

A Constraint-based Approach to Medical Guidelines and Protocols

Arjen HOMMERSOM^{a,1}, Perry GROOT^a, Peter LUCAS^a, Mar MARCOS^b, and Begoña MARTÍNEZ-SALVADOR^b

^a*Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen the Netherlands*

^b*Universitat Jaume I, Castellon, Spain*

Abstract. Medical guidelines and protocols are documents aimed at improving the quality of medical care by offering support in medical decision making in the form of management recommendations based on scientific evidence. Whereas medical guidelines are intended for nation-wide use, and thus omit medical management details that may differ among hospitals, medical protocols are aimed at local use, e.g., within hospitals, and, therefore, include more detailed information. Although a medical guideline and an associated protocol concerning the management of a particular disorder are related to each other, one question is to what extent they are different. Formal methods are applied to shed light on this issue. A Dutch medical guideline regarding the treatment of breast cancer, and a Dutch protocol based on it, are taken as an example.

Keywords. Adaptation, Verification, Model Checking

Introduction

Medical management is increasingly based on recommendations from the medical scientific community, summarised in medical guidelines and protocols. Medical guidelines are systematically developed, structured documents, containing conclusions and recommendations, based on scientific evidence [6]. These documents are called *evidence-based guidelines*. Medical protocols are local adaptations of medical guidelines.

The goal of the work described here is to better understand the differences and similarities between guidelines and protocols. First, insight is obtained into the relation of a medical guideline and protocol concerning the medical management of one particular disorder, breast cancer. Based on the results of this analysis, we have carried out a formal analysis of parts of both the guideline and the protocol for breast cancer treatment, which provides a rigorous method for finding such differences. This is done by looking at both medical protocols and guidelines as defining (logical) constraints on the medical management of patients performed in practice. This approach was inspired by a statement by Wiersma and Burgers that “recommendations in guidelines should not only be based on evidence extracted from scientific literature, but take into account the context of daily medical practice as well” [17]. In effect, this makes the comparison between guidelines

¹Corresponding Author: Arjen Hommersom, Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, the Netherlands; E-mail: arjenh@cs.ru.nl.

and protocols more realistic. In principle this approach would allow one to discover flaws or suboptimal management actions in the medical management in practice, assuming that a given protocol and guideline are correct, or to find incorrect or suboptimal medical management decisions in a protocol or guideline, assuming that the medical management in practice is correct and optimal. In the research described in this chapter we investigate whether this is possible using a combination of informal and formal, in particular model checking, methods.

1. Medical Guidelines and Protocols

A medical guideline is an extensive document, developed by a working group involving professionals involved in the management of the disorder covered by the guideline. By definition, a protocol is seen as a local version of a guideline, meant to be useful as a guide for daily clinical care. Hence, basically, a medical protocol is a summary of the most important sections that are in the guideline, mostly recommendations, supplemented with hospital-specific details concerning the treatment. This implies that many sections in a protocol may be very similar to related sections in a guideline. However, there may also be differences, partly due to differences in opinion between the guideline designers and protocol designers, and partly due to the difference in purpose of a guideline and protocol. The guideline that we have used in this study is the 2004 version of the Dutch CBO guideline on the treatment of breast cancer. The protocol that we have used is the protocol of the Dutch Integral Cancer Centre East (IKO in Dutch), which is based on the CBO guideline. To understand the differences between breast cancer treatment in the guideline and the protocol, we briefly review the result of an informal analysis of cases where the recommendations of the guideline and protocol differs.

Most of the differences between the CBO guideline and the IKO protocol that were found are due to the fact that the protocol is more specific than the guideline. Such differences are also referred to as ‘cookbook’ difference, indicating that the difference implies an insignificant refinement compared to the guideline. For example, in the protocol, an ultrasound axilla is suggested as default action during the sentinel node procedure to assess the stage of the disease, whereas the guideline does not provide such a default. Similarly, a protocol may choose a particular order between interventions to improve the efficiency of the health care process, whereas a guideline does not recommend any.

There are few real differences (i.e., differences that cannot be described in terms of a refinement) between the protocol and the guideline. The main reason for this is that this particular protocol is heavily based on the guideline and the developers are involved in both the guideline and the protocol. As a consequence, the evidence used is the same in both cases, and therefore the recommendations are very similar. An example of such a real difference is the case when tumour cells are isolated in the sentinel node. According to the guideline, axillary treatment can be omitted, in contrast to the IKO protocol where additional axillary treatment is recommended in any case. This difference is a significant change in advise and, assuming a closed world assumption on the interventions that may be performed, can be seen as a contradiction. However, it may be argued that the evidence underlying the guideline advice was based on retrospective studies and is therefore uncertain.

2. Medical Management in Breast Cancer

First, we give an informal description on the medical management as stated in the CBO guideline (and IKO protocol) that deals with locoregional treatment of operable breast cancer, i.e., T1-2 N0-1 M0 breast cancer according to the TNM classification system [8]. Thereafter, we discuss temporal logic as a means for formalising the medical management of breast cancer.

2.1. Informal Description of Medical Management

According to the CBO guideline there are only two options for local treatment of operable invasive breast cancer: breast-conserving therapy (BCT) or modified radical mastectomy (MRM). BCT implies ample local excision of the tumour, an axillary staging procedure, and radiotherapy of the breast. MRM involves a total resection of the breast (mastectomy) and dissection of the axillary nodes (AND). The aim of BCT is to achieve a survival rate comparable to MRM with an optimal cosmetic result in terms of the treated breast. BCT is usually the preferred treatment unless the patient has a clear preference for MRM and there are no contra indications for BCT, i.e., there is no (1) multicentricity (two or more tumour foci in different quadrants), or (2) diffuse malignant microcalcifications, or (3) previous radiotherapy of the breast. Another contra indication for BCT is obtained *during* surgery: (4) the margins of the local excision remain tumour-positive after repeated local excision attempts. In this case, local excision attempts are unsuccessful in removing the primary tumour and treatment therefore switches to MRM.

Treatment of the axillary nodes is also part of the treatment of breast cancer as the pathologic assessment of axillary lymph nodes remains the most important prognostic variable for the invasive breast cancer patient. An optimal assessment would be achievable by means of a complete axillary node dissection (AND). However, AND may lead to morbidity, e.g., pain, limited shoulder movement. An alternative for axillary staging is the sentinel node procedure (SNP), which only dissects the sentinel nodes, i.e., those nodes that drain the area of the breast where the primary tumour is located and thus are most likely to contain metastasis. The SNP is currently the standard procedure for axillary staging in breast cancer provided that there are no contra-indications, where contra-indications of SNP are defined as (1) suspected/proven malignancy in the axillary nodes, (2) tumour > T2, (3) multiple tumour foci, and (4) potentially disrupted lymph drainage due to recent axillary surgery or a large biopsy cavity following tumour excision.

When the SNP is not possible, complete axillary node dissection should be carried out. Furthermore, treatment of the axilla is indicated (i.e., dissection, radiotherapy) for all forms of lymph node metastasis.²

2.2. Temporal Logic Representation

The CBO guideline can be interpreted as (temporal) constraints on medical management. It has been shown in [10] that the step-wise, possibly iterative, execution of a guideline can be described precisely by means of temporal logic. The logic that we use here for specifying properties of medical guidelines is a combination of Computation Tree Logic (CTL) [3,4] and Linear Temporal Logic (LTL) [13].

²Here, the CBO guideline differs from the IKO protocol as it makes an exception for isolated tumour cells.

CTL uses atomic propositions and Boolean connectives (e.g., \neg, \vee, \wedge) to build up more complicated expressions for describing properties of states. Furthermore, CTL formulas can be composed of *path quantifiers* and *temporal operators* for describing properties of *computation trees*, i.e., all paths that are possible from a certain state. The path quantifiers **A** and **E** specify that all of the paths or some of the paths starting at a specific state have some property. The temporal operators describe properties of a path through the tree. The four temporal operators are **X**, **G**, **F**, and **U**, where **X** φ is true if φ holds in the next state, **G** φ if φ holds in the current and in all future states, **F** φ if φ holds in some state in the future (or is true in the current state), and φ **U** ψ if φ holds until ψ holds.

LTL provides operators for describing events along a single computation path. Each formula is of the form **A** f , where f is a path formula, which is either an atomic proposition or inductively defined as $\neg f, f \vee g, f \wedge g, \mathbf{X}f, \mathbf{F}f, \mathbf{G}f$, or $f\mathbf{R}g$ with f, g path formulas.

The language we use for atomic propositions consists of medical actions (*Actions*), medical plans (*Plans*), and data structures (*Data*):

$$\begin{aligned} \text{Actions} &: \{\text{tumour-excision, mastectomy, AND, SNP}\} \\ \text{Plans} &: \{\text{TREATMENT, BCT, MRM, AXILLA-STAGING}\} \\ \text{Data} &: \{\text{CI-BCT, CI-SN, TF, SN, ITC}\} \end{aligned}$$

where $\text{CI-BCT, CI-SN} \in \{\top, \perp\}$ denote the contra indications for BCT and SN, respectively, $\text{SN} \in \{\text{unknown, neg, pos}\}$ denotes whether there is a metastasis found in the lymph nodes after performing the SN procedure, $\text{TF} \in \{\text{unknown, } \top, \perp\}$ denotes whether the resection margins are tumour free, and $\text{ITC} \in \{\top, \perp\}$ denotes whether there are isolated tumour cells. In the formal analysis, we will only concern ourselves with the surgical part of the treatment and omit radiotherapy.

3. Formalisation of Medical Management

In this section, we give a constraint-based representation of a fragment of the CBO guideline using the temporal logic representation discussed in the previous section. Furthermore, we interpret the recommendations in the IKO protocol and represent them in a more or less executable model. The goal is to verify whether the model of the protocol complies with the recommendations of the CBO guideline, or if there are differences, using a model checking approach [5].

3.1. Constraint-Based Representation of the Guideline

The final representation in temporal logic of the medical management in the CBO guideline is shown in Figure 1.

Some constraints given by the guideline are not easily expressible in temporal logic, as they involve other modalities different from time, such as the preference for BCT over MRM and the preference for the SNP over axilla-dissection for staging the axilla. Other assumptions regarding the patient data are implicit in the guideline, e.g., the status of the resection margins, i.e., whether they are tumour free (TF) or not (\neg TF), only becomes known after excision of the tumour and the existence of metastasis ($\text{SN}=\text{pos}$ or $\text{SN}=\text{neg}$) only becomes known after the SNP. Here we have chosen not to consider these more implicit constraints.

Constraints related to control structure
(1) $\mathbf{AG}(\text{TREATMENT} \rightarrow \mathbf{AF}(\text{BCT} \vee \text{MRM}))$
(2) $\mathbf{AG}(\text{CI-BCT} \rightarrow \neg \text{BCT})$
(3) $\mathbf{AG}(\text{BCT} \rightarrow \mathbf{AF}(\text{AXILLA-STAGING} \vee \text{MRM}) \wedge \mathbf{AF} \text{ tumour-excision})$
(4) $\mathbf{AG}(\text{MRM} \rightarrow \mathbf{AF} \text{ AND} \wedge \mathbf{AF} \text{ mastectomy})$
(5) $\mathbf{AG}(\text{AXILLA-STAGING} \rightarrow \mathbf{AF} (\text{AND} \vee \text{SNP}))$
(6) $\mathbf{AG}(\text{CI-SN} \rightarrow \neg \text{SNP})$
(7) $\mathbf{AG}(\text{tumour-excision} \rightarrow ((\text{TF} = \perp \rightarrow \mathbf{AF} \text{ MRM}) \wedge (\text{TF} = \top \rightarrow \mathbf{AG} \neg \text{MRM})))$
(8) $\mathbf{AG}(\text{SNP} \rightarrow (\text{SN} = \text{pos} \wedge \neg \text{ITC} \rightarrow \mathbf{AF} \text{ AND}))$
(9) $(\mathbf{G} \neg \text{MRM}) \rightarrow \mathbf{AG}(\text{SNP} \rightarrow \mathbf{AG}(\text{ITC} \rightarrow \mathbf{AG} \neg \text{AND}))$
(10) $\mathbf{AG}(\text{TREATMENT} \rightarrow (\text{CI-SN} \rightarrow \mathbf{AF} \text{ AND}))$
Constraints related to data
(11) $(\text{CI-BCT} \rightarrow \mathbf{AG} \text{ CI-BCT}) \wedge (\neg \text{CI-BCT} \rightarrow \mathbf{AG} \neg \text{CI-BCT})$
(12) $(\text{CI-SN} \rightarrow \mathbf{AG} \text{ CI-SN}) \wedge (\neg \text{CI-SN} \rightarrow \mathbf{AG} \neg \text{CI-SN})$

Figure 1. Constraint-based representation of the CBO guideline. BCT = breast conserving treatment, MRM = modified radical mastectomy, CI-BCT = contra indications for BCT, SN = result of sentinel node procedure, CI-SN = contra indications for SNP, tumour-excision = segmental tumour excision, TF = tumour free resection margins, ITC = isolated tumour cells.

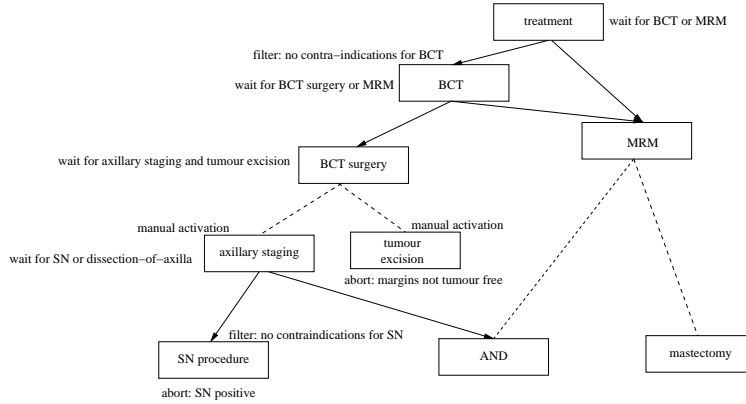


Figure 2. Asbru interpretation of IKO protocol. Arrows represent sequential plans, dotted lines represent unordered sub-plans

3.2. Asbru Representation of the IKO Protocol

Much research has already been devoted to the development of representation languages for medical guidelines. Most of them consider guidelines as a composition of actions, controlled by conditions. However, many languages are not formal enough for the purpose of our research as they often incorporate free-text elements which do not have a clear semantics. Exceptions to this are *PROforma* [7] and *Asbru* [15]. Here we use *Asbru*, because in previous research its semantics has been defined precisely [1] and can be translated automatically into SMV for model checking purposes [2].³

³<http://www.cis.ksu.edu/santos/smv-doc/> [accessed January 2008]

The overall structure of the Asbru model is given in Figure 2. It consists of nine plans ordered in a hierarchy. The top level plan ‘treatment’ will start by selecting the BCT plan, which may be rejected in case there are contra indications against doing breast conserving therapy. In that case, treatment will continue with a modified radical mastectomy (MRM). In case BCT is successfully completed, the treatment also completes and the MRM plan will not be started. The ‘BCT surgery’ plan consists of axillary staging and tumour excision, which are modelled as unordered plans, as the protocol does not explicitly state an order. To allow for a specific ordering of these two sub-plans we include a manual activation and assume that the activation will be performed by a doctor eventually. In case of BCT, the axillary staging starts with an investigation of the sentinel nodes provided that there are no contra indications. In case it is rejected or, because the sentinel nodes are positive, the plan is aborted, and an axillary dissection has to be performed. Furthermore, it is possible that the excision aborts because the margins are not tumour free. Since BCT surgery waits for this sub-plan, in that case BCT surgery has to be aborted and therefore it is mandatory to do a MRM. Finally, MRM is defined as both a dissection of the axilla and a mastectomy as defined by the protocol. No particular order between the two is given.

The formal semantics of the Asbru model in Figure 2 is based on the plan state model described in [1], of which an SMV model was constructed using the method and tool described in [2]. Most variables dealing with patient data are initialised as *unknown* and receive an indeterministic value in the second step to make sure there is only one root of the model. Furthermore, we assume that they do not change during the treatment. The only variables that are initialised at a later stage are the status of the sentinel node, which becomes known during the SNP and whether or not the tumour margins that have been resected are tumour free, which becomes known at the excision of the tumour. Furthermore, fairness constraints have been added to ensure that the manual activation of both the axilla surgery and the tumour excision eventually occurs. In other words, the patient will not wait indefinitely for the treatments to start.

Using the above formalisation, the IKO protocol can be verified using the constraints of the CBO guideline using standard model checking techniques. However, guidelines and protocols are usually under-constrained, thereby allowing many treatment paths not occurring in medical practice. We therefore look at the inclusion of medical management in practice in the following section.

4. Comparison Using Background Knowledge

In this section, we use the textbook of Roses [14] to create a precise model of medical management in practice. This model will be formalised into a decision tree, referred to as *background knowledge*, which will be used to select the part of the IKO protocol that is consistent with [14] and then verify for only this selected part whether it complies with the constrained based representation of the CBO guideline.

4.1. Medical Management in Practice

According to [14], the sentinel node procedure (SNP) is started before segmental excision (i.e., used in BCT) or mastectomy. The sentinel nodes (SNs) are then immediately

sent to the pathology lab, where they are examined during surgery. If the SNs are found to be positive, axillary dissection can be completed during the primary breast surgery in one setting.

Furthermore, [14] differs from the CBO guideline and IKO protocol in the case of recurrent tumour positive resection margins in the BCT treatment. Whereas CBO and IKO recommend to switch the treatment to MRM, which includes axillary dissection, [14] only recommends a mastectomy with axillary dissection depending on sentinel node histopathology.

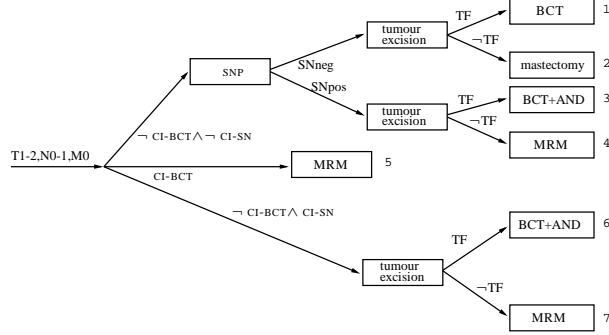


Figure 3. Background knowledge: possible treatment paths for surgery of operable invasive breast cancer. CI-BCT = contra indications BCT, CI-SN = contra indications SNP, TF = tumour free resection margins, AND = axillary node dissection.

Information from [14] can be represented in a decision tree as shown in Figure 3, which deals with the ordering of medical actions treating the primary tumour (BCT and MRM) and the axilla (SNP and/or AND).⁴ Nodes represent medical actions or plans, arcs represent constraints. A path from the root node to a leaf node represents a treatment path, which defines the order of medical actions when the constraints on the path are satisfied. As mentioned above, the guideline recommends MRM in path (2) instead of mastectomy.

4.2. Comparing Medical Management with the IKO Protocol

Clearly, the medical management stated by the IKO protocol is less precise than the medical management performed in practice. Typically, one would expect the medical management in the protocol to be under constrained when compared to the medical management in practice. To verify this for the IKO protocol, we have transformed the 7 possible treatment paths in Figure 3 into a number of CTL properties (2 shown below) and verified whether these paths occur in the protocol.

- (1) $\mathbf{EX}(\neg\text{CI-BCT} \wedge \neg\text{CI-SN} \wedge \mathbf{EF}(\text{SNP} \wedge \text{SNP} = \text{neg} \wedge \mathbf{EF}(\text{tumour-excision} \wedge \text{TF} \wedge \mathbf{AG}(\neg\text{mastectomy} \wedge \neg\text{AND}))))$
- (2) $\mathbf{EX}(\neg\text{CI-BCT} \wedge \neg\text{CI-SN} \wedge \mathbf{EF}(\text{SNP} \wedge \text{SNP} = \text{neg} \wedge \mathbf{EF}(\text{tumour-excision} \wedge \neg\text{TF} \wedge \mathbf{EF}(\text{mastectomy}) \wedge \mathbf{AG}(\neg\text{AND}))))$

⁴We abstract from isolated tumour cells.

With the SMV model checker we were able to verify that all paths, except (2), can occur in the IKO protocol. Path (2) does not hold in the IKO protocol because it recommends a MRM whereas [14] recommends a mastectomy, i.e., axillary dissection is included in the medical management according to the protocol, but not according to [14]. Whether the protocol or the textbook is incomplete or incorrect should be discussed with medical experts.

4.3. Selective Comparison of Guideline Constraints and Protocol

Clearly medical management is much less precisely defined in the CBO guideline and the IKO protocol than in the medical textbook of Roses [14]. Hence, any model that is only based on a written document of a guideline or protocol without the inclusion of background knowledge, will include many paths in which medical actions are unrealistically ordered. Many rightful properties of medical management may therefore not hold for the model constructed. Either one can choose to improve the model such that it adheres to medical practice (but not to the guideline document), or one can select only those paths in the model that also occur in medical practice for which then the property needs to be proven.

One approach to accomplish this is by including assertions to the model of the protocol or guideline. Assertions are statements that should hold in every execution path of the protocol, which, in SMV, are written down in the form of linear time logic (LTL) properties. This makes it possible to state properties about the relation of medical actions in time. In order to do this, the background knowledge formalised in terms of a decision tree, needs to be interpreted in terms of such LTL assertions. Here, we consider the following LTL assertions.

- (1) $(\neg \text{CI-BCT} \wedge \neg \text{CI-SN}) \leftrightarrow \mathbf{F} \text{ SNP}$
- (2) $(\mathbf{F} \text{ SNP}) \rightarrow ((\neg \text{tumour-excision} \mathbf{U} \text{ SNP}) \wedge \mathbf{F} \text{ tumour-excision})$
- (3) $((\mathbf{F} \text{ SNP}) \wedge \text{SNP} = \text{neg} \wedge (\mathbf{F} \text{ TF})) \rightarrow \mathbf{G}(\neg \text{mastectomy} \wedge \neg \text{AND})$
- (4) $((\mathbf{F} \text{ SNP}) \wedge \text{SNP} = \text{neg} \wedge (\mathbf{F} \neg \text{TF})) \rightarrow ((\mathbf{F} \text{ mastectomy}) \wedge (\mathbf{G} \neg \text{AND}))$
- (5) $((\mathbf{F} \text{ SNP}) \wedge \text{SNP} = \text{pos} \wedge (\mathbf{F} \text{ TF})) \rightarrow ((\mathbf{F} \text{ AND}) \wedge (\mathbf{G} \neg \text{MRM}))$
- (6) $((\mathbf{F} \text{ SNP}) \wedge \text{SNP} = \text{pos} \wedge (\mathbf{F} \neg \text{TF})) \rightarrow \mathbf{F} \text{ MRM}$
- (7) $(\text{CI-BCT} \rightarrow ((\mathbf{G} \neg \text{tumour-excision}) \wedge (\mathbf{F} \text{ MRM})))$
- (8) $(\neg \text{CI-BCT} \wedge \text{CI-SN}) \rightarrow \mathbf{F} \text{ tumour-excision}$
- (9) $(\neg \text{CI-BCT} \wedge \text{CI-SN} \wedge (\mathbf{F} \text{ TF})) \rightarrow ((\mathbf{F} \text{ AND}) \wedge (\mathbf{G} \neg \text{MRM}))$
- (10) $(\neg \text{CI-BCT} \wedge \text{CI-SN} \wedge (\mathbf{F} \neg \text{TF})) \rightarrow \mathbf{F} \text{ MRM}$

Assertions (1) and (2) deal with the use of sentinel node procedure and the order between this and the excision of the tumour. Assertions (3) to (6) are concerned with paths (1) to (4). Assertion (7) deals with path (5). Finally assertions (8) and (9) deal with path (6) and (7). However, we have seen in the previous section that (4), which corresponds to path (2), is not coherent with the model (i.e., from (4) it follows the antecedent of (4) is false), so in this form it is not usable. We could therefore either adapt the assertions so that it corresponds to the guideline or omit it. Here, we have omitted it.

Verifying the guideline constraints with SMV on the Asbru model of the IKO protocol using these assertions, shows that, indicating a difference between protocol and guideline with respect to medical management in practice. Although, in this case the dif-

ference between protocol and guideline is clear and could also have more easily been found through an informal analysis, this is largely because the protocol and guideline have a very similar structure and their recommendations are almost identical. However, the approach taken is independent of the underlying structure of the protocol and guideline. Therefore, this case study shows that formal techniques can be used to compare guideline and protocol independent of their underlying document structure.

5. Discussion

The aim of this work was to obtain insight into the differences and similarities between guidelines and protocols, based on the assumption that protocols should be looked upon as local modifications of guidelines. As a guideline is a starting point for drafting a protocol concerning the same topic, the development of a protocol based on a guideline can be seen as a transformation process. In this work, we have only been able to find end point protocols; as a consequence, the transformation process could only be described as consisting of a single step. In reality, it may be a more iterative process to design a protocol on the basis of an available guideline. This view on both guidelines and protocols raises a number of issues currently not addressed in literature.

First, guidelines are typically under-constrained thereby omitting many details about treatment order. Our work contrasts on this point with [16] for example, in which guidelines are more viewed as programs, but in which no execution paths are excluded that are illogical for medical management in practice. Clearly, additional medical background knowledge is needed to supplement the knowledge in the guideline document as was already acknowledged in previous work [9]. Whereas in previous work we incorporated background knowledge into the model, here we have used background knowledge to restrain the number of possible execution paths.

Second, researchers have focused on the verification of the quality of medical guidelines. However, verification of guidelines still takes a lot of effort. By using formal methods to find differences between a protocol and a guideline, one could reuse verification results of the guideline for the protocol and only focus on those parts that are different. Current work on verification of guidelines only considers guidelines to be solitary objects. No reference is made to verifying adaptations of guidelines.

Third, locating differences between guidelines and protocols is a novel topic, which has previously only been looked at from an informal angle [12]. The formal techniques used in our research extends previous work on model checking medical guidelines [2] and complements the techniques used in earlier work on quality checking medical guidelines [16,9]. The authors of [11] also investigate guideline-protocol relationships using model checking, but take a different approach as they view guidelines and protocols as programs rather than constraints on medical management.

One of the questions that emerged in the course of the research was whether the guideline or protocol ought to be adopted as the gold standard for comparison. Based on insights obtained by consulting literature on guideline development, we decided to take neither the guideline nor the protocol as the gold standard, but medical management in practice up to the point where it is consistent with the guideline and/or protocol. Using model-checking as principal tool, the guideline and protocol, now seen as defining logical constraints to medical management, were compared to a decision tree describing the

medical management. Some of the outcomes of this research cast doubts on the content of both guideline and protocol, in the sense that at least some sort of explanation is needed in order to understand why there are differences between the decision tree, on the one hand, and the guideline and protocol, on the other hand. We believe that these results give a promising starting point for further investigating the relations between guidelines, protocols, and medical management in practice.

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