding
 299 values, respectively, in the clinical knowledge model that construct the basic *Condition*.
 300
 301

Definitions and declarations		Relations	
a, b	Identifiers	$A \leftrightarrow B$	Binary relation
p, q	Predicates	$\text{dom } R$	Relation domain
s, t	Sequences	$\text{ran } R$	Relation range
x, y	Expressions	R^{\sim}	Relational inverse (relational transpose)
A, B	Sets	$A \triangleleft R$	Domain restriction
R, S	Relations	$A \triangleright R$	Range restriction
$d; e$	Declarations	$A \triangleleft R$	Domain subtraction (Anti-domain restriction)
$a == x$	Abbreviated definition	$A \triangleright R$	Range subtraction (Anti-range restriction)
$[A]$	Given set	$R \oplus S$	Relation overriding
$A ::= b \langle\langle B \rangle\rangle \mid c \langle\langle C \rangle\rangle$	Free type declaration	$R \times S$	Cartesian product
let $a == x$	Local variable declaration	$a \mapsto b$	Maplet (order pair: same as (a,b))
Logic		Sequences	
$\neg p$	Logical negation	$\text{Seq } A$	Sequence
$p \wedge q$	Logical conjunction	$\text{seq}_1 A$	Non-Empty sequence
$p \vee q$	Logical disjunction	$\langle \rangle$	Empty sequence
$p \Rightarrow q$	Logical implication	$\langle x, y, \dots \rangle$	Sequence
$p \Leftrightarrow q$	Logical equivalence	$s \sim t$	Concatenation
$\forall x: p$	Universal quantification	$A \upharpoonright s$	Extract ($\{1,3,6\} \upharpoonright \langle a, b, c, d \rangle$ will give $\langle a, c \rangle$)
$\exists x: q$	Existential quantification	$s \upharpoonright A$	Filter ($\langle a, b, c, d \rangle \upharpoonright \{b, d, e\}$ will give $\langle b, d \rangle$)
$\exists! x: q$	Existential quantification (exactly one element)	$s \text{ in } t$	Is in ($\langle a, b \rangle$ in $\langle w, y, a, b, c \rangle$ is true. $\langle b, a \rangle$ in $\langle w, y, a, b, c \rangle$ is false)
if p then q else r	structural conditional logic	Schema Notation	
Sets			Schema
$x \in y$	Set membership	$\begin{array}{ c} s \\ \hline d \\ \hline p \end{array}$	
$\{ \}$	Empty set	$\begin{array}{ c} d \\ \hline p \end{array}$	Axiomatic definition
\mathbb{N}	Set of natural numbers		
$A \subseteq B$	Set inclusion	$\begin{array}{ c} T \\ \hline S \\ \hline d \\ \hline p \end{array}$	Schema inclusion
$\{x, y, \dots\}$	Set of elements		
$\langle x, y, \dots \rangle$	Ordered tuple		
$\mathbb{P}A$	Power set		
\mathbb{P}_1A	Non-empty power set		
$A \cap B$	Set intersection		
$A \cup B$	Set union		
$A \setminus B$	Set difference	ΔS	Change in schema
$\bigcup A$	Generalization union	ΞS	No schema change
$\bigcap A$	Generalization intersection	$S \cong T \wedge V$	Schema definition as value of schema expression
$\#A$	Size of finite set	$a?$	Input to an operation
$\{d; e \dots \mid p \bullet x\}$	Set comprehension	$a!$	Output of an operation
Functions		a'	State component after operation
$A \mapsto B$	Partial function	S'	State schema after operation
$A \rightarrow B$	Total function		

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Figure 4: Z notation concepts overview

Abbreviation: Abbreviation introduces another name to an existing object. For example, type definition (2) in Figure 5 is the abbreviation for cancer treatments.

Free type: Free type allows a variety of data structures to be represented using sets with explicit structuring information. For example, type definition (3) in Figures 5 highlights three different object definitions. *ConditionOperator* is a free type that distinctly represents the set of operators used in the *Condition*. The *Condition* further expresses the complex definition of the conditions used in the clinical

312 rules. *treatmentSet* is a free type that covers high-level semantics for cancer treatments that provided
 313 to a patient in a proper sequence by using the guidelines.
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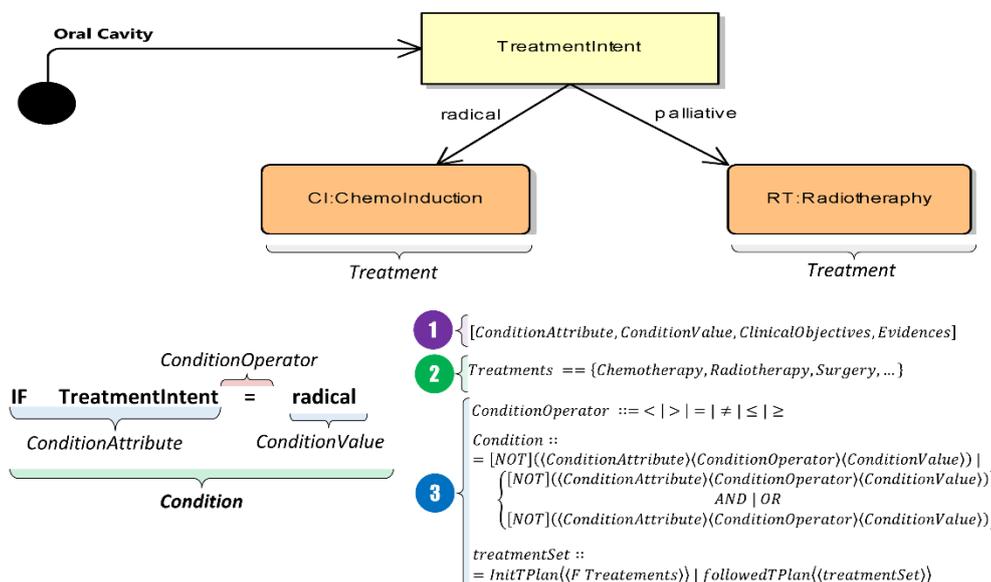


Figure 5: Declaration, abbreviation and free type examples

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 318
 319 *Axiom*: Axiom provides the ability to define objects and includes constraints upon it. In an
 320 axiomatic definition, the object definition represents in two compartments: declarations and
 321 predicates. Declarations represent the content structure of an object and predicates introduce
 322 constraints on the contents. Figure 6 shows an example of the axiomatic definition for CKM
 323 specification.
 324

325 *Schema*: Schema is the most powerful artifact in Z notation and describes the system behavior.
 326 Similar to an axiom, it defines objects using declarations and predicates. However, the schema can
 327 take different forms such as a modeling static structure, modeling operations, and modeling different
 328 states of the object after operations. Figure 6 shows an example of modeling CKM as a
 329 "ClinicalKnowledgeModel" schema.

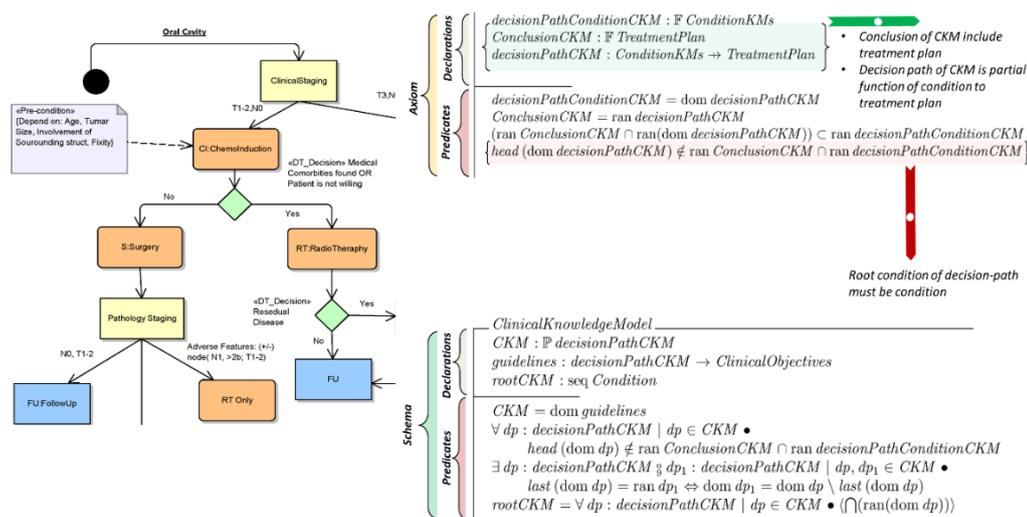


Figure 6: Axiomatic definition and schema example

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 331

332 3.2. *The motivation for formal methods*

333 The ability of domain experts to trust knowledge content is a key factor that influences the
334 success of CDSS implementation. The trust in knowledge primarily depends on how well the
335 knowledge contents have passed through a sophisticated validation process to ensure consistencies
336 in the refined knowledge model. According to a systematic review by Mor Peleg [2], formal
337 verification techniques are used to validate the clinical knowledge for internal consistencies and to
338 check for the fulfillment of the desired properties and specifications. There are two broad categories
339 of these techniques: model checking and theorem proving [2]. In model checking, the knowledge
340 transformed into an appropriate model-checker format, and the model checker verifies the
341 consistency of the knowledge model for the fulfillment of the desired properties. Alessio Bottrighi et
342 al. applied the model checking approach to integrating the computerized guideline management
343 system with a model checker [30]. The guideline representation language GLARE is used and
344 integrated with the SPIN model checker to verify the clinical guidelines. Theorem proving uses the
345 logical derivation of theorems in order to prove the consistency of the knowledge contents available
346 in the formal specification. Annette T. Teije et al. [31] used KIV-based formalism to represent medical
347 protocols and defined semantics of the desired properties. The desired properties of the protocol are
348 verified using formal proof of the KIV theorems.

349 Based on the substantial advantages and the need for formalism in knowledge validation and
350 verification, we introduced the formal verification process as a formal method content into the
351 development framework of Smart CDSS. Selection of an appropriate formal method requires formal
352 guidelines to find the best fit for a knowledge representation scheme. In this work, we used the Z
353 notation as the formal representation language for knowledge representation and for modeling the
354 validation method features. We used the formal theorem proving mechanism to remove
355 inconsistencies in the method, which ultimately ensures a consistent and valid knowledge model.
356 Following are fundamental features of Z notation, which compels its suitability for clinical
357 knowledge modeling and verification of the acquisition process.

358

359 1. *Easy knowledge modeling*: While using the Z notation, it is simple to decompose the know-
360 wledge specifications into small pieces and formally define the static and dynamic asp-
361 ects of the knowledge acquisition (i.e., the knowledge representation and validation pr-
362 ocess [25]). The "Schema" represents this aspect of Z notation, where the first-order pre-
363 dicate logic uses for the constraints on the typed knowledge contents. Moreover, dyna-
364 mic schema represents the validation process that operates within the boundaries of th-
365 e knowledge representation schema. The subsequent sections will elaborate, detailed co-
366 ntents of the formal verification process for the knowledge acquisition method in term-
367 s of Z specifications.

368 2. *Data-rich formalism*: Another aspect of Z notation is the notion of "types" [26]. Z types
369 are mathematical data types that can be used to represent any object in a system uniq-
370 uely. They specifically obey a rich collection of mathematical laws, which make it poss-
371 ible to determine the behavior of the system [25,26]. This aspect of Z leverage, toward-
372 s data-rich formalism of knowledge contents and the resulting artifacts, can be easily
373 mapped to standard viewpoints of RM-ODP [32] (e.g., the information viewpoint). H.
374 Bowman et al. used Z notation for consistency checking of the two views in the infor-
375 mation viewpoint [33]. Similarly, artifacts of Z notation can also map to the "analysis"
376 and "design" disciplines of the RUP framework.

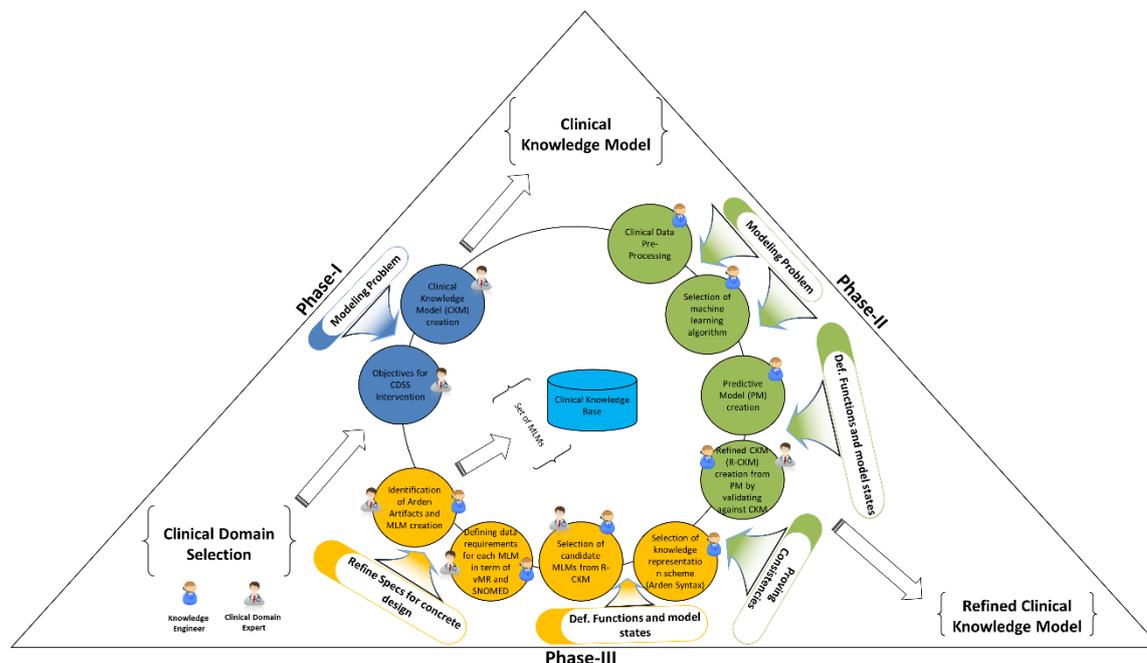
377 3. *Support of tools*: The Z specification language not only enables formal specifications for
378 a system and a language but also allows for the systematic reduction of such specifica-
379 tions into implementations [27]. Moreover, there is a wide range of tools available to c-
380 heck for syntax and type consistency in the specifications

381

382 4. Methods and Materials

383 4.1. Refined Knowledge Acquisition (ReKA) method

384 ReKA method is an enhancement of our hybrid knowledge acquisition method. It follows the
 385 same three-phase model used for hybrid knowledge acquisition method. It uses all the steps of hybrid
 386 knowledge acquisition described in section 2.1. Besides, it introduces new processes that involve the
 387 formal verification artifacts at different phases of the three-phase model. Figure 7 shows the extended
 388 three-phase model used by ReKA method. The extended processes are reflected as an additional layer
 389 on the basic processes.
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394 **Figure 7: Extended three-phase model for ReKA**

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This study focuses on the newly adopted processes of formal verification, so we skip details of the common process used with hybrid knowledge acquisition. The model created for oral cavity cancer in the earlier study is re-used for this study with new patient cases of 1229 from Shaukat Khanum Memorial Cancer Hospital (SKMCH), Lahore, Pakistan. Example scenarios have been created by physicians to modify our earlier oral cavity treatment model. Based on the earlier hybrid knowledge acquisition method, the modifications are valid; however, as demonstrated in the result section, ReKA identified that the modifications are not valid because it creates inconsistencies in the final knowledge model. Furthermore, we have also compared ReKA approach with the most relevant hybrid model acquisition approach. The subsequent sections further discuss the technical details of the formal verification processes used in the ReKA method.

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404 4.2. Establishing a formal modeling process

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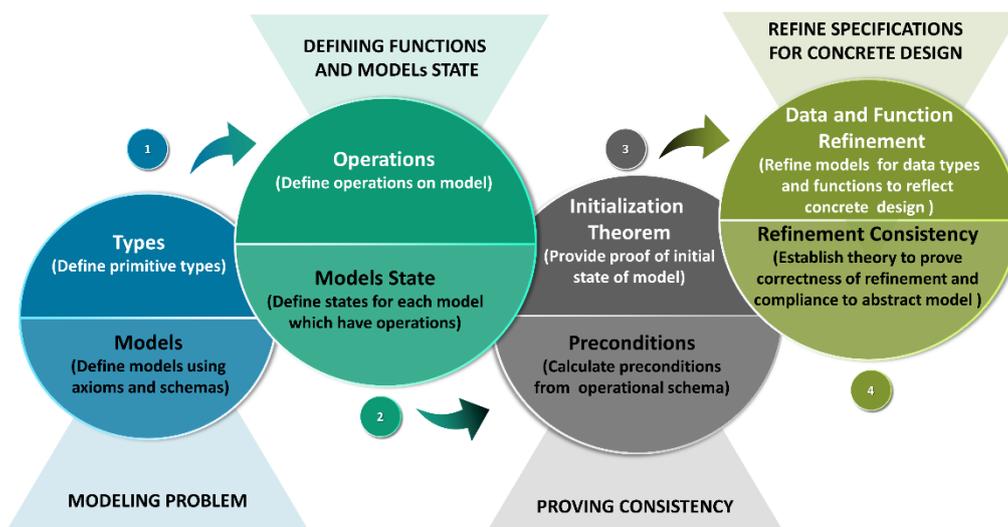
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To the best of our knowledge, no substantial evidence exists in a knowledge engineering discipline that discusses Z notation with discrete processes having proper guidance. Based on the capabilities of Z notation and the guidance available for applying different concepts of Z notation to formal modeling [25,26], we formulate a formal modeling process for knowledge acquisition method. It comprises four distinct processes: "modeling problem", "defining function and model states", "proving consistency", and "refine specification for concrete design". Below is a brief discussion of each of these processes. Figure 8 shows an abstract view.

413 1. *Modeling problem*: This includes tasks used to analyze the problem context and identify all
 414 of the relevant concepts that contribute to the final objectives. Different constructs of the
 415 selected formalism technique are used to model concepts at different granularity levels.
 416 Primitive types, axioms, free types, and schema are the candidate constructs in Z notations
 417 that assist in modeling the problem under consideration. During the knowledge acquisition
 418 method, various models created which include PM, CKM, and R-CKM. Different constructs
 419 of Z notation used in representing these models. The outcomes of this process produce
 420 primitive types, free types, sets of axioms, and sets of the static schema, which represents
 421 the knowledge models.
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Figure 8: Formal modeling process

426 2. *Defining functions and models state*: This includes tasks to define the behavioral aspects of the
 427 system under consideration. Defining operations related to the candidate models and
 428 associating the appropriate state model (as a consequence of the operation on the model)
 429 are the main activities of this process. Schemas are the central construct in Z and can
 430 represent the operations and states of the models. For the knowledge acquisition method,
 431 operations are defined for the retrieval of contents from PM, and CKM models. These
 432 operations will not affect changing the state of the corresponding models. Different
 433 operations define for the R-CKM model in order to validate the candidate decision path
 434 from PM against the CKM model and to evolve the final R-CKM model. As a result of the
 435 evolution of the R-CKM model, the corresponding state model is defined to formally
 436 represent possible changes in the contents of the R-CKM model.
 437 3. *Proving consistency*: Identifying inconsistencies in the specifications of the modeled problem
 438 is the ultimate goal of formal methods. The main task is to make sure that the defined models
 439 are consistent and have no contradictions with their desired requirements. Moreover, it is
 440 desirable to verify that the operations defined in various models are consistent and that their
 441 outcomes are within the intended boundaries of the domain. Z specification provides a well-
 442 established way to achieve both of these goals. The first part achieves, to prove the constraint
 443 part of the state schema of the model is satisfiable using "*initialization theorem*" - to indicate
 444 that an initial state, at least, exists. The second part requires to investigate "*preconditions*"
 445 for the candidate operations - that may be calculated from the operational schema using the
 446 one-point rule. For the knowledge acquisition method, the "*initialization theorem*" proves the
 447 satisfiability of the R-CKM state schema. Moreover, "*preconditions*" investigate for all
 448 operations that evolve the R-CKM model.

449 4. *Refining specification for concrete design*: The refinement process tends to construct and
 450 describe another model that complies with the original model of the design but is closer to
 451 implementation. The refinement process comprises large tasks that are applied in
 452 consecutive iterations at the data and function levels to ensure that the specifications are
 453 free of any uncertainty. These specifications are closer than previously modeled
 454 specification to executable program code. In order to prove that refinements are consistent
 455 within themselves and appropriately represent the original design model, it is necessary to
 456 establish a theory for refinement that includes a set of rules for proving the correctness.
 457

458 In this research work, we exploit the first three processes to model the clinical knowledge and
 459 the validation process in order to prove that the knowledge acquisition is sufficiently consistent with
 460 always producing valid final knowledge model. The refinement process is helpful for systems where
 461 the outcomes of the design are required to be sufficiently close for direct conversion into executable
 462 code. This process is included purposefully because our knowledge specification can be easily
 463 converted into the executable code if we properly exploit the Z refinement mechanism. Furthermore,
 464 we are presenting the "*Proving consistency*" step in the results section to emphasize the outcome of the
 465 formal verification process.

466 4.3. Modeling problem

467 The modeling problem investigates the basic concepts used in knowledge acquisition for Smart
 468 CDSS, which target the clinical objectives. The fundamental concepts used in Smart CDSS are PM,
 469 CKM, and R-CKM, which represent the clinical treatment plan for head and neck cancer. Primitive
 470 types, free types, axioms, and schema in Z notation are candidate constructs to represent these
 471 concepts.

472 4.3.1. Primitive types

473 Primitive types constitute the basic building blocks of the problem under consideration. In Smart
 474 CDSS, the concepts relevant to the clinical knowledge, which play a pivotal role in knowledge
 475 acquisition and validation, are cancer treatments (e.g., chemotherapy, radiotherapy, and surgery),
 476 clinical objectives (e.g., intervention for a treatment plan), and evidence (e.g., combined chemo-
 477 radiotherapy has a significant effect on patient survival; a success rate of 92%). These concepts are
 478 represented as a set using primitive types (Type Definition 1 :line 1). Furthermore, cancer treatment
 479 is abbreviated (line 3) as a general treatment to provide clarity in further specifications.
 480

Type Definition 1 Primitive types for clinical knowledge modelling

$[CancerTreatment, ClinicalObjectives, Evidences]$	(1)
$[Condition, ConditionAttribute, ConditionOperator, ConditionValue]$	(2)
$Treatments == \{CancerTreatment\}$	(3)

481 In order to define the formal representation of the knowledge model, primitive types are needed
 482 to capture the basic concepts used in the knowledge representation scheme. In Smart CDSS, the
 483 knowledge models follow decision tree representations where the combination of conditions with
 484 logical relationships constitutes the decision path. The *Condition* includes clinical concepts as an
 485 attribute with an exact value or a range of value sets. For example, a condition in the decision tree
 486 test node $TreatmentIntent = radical$ represents a patient categorization primarily based on the severity
 487 of cancer. Z primitive types (shown in Type Definition 1 (line 2) represents these concepts, and Type
 488 Definition 2 provides the corresponding language syntax for the condition.
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Type Definition 2 BNF for some primitive types

$$\text{Condition} ::= [\text{NOT}]((\langle \text{ConditionAttribute} \rangle \langle \text{ConditionOperator} \rangle \langle \text{ConditionValue} \rangle) | \{[\text{NOT}]((\langle \text{ConditionAttribute} \rangle \langle \text{ConditionOperator} \rangle \langle \text{ConditionValue} \rangle)\text{AND} | \text{OR} [\text{NOT}]((\langle \text{ConditionAttribute} \rangle \langle \text{ConditionOperator} \rangle \langle \text{ConditionValue} \rangle))\}) \quad (1)$$

$$\text{ConditionOperator} ::= < | > | = | \neq | \leq | \geq \quad (2)$$

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Moreover, free types in Smart CDSS reflects the semantics of the clinical concepts and provides conformance to decision tree representation formalism. For example, treatments provided to patients follow a sequence according to standard guidelines and protocols; ChemoInduction follows radiotherapy treatments and surgery for radical patients (from CKM). In order to capture these semantics, Type Definition 3 defines two free types: *TreatmentSet* and *TreatmentPlan* (line 1 and line 2, respectively).

Type Definition 3 Free types to capture semantics of knowledge artifacts

$$\text{treatmentSet} ::= \text{InitTPlan}(\langle \mathbb{R} \text{ Treatments} \rangle) | \text{followedTPlan}(\langle \text{treatmentSet} \rangle) \quad (1)$$

$$\text{TreatmentPlan} ::= \text{treatmentSet}(\langle \mathbb{N} \times \text{seq TreatmentPlan} \rangle) \quad (2)$$

$$\text{ConditionKMs} ::= \text{seq Condition} \cap \text{TreatmentPlan} \quad (3)$$

$$\text{RefinedTreatmentPlan} ::= \mathbb{N} \times \text{TreatmentPlan} \quad (4)$$

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In Smart CDSS, the knowledge model typically uses decision tree representation; however, PM is different from CKM and R-CKM in terms of the decision path. PM does not include treatments as a condition. To distinctly represent this formalism, *ConditionCKs* (line 3) defines a particular condition as a free type for CKM and R-CKM. Similarly, *RefinedTreatmentPlan* (line 4) represents refinement in final R-CKM, which dictates the addition of a treatment to R-CKM as a type of refinement (indicating the placement of treatment plan at a particular position in the decision path).

507 4.3.2. Knowledge models

508 Clinical knowledge models, such as PM, CKM, and R-CKM, are represented as axioms and
509 schemas. Subsequent sections explain the specifications for these models.

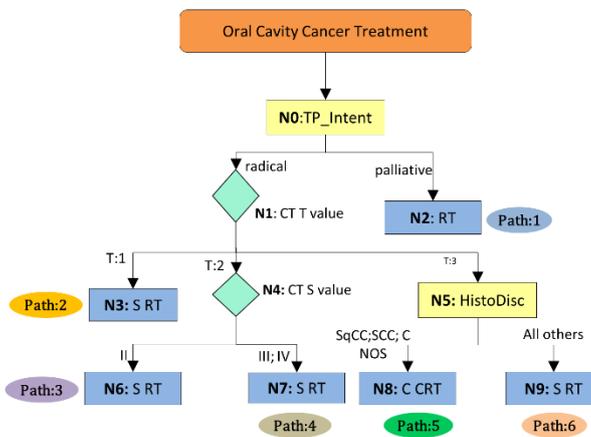
510 **Prediction model specifications:** Prediction model specifications cover the properties associated
511 with PM by decision tree formalism. Figure 9 shows the PM created (using CHAID decision tree) for
512 oral cavity cancer treatment intervention [17] with details of corresponding attributes and their
513 formalism semantics. The PM specifications are created using an axiom (Axiom 1) and the
514 *PredictionModel* schema (Schema 1). The axiomatic definition for PM represents the basic constructs
515 of PM using decision tree formalism. Accordingly, the decision paths are the main constituents of the
516 decision tree skeleton where a combination of logically related conditions makes a single decision
517 path that has one conclusion. The conditions and conclusion are also known as nodes of the decision
518 tree, where the conclusion is always a leaf node. The decision tree obtained from the data (using
519 machine-learning approaches) also has accuracy in terms of possessing correctly classified data cases
520 (i.e., using 10-fold cross-validation).

521

Axiom 1 Prediction model specifications

- $decisionPathConditionPM : \mathbb{F} seq Condition$ (1)
- $Conclusion : \mathbb{F} TreatmentPlan$ (2)
- $decisionPath : Condition \rightarrow TreatmentPlan$ (3)
- $accuracy : \mathbb{Z}$ (4)
- $decisionPathAccuracy : decisionPath \rightarrow accuracy$ (5)
- $evidences : \mathbb{F} Evidences$ (6)
- $decPathEvidences : decisionPath \rightarrow Evidences$ (7)
- $0 \leq accuracy \leq 100$ (8)
- $decisionPathConditionPM = dom decisionPath$ (9)
- $Conclusion = ran decisionPath$ (10)
- $\forall con : Condition \mid con \in decisionPathConditionPM \bullet$ (11)
 - $\exists conclusion : TreatmentPlan \mid conclusion \in Conclusion \bullet$
 - $decisionPath(con) = conclusion$
- $evidences = ran decPathEvidences$ (12)

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Attribute	Formalism	Remarks
RootNode	Only one; starting node; condition node	TP_Intent
LeafNode(s)	One or more; End of decision path; indicate conclusion	RT, S RT, C CRT
Condition Node(s)	One or more; indicate condition; must not be leaf node	CT S value; CT T value; HistoDisc
Decisionpath	Set of nodes (conjunction) with conclusion: start with root node, set of condition nodes, ends with leaf node	1. TP_Intent: palliative → RT; 2. TP_Intent: radical → CT T value; T:1 → S RT; (4 other paths)
Decisionpath Accuracy	Each path must have accuracy in range of 0 and 100	Decisionpath 1: 40.6 %; Decisionpath 2: 95.7 %
PM Accuracy	Mean accuracy of all decision paths; PM accuracy must be in range 0 and 100	PM accuracy for 6 paths: 59 %

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Figure 9: PM for treatment intervention in oral cavity cancer and its formalism (C CRT: Chemo Induction followed by chemotherapy; C NOS: Carcinoma NOS; CT S: clinical stage S value; CT T: clinical stage T value; HistoDisc: Histology description; RT: radiotherapy; SCC: Small cell carcinoma; SqCC: Squamous cell carcinoma; S RT: Surgery followed by RT; TP_Intent: Treatment Plan Intent)

Schema 1 Prediction model specifications

<i>PredictionModel</i>	
$PM : \mathbb{F} \text{ decisionPath}$	(1)
$accuracyPM : \mathbb{F} \mathbb{Z}$	(2)
$predictionModels : \text{decisionPath} \rightarrow \text{ClinicalObjectives}$	(3)
$predictionModelsAccuracy : PM \rightarrow accuracy$	(4)
$rootPM : \text{seq Condition}$	(5)
$0 \leq accuracyPM \leq 100$	(6)
$PM = \text{dom predictionModels}$	(7)
$accuracyPM = (\text{let } pathsAcc == \{pathsAcc : \mathbb{Z} \mid (\forall dp : \text{decisionPath} \mid dp \in PM \bullet$	(8)
$pathsAcc = \text{decisionPathAccuracy}(dp) + pathsAcc\}) / \#PM$	
$rootPM = \forall dp : \text{decisionPath} \mid dp \in PM \bullet \langle \cap(\text{ran}(\text{dom } dp)) \rangle$	(9)

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535 In Smart CDSS, PM follows decision tree formalism, which is obtained from patient medical
536 records where conditions are used to represent patient information (e.g., symptoms, problems
537 (diseases), clinical observations, and other demographic information (patient history)) and the
538 conclusion represents the treatment plan. Axiom 1 includes declarations for the decision path as a
539 partial function from the condition to the treatment plan (line 3). Its accuracy represented by a total
540 function from the decision path to the accuracy (line 5). The decision path conditions are represented
541 as a finite set of the Condition (line 1), and the conclusion represented by a finite set of the
542 TreatmentPlan (line 2). In order to reinforce the basic properties of the PM decision path, predicates
543 are used to constrain the defined properties. For example, the PM decision path accuracy must lie
544 between 0 and 100 (line 8). For all decision paths, there must exist one conclusion, and the conclusion
545 must be a TreatmentPlan (line 11).

546 Moreover, for validation purposes, we also associate the evidence (if it exists) with the treatment
547 plan recommendation that is provided by the decision path in PM. The evidence is a finite set (line
548 6), which can represent the effectiveness of the treatment plan in given patient cases in terms of the
549 success rate (as a percentage). It may also include external evidence from other research works.
550 Therefore, the decision path may have evidence represented by a partial function from the decision
551 path to the set of evidence (line 7 and line 12).

552 Prediction model specification is further extended through the PredictionModel schema
553 (Schema 1). PM is formally represented as a decision tree that is associated with the clinical objectives
554 using the injective function from the decision path to the clinical objectives (lines 1, 3, and 7). The PM
555 is associated with accuracy, which is the weighted mean accuracy of all of the decision paths in PM
556 (lines 2, 4, and 8). For simplicity, we consider an equal number of patient cases for each decision path;
557 this simplifies the accuracy of PM (line 8). Also, PM is a decision tree, which means it must include
558 one root node that must be a condition (lines 5 and 9).

559 **Clinical knowledge model specifications:** Clinical knowledge model specification represents the
560 formalism of CKM as an axiom (Axiom 2) and the schema *ClinicalKnowledgeModel* (Schema 2). CKM
561 is a knowledge model that represents clinical guidelines using a decision tree formalism. Figure 10 is
562 reference CKM created from clinical guidelines [17]. For the brevity purpose, we are not displaying
563 the pictorial representation of the formalism as it shares most of the structure artifacts with the R-
564 CKM and hence Figure 11 shows a formalism used as a reference for CKM.

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Axiom 2 Clinical knowledge model specifications

$decisionPathConditionCKM : \mathbb{F} \text{ ConditionKMs}$	(1)
$ConclusionCKM : \mathbb{F} \text{ TreatmentPlan}$	(2)
$decisionPathCKM : \text{ConditionKMs} \rightarrow \text{TreatmentPlan}$	(3)
$decisionPathConditionCKM = \text{dom } decisionPathCKM$	(4)
$ConclusionCKM = \text{ran } decisionPathCKM$	(5)
$(\text{ran } ConclusionCKM \cap \text{ran}(\text{dom } decisionPathCKM)) \subset \text{ran } decisionPathConditionCKM$	(6)
$\text{head}(\text{dom } decisionPathCKM) \notin \text{ran } ConclusionCKM \cap \text{ran } decisionPathConditionCKM$	(7)

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568 As described in a previous section, unlike PM, the CKM decision path also considers the
 569 treatment plan as a condition, and the conclusion is always a treatment plan. Therefore, decision path
 570 represented by a partial function from free type *ConditionKMs* to the treatment plan with axiomatic
 571 definition Axiom 2 (line 3). The constraint defined by a predicate at Axiom 2 (line 6) reinforce the idea
 572 of the CKM decision path that may contain treatment plans in condition. Moreover, every decision
 573 path must have a starting condition other than a treatment plan, which defined by a predicate at
 574 Axiom 2 (line 7). Axiom 2 (line 1,4 and 2,5) are representing the conditions
 575 (*decisionPathConditionCKM*) and conclusion (*ConclusionCKM*) of decision path in CKM as finite set of
 576 *ConditionKMs* and *TreatmentPlan* respectively.
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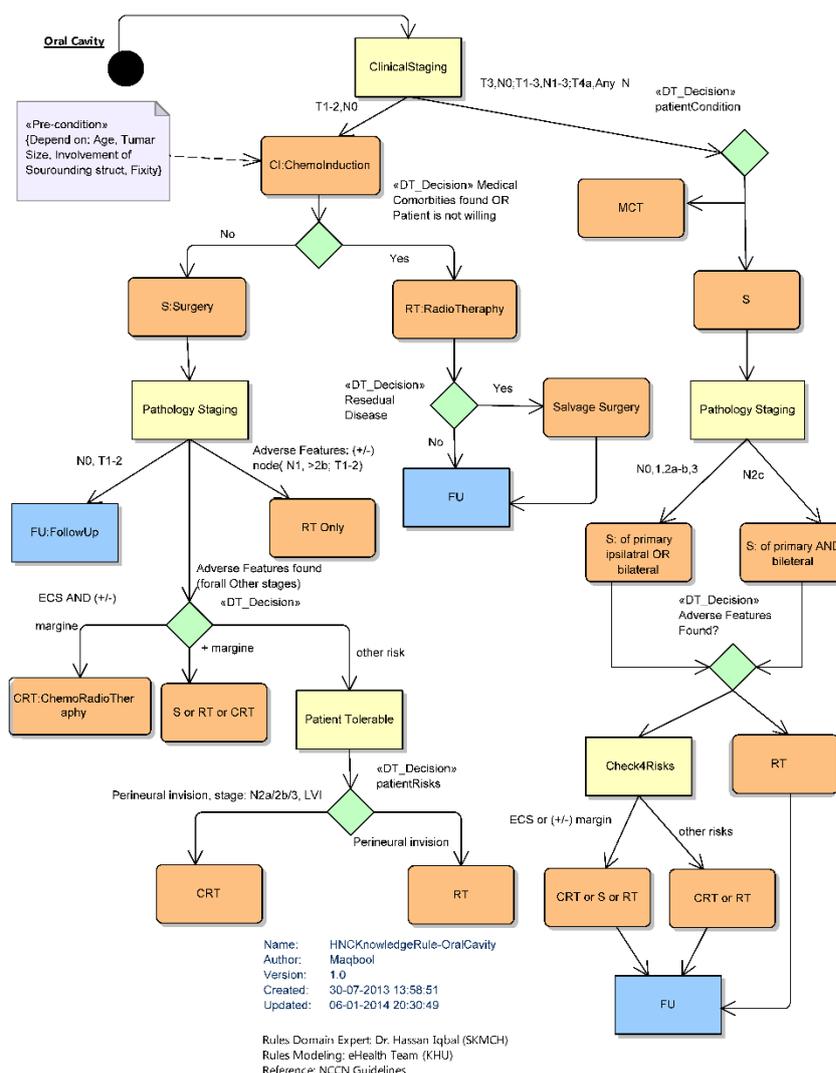
Schema 2 Clinical knowledge model specifications

<i>ClinicalKnowledgeModel</i>	
$CKM : \mathbb{P} \text{ decisionPathCKM}$	(1)
$guidelines : \text{ decisionPathCKM} \rightarrow \text{ ClinicalObjectives}$	(2)
$\text{rootCKM} : \text{ seq Condition}$	(3)
$CKM = \text{ dom guidelines}$	(4)
$\forall dp : \text{ decisionPathCKM} \mid dp \in CKM \bullet$ $\text{ head } (\text{ dom } dp) \notin \text{ ran ConclusionCKM} \cap \text{ ran decisionPathConditionCKM}$	(5)
$\exists dp : \text{ decisionPathCKM} \exists dp_1 : \text{ decisionPathCKM} \mid dp, dp_1 \in CKM \bullet$ $\text{ last } (\text{ dom } dp) = \text{ ran } dp_1 \Leftrightarrow \text{ dom } dp_1 = \text{ dom } dp \setminus \text{ last } (\text{ dom } dp)$	(6)
$\text{ rootCKM} = \forall dp : \text{ decisionPathCKM} \mid dp \in CKM \bullet \langle \bigcap (\text{ ran } (\text{ dom } dp)) \rangle$	(7)

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 579
 580 The *ClinicalKnowledgeModel* schema (Schema 2) further extends the CKM semantics. According
 581 to the definition of CKM, it covers-up the guidelines and follows decision tree formalism.
 582 Furthermore, it is associated with clinical objectives. For example, CKM (in Smart CDSS) consults
 583 NCCN guidelines, and its main objective is the provision of standard-based treatment plans for
 584 tumors in oral cavities. By using the schema definition (Schema 2), the guideline is a *total function*
 585 from the standard decision paths to the clinical objectives (line 2). CKM is a set of logically related
 586 decision paths in the guidelines that fulfill target clinical objectives (lines 1 and 4).
 587

588 Every decision path in CKM must start with a condition (other than a treatment plan), and CKM
 589 must have only one root condition (line 3) shared by all decision paths. Schema (Schema 2) defines
 590 these constraints by predicates at (lines 5 and 7).

591 In CKM, the treatment plan comes as a condition in one decision path and may act as a
 592 conclusion for another decision path. In other words, the CKM conclusion may occur in an
 593 intermediate node. Schema 2 defines a predicate (at line 6) to reflect this semantic.
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597 **Figure 10: CKM for treatment intervention in oral cavity cancer(CI: Chemoinduction; CRT:**
 598 **Chemotherapy; CT N: clinical stage N value; CT S: clinical stage S value; CT T: clinical stage T value;**
 599 **ECS: Extracapsular spread; FU: Follow-up; MCT: Multidisciplinary consultation; RT: radiotherapy;**
 600 **S: Surgery) [17]**

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604 *Refined clinical knowledge model specifications:* Refined clinical knowledge model
 605 specifications represent R-CKM formalism as an axiom (Axiom 3) and a schema
 606 (*RefinedClinicalKnowledgeModel*, Schema 3). R-CKM follows the formalism of CKM in that it also uses
 607 decision tree representation, which includes decision paths that have been formally validated from
 608 standard guidelines or possess sufficient evidence to prove their effectiveness. Figure 11 shows the
 609 R-CKM of a treatment plan for oral cavity cancer [17] with precise semantics and formalism. In this
 610 respect, the R-CKM decision path modeled (similar to CKM) by a *partial function* from free type
 611 *ConditionKMs* to the treatment plan; this is shown in the axiomatic definition (line 3).

Axiom 3 Refined clinical knowledge model specifications

$decisionPathConditionRCKM : \mathbb{F} ConditionKMs$	(1)
$ConclusionRCKM : \mathbb{F} TreatmentPlan$	(2)
$decisionPathRCKM : ConditionKMs \rightarrow TreatmentPlan$	(3)
$accuracy : \mathbb{Z}$	(4)
$decPathRCKMAccuracy : decisionPathRCKM \rightarrow accuracy$	(5)
$evidences : \mathbb{F} Evidences$	(6)
$decPathRCKMEvidences : decisionPathRCKM \rightarrow Evidences$	(7)
$refinedTPlan : \mathbb{F} RefinedTreatmentPlan$	(8)
$refinementsDecPath : RefinedTreatmentPlan \rightarrow decisionPath$	(9)
$0 \leq accuracy \leq 100$	(10)
$decisionPathConditionRCKM = \text{dom } decisionPathRCKM$	(11)
$ConclusionRCKM = \text{ran } decisionPathRCKM$	(12)
$(\text{ran } ConclusionRCKM \cap \text{ran } decisionPathConditionRCKM) \subset \text{ran } decisionPathConditionRCKM$	(13)
$\text{head}(decisionPathConditionRCKM) \notin \text{ran } ConclusionRCKM \cap \text{ran } decisionPathConditionRCKM$	(14)
$evidences = \text{ran } decPathRCKMEvidences$	(15)
$refinedTPlan = \text{dom } refinementsDecPath$	(16)

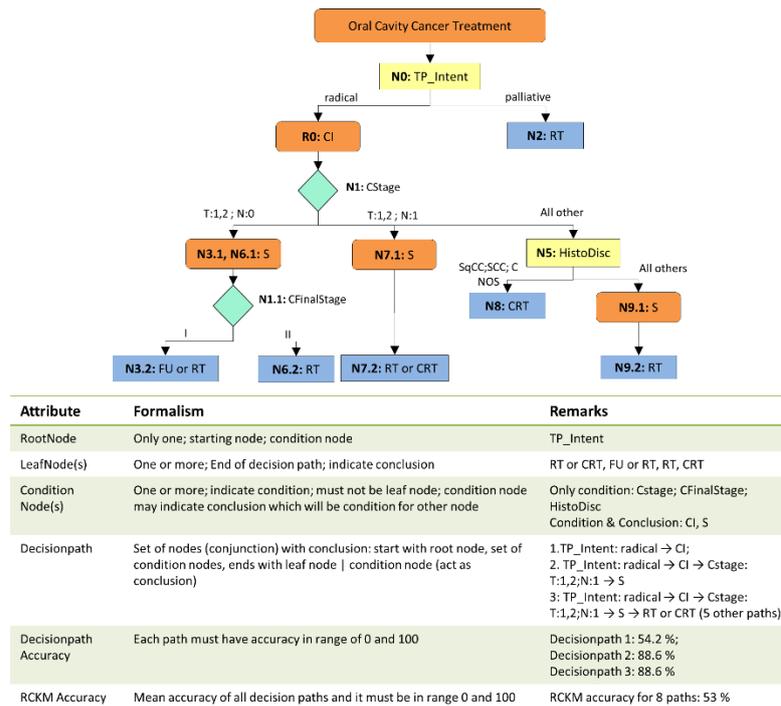
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As a result of refinements, the decision path of R-CKM may fully not conform to guidelines (CKM). In such cases, the evidence is required to justify the effectiveness of the refinements made to the decision path of R-CKM. To capture this context, a finite set of *Evidences* (line 6) is associated with the decision path of R-CKM as a *partial function* (line 7,15).

Schema 3 Refined clinical knowledge model specifications

$RefinedClinicalKnowledgeModel$	(1)
$PredictionModel$	(2)
$ClinicalKnowledgeModel$	(3)
$RCKM : \mathbb{F} decisionPathRCKM$	(4)
$refinedCKM : decisionPathRCKM \rightarrow CKM$	(5)
$rootRCKM : \text{seq } Condition$	(6)
$accuracyRCKM : \mathbb{F} \mathbb{Z}$	(7)
$refinedCKMsAccuracy : RCKM \rightarrow accuracy$	(8)
$0 \leq accuracyRCKM \leq 100$	(9)
$RCKM = \text{dom } refinedCKM$	(10)
$\forall dp : decisionPathRCKM \mid dp \in RCKM \bullet$	(11)
$\text{head}(\text{dom } dp) \notin \text{ran } ConclusionRCKM \cap \text{ran } decisionPathConditionRCKM$	(12)
$\exists dp : decisionPathRCKM \ni dp_1 : decisionPathRCKM \mid dp, dp_1 \in RCKM \bullet$	(13)
$\text{last}(\text{dom } dp) = \text{ran } dp_1 \Leftrightarrow \text{dom } dp_1 = \text{dom } dp \setminus \text{last}(\text{dom } dp)$	(14)
$accuracyRCKM = (\text{let } pathsAcc == \{pathsAcc : \mathbb{Z} \mid RCKM \neq \emptyset \wedge$	(15)
$(\forall dp : decisionPathRCKM \mid dp \in RCKM \bullet pathsAcc =$	(16)
$decPathRCKMAccuracy(dp) + pathsAcc\}) / \#RCKM$	(17)
$\forall p_{rckm} : decisionPathRCKM \mid p_{rckm} \in RCKM \bullet$	(18)
$\exists p_{pm} : decisionPath, p_{ckm} : decisionPathCKM \mid$	(19)
$p_{pm} \in PM \wedge p_{ckm} \in CKM \bullet \text{dom } p_{rckm} = \text{dom } p_{pm} \cup \text{dom } p_{ckm}$	(20)
$rootRCKM = \forall dp : decisionPathRCKM \mid dp \in RCKM \bullet \langle \cap(\text{ran}(\text{dom } dp)) \rangle$	(21)

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Figure 11: R-CKM for treatment intervention in oral cavity cancer and its formalism (CI: Chemoinduction; C NOS: Carcinoma NOS; CRT: Chemotherapy; CT N: clinical stage N value; CT S: clinical stage S value; CT T: clinical stage T value; ECS: Extracapsular spread; FU: Follow-up; HistoDisc: Histology description; RT: radiotherapy; S: Surgery; SCC: Small cell carcinoma; SqCC: Squamous cell carcinoma; TP_Intent: Treatment Plan Intent)

The predicates defined in Axiom 3 (lines 13, 14) capture the semantics of the decision path in R-CKM; a treatment plan can be a condition in the decision path, and the decision path must start with a condition (this should not be a treatment plan).

In addition to CKM formalism, decision paths in R-CKM become a part of the model after passing through a formal validation process and refinements (Figure 3). In this respect, the decision path in R-CKM has an accuracy represented by a *total function* from the decision path to the accuracy (line 5). Also, the accuracy of the decision path must be a finite value bounded interval [0,100] indicated in line (4,10). The refinement in R-CKM is represented by an *injective function* as shown in (line 9, 16) which maps the refined treatment plan (a free type, line 4, Type Definition 3) to the PM decision path (line 8).

The declarations and predicates of schema *RefinedClinicalKnowledgeModel* (Schema 3) are mostly similar to those of CKM (Schema 2); both share the same formalism. A *total function* (line 7) defines the new contents to support the overall accuracy of R-CKM. The intended accuracy calculated by the weighted mean accuracy for all of the decision paths in R-CKM (line 12).

Moreover, R-CKM is derived from PM and validated against CKM (guidelines); thus, the *total function* defines from the R-CKM decision paths to the intended CKM (line 4), and R-CKM modeled by a finite set of related decision paths (line 3) associated with CKM (line 9). Furthermore, a predicate adds to the schema (line 13), which constrains all of the decision paths; these must be derived from PM and aligned to CKM. Similarly, using schema inclusion, *PredictionModel* (Schema 1) and *ClinicalKnowledgeModel* (Schema 2) are also included (lines 1 and 2) into the *RefinedClinicalKnowledgeModel* (Schema 3) in order to make the contents of PM and CKM available to the R-CKM model.

Validation process specifications: Validation process specifications encompass the validation process (Figure 3) and properly represent the validation criteria defined for final knowledge model - R-CKM (See step 1: *Setting validation criteria* at Section 2.2). The schema *PMPPathValidation* (Schema 4)

654 models the basic semantics of the validation process. It includes schema
 655 *RefinedClinicalKnowledgeModel* (line 1), which is used to associate the validation process with R-CKM.
 656 It also provides a declaration for the two inputs that the validation process is supposed to consume:
 657 the PM decision path (line 2) and the minimal accuracy (assigned by a domain expert and acceptable
 658 for R-CKM) that requires for the PM decision path (line 3).
 659

Schema 4 Validation process specifications

<i>PMPathValidation</i>	
<i>RefinedClinicalKnowledgeModel</i>	(1)
$dp_{pm} ? : \text{decisionPath}$	(2)
$qualifiedAcc ? : \mathbb{Z}$	(3)
$dp_{pm} ? \in PM \wedge \text{decisionPathAccuracy}(dp_{pm} ?) \geq \text{qualifiedAcc} ?$	(4)
$\forall t_1, t_2 : \text{treatmentSet} \mid t_1, t_2 \in \text{ran}(\text{ran}(dp_{pm} ?)) \wedge \text{TreatmentPlan} \sim (t_1) > \text{TreatmentPlan} \sim (t_2) \bullet$	
$\exists dp_{ckm} : \text{decisionPathCKM}; t_3, t_4 : \text{treatmentSet} \mid dp_{ckm} \in \text{CKM},$	
$t_3, t_4 \in (\text{ran}(\text{dom}(dp_{ckm})) \cap \text{ran}(\text{ConclusionCKM})) \cup \text{ran}(\text{ran}(dp_{ckm})) \bullet$	
$(t_3 = t_1 \wedge t_4 = t_2) \Rightarrow \text{TreatmentPlan} \sim (t_3) > \text{TreatmentPlan} \sim (t_4)$	(5)
$\text{decPathEvidences}(dp_{pm} ?) \neq \emptyset \vee$	(6)
$\exists dp_{ckm} : \text{decisionPathCKM} \mid dp_{ckm} \in \text{CKM} \bullet$	
$(\text{ran}(\text{dom}(dp_{pm} ?)) \subseteq \text{ran}(\text{dom}(dp_{ckm}))) \Rightarrow$	
$\text{ran}(\text{ran}(dp_{pm} ?)) \subseteq$	
$(\text{ran}(\text{dom}(dp_{ckm})) \cap \text{ran}(\text{ConclusionCKM})) \cup \text{ran}(\text{ran}(dp_{ckm})))$	(7)

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662 The validation criteria defined in the validation process of the knowledge acquisition method
 663 reflected by predicates in the schema *PMPathValidation* (lines 4-7). The first two primaries
 664 (compulsory) criteria defined in the schema by conjunction predicates (lines 4 and 5) and two other
 665 criteria represented by disjunction predicates (lines 6 and 7).

666 4.4. Defining functions and state models

667 The main functions of knowledge models are to evolve R-CKM based on the validation of the
 668 decision path. The only evolving model is R-CKM, so the state model for R-CKM is presented.

669 4.4.1. Operations on knowledge models

670 Two types of operations defined for the knowledge model. For PM and CKM, only retrieval
 671 operations are required to represent access to different components of the model. So for as R-CKM is
 672 concerned, it requires specifications for both retrieval and state change operations.

673 *Operations for PM and CKM:* PM and CKM specification provide a set of operational schema
 674 related retrieval of various components of the PM and CKM, respectively. For the brevity purpose,
 675 we concentrate on operational schema related to the evolution of the knowledge model. Retrieval
 676 schema for the PM and CKM are straight forward, and we shall not discuss it further.

677 *Operations for R-CKM:* R-CKM is the only knowledge model that evolves through proper
 678 validation processes using PM and CKM. Therefore, in addition to retrieval operations, R-CKM also
 679 requires definitions for operations that represent the addition of new decision paths into the final
 680 model (in the presence of the validation criteria). For brevity purposes, we only concentrate on
 681 operations that are related to the evolution of R-CKM.

682 *EvolveRCKM* (Schema 5) is an operational schema that mainly represents the evolution of the R-
 683 CKM model. The evolution of R-CKM mainly describes as a two-step process after setting the
 684 validation criteria: (1) a decision path from PM is evaluated against the validation criteria and (2) the
 685 selected decision path is refined further (if needed) and added to the R-CKM.
 686

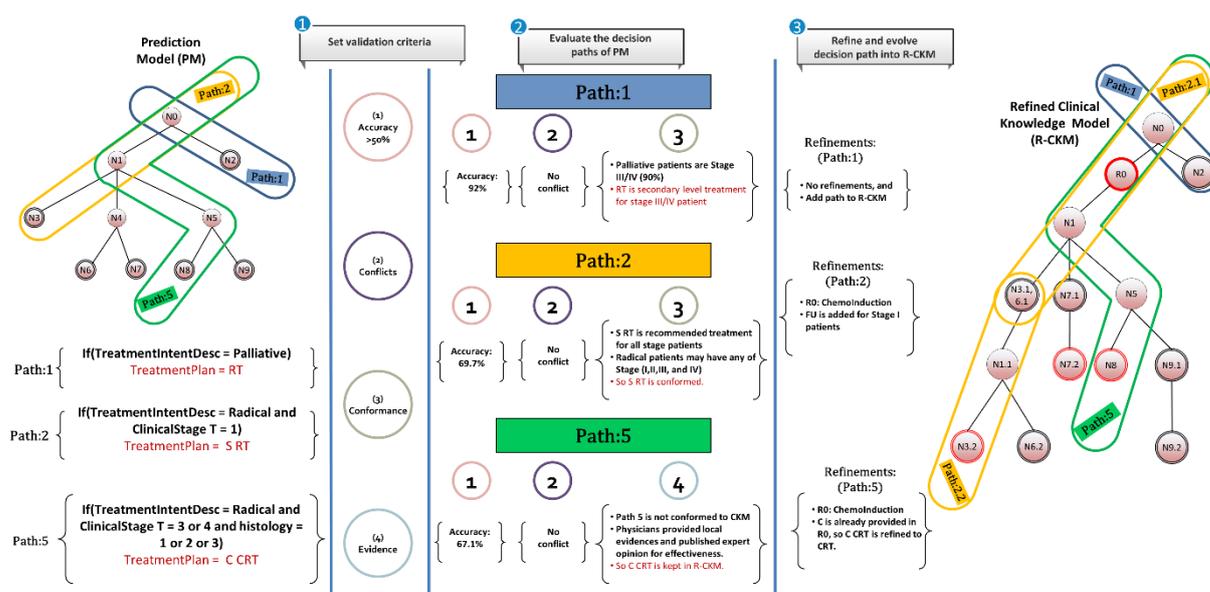
Schema 5 Evolution of R-CKM

EvolveRCKM $\hat{=}$ *PMPathValidation* \wedge *AddPathRCKM*

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689 Accordingly, *EvolveRCKM* (Schema 5) is defined as a composite operational schema to reflect
 690 these steps. This composition is modeled as a combination of two schemas: *PMPPathValidation* (Schema
 691 4) and *AddPathRCKM* (Schema 6).

692 To get a clear picture of this process, Figure 12 demonstrates three paths of the PM (Figure 9) in
 693 the context of the validation process (Figure 3) and produce the R-CKM (Figure 11). The two paths
 694 (path 1 and path 2) are fulfilling the first two compulsory criteria (having a minimum threshold of
 695 accuracy without any conflicts with CKM) and passing the criteria regarding conformance to CKM
 696 (Figure 10). Path 3 fulfilling the compulsory criteria; however, it goes for alternate criterion
 697 "Evidence" because of the suggested treatment plan does not conform to CKM. In the refinement step,
 698 path 2 and path 5 are refined to path 2.1, 2.2, and path 5, respectively. So far as path 1 is used without
 699 any refinements.
 700



701
702 **Figure 12: A running example of validation and refinement of three decision paths of PM**
703

704 *AddPathRCKM* is the main operational schema (Schema 6) that evolves the R-CKM and changes
 705 the original state of the model (Schema 3: *RefinedClinicalKnowledgeModel*), which represented by a
 706 change state in the schema (line 1). In order to understand the complexity of the *AddPathRCKM*
 707 operational schema, we divide the declarations and predicates into the following explanatory
 708 sections:

709 *AddPathRCKM* is the main operational schema (Schema 6) that evolves the R-CKM and changes
 710 the original state of the model (Schema 3: *RefinedClinicalKnowledgeModel*), which represented by a
 711 change state in the schema (line 1). In order to understand the complexity of the *AddPathRCKM*
 712 operational schema, we divide the declarations and predicates into the following explanatory
 713 sections:

- 714
- 715 ● *Declaration (Input)*: The *AddPathRCKM* schema expects two inputs: a candidate decision path from PM (line 2) and the desired treatment plan refinements in the decision path (line 3).
 - 716 ● *Declaration (Output)*: The final decision path of R-CKM, after refinements, is considered to be an output for the schema *AddPathRCKM* (line 4).
 - 717
 - 718 ● *Predicates (Pre-conditions)*: These include a set of predicates (lines 5-12) that must be met before any changes are made to the R-CKM model (Schema 3: *RefinedClinicalKnowledgeModel*). Most of these pre-conditions are not known in advance but are calculated using the one-point rule and simplification proofs. We shall describe some important pre-conditions, as evaluation results, for the formal verification process in Section 5.
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Schema 6 Adding PM decision path to R-CKM

<i>AddPathRCKM</i>	
Δ RefinedClinicalKnowledgeModel	(1)
$dp_{pm}?$: decisionPath	(2)
refinements? : \mathbb{F} RefinedTreatmentPlan	(3)
rckmPath! : decisionPathRCKM	(4)
$RCKM \neq \emptyset \Rightarrow head(dom dp_{pm}?) = rootRCKM$	(5)
$\forall pos : \mathbb{N} \mid pos \in dom refinements? \bullet pos > 1 \wedge$	
$pos \leq (\#(dom dp_{pm}?) + \#(ran dp_{pm}?)$	(6)
$ran(dom rckmPath!) \subset ran decisionPathConditionRCKM$	(7)
$ran(ran rckmPath!) \subset ran ConclusionRCKM$	(8)
$(ran(ran rckmPath!) \cap ran decisionPathConditionRCKM) \subset$	
$ran decisionPathConditionRCKM$	(9)
$0 \leq decPathRCKMAccuracy(rckmPath!) \leq 100$	(10)
$head(dom rckmPath!) \notin ran ConclusionRCKM \cap ran decisionPathConditionRCKM$	(11)
$\exists dp : decisionPathRCKM \mid dp \in RCKM \bullet$	
$dom rckmPath! = dom dp \setminus last(dom dp) \Rightarrow last(dom dp) = ran rckmPath!$	(12)
$dom rckmPath! = \exists p_{ckm} : decisionPathCKM \mid p_{ckm} \in CKM \bullet$	
$dom(p_{pm}?) \cup dom p_{ckm}$	(13)
$ran rckmPath! = ran dp_{pm}?$	(14)
$\forall r : RefinedTreatmentPlan \mid r \in refinements? \bullet$	
$rckmPath! = \bigcap / \{ \{ t_p : TreatmentPlan \bullet (1..dom r, t_p) \} \mid dom rckmPath!, ran r,$	
$\{ t_p : TreatmentPlan \bullet (dom r + 1.. \#(dom rckmPath!), t_p) \} \mid dom rckmPath! \}$	(15)
$decisionPathRCKM' = decisionPathRCKM \cup \{ dom rckmPath! \mapsto ran rckmPath! \}$	(16)
$decisionPathConditionRCKM' = decisionPathConditionRCKM \cup dom rckmPath!$	(17)
$refinedTPlan' = refinedTPlan \cup refinements?$	(18)
$refinementsDecPath' = refinementsDecPath \cup \{ refinements? \mapsto dp_{pm}? \}$	(19)
$ConclusionRCKM' = ConclusionRCKM \cup ran rckmPath!$	(20)
$decPathRCKMAccuracy' = decPathRCKMAccuracy \cup$	
$\{ rckmPath! \mapsto decPathRCKMAccuracy(rckmPath!) \}$	(21)
$accuracyRCKM' = \frac{accuracyRCKM \times \#RCKM + \#RCKM \mid decPathRCKMAccuracy'(rckmPath!)}{\#RCKM + 1}$	(22)
$\#RCKM' = \#RCKM + 1$	(23)
$evidences' = evidences \cup decPathEvidences(dp_{pm}?)$	(24)
$decPathRCKMEvidences' = decPathRCKMEvidences \cup$	
$\{ rckmPath! \mapsto decPathEvidences(dp_{pm}?) \}$	(25)
$RCKM' = RCKM \oplus \{ dom rckmPath! \mapsto ran rckmPath! \}$	(26)
$refinedCKM' = refinedCKM \oplus \{ rckmPath! \mapsto CKM \}$	(27)
$rootRCKM' = rootRCKM = head(dom dp_{pm}?)$	(28)

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- *Predicates (Refinements)*: The refinement process performed on the candidate decision path of PM (line 14), and the modified path (line 15) according to the necessary treatment plan that is mentioned by the suggested refinements, provided by an input (line 3).

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- *Predicates (Evolution)*: The R-CKM is evolved with the newly refined decision path. All of the relevant components of the *RefinedClinicalKnowledgeModel* schema are indicated through primed statements in the operational schema (lines 16-28). These primed statements primarily represent the new change state of the R-CKM model; subsequent sections explain further details.

734 4.4.2. Model states for knowledge models

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Modifications are only made to R-CKM upon evolution through the *EvolveRCKM* (Schema 5) operational schema using the combination of schema *AddPathRCKM* and schema *PMPATHValidation*. *PMPATHValidation* (Schema 4) validates a decision path of PM against the validation criteria and makes no change to the R-CKM model. Thus, *AddPathRCKM* (Schema 6) makes refinements to the decision path of PM and adds the refined path to R-CKM, which ultimately makes changes to the relevant components of the R-CKM. In this respect, the state model of *RefinedClinicalKnowledgeModel* (Schema 3) reflects changes following the *AddPathRCKM* operational schema. The schema *RefinedClinicalKnowledgeModel'* (Schema 7) represents the R-CKM model state, which encapsulates all of the relevant statements from R-CKM specifications (Axiom 3 and Schema 3).

The *AddPathRCKM* operational schema is invoked in conjunction with *PMPATHValidation* through the *EvolveRCKM* operational schema, and *PMPATHValidation* validates the decision path of PM. The changes made to the R-CKM model (*RefinedClinicalKnowledgeModel'*: Schema 7) by *AddPathRCKM* operational schema are summarized as follows:

Schema 7 R-CKM state after modification

$RefinedClinicalKnowledgeModel'$	
$PredictionModel$	(1)
$ClinicalKnowledgeModel$	(2)
$decisionPathConditionRCKM' : \mathbb{F} ConditionKMs$	(3)
$ConclusionRCKM' : \mathbb{F} TreatmentPlan$	(4)
$decisionPathRCKM' : ConditionKMs \rightarrow TreatmentPlan$	(5)
$decPathRCKMAccuracy' : decisionPathRCKM' \rightarrow accuracy$	(6)
$evidences' : \mathbb{F} Evidences$	(7)
$decPathRCKMEvidences' : decisionPathRCKM' \rightarrow Evidences$	(8)
$refinedTPlan' : \mathbb{F} RefinedTreatmentPlan$	(9)
$refinementsDecPath' : RefinedTreatmentPlan \rightarrow decisionPath$	(10)
$RCKM' : \mathbb{F} decisionPathRCKM$	(11)
$refinedCKM' : decisionPathRCKM' \rightarrow CKM$	(12)
$rootRCKM' : seq Condition$	(13)
$accuracyRCKM' : \mathbb{F} \mathbb{Z}$	(14)
$refinedCKMsAccuracy' : RCKM' \rightarrow accuracy$	(15)
$decisionPathConditionRCKM' = \text{dom } decisionPathRCKM'$	(16)
$ConclusionRCKM' = \text{ran } decisionPathRCKM'$	(17)
$(\text{ran } ConclusionRCKM' \cap \text{ran } decisionPathConditionRCKM') \subset \text{ran } decisionPathConditionRCKM'$	(18)
$\text{head } (decisionPathConditionRCKM') \notin \text{ran } ConclusionRCKM' \cap \text{ran } decisionPathConditionRCKM'$	(19)
$evidences' = \text{ran } decPathRCKMEvidences'$	(20)
$refinedTPlan' = \text{dom } refinementsDecPath'$	(21)
$0 \leq accuracyRCKM' \leq 100$	(22)
$RCKM' = \text{dom } refinedCKM'$	(23)
$\forall dp : decisionPathRCKM' \mid dp \in RCKM' \bullet$ $\text{head } (\text{dom } dp) \notin \text{ran } ConclusionRCKM' \cap \text{ran } decisionPathConditionRCKM'$	(24)
$\exists dp : decisionPathRCKM' \S dp_1 : decisionPathRCKM' \mid dp, dp_1 \in RCKM' \bullet$ $\text{last } (\text{dom } dp) = \text{ran } dp_1 \Leftrightarrow \text{dom } dp_1 = \text{dom } dp \setminus \text{last } (\text{dom } dp)$	(25)
$accuracyRCKM' = (\text{let } pathsAcc == \{pathsAcc : \mathbb{Z} \mid RCKM' \neq \emptyset \wedge$ $(\forall dp : decisionPathRCKM' \mid dp \in RCKM' \bullet pathsAcc =$ $decPathRCKMAccuracy'(dp) + pathsAcc\}) / \#RCKM'$	(26)
$\forall p_{ckm} : decisionPathRCKM' \mid p_{ckm} \in RCKM' \bullet$ $\exists p_{pm} : decisionPath, p_{ckm} : decisionPathCKM \mid$ $p_{pm} \in PM \wedge p_{ckm} \in CKM \bullet \text{dom } p_{ckm} = \text{dom } p_{pm} \cup \text{dom } p_{ckm}$	(27)
$RCKM' \neq \emptyset \Rightarrow \text{rootRCKM}' = \text{rootRCKM}$	(28)

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- A new decision path added to R-CKM; this adds new conditions to the set of R-CKM conditions ((Schema 6: Lines 16 and 17)). These changes represented in the state model (Schema 7) at lines 3, 5, and 16.
 - New refinements introduced to a set of the R-CKM model, which results in the addition of a PM path with the associated refinements (Schema 6: Lines 18 and 19). These states reflected in lines 9, 10, and 21 in Schema 7.
 - With the new decision path, the R-CKM model evolved for a new conclusion (Schema 6: Line 20), which yields new states in the model properties of $RCKMConclusion$, as indicated in the state model schema at lines 4 and 17.
 - For the new R-CKM path, the accuracy of the path will be associated, and the overall R-CKM accuracy is recalculated (Schema 6: Lines 21, 22, and 23). The resulting state changes reflected at lines 6, 14, 15, 22, and 26 in the state model schema.
 - Evidence of the PM's decision path associated with the refined decision path in R-CKM (Schema 6: Lines 24 and 25). These changes reflected in lines 7, 8, and 20 in the state model schema.
 - Finally, R-CKM evolved with the addition of a new decision path, and the root condition re-evaluated (Schema 6: Lines 26, 27, and 28). These evolutions change the states at multiple statements in the state model schema, as indicated in lines 11, 12, 13, 18, 19, 23, 24, 25, 27, and 28.

770 5. Results and evaluation

771 This section explains the evaluation of the proposed work using two perspectives. First, it
772 demonstrates the theorem proving mechanism to show inconsistencies in the hybrid knowledge
773 acquisition method before formal verification. The outcome of the formal verification is presented as
774 an enhanced knowledge acquisition method – as ReKA method. We evaluate the enhanced method
775 (in the context of formal verification) against our initial approach and describes its discrepancies

776 using real clinical scenarios. Second, we compare our enhanced approach with one of the existing
777 relevant approaches developed by Tossie et al. [22].

778 5.1. Proving consistency of the knowledge acquisition method

779 5.1.1. Consistency proof using the Initialization Theorem

780 The *initialization theorem* provides a mechanism to prove that the model (R-CKM) is consistent
781 and fulfills the requirements. It determines the model has at least an initial state. Definition 1 defines
782 the initialization theorem.

Definition 1: For the system state "State" and its initial state "StateInit", the initialization theorem takes the following form:

$$\exists \text{State}' \bullet \text{StateInit}$$

783 Definition 1: Initialization Theorem

784 For the R-CKM model represented in the schema *RefinedClinicalKnowledgeModel* (Schema 3), the
785 initial state is defined using the state schema *InitRCKM* (Schema 8).
786

Schema 8 R-CKM Initial state

<i>InitRCKM</i>	
<i>RefinedClinicalKnowledgeModel'</i>	(1)
<i>accuracyRCKM'</i> = 0	(2)
<i>RCKM'</i> = \emptyset	(3)
<i>refinedCKM'</i> = \emptyset	(4)
<i>rootRCKM'</i> = \emptyset	(5)
<i>refinedCKMsAccuracy'</i> = \emptyset	(6)
<i>decisionPathRCKM'</i> = \emptyset	(7)
<i>decisionPathConditionRCKM'</i> = \emptyset	(8)
<i>ConclusionRCKM'</i> = \emptyset	(9)
<i>decPathRCKMAccuracy'</i> = \emptyset	(10)
<i>evidences'</i> = \emptyset	(11)
<i>decPathRCKMEvidences'</i> = \emptyset	(12)

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789 For the given initial state *InitRCKM* of the R-CKM model's schema
790 *RefinedClinicalKnowledgeModel*, the initialization theorem is represented by Theorem 1; this is inspired
791 by the basic definition provided in Definition 1.
792

Theorem 1 Initialization theorem for initial state of R-CKM

$$\exists \text{RefinedClinicalKnowledgeModel}' \bullet \text{InitRCKM}$$

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795 The proof of this initialization theorem leads to consistent specifications for the R-CKM model.
796 It is almost impossible to prove the initial state of the modeling specifications, which include
797 contradictions. Hence, it can conclude that the model does not fulfill the desired requirements.

798 In order to prove the *initialization theorem*, we can take advantage of the *one-point rule* as well as
799 some other set theory laws and fundamental definitions. The *one-point rule* helps to replace the
800 existential quantifier when the bound variable has an identity within the boundaries of the
801 quantification expression. For the one-point rule, Definition 2 provides the essential background
802 related to replacing the existential quantifier.

803 Following the definition of the *one-point rule*, and other fundamental laws and definitions, the
804 proof of *initialization theorem* is given in Proof 1. The proof is straightforward, and each step is
805 explained with instructive definitions.
806

Definition 2: For the given predicate:

$$\exists x : a \bullet p \wedge x = t$$

The one-point rule gives the following equivalence for the given existential quantifier.

$$(\exists x : a \bullet p \wedge x = t) \Leftrightarrow t \in a \wedge p[t/x]$$

Definition 2: The one-point rule

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Proof 1 Proving initial state of R-CKM using initialization theorem (*Theorem 1*)

$$\begin{aligned} & \exists \text{RefinedClinicalKnowledgeModel}' \bullet \text{InitRCKM} \\ & \Leftrightarrow \text{RefinedClinicalKnowledgeModel}' \bullet \\ & \quad | \text{RefinedClinicalKnowledgeModel}' | \\ & \quad \text{accuracyRCKM}' = 0 \wedge \\ & \quad \text{RCKM}' = \emptyset \wedge \\ & \quad \text{refinedCKM}' = \emptyset \wedge \\ & \quad \text{rootRCKM}' = \emptyset \wedge \\ & \quad \text{refinedCKMsAccuracy}' = \emptyset] \\ & \Leftrightarrow \exists \text{RefinedClinicalKnowledgeModel}' \bullet \quad [\text{schema quantification}] \\ & \quad \text{accuracyRCKM}' = 0 \wedge \\ & \quad \text{RCKM}' = \emptyset \wedge \\ & \quad \text{refinedCKM}' = \emptyset \wedge \\ & \quad \text{rootRCKM}' = \emptyset \wedge \\ & \quad \text{refinedCKMsAccuracy}' = \emptyset \\ & \Leftrightarrow \exists \text{RCKM}' : \mathbb{P} \text{ decisionPathRCKM}, \quad [\text{definition : RefinedClinicalKnowledgeModel}] \\ & \quad \text{rootRCKM}' : \text{decisionPathConditionRCKM}, \text{accuracyRCKM}' : \mathbb{Z} \bullet \\ & \quad \exists \text{refinedCKM}' : \text{RCKM} \rightarrow \text{CKM}, \\ & \quad \text{refinedCKMsAccuracy}' : \text{RCKM} \rightarrow \text{accuracyRCKM} \bullet \\ & \quad 0 \leq \text{accuracyRCKM}' \leq 100 \wedge \\ & \quad \text{RCKM}' = \text{dom refinedCKM}' \wedge \\ & \quad \text{accuracyRCKM}' = (\text{let pathsAcc} == \{ \text{pathsAcc} : \mathbb{Z} \mid \text{RCKM}' \neq \emptyset \wedge \\ & \quad (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \text{pathsAcc} = \\ & \quad \text{refinedCKMsAccuracy}'(dp) + \text{pathsAcc}) \} / \# \text{RCKM}' \wedge \\ & \quad \text{rootRCKM}' = \text{rootRCKM}' \wedge \\ & \quad \text{accuracyRCKM}' = 0 \wedge \\ & \quad \text{RCKM}' = \emptyset \wedge \\ & \quad \text{refinedCKM}' = \emptyset \wedge \\ & \quad \text{rootRCKM}' = \emptyset \wedge \\ & \quad \text{refinedCKMsAccuracy}' = \emptyset \\ & \Leftrightarrow \emptyset \in \mathbb{P} \text{ decisionPathRCKM} \wedge \quad [\text{one - point rule : 5 - times}] \\ & \quad \emptyset \in \text{decisionPathConditionRCKM} \wedge \\ & \quad 0 \in \mathbb{Z} \wedge \\ & \quad \emptyset \in \text{RCKM} \rightarrow \text{CKM} \wedge \\ & \quad \emptyset \in \text{RCKM} \rightarrow \text{accuracyRCKM} \end{aligned}$$

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811 5.1.2. R-CKM evolution consistency proof using simplified pre-conditions and proving the property
812 composition

813 The pre-conditions of an operational schema represent a set of states, for which the outcome of
814 the operations is properly defined. The pre-condition of operation is another schema, obtained from
815 a given operation, that hides components related to the state after the operation and provides an
816 output that results from an operation.

817 We establish a theorem (*Theorem 2*), which is based on the basic definition of the pre-condition
818 schema (*Definition 3*), to calculate the pre-conditions for the operational schema *AddPathRCKM*
819 (*Schema 6*).

820

Definition 3: For the operational schema "operation," the state of the system modeled by "state" and the "output" is the list of outputs associated with the operation. Then, the following is equation represents the pre-condition of the schema.

$$\text{pre operation} = \exists \text{state}' \bullet \text{operation}$$

Definition 3: Precondition of an operation

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Calculation of pre-condition requires simplification of predicate part of the theorem (*Theorem 2*) which involves expansion of all schemas. After the expansion of all possible schemas, the one-point rule plays a pivotal role in simplifying and proving the primed statements in the schema. Due to space limits, the proof is provided as supplementary appendices. The Supplementary Appendix A explains the proof with instructive definitions at each evolving step of the schema. For brevity purposes, the proof does not discuss the pre-condition calculation in detail; however, we believe that

828 the given explanation is sufficient to determine the pre-conditions for the *AddPathRCKM* operational
 829 schema.
 830

Theorem 2 Pre-conditions calculation for R-CKM evolution operation

pre *AddPathRCKM* = \exists *RefinedClinicalKnowledgeModel!*
 • *AddPathRCKM*

<pre>pre <i>AddPathRCKM</i> <i>RefinedClinicalKnowledgeModel</i> <i>dp_{pm}?</i> : <i>decisionPath</i> <i>qualifiedAcc?</i> : \mathbb{Z} <i>refinements?</i> : \mathbb{F} <i>RefinedTreatmentPlan</i></pre>

<pre>\exists <i>RefinedClinicalKnowledgeModel!</i>; <i>rckmPath!</i> : <i>decisionPathRCKM</i> • <i>AddPathRCKM</i></pre>
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Although the simplification process seems quite complicated in terms of resolving all of the primed statements, however using set theory fundamental laws and the *one-point rule*, it becomes straightforward. Additionally, another aspect is that it reveals new pre-condition predicates that were not known in advance. The next section provides a detailed evaluation of the newly discovered pre-condition, which gives birth to an enhanced ReKA method. The primed predicates in Proof 2 (at Supplementary Appendix A) are underlined (numbered 1-13). The prime predicates require simplifications to conclude the proof. To save space, the Supplementary Appendix B presents the simplification proofs.

842 *5.2. Evaluation: Comparative analysis of ReKA and hybrid knowledge acquisition method*

843 As a consequence of "Proving consistency" mechanism, the main problem is regarding
 844 inconsistencies identified in step-3 (selection and refinement of the selected PM decision path) of the
 845 validation process in the hybrid knowledge acquisition method. The inconsistencies are covered-up
 846 by introducing nine additional criteria (see Table 1), that are placed after refinement. As an outcome
 847 of the formal verification, the enhanced ReKA method introduces to accommodate the newly
 848 discovered criteria. The ReKA criteria cover the broad categories of inconsistencies defined below.
 849 Each criterion contributes to one or more categories of inconsistencies.

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1. *Category-1 (Violating formalism of the R-CKM)*: These inconsistencies occur because of bypassing the construction norms of the R-CKM. This category of inconsistencies makes the final model invalid in terms of affecting outcomes of other decision paths. Criteria 1, 2, and 7 ensures avoiding inconsistencies related to R-CKM formalism.
2. *Category-2 (Violating conformance to guidelines (CKM))*: This category represents refinements, which produce inconsistencies in a decision path that does not conform to clinical guidelines without associating any additional significant evidences. These criteria were in place during the initial steps of the acquisition process (in the hybrid knowledge acquisition method); however, it was not available to ensure the conformance after refinements. Criteria 5 and 9 explicitly discuss that each refined path must conform to CKM.
3. *Category-3 (Compromising quality of R-CKM)*: These inconsistencies are related to the quality of R-CKM, which are mainly instigating from the refinements to existing PM decision path without re-evaluation on patient data. Criteria 6 defines performance (such as accuracy) associated with each refined decision path after evaluating against existing patient data.
4. *Category-4 (Introducing out-bounded refinements)*: This category discusses the inconsistencies in decision path that comes intentionally or unintentionally by introducing conditions or treatment plans which do not exist in the hospital information system or out of the scope of the healthcare

868 provider. Criteria 3 and 4 dictates that a domain expert must include only appropriate conditions
869 and treatments that exist within the boundary of the capacity of the healthcare provider.

Table 1. Evolution criteria derived from formal verification

C.No	Criteria	Remarks
1.	$RCKM \neq \emptyset \Rightarrow head(\text{dom } dp_{pm}?) = rootRCKM$	<ul style="list-style-type: none"> • Root of the R-CKM remains the same for any decision path when R-CKM already has some decision paths. • Root of the R-CKM will be the first condition for the decision path when R-CKM has no decision path.
2.	$\{\forall pos : \mathbb{N} \mid pos \in \text{dom } refinements? \bullet pos > 1 \wedge pos \leq (\#(\text{dom } dp_{pm}?) + \#(\text{ran } dp_{pm}?)\}$	<ul style="list-style-type: none"> • Refinements in the PM decision path for treatment must be conformed. • Example: Treatment refinements in the root of the decision path are not conformed.
3.	$\text{ran}(\text{dom } rckmPath!) \subset \text{ran } decisionPathConditionRCKM$	<ul style="list-style-type: none"> • Conditions in the refined decision path must come from the defined condition set of the R-CKM. • Example: Conditions outside the condition set make R-CKM non-integrable to HIS workflows.
4.	$\text{ran}(\text{ran } rckmPath!) \subset \text{ran } ConclusionRCKM$	<ul style="list-style-type: none"> • Conclusion in the refined decision path must be within the scope of the defined treatments. • Example: Conclusions for the treatment plan must be valid cancer treatment.
5.	$(\text{ran}(\text{ran } rckmPath!) \cap \text{ran } decisionPathConditionRCKM) \subset \text{ran } decisionPathConditionRCKM$	<ul style="list-style-type: none"> • Conclusion of the refined path may be the condition of another decision path in R-CKM. • Example: The refined path may be an extension of an existing decision path.
6.	$0 \leq decPathRCKMAccuracy(rckmPath!) \leq 100$	<ul style="list-style-type: none"> • Refined decision path accuracy must be within the range of 0 to 100. • Example: The refined decision path should be tested for the set of patient data.
7.	$head(\text{dom } rckmPath!) \notin \text{ran } ConclusionRCKM \cap \text{ran } decisionPathConditionRCKM$	<ul style="list-style-type: none"> • The first condition in the refined decision path must not be a treatment plan. • Example: A treatment plan is given based on some available symptoms (conditions).
8.	$\exists dp : decisionPathRCKM \mid dp \in RCKM \bullet \text{dom } rckmPath! = \text{dom } dp \setminus last(\text{dom } dp) \Rightarrow last(\text{dom } dp) = \text{ran } rckmPath!$	<ul style="list-style-type: none"> • Detailed explanation of the criteria 5.
9.	$\text{dom } rckmPath! = \exists p_{ckm} : decisionPathCKM \mid p_{ckm} \in CKM \bullet \text{dom}(p_{pm}?) \cup \text{dom } p_{ckm}$	<ul style="list-style-type: none"> • Refined decision path must be conformed to CKM. • Example: The refined path is obtained from PM and refined after confirmation from CKM.

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5. *Category-5 (Introducing inconsistencies due to complexities)*: This category is related to Category-1. However, it further covers the inconsistencies that occur due to lack of availability of descriptions for the construction of R-CKM. Criteria 8 is the detailed formal description of how to refine the path in order to avoid any inconsistencies. Criteria 1, 2, and 7 of Category-1 also comes under this category.

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880**Table 2: ReKA method Vs. earlier hybrid knowledge acquisition method (Knowledge validation perspective: All refinements are valid in earlier method)**

<i>Invalid Refinements to decision path #2</i>	<i>ReKA Validation</i>
Given decision path: <i>TreatmentIntent: palliative → Treatment Plan: RT (Radiotherapy)</i>	
Scenario 1: Modified decision path after refinements: <i>TreatmentIntent: palliative → Treatment Plan(RT): done → Surgery</i>	Criteria violation: Category: 2 Specific Criteria: 9
A rationale for violation: The guidelines (CKM) recommends follow-up after RT for palliative patients.	
Scenario 2: Modified decision path after refinements: <i>Treatment Plan(RT): done → TreatmentIntent: palliative → Follow-up</i>	Criteria violation: Category: 1, 5 Specific Criteria: 1, 2, 7
A rationale for violation: The treatment path after modification represents valid guideline-based treatment. However, it violates the formalism of the decision tree because modification in root node affects other decision paths.	
Scenario 3: Modified decision path after refinements: 1. <i>TreatmentIntent: palliative → Check for risk. ECS: Yes → Treatment Plan: RT or Surgery</i> 2. <i>TreatmentIntent: palliative → Check for risk. PNI: Yes → Treatment Plan: RT</i>	Criteria violation: Category: 4 Specific Criteria: 3 Category: 3 Specific Criteria: 6
A rationale for violation: Although the refinement 1 and refinement 2 conform to the guidelines (CKM), they are invalid due to the following reasons: <u>Category-4:</u> The hospital healthcare information system (HIS) at current stage maintain data for essential adverse histopathologic risk factors such as extracapsular spread (ECS). It keeps all other related factors such as perineural invasion (PNI) and lymphovascular invasion (LVI) in a broad category of others-histopathologic risks. Hence introducing PNI as a discrete data item raises an issue of the direct integration of the decision path to HIS workflows. Furthermore, the HIS records the risk of ECS to the patient with the radical status of treatment intent. So based on the above discussion; refinement#1 is not valid knowledge within the scope of local practices, and refinement#2 is also invalid as it introduces unknown data items. <u>Category-3:</u> Violation of criteria 3 in category-4 leads to the undefined quality of final RCKM. The decision path acquired from refinement#1 and refinement#2 cannot evaluate against patient data because of the unavailability of the missing data for ECS and PNI risk factor respectively.	
Scenario 4: Modified decision path after refinements: <i>TreatmentIntent: palliative and Treatment Plan(RT): done → Salvage Surgery: done → Follow-up</i>	Criteria violation: Category 4: Specific Criteria: 4 Category: 3 Specific Criteria: 6 Category: 2 Specific Criteria: 9 and 5
A rationale for violation: The Salvage Surgery refers to surgical treatment which uses after the failure of initial treatment. It is recommended explicitly having residual disease exist after RT for neck metastasis. The refinement for decision path with extended Salvage Surgery is invalid due to the following reasons: <u>Category-4 and Category-3:</u> It creates an issue of direct integration to HIS workflows because the existing treatment plan cannot differentiate between standard surgery and salvage surgery. This specific violation in turns raises category-3 violation which has the same interpretation mentioned in Scenario 3. <u>Category-2:</u> The refinements do not conform to the given guideline (CKM) even after interpretation of salvage surgery to standard surgery. The main reason is the salvage surgery is applicable for patients who are categorized as radical by TreatmentIntent.	

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The ReKA method can elaborate on the ambiguous steps in the validation process related to refinements. To better understand the impact of the ReKA method, Table 2 discusses four refinement

885 scenarios to decision path by the domain expert(see Path-2 in Figure 12). Each of these scenarios
 886 introduces inconsistencies which relate to one or more categories. It is important to note that these
 887 refinements are valid according to the hybrid knowledge acquisition method.
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889 Figure 13 depicts the enhancements made in the knowledge acquisition method in the validation
 890 process. Figure. 13a shows the initially proposed hybrid knowledge acquisition method with detailed
 891 steps of the validation process. The ReKA method, with the suggested improvements due to formal
 892 verification, is depicted in Figure. 13b. The ReKA method enhances the hybrid acquisition method
 893 by introducing the following specific sub-steps:
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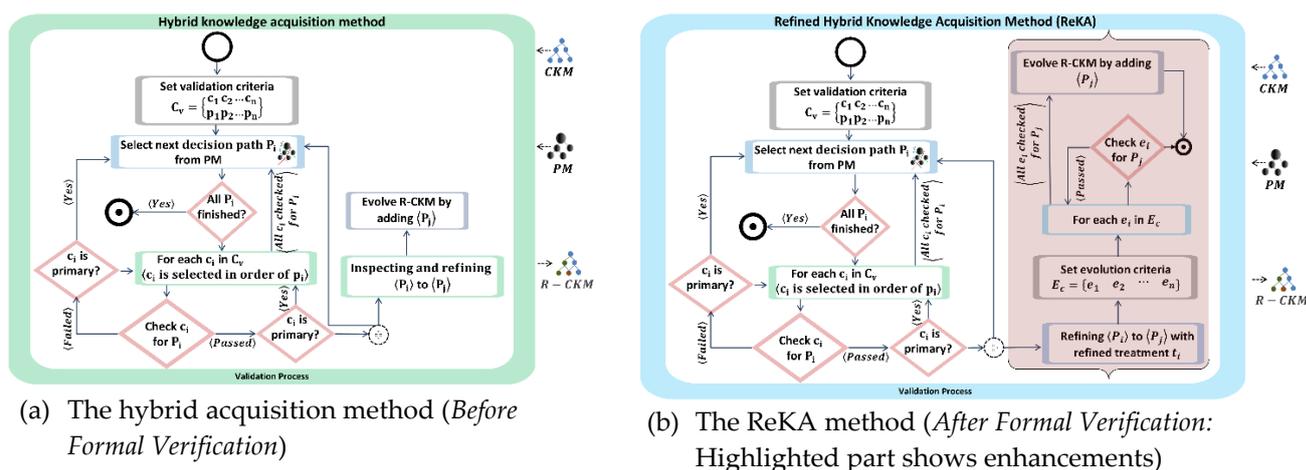


Figure 13: Comparison of ReKA with earlier hybrid knowledge acquisition method (Process enhancement perspective)

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- *Evolution criteria setting*: Any refinement in the decision path suggested by domain expert must be evaluated against a set of evolution criteria (specified in Table 1) to avoid inconsistencies as mentioned earlier in the R-CKM.
 - *Criteria checking*: All evolution criteria are compulsory and refined decision path in R-CKM must fulfill each criterion. Any refinement to decision path which is not fulfilling any of the nine criteria lists must not be considered, and the domain expert is prompted for the violation and indicated with a non-valid evolution of the R-CKM model.
 - *Evolution of R-CKM*: After passing the evolution criteria, the refined decision path becomes part of the R-CKM, and the process terminates faithfully.
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905 5.3. Comparison with the existing approach

906 One way of combining the traditional data-driven approach and guideline-based approach is to
 907 use PM as a source, and transforming it into the final knowledge model R-CKM, after rigorous
 908 validation process which conforms the transformation from CKM - the guidelines. However, the
 909 combination of these approaches can be done in another manner - considering CKM as a source
 910 and adding the decision paths from PM, which are missing in the CKM. In this section, we will discuss
 911 one of the existing most relevant approaches [22], which lies in the second category and draw a
 912 comparative analysis with our approach. In order to know the detailed description, Figure 14 shows
 913 the high-level steps in both knowledge acquisition approaches. These are given the same CKM and
 914 PM as an input. The resulting outcome - we called the R-CKM model is different with both
 915 approaches.

916 The main limitations of the existing approach are highlighted in Figure 14, and a detailed
 917 discussion is provided in Table 3.

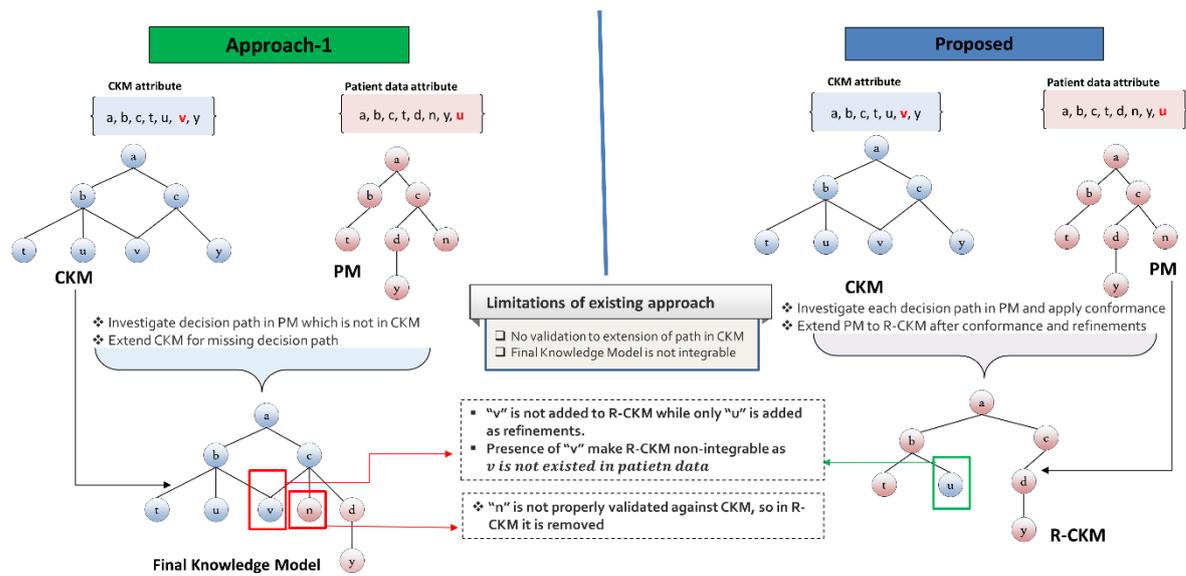


Figure 14: Demonstration of existing approach vs. proposed approach [22]

Table 3: Detailed description of guideline-enabled data-driven formally verified approach vs. existing approach

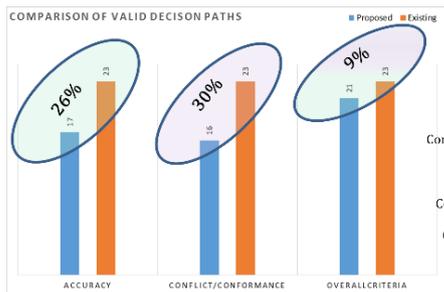
SNO	Proposed Approach	Existing Approach	Remarks
1.	Evolve the PM into R-CKM using CKM	Evolve the CKM using PM	Existing approach is not integrable Example: Concept "v" is not existed in patient data.
2.	Evolving decision path based on conformance criteria from CKM	Evolving decision path is considered, based on performance (accuracy)	Every decision path is eligible: Only based on performance. (No validation) Example:
3.	Evolving decision path if it has no conflict with guidelines		i. "n" is not validated against CKM, so, removed from R-CKM.
4.	Evolving decision path if not conformed from CKM, only if sufficient evidences exists.		ii. "d" is added in final R-CKM, based, on evidence support.

In a nutshell, the existing approach tends to use the PM as a key source to refine the decision paths in the CKM while compromising the quality of the model (missing rigorous validation) and integration to existing healthcare workflows. We also applied the existing approach on the SKMCH data set of 1229 oral cavity cancer patients and used the CKM as a reference guideline model (derived for oral cavity NCCN guidelines). In the final knowledge model, we identified that 26% of the decision paths were violating the quality criteria of lower accuracy (in our case, it should be greater than 50%), 30% of the decision paths were not conformed to guidelines, and 9% decision paths were violating multiple criteria, i.e., lower accuracy and non-conformance. Overall, 47.8% of decision paths lacked to pass the validation criteria. Figure 15 shows the details of the decision tree C4.5 algorithm (which is referred by Toussi et al.) with highlighted decision paths lacking one or more validation criteria.

As described in Table 3, the final model obtained from Toussi et al. approach is not necessarily integrable to evaluate its performance against patient data available at a local organization. However, as shown in Figure 15, the source model for Toussi et al. approach is C4.5, which has overall accuracy of 69.7% on SKMCH dataset. Even considering the Toussi et al. approach produces the final knowledge integrable to existing healthcare workflow, still there exists a chance that overall model accuracy will fall from 69.7% because of its generalization. In the case of proposed work, we have a rigorous selection process for choosing the appropriate machine learning algorithm and as indicated the CHAID decision tree is a candidate algorithm with an accuracy of 71% on a data set of 1229 oral

945 cavity patients (see [17] for details of part of knowledge acquisition related to this part). Moreover,
 946 the final knowledge model – R-CKM performance is improved to 72.57%, as shown in Figure 16. To
 947 conclude, the proposed approach also gives greater performance over Toussi et al. on the local
 948 SKMCH dataset.
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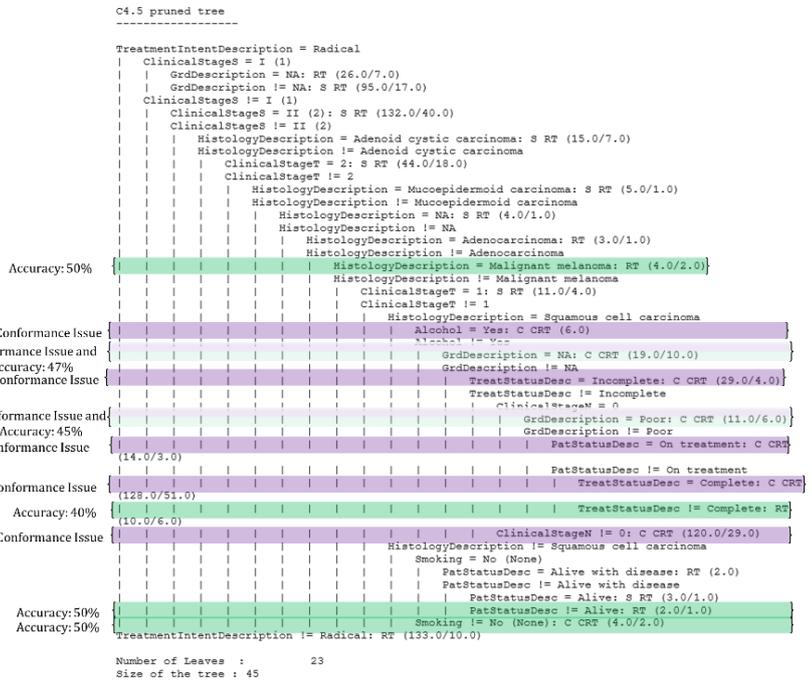
Algorithm: C4.5 (with accuracy 69.7%)
Dataset: 1229 (H&N cancer dataset of SKMCH)
Guideline: NCCN
Total decision paths: 23



Six (6) decision paths have lower accuracy than the targeted

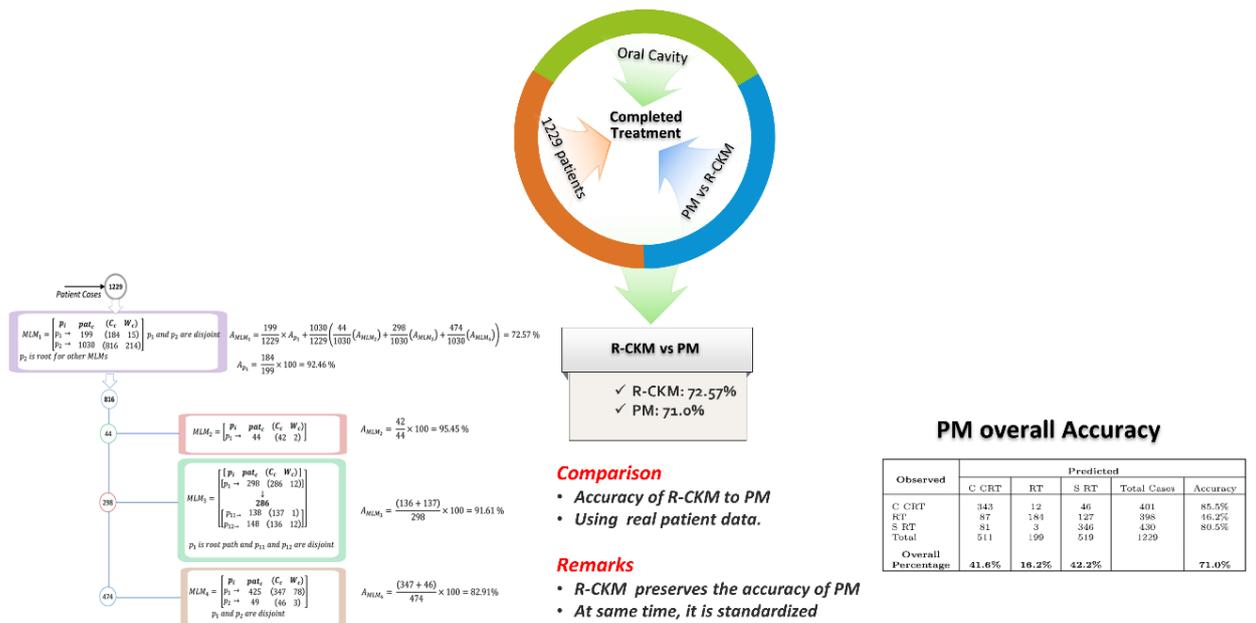
Seven (7) decision paths are not conformed

Two(2) decision paths are not conformed and having lower accuracy



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Figure 15: Comparison of the proposed approach with the existing approach using SKMCH oral cavity cancer data [22]



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Figure 16: R-CKM results using oral cavity cancer data [R-CKM is implemented as set a of HL7 MLMs and the evaluation results drawn are based on the structure of MLMs]

959 6. Discussion

960 6.1. *Is verification always required for clinical knowledge modeling?*

961 Validation and verifications are the key pillars of trust on the domain knowledge. However, the
962 use of applying both processes mainly contributed towards the criticality and complexity of the
963 clinical knowledge modeling method and the final knowledge models. In other words, for less critical
964 and less complex clinical knowledge acquisition methods and models, validation only may play a
965 role to establish the required level of trust on the knowledge. Consider an example of calculating
966 TNM staging for cancer [34]. Predefined rules or algorithms and deterministic mappings use for final
967 knowledge modeling of TNM staging. The TNM staging knowledge model does not need exhaustive
968 validation. It requires a limited set of validation cases to test the validity of complete knowledge.

969 In contrast, validation and verification should be in place for the knowledge acquisition method,
970 which involves different sources of knowledge with diverse structure and semantics. In this research
971 work, the ReKA method involves diverse knowledge sources; CPGs, decision trees (from patient
972 data), and domain expert heuristics (in refinements) where each of them has different nature of
973 structure and semantics. Therefore, the only validation could not guarantee that the knowledge
974 model is always valid. The formal verification in the ReKA method introduced the necessarily
975 missing steps in our previously hybrid knowledge acquisition method, which only relied on the
976 validation process. The outcomes of the ReKA method have been evaluated through a set of the real
977 clinical scenarios provided in Table 2.

978 6.2. *What is the overhead of the formal verification process and to which extent the formalism is required?*

979 Formal verification has significant overhead in terms of time and selection of expert resource
980 who have sufficient skills to model the domain knowledge mathematically. It is important to note
981 that the applicability of the formally verified model is not reduced in terms of efficiency rather delay
982 is expected in the delivery of the final knowledge model. Therefore, to tune the trade-off of timely,
983 cost-effective delivery with producing high-quality knowledge model, the maximum extent of
984 formalism is identified during clinical knowledge modeling.

985 In ReKA method, the formal verification is involved in the first two phases of modeling of CPGs
986 (CKM), decision trees (PM) and final model (R-CKM). In the third phase, R-CKM is converted into
987 standard executable knowledge representation of HL7 MLM (medical logic modules). There was a
988 choice of applying the formal verification (Z refinements) in the third phase of the transformation of
989 R-CKM to MLMs. However, we already demonstrated in [17] that the conversion is straight forward,
990 and the MLMs are easily validated against the real patient cases, as shown in Figure 16.

991 6.3. *Whether validation or semi or less formalism sufficient for consistency of complex knowledge acquisition 992 models or methods?*

993 As discussed earlier, only validation is not enough for complex knowledge acquisition methods
994 or models. Similarly, semi or less formal analysis of knowledge acquisition method does not always
995 guarantee consistent and valid knowledge. As an example, Grando et al. have demonstrated that
996 using the formal analysis for the expressiveness of CIG languages found satisfiability of some
997 patterns which was ignored or not detected by the less formal analysis method [35].

998 In the hybrid knowledge acquisition method [17], initially, we relied on a rigorous validation
999 process, the partial formalism of the decision tree and freedom of domain expert to modify existing
1000 knowledge model with additional constraints. While using ReKA method, it has realized that relying
1001 upon only the validation process and partial formalism support of decision tree, the final knowledge
1002 model is not always valid. The ReKA method highlighted a set of inconsistencies which includes
1003 violation of knowledge representation formalism (R-CKM), conformance to CPGs, compromising the
1004 quality of the model, outbound refinements in the model, and inconsistencies due to the complexity
1005 of the knowledge. Each category of inconsistency is demonstrated with real clinical knowledge
1006 modeling scenarios, as shown in Table 2.

1007 6.4. Whether formally verified clinical knowledge models or methods always guarantee consistency
1008 concerning the essential context of the domain?

1009 According to Boehm definition, validation is all about, “are we building the right product?” and
1010 the verification is all about, “are we building the product right?” [36]. In terms of clinical knowledge
1011 modeling, we can interpret the definition in simple words as: “do we create right knowledge model
1012 for the clinical domain under consideration?” and “do the method of acquisition is right to reflect all
1013 essential context of the clinical domain in the creation of knowledge model?”. At this stage, knowing
1014 all the essential context of the clinical domain is important. The verification process will make sure
1015 to find the inconsistencies in the acquisition process according to the context provided during the
1016 validation process. As a conclusion, the formal method always guarantees the consistency of the
1017 model based on the given domain context. However, if the essential context of the domain is missing
1018 or wrongly perceived in the design, then formal verification is also not the ultimate solution to
1019 discover the missing or detect the wrongly perceived knowledge.

1020 7. Conclusion

1021 This paper introduced enhanced ReKA method as a result of the formal verification using Z
1022 notation. Z notation proves the consistency of the acquisition process and hence, improved the hybrid
1023 knowledge acquisition method. ReKA method is established based on the three steps formal
1024 verification process to represent the knowledge models formally. Also, it involves the associated
1025 validation process of hybrid knowledge acquisition using various artifacts of Z notation.
1026 Subsequently, the mechanism of theorem proving in formal verification has identified inconsistencies
1027 in the previously established knowledge acquisition by introducing nine additional criteria. These
1028 criteria address the broad categories of inconsistencies related to the formalism of knowledge,
1029 conformance to CPGs, quality of knowledge, and complexities of knowledge acquisition artifacts.
1030 The ReKA method produces guideline-enabled data-driven knowledge model which support the
1031 high-quality recommendation, global evidence, local practices, and always consistent model
1032 compared to existing hybrid knowledge models. It is important to mention that the key advantages
1033 of ReKA method include its generality, that can be easily adapted in other cancer domains. Moreover,
1034 to the best of our knowledge, this is the first attempt, to use Z notation in the modeling of medical
1035 knowledge, and to align its core step as contents of method plugin, in the Smart CDSS development
1036 framework.

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1038 assisted in the evaluation of results. TA helped in the implementation of the models into the real healthcare
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1128 Supplementary Appendices

1129 Supplementary Appendix A. Calculating pre-conditions for R-CKM evolution

Proof 2 Pre-condition calculation proof using one-point rule

$$\begin{aligned}
& \text{pre } \text{AddPathRCKM} \Leftrightarrow & (2.01) \\
& \exists \text{ RefinedClinicalKnowledgeModel}^f; \text{ rckmPath!} : \text{decisionPathRCKM} \bullet & [\text{def.pre AddPathRCKM}] \quad (2.02) \\
& \quad \text{AddPathRCKM} \\
& \Leftrightarrow \\
& = \text{ RefinedClinicalKnowledgeModel}^f; \text{ rckmPath!} : \text{decisionPathRCKM} \bullet & [\text{def.AddPathRCKM}] \quad (2.03) \\
& \text{RCKM} \neq \emptyset \Rightarrow \text{head}(\text{dom } \text{dppm}?) = \text{rootRCKM} \wedge & (2.04) \\
& \forall \text{ pos} : \mathbb{N} \quad \text{pos} \in \text{dom } \text{refinements}^? \bullet \text{pos} > 1 \wedge & (2.05) \\
& \quad \text{pos} < (\#\{\text{dom } \text{dppm}?\} + \#\{\text{ran } \text{dppm}?\}) \wedge \\
& \text{ran}(\text{dom } \text{rckmPath!}) \subseteq \text{ran } \text{decisionPathConditionRCKM} \wedge & (2.06) \\
& \text{ran}(\text{ran } \text{rckmPath!}) \subseteq \text{ran } \text{ConclusionRCKM} \wedge & (2.07) \\
& (\text{ran}(\text{ran } \text{rckmPath!}) \cap \text{ran } \text{decisionPathConditionRCKM}) \subseteq & (2.08) \\
& \quad \text{ran } \text{decisionPathConditionRCKM} \wedge \\
& 0 \leq \text{decPathRCKMAccuracy}(\text{rckmPath!}) \leq 100 \wedge & (2.09) \\
& \text{head}(\text{dom } \text{rckmPath!}) \notin \text{ran } \text{ConclusionRCKM} \cap \text{ran } \text{decisionPathConditionRCKM} \wedge & (2.10) \\
& \text{dp} : \text{decisionPathRCKM} \quad \text{dp} \in \text{RCKM} \bullet & (2.11) \\
& \quad \text{dom } \text{rckmPath!} \rightarrow \text{dom } \text{dp} \setminus \text{last}(\text{dom } \text{dp}) \rightarrow \text{last}(\text{dom } \text{dp}) \rightarrow \text{ran } \text{rckmPath!} \wedge \\
& \text{dom } \text{rckmPath!} \rightarrow \exists \text{ pckm} : \text{decisionPathCKM} \mid \text{pckm} \in \text{CKM} \bullet & (2.12) \\
& \quad \text{dom}(\text{dppm}?) \cup \text{dom } \text{pckm} \wedge \\
& \text{ran } \text{rckmPath!} \rightarrow \text{ran } \text{dppm}^? \wedge & (2.13) \\
& \forall r : \text{ RefinedTreatmentPlan} \mid r \in \text{refinements}^? \bullet \\
& \quad \text{rckmPath!} \rightarrow \bigcap \{ \{ \text{tp} : \text{TreatmentPlan} \bullet \{1 \dots \text{dom } r, \text{tp}\} \} \mid \text{dom } \text{rckmPath!}, \text{ran } r, & (2.14) \\
& \quad \{ \text{tp} : \text{TreatmentPlan} \bullet (\text{dom } r + 1 \dots \#\{\text{dom } \text{rckmPath!}\}, \text{tp}) \} \mid \text{dom } \text{rckmPath!} \} \wedge \\
& \text{decisionPathRCKM}^f = \text{decisionPathRCKM} \cup \{ \text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!} \} \wedge & (2.15) \\
& \text{decisionPathConditionRCKM}^f = \text{decisionPathConditionRCKM} \cup \{ \text{dom } \text{rckmPath!} \} \wedge & (2.16) \\
& \text{refinedTPlan}^f \rightarrow \text{refinedTPlan} \rightarrow \text{refinements}^? \wedge & (2.17) \\
& \text{refinementsDecPath}^f = \text{refinementsDecPath} \cup \{ \text{refinements}^? \rightarrow \text{dppm}^? \} \wedge & (2.18) \\
& \text{ConclusionRCKM}^f = \text{ConclusionRCKM} \cup \text{ran } \text{rckmPath!} \wedge & (2.19) \\
& \text{decPathRCKMAccuracy}^f = \text{decPathRCKMAccuracy} \cup & (2.20) \\
& \quad \{ \text{rckmPath!} \mapsto \text{decPathRCKMAccuracy}(\text{rckmPath!}) \} \wedge \\
& \text{accuracyRCKM}^f = \frac{\text{accuracyRCKM} \times \#\text{RCKM} \quad \text{decPathRCKMAccuracy}^f(\text{rckmPath!})}{\#\text{RCKM} - 1} \wedge & (2.21) \\
& \#\text{RCKM}^f = \#\text{RCKM} + 1 \wedge & (2.22) \\
& \text{evidences}^f = \text{evidences} \cup \text{decPathEvidences}(\text{dppm}^?) \wedge & (2.23) \\
& \text{decPathRCKMEvidences}^f = \text{decPathRCKMEvidences} \cup & (2.24) \\
& \quad \{ \text{rckmPath!} \mapsto \text{decPathEvidences}(\text{dppm}^?) \} \wedge \\
& \text{RCKM}^f = \text{RCKM} \Leftrightarrow \{ \text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!} \} \wedge & (2.25) \\
& \text{refinedCKM}^f \rightarrow \text{refinedCKM} \Leftrightarrow \{ \text{rckmPath!} \mapsto \text{CKM} \} \wedge & (2.26) \\
& \text{rootRCKM}^f = \text{rootRCKM} = \text{head}(\text{dom } \text{dppm}^?) & (2.27) \\
& \Leftrightarrow \\
& = \text{rckmPath!} : \text{decisionPathRCKM}; & [\text{def.RefinedClinicalKnowledgeModel}^f] \quad (2.28) \\
& \text{decisionPathConditionRCKM}^f : \mathbb{F} \text{ ConditionKMs}; & (2.29) \\
& \text{ConclusionRCKM}^f : \mathbb{T} \text{ TreatmentPlan}; & (2.30) \\
& \text{decisionPathRCKM}^f : \text{ConditionKMs} \rightarrow \text{TreatmentPlan}; & (2.31) \\
& \text{decPathRCKMAccuracy}^f : \text{decisionPathRCKM}^f \rightarrow \text{accuracy}; & (2.32) \\
& \text{evidences}^f : \mathbb{F} \text{ Evidences}; & (2.33) \\
& \text{decPathRCKMEvidences}^f : \text{decisionPathRCKM}^f \rightarrow \text{Evidences}; & (2.34) \\
& \text{refinedTPlan}^f : \mathbb{T} \text{ RefinedTreatmentPlan}; & (2.35) \\
& \text{RCKM}^f : \mathbb{T} \text{ decisionPathRCKM}; & (2.36) \\
& \text{refinedCKM}^f : \text{decisionPathRCKM}^f \rightarrow \text{CKM}; & (2.37) \\
& \text{refinementsDecPath}^f : \text{ RefinedTreatmentPlan} \rightarrow \text{decisionPath}; & (2.38) \\
& \text{rootRCKM}^f : \text{seq } \text{Condition}; & (2.39) \\
& \text{accuracyRCKM}^f : \mathbb{T} \mathbb{E}; & (2.40) \\
& \text{refinedCKMsAccuracy}^f : \text{RCKM}^f \rightarrow \text{accuracy} \bullet & (2.41) \\
& (1) \cdot \text{decisionPathConditionRCKM}^f \rightarrow \text{dom } \text{decisionPathRCKM}^f \wedge & (2.42) \\
& (2) \cdot \text{ConclusionRCKM}^f = \text{ran } \text{decisionPathRCKM}^f \wedge & (2.43) \\
& (3) \cdot (\text{ran } \text{ConclusionRCKM}^f \cap \text{ran } \text{decisionPathConditionRCKM}^f) \subseteq \text{ran } \text{decisionPathConditionRCKM}^f \wedge & (2.44) \\
& (4) \cdot \text{head}(\text{decisionPathConditionRCKM}^f) \notin \text{ran } \text{ConclusionRCKM}^f \cap \text{ran } \text{decisionPathConditionRCKM}^f \wedge & (2.45) \\
& (5) \cdot \text{evidences}^f = \text{ran } \text{decPathRCKMEvidences}^f \wedge & (2.46) \\
& (6) \cdot \text{refinedTPlan}^f = \text{dom } \text{refinementsDecPath}^f \wedge & (2.47)
\end{aligned}$$

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Continued.. 1 from Proof 2

$$(7) \neg 0 \leq \text{accuracyRCKM}' \leq 100 \wedge \quad (2.48)$$

$$(8) \neg \text{RCKM}' = \text{dom refinedCKM}' \wedge \quad (2.49)$$

$$(9) \neg \forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \frac{\text{head}(\text{dom } dp) \notin \text{ran ConclusionRCKM}' \cap \text{ran decisionPathConditionRCKM}' \wedge}{\text{last}(\text{dom } dp) = \text{ran } dp_1 \Leftrightarrow \text{dom } dp_1 = \text{dom } dp \setminus \text{last}(\text{dom } dp) \wedge} \quad (2.50)$$

$$(10) \neg \exists dp : \text{decisionPathRCKM}' \circ dp_1 : \text{decisionPathRCKM}' \mid dp, dp_1 \in \text{RCKM}' \bullet \frac{\text{last}(\text{dom } dp) = \text{ran } dp_1 \Leftrightarrow \text{dom } dp_1 = \text{dom } dp \setminus \text{last}(\text{dom } dp) \wedge}{\text{accuracyRCKM}' = (\text{let pathsAcc} == \{\text{pathsAcc} : \mathbb{Z} \mid \text{RCKM}' \neq \emptyset \wedge (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \text{pathsAcc} = \frac{\text{decPathRCKMAccuracy}'(dp) + \text{pathsAcc}}{\#\text{RCKM}' \wedge} \}}) / \#\text{RCKM}' \wedge} \quad (2.51)$$

$$(11) \neg \frac{\text{accuracyRCKM}' = (\text{let pathsAcc} == \{\text{pathsAcc} : \mathbb{Z} \mid \text{RCKM}' \neq \emptyset \wedge (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \text{pathsAcc} = \frac{\text{decPathRCKMAccuracy}'(dp) + \text{pathsAcc}}{\#\text{RCKM}' \wedge} \}}) / \#\text{RCKM}' \wedge}{\exists p_{pm} : \text{decisionPath, } p_{ckm} : \text{decisionPathCKM} \mid \frac{p_{pm} \in \text{PM} \wedge p_{ckm} \in \text{CKM} \bullet \text{dom } p_{rckm} = \text{dom } p_{pm} \cup \text{dom } p_{ckm} \wedge}{\text{RCKM}' \neq \emptyset \Rightarrow \text{rootRCKM}' = \text{rootRCKM} \wedge} \quad (2.52)$$

$$(12) \neg \forall p_{rckm} : \text{decisionPathRCKM}' \mid p_{rckm} \in \text{RCKM}' \bullet \frac{\exists p_{pm} : \text{decisionPath, } p_{ckm} : \text{decisionPathCKM} \mid \frac{p_{pm} \in \text{PM} \wedge p_{ckm} \in \text{CKM} \bullet \text{dom } p_{rckm} = \text{dom } p_{pm} \cup \text{dom } p_{ckm} \wedge}{\text{RCKM}' \neq \emptyset \Rightarrow \text{rootRCKM}' = \text{rootRCKM} \wedge} \quad (2.53)$$

$$(13) \neg \text{RCKM}' \neq \emptyset \Rightarrow \text{rootRCKM}' = \text{rootRCKM} \wedge \quad (2.54)$$

$$\text{RCKM}' \neq \emptyset \Rightarrow \text{head}(\text{dom } dp_{pm}?) = \text{rootRCKM} \wedge \quad (2.55)$$

$$\forall \text{pos} : \mathbb{N} \mid \text{pos} \in \text{dom refinedCKM}' \bullet \text{pos} > 1 \wedge \quad (2.56)$$

$$\text{pos} \leq (\#\text{dom } dp_{pm}?) + (\#\text{ran } dp_{pm}?) \wedge \quad (2.57)$$

$$\text{ran}(\text{dom } rckmPath!) \subset \text{ran decisionPathConditionRCKM} \wedge \quad (2.58)$$

$$\text{ran}(\text{ran } rckmPath!) \subset \text{ran ConclusionRCKM} \wedge \quad (2.59)$$

$$(\text{ran}(\text{ran } rckmPath!) \cap \text{ran decisionPathConditionRCKM}) \subset \text{ran decisionPathConditionRCKM} \wedge \quad (2.60)$$

$$0 \leq \text{decPathRCKMAccuracy}(rckmPath!) \leq 100 \wedge \quad (2.61)$$

$$\text{head}(\text{dom } rckmPath!) \notin \text{ran ConclusionRCKM} \cap \text{ran decisionPathConditionRCKM} \wedge \quad (2.62)$$

$$\exists dp : \text{decisionPathRCKM} \mid dp \in \text{RCKM} \bullet \frac{\text{dom } rckmPath! = \text{dom } dp \setminus \text{last}(\text{dom } dp) \Rightarrow \text{last}(\text{dom } dp) = \text{ran } rckmPath! \wedge}{\text{dom } rckmPath! = \exists p_{ckm} : \text{decisionPathCKM} \mid p_{ckm} \in \text{CKM} \bullet \frac{\text{dom}(p_{pm}?) \cup \text{dom } p_{ckm} \wedge}{\text{ran } rckmPath! = \text{ran } dp_{pm}? \wedge} \quad (2.63)$$

$$\text{dom } rckmPath! = \exists p_{ckm} : \text{decisionPathCKM} \mid p_{ckm} \in \text{CKM} \bullet \frac{\text{dom}(p_{pm}?) \cup \text{dom } p_{ckm} \wedge}{\text{ran } rckmPath! = \text{ran } dp_{pm}? \wedge} \quad (2.64)$$

$$\text{ran } rckmPath! = \text{ran } dp_{pm}? \wedge \quad (2.65)$$

$$\forall r : \text{RefinedTreatmentPlan} \mid r \in \text{refinements?} \bullet \frac{\text{rckmPath!} = \bigcap \{t_p : \text{TreatmentPlan} \bullet (1.. \text{dom } r, t_p)\} \mid \text{dom } rckmPath!, \text{ran } r, \{t_p : \text{TreatmentPlan} \bullet (\text{dom } r + 1.. \#\text{dom } rckmPath!, t_p)\} \mid \text{dom } rckmPath! \wedge}{\text{rckmPath!} = \bigcap \{t_p : \text{TreatmentPlan} \bullet (1.. \text{dom } r, t_p)\} \mid \text{dom } rckmPath!, \text{ran } r, \{t_p : \text{TreatmentPlan} \bullet (\text{dom } r + 1.. \#\text{dom } rckmPath!, t_p)\} \mid \text{dom } rckmPath! \wedge} \quad (2.65)$$

$$\text{rckmPath!} = \bigcap \{t_p : \text{TreatmentPlan} \bullet (1.. \text{dom } r, t_p)\} \mid \text{dom } rckmPath!, \text{ran } r, \{t_p : \text{TreatmentPlan} \bullet (\text{dom } r + 1.. \#\text{dom } rckmPath!, t_p)\} \mid \text{dom } rckmPath! \wedge \quad (2.65)$$

$$\text{decisionPathRCKM}' = \text{decisionPathRCKM} \cup \{\text{dom } rckmPath! \mapsto \text{ran } rckmPath!\} \wedge \quad (2.66)$$

$$\text{decisionPathConditionRCKM}' = \text{decisionPathConditionRCKM} \cup \text{dom } rckmPath! \wedge \quad (2.67)$$

$$\text{refinedTPlan}' = \text{refinedTPlan} \cup \text{refinements?} \wedge \quad (2.68)$$

$$\text{refinementsDecPath}' = \text{refinementsDecPath} \cup \{\text{refinements?} \mapsto dp_{pm}?\} \wedge \quad (2.69)$$

$$\text{ConclusionRCKM}' = \text{ConclusionRCKM} \cup \text{ran } rckmPath! \wedge \quad (2.70)$$

$$\text{decPathRCKMAccuracy}' = \text{decPathRCKMAccuracy} \cup \{\text{rckmPath!} \mapsto \text{decPathRCKMAccuracy}(rckmPath!)\} \wedge \quad (2.71)$$

$$\text{accuracyRCKM}' = \frac{\text{accuracyRCKM} \bullet \#\text{RCKM} - \text{decPathRCKMAccuracy}(rckmPath!)}{\#\text{RCKM} - 1} \wedge \quad (2.72)$$

$$\#\text{RCKM}' = \#\text{RCKM} + 1 \wedge \quad (2.73)$$

$$\text{evidences}' = \text{evidences} \cup \text{decPathEvidences}(dp_{pm}?) \wedge \quad (2.74)$$

$$\text{decPathRCKMEvidences}' = \text{decPathRCKMEvidences} \cup \{\text{rckmPath!} \mapsto \text{decPathEvidences}(dp_{pm}?)\} \wedge \quad (2.75)$$

$$\text{RCKM}' = \text{RCKM} \oplus \{\text{dom } rckmPath! \mapsto \text{ran } rckmPath!\} \wedge \quad (2.76)$$

$$\text{refinedCKM}' = \text{refinedCKM} \oplus \{\text{rckmPath!} \mapsto \text{CKM}\} \wedge \quad (2.77)$$

$$\text{rootRCKM}' = \text{rootRCKM} = \text{head}(\text{dom } dp_{pm}?) \quad (2.78)$$

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11371138 **Supplementary Appendix B. Simplification of primed statements using logical proof**

1139 This section describes the detailed steps used to prove the primed statements in Proof 2 (line
1140 2.42 to 2.54). The primed statements are evolved using fundamental laws of set theory and deduction
1141 rules to obtain the simplified form. All proofs (Proof 5 - 15) are straightforward, and instructions are
1142 provided for each logical statement.

1143 We introduce the necessary definitions (if required) before each proof in order to clarify the
1144 logical steps in the corresponding and subsequent proofs. Proof 3 provides the simplification of the
1145 first prime statement in Proof 2 (line 2.42), which is concluded to the simplified statement of the R-
1146 CKM model ((Axiom 3: line 11). In addition to the *one-point rule* (Definition 2), the following basic
1147 definitions (Definitions 4, 5) are used to deduce the final conclusion.

1148 Proof 4 simplifies the primed statement in Proof 2 (line 2.43) to the refined statement of the R-
1149 CKM model (Axiom 3: line 12). Using the *one-point rule* (line 4.02), set subtraction, and *ran* properties
1150 (line 4.03- 4.05), the proof is easily concluded. The *ran* property for the union is defined as follows.

Definition 4: For any two functions f and g , the dom property for the union is defined as follows;

$$\text{dom}(f \cup g) \Leftrightarrow \text{dom}f \cup \text{dom}g$$

Definition 4: dom over union

Definition 5: For any two sets a and b , the set subtraction is formally defined as follows;

$$a \setminus b = \{x \in a \mid x \notin b\}$$

Definition 5: Set subtraction

Definition 6: For any two functions f and g , the ran property for the union is defined as follows;

$$\text{ran}(f \cup g) \Leftrightarrow \text{ran}f \cup \text{ran}g$$

Definition 6: ran over union

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Proof 5 simplifies the primed statement in Proof 2 (line 2.44) using the *one-point rule* (line 5.02), the definition of range (line 5.03 using Definition 6), and other laws and principles of set theory, which are described in the following definitions.

Definition 7: For any two sets a and b , the following property holds;

$$a \cup b = a \Leftrightarrow b \subset a$$

Definition 7: Union Properties

Definition 8: Set intersection is distributive over A set union. For sets r , s , and t , the set intersection distribution over a union set can be defined as follows;

$$r \cap (s \cup t) = (r \cap s) \cup (r \cap t)$$

Definition 8: Set intersection distribution law over union

Definition 9: For sets a , b , and c , the following definition holds;

$$a \cup b \subset c \Rightarrow (a \subset c \wedge b \subset c)$$

Definition 9: Set union and proper subset

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Using the one-point rule (line 6.01) and definitions of basic set theory (lines 6.02 - 6.04), Proof 6 concludes the primed statement in Proof 2 (line 2.45) into the R-CKM model (Axiom 3: line 14).

Proof 7 concludes the primed statement in Proof 2 (line 2.46) into the R-CKM model (Axiom 3: line 15) using the one-point rule (line 7.02) and definitions of basic set theory (lines 7.03 - 7.05).

Using the one-point rule (line 8.02) and definitions of basic set theory (lines 8.03 - 8.05), Proof 8 concludes the primed statement in Proof 2 (line 2.47) into the R-CKM model (Axiom 3: line 16).

Proof 9 concludes the primed statement in Proof 2 (line 2.48) into the R-CKM model (Schema 3: line 8). This proof is straightforward, and its conclusion is reached by using the one-point rule (line 9.02, 9.09) and solving the inequalities with fundamental mathematics. The proof is logically decomposed into two parts (lines 9.03-9.07 and lines 9.08-9.11). Each part is proven separately, and the final statement is concluded (line 9.12).

Definition 10: The union (\cup) of two functions is not always a function. However, \oplus is the same as a union but ensures that combinations of the two functions are also a function. For two functions f and g , \oplus is defined as follows:

$$f \oplus g = (\text{dom } g \triangleleft f) \cup g$$

For functions f and g , the dom property for \oplus is defined as follows:

$$\text{dom}(f \oplus g) \Leftrightarrow \text{dom } f \oplus \text{dom } g$$

Definition 10: dom property over \oplus

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Definition 11: Modus ponens, or implication elimination, is a simple argument form and rule inference in logic. For predicates p and q , the modus ponens can be formally represented as follows:

$$p \Rightarrow q, q \vdash p$$

Definition 11: Modus ponens

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The remaining proofs (Proof 10-Proof 15) use the same pattern of logical proofs to simplify the remaining primed statements of Proof 2 (line 2.49-line 2.54). Each step in the proofs is provided with instructive definitions, and necessary definitions are included where the explanation is required.

Proof 3 Simplification of primed statement-(1)

$$\text{decisionPathConditionRCKM}' - \text{dom decisionPathRCKM}' \quad (3.01)$$

$$\text{decisionPathConditionRCKM}' \cup \text{dom rckmPath}' - \text{dom}(\text{decisionPathRCKM}' \cup \{\text{dom rckmPath}' \mapsto \text{ran rckmPath}'\}) \quad \text{Def.2 : [one - point rule]} \quad (3.02)$$

$$\text{decisionPathConditionRCKM}' \cup \text{dom rckmPath}' - \text{dom decisionPathRCKM}' \cup \text{dom}(\text{dom rckmPath}' \mapsto \text{ran rckmPath}') \quad \text{Def.4 : [dom property over } \cup \text{]} \quad (3.03)$$

$$\text{decisionPathConditionRCKM}' \cup \text{dom rckmPath}' = \text{dom decisionPathRCKM}' \cup \text{dom rckmPath}' \quad [\text{dom def.}] \quad (3.04)$$

$$\text{decisionPathConditionRCKM}' = \text{dom decisionPathRCKM}' \quad \text{Def.5 : [Set subtraction]} \quad (3.05)$$

Proof 4 Simplification of primed statement-(2)

$$\text{ConclusionRCKM}' = \text{ran decisionPathRCKM}' \quad (4.01)$$

$$\text{ConclusionRCKM}' \cup \text{ran rckmPath}' = \text{ran}(\text{decisionPathRCKM}' \cup \{\text{dom rckmPath}' \mapsto \text{ran rckmPath}'\}) \quad \text{Def.2 : [one - point rule]} \quad (4.02)$$

$$\text{ConclusionRCKM}' \cup \text{ran rckmPath}' = \text{ran}(\text{decisionPathRCKM}' \cup \text{ran}(\text{dom rckmPath}' \mapsto \text{ran rckmPath}')) \quad \text{Def.6 : [ran property over } \cup \text{]} \quad (4.03)$$

$$\text{ConclusionRCKM}' \cup \text{ran rckmPath}' = \text{ran decisionPathRCKM}' \cup \text{ran rckmPath}' \quad [\text{ran def.}] \quad (4.04)$$

$$\text{ConclusionRCKM}' = \text{ran decisionPathRCKM}' \quad \text{Def.5 : [Set subtraction]} \quad (4.05)$$

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Proof 5 Simplification of primed statement-(3)

$$\begin{aligned} & (\text{ran ConclusionRCKM}^f \cap \text{ran decisionPathConditionRCKM}^f) \subseteq \text{ran decisionPathConditionRCKM}^f & (5.01) \\ & (\text{ran}(\text{ConclusionRCKM} \cup \text{ran rckmPath}) \cap \text{ran}(\text{decisionPathConditionRCKM} \cup \text{dom rckmPath})) \subseteq \text{ran}(\text{decisionPathConditionRCKM} \cup \text{dom rckmPath}) \text{Def.2: [one - point rule]} & (5.02) \\ & (\text{ran ConclusionRCKM} \cup \text{ran}(\text{ran rckmPath})) \cap (\text{ran decisionPathConditionRCKM} \cup \text{ran}(\text{dom rckmPath})) \subseteq \text{ran decisionPathConditionRCKM} \cup \text{ran}(\text{dom rckmPath}) \text{Def.6: [ran property over } \cup] & (5.03) \\ & ((\text{ran ConclusionRCKM} \cup \text{ran}(\text{ran rckmPath})) \cap \text{ran decisionPathConditionRCKM}) \subseteq \text{ran decisionPathConditionRCKM} \text{Def.7: [} a \cup b = a \triangleleft b \subseteq a] & (5.04) \\ & (\text{ran ConclusionRCKM} \cap \text{ran decisionPathConditionRCKM}) \cup (\text{ran}(\text{ran rckmPath}) \cap \text{ran decisionPathConditionRCKM}) \subseteq \text{ran decisionPathConditionRCKM} \text{Def.8: [Distribution law for } \cap] & (5.05) \\ & (\text{ran ConclusionRCKM} \cap \text{ran decisionPathConditionRCKM}) \subseteq \text{ran decisionPathConditionRCKM} \wedge \text{ran}(\text{ran rckmPath}) \cap \text{ran decisionPathConditionRCKM} \subseteq \text{ran decisionPathConditionRCKM} \text{Def.9: [} a \cup b \subseteq c \Rightarrow (a \subseteq c \wedge b \subseteq c)] & (5.06) \\ & (\text{ran ConclusionRCKM} \cap \text{ran decisionPathConditionRCKM}) \subseteq \text{ran decisionPathConditionRCKM} \text{[} a \wedge \text{true} = a] & (5.07) \end{aligned}$$

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1183**Proof 6 Simplification of primed statement-(4)**

$$\begin{aligned} & \text{head}(\text{decisionPathConditionRCKM}^f) \subseteq \text{ran ConclusionRCKM}^f \cap \text{ran decisionPathConditionRCKM}^f & (6.01) \\ & \text{head}(\text{decisionPathConditionRCKM} \cup \text{dom rckmPath}) \subseteq \text{ran}(\text{ConclusionRCKM} \cup \text{ran rckmPath}) \cup \text{ran}(\text{decisionPathConditionRCKM} \cup \text{dom rckmPath}) \text{Def.2: [one - point rule]} & (6.02) \\ & \text{head}(\text{decisionPathConditionRCKM} \cup \text{dom rckmPath}) \subseteq \text{ran}(\text{ConclusionRCKM} \cup \text{ran}(\text{ran rckmPath})) \cup \text{ran}(\text{decisionPathConditionRCKM} \cup \text{dom rckmPath}) \text{Def.6: [ran property over } \cup] & (6.03) \\ & \text{head}(\text{decisionPathConditionRCKM}) \subseteq \text{ran ConclusionRCKM} \cup \text{ran decisionPathConditionRCKM} \text{Def.7: [} a \cup b = a \Leftrightarrow b \subseteq a] & (6.04) \end{aligned}$$

Proof 7 Simplification of primed statement-(5)

$$\begin{aligned} & \text{evidences}^f = \text{ran decPathRCKMEvidences}^f & (7.01) \\ & (\text{evidences} \cup \text{decPathEvidences}(dppm?)) = \text{ran}(\text{decPathRCKMEvidences} \cup \text{rckmPath} \mapsto \text{decPathEvidences}(dppm?)) \text{Def.2: [one - point rule]} & (7.02) \\ & (\text{evidences} \cup \text{decPathEvidences}(dppm?)) = \text{ran}(\text{decPathRCKMEvidences} \cup \text{ran}\{\text{rckmPath} \mapsto \text{decPathEvidences}(dppm?)\}) \text{Def.6: [ran property over } \cup] & (7.03) \\ & (\text{evidences} \cup \text{decPathEvidences}(dppm?)) = \text{ran}(\text{decPathRCKMEvidences} \cup \text{decPathEvidences}(dppm?)) \text{[ran def.]} & (7.04) \\ & \text{evidences} = \text{ran}(\text{decPathRCKMEvidences}) \text{Def.5: [Set subtraction]} & (7.05) \end{aligned}$$

Proof 8 Simplification of primed statement-(6)

$$\begin{aligned} & \text{refinedTPPlan}^f = \text{dom refinementsDecPath}^f & (8.01) \\ & \text{refinedTPPlan} \cup \text{refinements?} = \text{dom}(\text{refinementsDecPath} \cup \{\text{refinements?} \mapsto dppm?\}) \text{Def.2: [one - point rule]} & (8.02) \\ & \text{refinedTPPlan} \cup \text{refinements?} = \text{dom}(\text{refinementsDecPath} \cup \text{dom}\{\text{refinements?} \mapsto dppm?\}) \text{Def.4: [dom property over } \cup] & (8.03) \\ & \text{refinedTPPlan} \cup \text{refinements?} = \text{dom}(\text{refinementsDecPath} \cup \text{refinements?}) \text{[dom def.]} & (8.04) \\ & \text{refinedTPPlan} = \text{dom}(\text{refinementsDecPath}) \text{Def.5: [Set subtraction]} & (8.05) \end{aligned}$$

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Proof 9 Simplification of primed statement-(7)

$$\begin{aligned}
0 \leq accuracyRCKM' &\leq 100 && (9.01) \\
\Leftrightarrow accuracyRCKM' \geq 0 \wedge accuracyRCKM' \leq 100 &&& (9.02) \\
accuracyRCKM' &\geq 0 && \text{[Let consider } P_1 \text{]} \quad (9.03) \\
\frac{accuracyRCKM \times \#RCKM + decPathRCKM Accuracy(rckmPath)}{\#RCKM + 1} &\geq 0 && \text{Def.2 : one - point rule} \quad (9.04) \\
accuracyRCKM \times \#RCKM - decPathRCKM Accuracy(rckmPath) &> 0 && \text{[multiplication]} \quad (9.05) \\
accuracyRCKM \times \#RCKM &\geq 0 && a - b \geq 0 \wedge b \geq 0 \rightarrow a \geq 0 \quad (9.06) \\
accuracyRCKM &> 0 && \text{Division} \quad (9.07) \\
accuracyRCKM' < 100 &&& \text{[Let consider } P_2 \text{]} \quad (9.08) \\
\frac{accuracyRCKM \times \#RCKM + decPathRCKM Accuracy(rckmPath)}{\#RCKM + 1} &\leq 100 && \text{Def.2 : one - point rule} \quad (9.09) \\
accuracyRCKM \times \#RCKM - decPathRCKM Accuracy(rckmPath) &< 100 \times (\#RCKM + 1) && \text{[multiplication]} \quad (9.09) \\
accuracyRCKM \times \#RCKM < 100 \times (\#RCKM + 1) &&& [ax + y < c.(a + 1) \wedge y < c \rightarrow ax < c.(a + 1)] \quad (9.10) \\
accuracyRCKM &\leq 100 && [ax \leq c.(a + 1) \Rightarrow x \leq c] \quad (9.11) \\
0 \leq accuracyRCKM \leq 100 &&& [P_1 \text{ and } P_2 \text{ proofs}] \quad (9.12)
\end{aligned}$$

Proof 10 Simplification of primed statement-(8)

$$\begin{aligned}
RCKM' - dom.refinedCKM' &&& (10.01) \\
RCKM \equiv \{ \{ dom.rckmPath \rightarrow ran.rckmPath \} - &&& \text{Def.2 : [one - point rule]} \quad (10.02) \\
dom.refinedCKM \odot \{ rckmPath \rightarrow CKM \} \} &&& \\
RCKM \equiv \{ \{ dom.rckmPath \rightarrow ran.rckmPath \} - &&& \text{Def.10 : [dom over \cap]} \quad (10.03) \\
dom.refinedCKM \odot dom\{ rckmPath \rightarrow CKM \} \} &&& \\
RCKM \equiv \{ \{ dom.rckmPath \rightarrow ran.rckmPath \} - &&& \text{[dom def.]} \quad (10.04) \\
dom.refinedCKM \odot rckmPath \} &&& \\
RCKM \odot rckmPath - dom.refinedCKM \odot rckmPath &&& \text{Simplification} \quad (10.05) \\
RCKM - dom.refinedCKM &&& \text{Def.5 : [Set subtraction]} \quad (10.06)
\end{aligned}$$

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Proof 11 Simplification of primed statement-(9)

$$\begin{aligned}
\forall dp : decisionPathRCKM' \mid dp \in RCKM' \bullet &&& (11.01) \\
head(dom dp) \notin ran ConclusionRCKM' \cap ran decisionPathConditionRCKM' &&& \\
\forall dp : (decisionPathRCKM \cup \{ \{ dom.rckmPath \rightarrow ran.rckmPath \} \} \mid &&& \text{Def.2 : [one - point rule]} \quad (11.02) \\
dp \in (RCKM \odot \{ \{ dom.rckmPath \rightarrow ran.rckmPath \} \}) \bullet &&& \\
head(dom dp) \notin ran(ConclusionRCKM \cup ran.rckmPath) \cap &&& \\
ran(decisionPathConditionRCKM \cup dom.rckmPath) &&& \\
\forall dp : decisionPathRCKM \mid dp \in RCKM \bullet &&& \forall \text{ simplification} \quad (11.03) \\
head(dom dp) \notin ran ConclusionRCKM \cap ran decisionPathConditionRCKM \wedge &&& \\
head(dom\{ rckmPath \rightarrow ran.rckmPath \}) \notin ran(ConclusionRCKM \cup ran.rckmPath) \cap &&& \\
ran(decisionPathConditionRCKM \cup dom.rckmPath) &&& \\
\forall dp : decisionPathRCKM \mid dp \in RCKM \bullet &&& \text{Def.4, 6 : [dom def. and ran over \cup]} \quad (11.04) \\
head(dom dp) \notin ran ConclusionRCKM \cap ran decisionPathConditionRCKM \wedge &&& \\
head(dom.rckmPath) \notin ran ConclusionRCKM \cup ran(rckmPath) \cap &&& \\
ran decisionPathConditionRCKM \cup ran(dom.rckmPath) &&& \\
\forall dp : decisionPathRCKM \mid dp \in RCKM \bullet &&& \text{Def.7 : [a - b - a \rightarrow b \subset a]} \quad (11.05) \\
head(dom dp) \notin ran ConclusionRCKM \cap ran decisionPathConditionRCKM \wedge &&& \\
head(dom.rckmPath) \notin ran ConclusionRCKM \cap &&& \\
ran decisionPathConditionRCKM &&& \\
\forall dp : decisionPathRCKM \mid dp \in RCKM \bullet &&& [a \wedge true \equiv a] \quad (11.06) \\
head(dom dp) \notin ran ConclusionRCKM \cap ran decisionPathConditionRCKM &&&
\end{aligned}$$

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Proof 12 Simplification of primed statement-(10)

$$\perp dp : \text{decisionPathRCKM}' \circ dp_1 : \text{decisionPathRCKM}' \bullet dp, dp_1 \in \text{RCKM}' \bullet \\ \text{dom } dp_1 = \text{dom } dp \setminus \text{last}(\text{dom } dp) \Rightarrow \text{last}(\text{dom } dp) = \text{ran } dp_1 \quad (12.01)$$

$$\perp dp : (\text{decisionPathRCKM}' \cup \{\text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}\}) \circ dp_1 : (\text{decisionPathRCKM}' \cup \{\text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}\}) \bullet \\ dp, dp_1 \in (\text{RCKM}' \cup \{\text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}\}) \bullet \\ \text{dom } dp_1 = \text{dom } dp \setminus \text{last}(\text{dom } dp) \Rightarrow \text{last}(\text{dom } dp) = \text{ran } dp_1 \quad \text{Def.2 : [one - point rule]} \quad (12.02)$$

$$\perp dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \\ \text{dom } \text{rckmPath!} \setminus \text{dom } dp \setminus \text{last}(\text{dom } dp) \mapsto \text{last}(\text{dom } dp) \setminus \text{ran } \text{rckmPath!} \\ \Rightarrow \\ \exists dp : \text{decisionPathRCKM}' \circ dp_1 : \text{decisionPathRCKM}' \bullet dp, dp_1 \in \text{RCKM}' \bullet \\ \text{dom } dp_1 \setminus \text{dom } dp \setminus \text{last}(\text{dom } dp) \mapsto \text{last}(\text{dom } dp) \setminus \text{ran } dp_1 \quad [_] \text{expansion} \quad (12.03)$$

$$\exists dp : \text{decisionPathRCKM}' \circ dp_1 : \text{decisionPathRCKM}' \mid dp, dp_1 \in \text{RCKM}' \bullet \\ \text{dom } dp_1 \setminus \text{dom } dp \setminus \text{last}(\text{dom } dp) \mapsto \text{last}(\text{dom } dp) \setminus \text{ran } dp_1 \quad \text{Def.11 : [Modus ponens]} \quad (12.04)$$

Proof 13 Simplification of primed statement-(11)

$$\text{accuracyRCKM}' - (\text{let } \text{pathsAcc} \leftarrow \{ \text{pathsAcc} : \mathbb{Z}, \text{RCKM}' \neq \emptyset \wedge \\ (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \text{pathsAcc} = \\ \text{decPathRCKMAccuracy}(dp) + \text{pathsAcc}) \} / \# \text{RCKM}' \quad (13.01)$$

$$\text{accuracyRCKM} \times \# \text{RCKM} \mid \text{decPathRCKMAccuracy}(\text{rckmPath!}) = \\ \frac{\# \text{RCKM} + 1}{\# \text{RCKM} + 1} \\ (\text{let } \text{pathsAcc} \leftarrow \{ \text{pathsAcc} : \mathbb{Z} \mid (\text{RCKM} \neq \emptyset \wedge \text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}) \neq \emptyset \wedge \\ (\forall dp : (\text{decisionPathRCKM}' \cup \{\text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}\}) \mid dp \in \\ (\text{RCKM}' \cup \{\text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}\}) \bullet \\ \text{pathsAcc} = (\text{decPathRCKMAccuracy}(dp) + \text{pathsAcc}) \\ + \text{decPathRCKMAccuracy}(\text{rckmPath!})) \} / (\# \text{RCKM} - 1) \quad \text{Def.2 : 'one - point rule'} \quad (13.02)$$

$$\text{accuracyRCKM} \times \# \text{RCKM} \mid \text{decPathRCKMAccuracy}(\text{rckmPath!}) = \\ \frac{\# \text{RCKM} + 1}{\# \text{RCKM} + 1} \\ (\text{let } \text{pathsAcc} \leftarrow \{ \text{pathsAcc} : \mathbb{Z} \mid \text{RCKM} \neq \emptyset \wedge \\ (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \\ \text{pathsAcc} = \text{decPathRCKMAccuracy}(dp) - \text{pathsAcc}) \} \} + \\ \text{decPathRCKMAccuracy}(\text{rckmPath!}) / (\# \text{RCKM} + 1) \quad [_] \text{simplification} \quad (13.03)$$

$$\text{accuracyRCKM} \times \# \text{RCKM} + \text{decPathRCKMAccuracy}(\text{rckmPath!}) = \\ (\text{let } \text{pathsAcc} \leftarrow \{ \text{pathsAcc} : \mathbb{Z}, \text{RCKM}' \neq \emptyset \wedge \\ (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \text{pathsAcc} = \\ \text{decPathRCKMAccuracy}(dp) + \text{pathsAcc}) \} \} \mid \text{decPathRCKMAccuracy}(\text{rckmPath!})) \quad [\text{multiplication} \quad (13.04)$$

$$\text{accuracyRCKM} \times \# \text{RCKM} = \\ (\text{let } \text{pathsAcc} \leftarrow \{ \text{pathsAcc} : \mathbb{Z}, \text{RCKM}' \neq \emptyset \wedge \\ (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \text{pathsAcc} = \\ \text{decPathRCKMAccuracy}(dp) - \text{pathsAcc}) \} \} \\ [\text{subtraction} \quad (13.05)$$

$$\text{accuracyRCKM} = \\ (\text{let } \text{pathsAcc} \leftarrow \{ \text{pathsAcc} : \mathbb{Z}, \text{RCKM}' \neq \emptyset \wedge \\ (\forall dp : \text{decisionPathRCKM}' \mid dp \in \text{RCKM}' \bullet \text{pathsAcc} = \\ \text{decPathRCKMAccuracy}(dp) - \text{pathsAcc}) \} \} / \# \text{RCKM} \quad [\text{division} \quad (13.06)$$

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1204**Proof 14** Simplification of primed statement-(12)

$$\forall p_{\text{rckm}} : \text{decisionPathRCKM}' \bullet p_{\text{rckm}} \in \text{RCKM}' \bullet \\ \exists p_{\text{pm}} : \text{decisionPath}, p_{\text{ckm}} : \text{decisionPathCKM} \mid \\ p_{\text{pm}} \in \text{PM} \wedge p_{\text{ckm}} \in \text{CKM} \bullet \text{dom } p_{\text{rckm}} = \text{dom } p_{\text{pm}} \cup \text{dom } p_{\text{ckm}} \quad (14.01)$$

$$\forall p_{\text{rckm}} : (\text{decisionPathRCKM}' \cup \{\text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}\}) \bullet \\ p_{\text{rckm}} \in (\text{RCKM}' \cup \{\text{dom } \text{rckmPath!} \mapsto \text{ran } \text{rckmPath!}\}) \bullet \\ \exists p_{\text{pm}} : \text{decisionPath}, p_{\text{ckm}} : \text{decisionPathCKM} \mid \\ p_{\text{pm}} \in \text{PM} \wedge p_{\text{ckm}} \in \text{CKM} \bullet \text{dom } p_{\text{rckm}} = \text{dom } p_{\text{pm}} \cup \text{dom } p_{\text{ckm}} \quad \text{Def.2 : [one - point rule]} \quad (14.02)$$

$$\forall p_{\text{rckm}} : \text{decisionPathRCKM}' \bullet p_{\text{rckm}} \in \text{RCKM}' \bullet \\ \exists p_{\text{pm}} : \text{decisionPath}, p_{\text{ckm}} : \text{decisionPathCKM} \mid \\ p_{\text{pm}} \in \text{PM} \wedge p_{\text{ckm}} \in \text{CKM} \bullet \text{dom } p_{\text{rckm}} = \text{dom } p_{\text{pm}} \cup \text{dom } p_{\text{ckm}} \wedge \\ \exists p_{\text{ckm}} : \text{decisionPathCKM} \bullet p_{\text{ckm}} \in \text{CKM} \bullet \\ \text{dom } \text{rckmPath!} \setminus \text{dom } (p_{\text{pm}}?) \cup \text{dom } p_{\text{ckm}} \quad \forall \text{expansion} \quad (14.03)$$

$$\forall p_{\text{rckm}} : \text{decisionPathRCKM}' \bullet p_{\text{rckm}} \in \text{RCKM}' \bullet \\ \exists p_{\text{pm}} : \text{decisionPath}, p_{\text{ckm}} : \text{decisionPathCKM} \mid \\ p_{\text{pm}} \in \text{PM} \wedge p_{\text{ckm}} \in \text{CKM} \bullet \text{dom } p_{\text{rckm}} = \text{dom } p_{\text{pm}} \cup \text{dom } p_{\text{ckm}} \quad 'a \wedge \text{true} \rightarrow a' \quad (14.04)$$

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1208**Proof 15** Simplification of primed statement-(13)

$$\text{RCKM} \neq \emptyset \Rightarrow \text{rootRCKM}' = \text{rootRCKM} \quad (15.01)$$

$$\text{RCKM} \neq \emptyset \Rightarrow \text{head}(\text{dom } dp_{\text{pm}}?) = \text{rootRCKM} \quad \text{Def.2 : [one - point rule]} \quad (15.02)$$

$$\text{RCKM} / \emptyset \mapsto \text{rootRCKM} \quad \text{rootRCKM} \quad [\text{Substitution} \quad (15.03)$$

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