The focus of this research is to offer new ways of supporting clinical processes through the use of information technology that is based on reusable evidence-based data structures, models and components. In the long term this can lead to the creation of customisable e-services for patient-specific decision making in health care. In particular, computerisation of clinical practice guidelines is explored using openEHR, a semantic technology for electronic health records.
The project is a collaboration between the Karolinska Institutet departments LIME, MedSolna and Clinical Neuroscience as well as with the company Cambio Healthcare Systems.

Nadim Anani holds the equivalent of B.Sc. and M.Sc. degrees in Medical Informatics from Heidelberg University, Germany.

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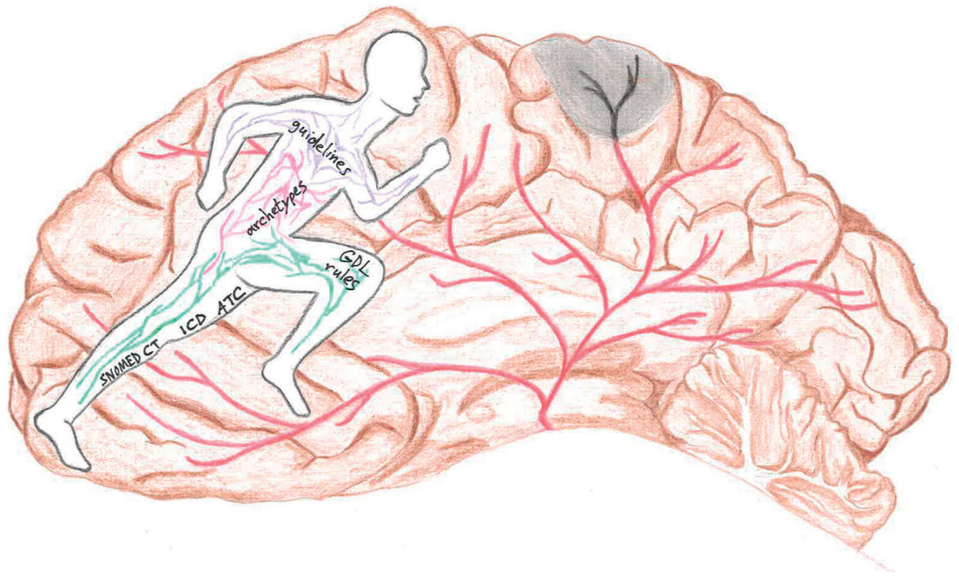

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EXPLORING OPENEHR-BASED CLINICAL GUIDELINES IN ACUTE STROKE CARE AND RESEARCH

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THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Largely speaking, health information systems today are not able to exchange data between each other and understand the data's meaning automatically by means of their information technology components. This lack of 'interoperability' also leads to patients experiencing an undesired discontinuity in their care. This thesis is a part of a health informatics field which tackles interoperability barriers by offering standardised information models for electronic health records. More specifically, this work explores possibilities of combining standardised information models offered by the openEHR interoperability approach with knowledge from evidence-based clinical practice guidelines. The applied methodology includes openEHR archetypes, the openEHR reference information model, standard medical terminologies such as SNOMED CT, the international stroke treatment registry SITS, a newly developed model for representing guideline knowledge (the 'Care Entry-Network Model'), and rules authored in the Guideline Definition Language, a formalism recently endorsed by openEHR as a part of its specifications. The study design used is based on evaluating the work done by means of retrospectively checking the compliance of completed patient cases with guidelines from the domain of acute stroke management in Europe, both experimentally and using thousands of real patient cases from SITS. Our overall findings are that i) the Care Entry-Network Model facilitates an intermediate step between narrative guideline text and computer-interpretable guidelines to be deployed in openEHR systems, ii) the Guideline Definition Language is practicable for creating and automatically running openEHR-based computer-interpretable guidelines, where we also provide detailed accounts of our employed GDL technologies, and iii) the Guideline Definition Language combined with real patient data from patient data registries can generate new clinical knowledge, which in our case has benefited stroke carers and researchers working with acute stroke thrombolysis. In conclusion, using our methodology, health care stakeholders would get evidence-based knowledge components in their electronic health records based on shareable, well maintainable information and knowledge models in the form of archetypes and GDL rules respectively. However, our approach still needs to be tested at the point of clinical decision making and compared to other approaches for providing exchangeable computer-interpretable guidelines.

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II. Anani N, Chen R, Prazeres Moreira T, Koch S. Retrospective checking of compliance with practice guidelines for acute stroke care: a novel experiment using openEHR's Guideline Definition Language. BMC Medical Informatics and Decision Making. 2014 May 10;14:39.

III. Anani N, Mazya MV, Chen R, Prazeres Moreira T, Bill O, Ahmed N, Wahlgren N, Koch S. Retrospective checking of compliance with practice guidelines: applying openEHR's Guideline Definition Language to the SITS international stroke treatment registry. Manuscript.

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FURTHER RELATED WORK

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CONTENTS

LIST OF ABBREVIATIONS

CIG	computer-interpretable guideline
EHR	electronic health record
GDL	Guideline Definition Language
guideline	clinical practice guideline

1 FIELD OF RESEARCH

1.1 ELECTRONIC HEALTH RECORDS

Information systems in health care (often referred to as 'health information systems') can serve as a facilitator in the development of health care organisations (Berg, 2011). Health information systems are hard to picture without information technology today and have been noted, by some, to be a key part in the 'reinvention of healthcare' (Coiera, 2004). A core component of health information systems is the electronic health record (EHR).

One can see an EHR to be the digital means of storing and retrieving data of a patient. The International Organization for Standardization (ISO) defines an EHR in its most generic purpose to be a 'repository of information regarding the status of a subject of care, in computer processable form' (International Organization for Standardization, 2005).

The ISO report also explains that an EHR should ideally be patient-centred and longitudinal, i.e. a life-long record. This means that an EHR should be able to reflect the complete health care journey of a patient throughout her whole life, irrespective of whether she was taken care of by one or one hundred organisations, whether these organisations were in the same city, region or country or whether different kinds of specialists, e.g. dermatologists, cardiologists or physiotherapists, were involved. This also relates to the concept of continuity of care (Shortell, 1976).

The definitions of ideal EHRs by ISO and other parties do not, however, reflect the reality of EHR usefulness in most health care settings today. The successes of EHRs in improving patient care and outcomes are still often reported to be modest, if making any impact at all (El-Kareh et al., 2013; Celi et al., 2015; Enriquez et al., 2015).

Nevertheless, several countries around the world are placing considerable efforts on defining their policies, plans and expectations around effective EHR implementation, including initiatives such as a national eHealth strategy in Sweden, the Meaningful Use programme in the USA and larger investments into EHR development by New Zealand to attract EHR vendors (Gray et al., 2011).

Also, hopes on the different roles EHRs can take on are high. Beside their primary function of supporting more effective patient care, EHRs are also expected to improve research decisively, empower patients in the form of personal health records and point out quality improvement measures in health care organisations (Angus, 2015; Prey et al., 2015; Bekelis et al., 2015).

All in all, the adoption of EHRs is already wide globally, but for them to also reach their full potential widely, they probably need to undergo more systematic evaluations to generate more evidence around them. At the same time, concerns about the ineffective use of EHRs, such as those raised in a complaint letter recently by prominent medical associations in the

USA, need to be addressed (American Academy of Family Physicians, 2015). Looking into the future, a balanced combination of different EHR development methods (including application of some of the concepts described in sections 1.2, 1.3 and 1.6 below) may remove risks of EHRs being a ‘trap’ and lead to reaping their benefits efficiently (Mandl and Kohane, 2012).

1.2 CLINICAL INFORMATION MODELLING

The idea behind clinical information modelling is basically reproducing realities from the clinical world in models that are systematic enough for computing clinical data as sophisticatedly as possible.

The purposes of clinical information models thus include facilitating detailed querying of patient data, computerised clinical decision support, improved quality management in health care and better clinical research (Goossen, 2014).

The levels on which clinical information modelling happens usually vary with differences occurring based on, for instance, whether the focus is more technical, more clinical or more to represent all definitions and relationships within a certain clinical, medical or scientific domain. The more technical level of clinical information modelling will usually be most helpful to software engineers, by providing relevant data types, classes and related functions tailored to health care computing. The more clinical level will usually deal with structuring established clinical concepts that all clinical professionals can relate to, such as electrocardiogram observations, blood glucose measurements, medication orders or diagnostic procedures. Ontologies, which constitute the third modelling level mentioned here, aim to be comprehensive representations of a part of reality, like the clinical world or human biology. Arguably a fourth level of information modelling is that of defining concrete use cases within health information systems, such as all the information appearing in a radiological summary on a clinician’s computer screen or mobile phone.

An example of a clinical information model with a technical focus is a data type representing a quantity in health care, which includes attributes such as value, unit and error margin as well as functions that set and retrieve these attributes. An example of a clinical information model with a more clinical focus is an agreed-upon definition of all elements of a clinical scoring system like an Apgar score. Examples of ontologies are the Disease Ontology, Common Anatomy Reference Ontology and Information Artifact Ontology (Smith et al., 2007; Ceusters, 2012). An example of a clinical use case information model is a definition of a graphical user interface’s information components at an ophthalmic clinic.

These different levels of clinical information modelling are often combined in specifications of health informatics standards (see *1.3 Health Informatics Standards*), with differing approaches (Goossen et al., 2010). The standards, in turn, often aim at creating more effective EHRs (see *1.1 Electronic Health Records*). Furthermore, some research shows that certain

ontological principles can be used to follow and define every detail of what happens in an EHR over time, through so-called 'referent tracking' (Rudnicki et al., 2007).

Table 1 summarises the different focuses within clinical information modelling.

Modelling Focus	**Description**
Technical	Typically targeted at software engineers, defines health care-specific data types and classes. Example: quantity data type or class with its attributes and functions.
Clinical	Typically targeted at both clinicians and software engineers, structures established clinical concepts. Example: structured model of an Apgar score.
Ontological	Comprehensive representation of a part of reality, with definitions and relationships between defined entities. Example: Common Anatomy Reference Ontology.
Use case-based	Typically addresses information needs of clinical use cases in concrete settings. Example: information components of a graphical user interface at an ophthalmic clinic.

Table 1. Different focuses within clinical information modelling.

1.3 HEALTH INFORMATICS STANDARDS

Over the past few decades, several organisations and initiatives have been defining health informatics standards or specifications for such standards. The overarching aim and vision of health informatics standards or standard specifications is enabling interoperability.

A commonly used definition of interoperability is that of the Institute of Electrical and Electronics Engineers (IEEE): 'Ability of a system or product to work with other systems or products without special effort on the part of the customer. Interoperability is made possible by the implementation of standards.' (Institute of Electrical and Electronics Engineers, 2015). What this essentially means is that interoperability is reached when system A sends information to system B, and system B is able not only to receive and read this information, but also to understand it automatically. An example from health information systems is that the health information system of hospital A sends a discharge summary to that of hospital B, and the information system of hospital B is not only able to read the discharge summary from

hospital A (e.g. because hospital B has software that can open the file type sent from hospital A), but also perform useful tasks towards patient care based on the received summary automatically without human intervention.

Thorough and wide interoperability that can cross various organisational borders has been more of a dream than reality so far, especially between the mostly heterogeneously structured health information systems of today (Jacob, 2015). The efforts in the following section aim to change that.

1.3.1 Types of Health Informatics Standards

1.3.1.1 Messaging Standards

Messaging standards try to achieve interoperability by standardising the structure of messages exchanged between health information systems, so that messages sent by one system can be understood by another system through the commonly agreed-upon message structure.

The most prominent and widely used messaging standard is probably HL7 V2 (Health Level Seven Version 2). HL7 V2 structures various types of messages, e.g. admission, discharge and transfer messages or laboratory request and result messages (Rajeev et al., 2010).

1.3.1.2 Structure and Content Standards

Some standards try to achieve interoperability by standardising the whole structure and content of EHRs, which is a more holistic approach than that used in messaging standards. To follow in this section are some efforts and initiatives which fall under this standardisation category. **From those efforts, the research in this thesis focuses on ideas and specifications from the openEHR approach (the description of which follows directly).**

The openEHR Foundation and its related community do not directly define standards as such, but provide a large and rich set of specifications, tools and other resources that deal with reaching wide interoperability and effective EHRs. The openEHR Foundation provides all of its resources free of charge and most openEHR-related software applications are open-sourced.

One of the key concepts within openEHR's approach to reaching interoperability is two-level modelling, which separates information modelling into archetypes and a reference information model (The openEHR Foundation openEHR Architecture Overview, 2015; Bird et al., 2003). Archetypes are clinical content models of coherent clinical concepts like a Glasgow Coma Scale measurement, catheter insertion, risk assessment or medication prescription. Archetypes have to be maximal datasets, i.e. they should contain all relevant data elements that anyone could possibly need in clinical practice in relation to the clinical concept the archetype represents, like a medication prescription. Making archetypes maximal datasets facilitates that any health care organisation can use the exact same archetype for a certain clinical concept by only extracting the parts this organisation needs from it. This constitutes one of the dimensions of interoperability in the openEHR approach, where the

vision is that as many organisations as possible use the same archetypes, e.g. the same archetype for making a fall risk assessment or the same archetype for prescribing medication. In order to assure archetype quality within the geographical context they are to be used in and reach archetype versions that all involved health care organisations can work with, there are archetype review processes that can occur on national as well as international levels. The Clinical Knowledge Manager, a state-of-the-art governance platform for archetypes, supports the review processes (Nasjonal IKT Clinical Knowledge Manager, 2015; NEHTA Clinical Knowledge Manager, 2015; openEHR Clinical Knowledge Manager, 2015). Figure 1 shows an example of an archetype as represented by a mind map.

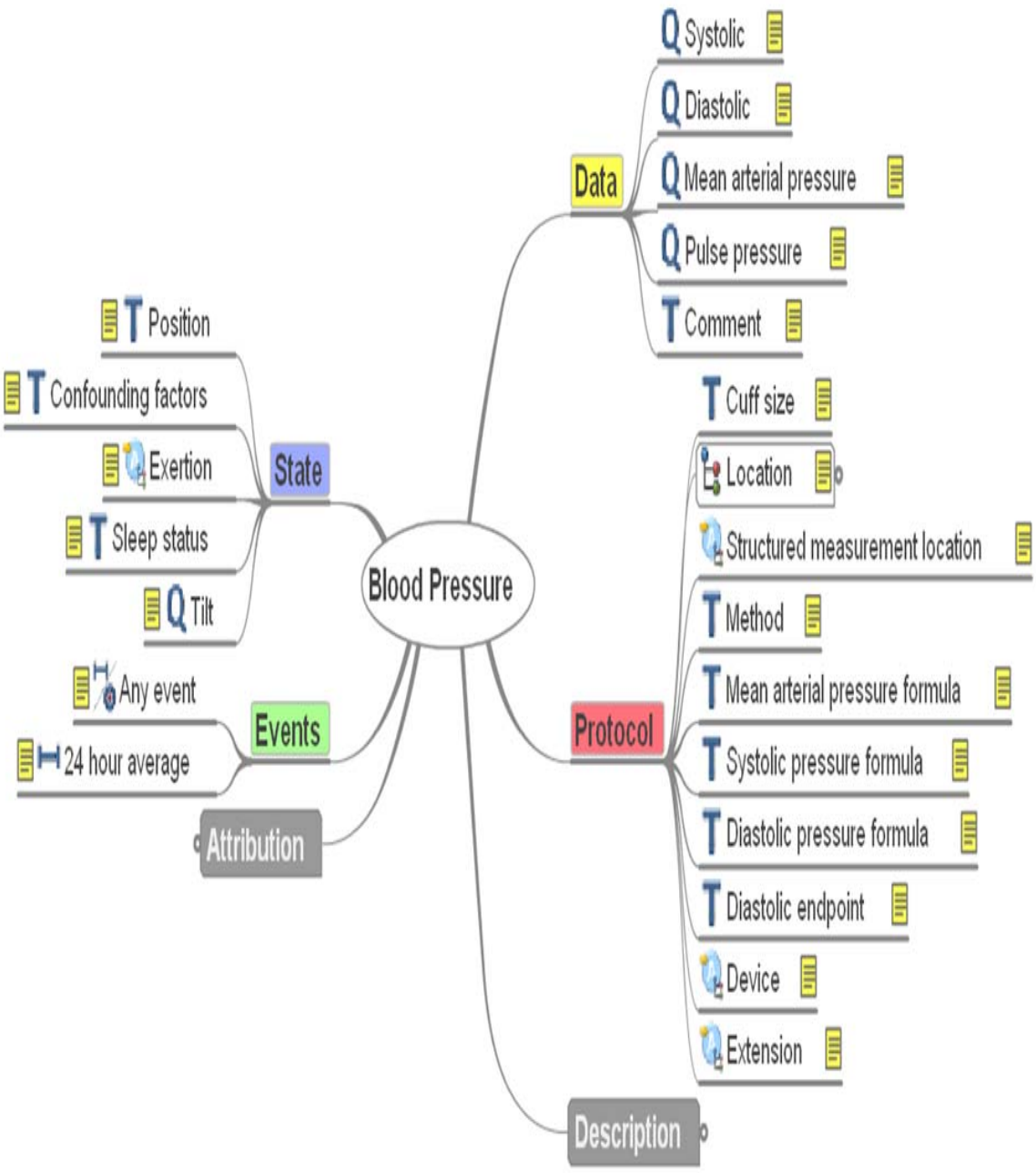

Figure 1. Blood pressure archetype after international consensus (reproduced with permission from openEHR Clinical Knowledge Manager, 2015).

Note that the different data categories in an archetype, such as `Protocol`, `Events` and `State` in Figure 1, will also depend on what sort of archetype it is. openEHR archetypes and archetype data types follow a so-called 'clinical investigator system', which is based on how openEHR believes the clinical problem-solving process takes place (The openEHR Foundation openEHR Architecture Overview, 2015). Within this problem-solving process, clinicians (or other investigators) make *observations*, which they can use as the basis for making *evaluations*, which in turn they can use for giving *instructions*, which in turn translate into *actions*. These phenomena translate into corresponding archetypes in openEHR, along with further kinds of archetypes like administrative or demographic archetypes.

Formal archetype definition takes place through the Archetype Definition Language (ADL), and archetype data instances can be queried through the Archetype Query Language (AQL). Also, archetype elements can be translated into any natural language (e.g. German, Arabic or Mandarin).

The reference information model, which is the other level of the two-level modelling concept in openEHR, provides standard data types, data structures and classes that are needed for health care computing. In Figure 1, the 'Q' and 'T' symbols, for example, represent quantity and text data types respectively from openEHR's reference information model. Further types supported are ones that facilitate classifying archetypes with respect to the clinical investigation process mentioned above, so the openEHR reference information model has the types `OBSERVATION`, `EVALUATION`, `INSTRUCTION` and `ACTION` too (they are subclasses of the abstract class `CARE_ENTRY`). It is worth noting that the reference information model to be used together with archetypes does not have to be the one released by openEHR, it can theoretically be any standard information model that archetypes can work with.

By using two-level modelling, the openEHR approach satisfies both the clinical (through archetypes) and technical (through a standard information model) focuses of information modelling (see *1.2 Clinical Information Modelling*, including Table 1). openEHR actually also satisfies the use case-based modelling focus through openEHR templates, which are aggregations of certain data elements from a collection of different archetypes. Furthermore, openEHR allows binding clinical data elements to terms from any standard terminology (see *1.3.1.3 Standard Medical Terminologies* below), which often have underlying ontologies. Terminology binding, together with identification and namespacing mechanisms for openEHR archetypes, constitute the utilisation of an ontological focus as well in openEHR's information modelling (The openEHR Foundation Archetype Technology Overview, 2015).

Beside openEHR, several other standardisation or interoperability specification efforts exist that often rely upon similar ideas such as having a standard information model or a model-driven approach that separates clinicians' requirements from those of software developers. The differences are often in the extent to which they offer such possibilities, where they see

their main focus to be or simply organisational, e.g. whether or not specifications are freely available or tools are open-sourced. Examples include the HL7 V3 Reference Information Model (RIM), HL7 V3 Clinical Document Architecture (CDA), the ISO standard 13606 (which is partly derived from openEHR specifications and uses archetypes as well), the Clinical Information Modeling Initiative (CIMI), Multi-Level Healthcare Information Modelling (MLHIM) and the recent HL7 Fast Healthcare Interoperability Resources (FHIR) (Moreno-Conde et al., 2015; MLHIM, 2015).

We chose to work with openEHR in this thesis in order to set a research scope, and because of the advantage of freely available and open-sourced resources. We had also gained some experience with and knowledge in openEHR prior to the start of this project. At the same time, this thesis' findings can serve as a basis for comparisons with modelling and implementation of computerised clinical guidelines using other standard specifications.

1.3.1.3 Standard Medical Terminologies

Standard medical terminologies are seen to have a vital role in reaching interoperability between different health information systems, as they allow for having a 'common denominator' when describing any part of the clinical world. Some, like the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT), have an ontological basis for their term hierarchies, while others, like the International Classification of Diseases (ICD) are pure classifications (International Health Terminology Standards Development Organisation, 2015; World Health Organization, 2015). An example of a SNOMED CT code is 169836001, which represents childbirth, whereas an example of an ICD code is E14, which represents diabetes (from the 10th edition of ICD). It is worth noting that SNOMED CT, containing over 300,000 terms, is more clinically comprehensive than ICD, as the latter focuses only on diseases.

Further examples of standard medical terminologies are Logical Observation Identifiers Names and Codes (LOINC), which focuses on laboratory terms, Anatomical Therapeutic Chemical (ATC) and the National Drug File – Reference Terminology (NDF-RT), the latter two being useful for finding codes for drugs (LOINC, 2015; WHO Collaborating Centre for Drug Statistics Methodology, 2015; U.S. National Library of Medicine, 2015).

As mentioned under *1.3.1.2 Structure and Content Standards*, clinical data elements from openEHR archetypes can be bound to terms from any standard medical terminology.

1.3.2 Regional, National and International Efforts

Different regions and countries have been defining policies, creating new institutions and making concrete implementation steps to reach better interoperability within or between them. The following examples are by no means exhaustive, but can give an idea of the adoption of health informatics standards in 'the real world'.

Several countries, such as Australia, Canada, Indonesia, Uruguay and Sweden, are members of the International Health Terminology Standards Development Organisation (IHTSDO), which indicates that they believe in using the standard medical terminology SNOMED CT (International Health Terminology Standards Development Organisation, 2015). Other countries, such as Norway, have nationally coordinated efforts to review and maintain archetypes (Ljosland Bakke, 2015).

At the same time, HL7 V2 messages have been connecting cross-border organisations for decades and the international openEHR archetype repository has been seeing people from all over the world contribute, translate and review archetypes together (Health Level Seven International, 2015; openEHR Clinical Knowledge Manager, 2015).

1.4 EVIDENCE-BASED PRACTICE GUIDELINES

Clinical practice guidelines are 'systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific circumstances' using the most recent evidence from research in the clinical field of interest, e.g. diabetes or hypertension management (Institute of Medicine (US) Committee to Advise the Public Health Service on Clinical Practice Guidelines, 1990). These patient and practitioner decisions can be diagnostic or treatment-related decisions, for instance. Clinical practice guidelines will be referred to as 'guidelines' throughout this thesis, or using the complete term 'clinical practice guidelines' at times.

The hopes placed on guidelines have been large in the past two decades, as guidelines form a part of evidence-based medicine. Following guidelines is expected to reduce or remove variations in health care provision due to a more systematic way of patient management, and thus lead to more fairness. Guideline use is also expected to improve outcomes through using the latest research evidence in patient care and reaching better cost-effectiveness (Sackett and Rosenberg, 1995). Additionally, guidelines are seen to have a role in empowering patients and achieving more patient-centredness (O'Connor et al., 2004).

Unfortunately, experience has shown that the benefits of guidelines cannot become a full reality without balanced health care management approaches, effective dissemination of guideline knowledge amongst clinicians and efficient implementation of guideline recommendations (Walshe and Rundall, 2001).

Guidelines also have their limitations, e.g. one set of guidelines most often deals with managing one specific disease, which does not necessarily correspond to the reality of patients, especially elderly patients, for instance, who tend to have comorbidities such as simultaneous diabetes and hypertension (Muth and Glasziou, 2015). This, in turn, owes to the fact that guidelines derive much of their content from randomised controlled trials, which seldom take comorbidities into consideration thoroughly (Jadad et al., 2011).

1.5 COMPUTER-INTERPRETABLE GUIDELINES

Computer-interpretable guidelines (CIGs) are representations of guidelines that a computer can execute. This CIG execution by a computer is often also referred to as 'enactment'.

1.5.1 Purpose and Desired Benefits

The purpose of creating CIGs is to be able to overcome some of the barriers in the way of achieving the benefits of guidelines (see also *1.4 Evidence-Based Practice Guidelines*). The idea is to offer guideline knowledge to clinicians at the point of care in the form of computerised clinical decision support provided through the health information system. This mostly overcomes the time and resources clinicians would otherwise need to update themselves about the latest guideline releases in their field and to retrieve or apply that knowledge correctly when they need it. This should eventually lead to more effective use of guidelines and better permeation of guideline knowledge into clinical practice (Latoszek-Berendsen et al., 2010).

1.5.2 CIG Formalisms

In order to create CIGs, several formalisms have been developed that specialise on offering the features needed for achieving computer-executable guidelines. These CIG formalisms can be seen as CIG programming languages to some extent, and are often also referred to as 'guideline representation models' (Wang et al., 2002).

Actions and decisions are the two core components that most CIG formalisms support. This is due to the fact that guideline recommendations are often formulated in terms of '*If X then Y*', where the *If X* part constitutes some sort of decision evaluating the condition *X*, and *Y* is some sort of action. An example could be '*If the patient's systolic blood pressure exceeds 180 mmHg then alert the treating physician*', where the decision is evaluating whether the patient's systolic blood pressure is above 180 mmHg, and the action to be taken is alerting the treating physician in case the condition of systolic blood pressure > 180 mmHg is met. Additionally, CIG formalisms typically also support scheduling constraints such as preconditions or postconditions, which have to be met before or upon taking a certain step in the guideline process respectively.

The most common form of CIG formalisms is task-network models which, as the name suggests, comprise a network of tasks. Most generically, these tasks are actions and decisions as described above, but depending on the particular features of every guideline formalism, there can be more task types. The network of the tasks arises by connecting them through conditions and nesting them into each other in a hierarchical manner. Figure 2 shows an example of a stroke guideline representation constructed with a task-network model, particularly the formalism PROforma. PROforma has the task types *action* (blue in the figure), *decision* (pink), *enquiry* (green) and *plan* (the actions, decisions and enquiries here are part of a plan). Plans, in turn, can be parts of another plan or be made up of other plans

(the nesting characteristic). Some of the strengths of PROforma include the possibility to define decision candidates, arguments for and against the candidates as well as weights for the arguments (in the figure, based on the 'CT Scan' enquiry, the 'Stroke Type' decision either results in an ischaemic or a haemorrhagic stroke type, which is not visible in the diagram but defined as properties of the respective tasks).

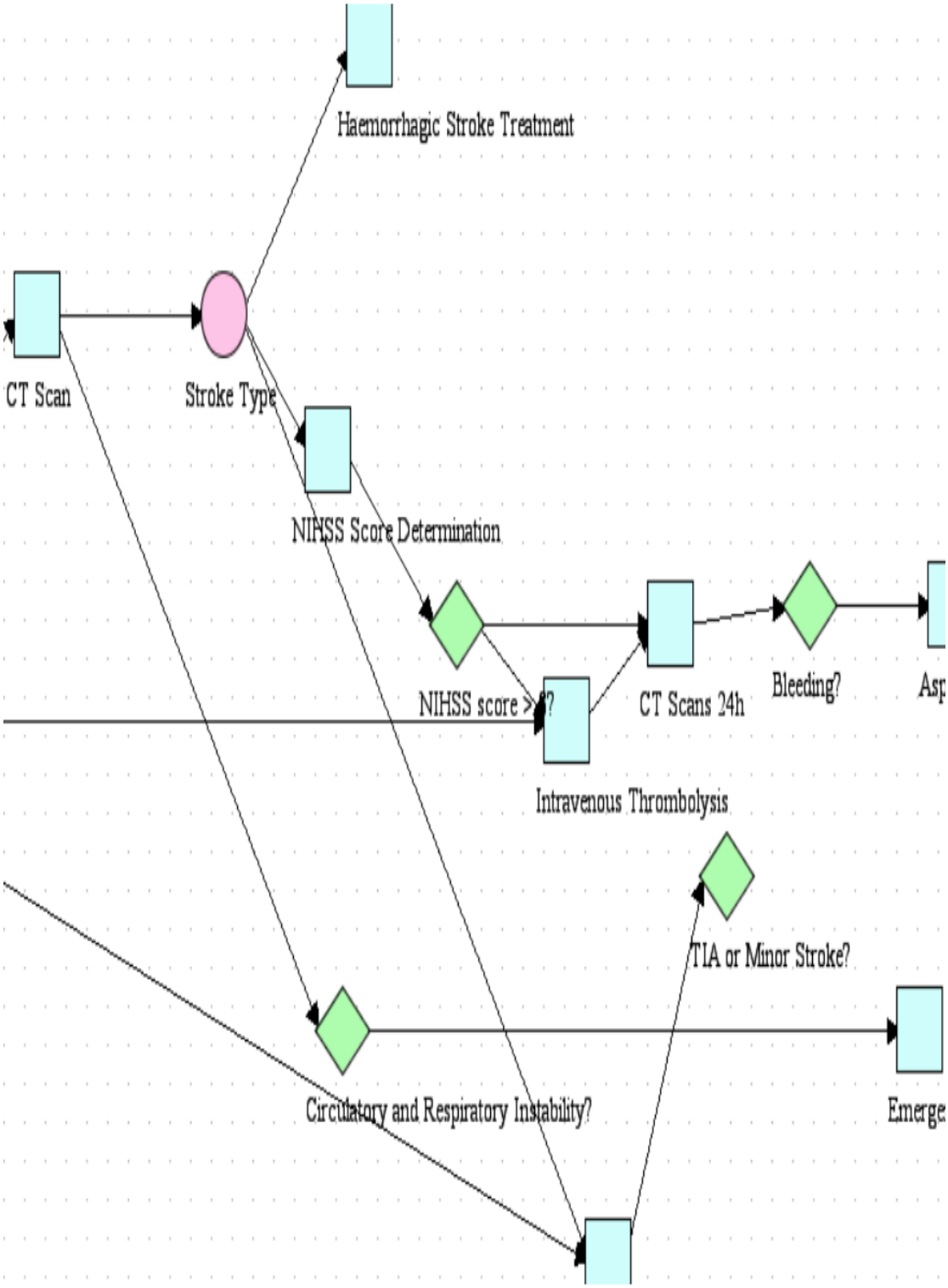

Figure 2. Stroke guideline representation by the task-network model PROforma.

Other task-network models include Asbru, which has thorough functionality for handling intentions in guideline-related processes, SAGE, which has an interoperability (i.e. CIG shareability) focus, GLIF3, which supports some HL7 features for representing patient data in guidelines and GUIDE (Peleg, 2013).

Beside task-network models, CIG formalisms can be rule languages or object-oriented constraint languages. An example of rule languages is one of the first-ever CIG formalisms – the Arden Syntax – and another one is the Guideline Definition Language (GDL), which plays a central role in this thesis (see *2.4 Emergence of the Guideline Definition Language*). An example of an object-oriented constraint language is the HL7-based GELLO.

1.5.3 Knowledge Modelling

Modelling knowledge from guidelines in one way or another is a typical step to take before reaching fully executable CIGs. The methods of visualising what is going on in the guidelines and defining all necessary execution steps can vary from flowcharts and business process models to using development environments offered for specific CIG formalisms, e.g. the Tallis Composer for PROforma CIGs (Ly et al., 2015; Sutton and Fox, 2003).

This step in the development process of CIGs can prove to be the most tedious and time-consuming, since guideline knowledge is often released in a narrative, unstructured format. Barriers in turning this unstructured knowledge into more structured knowledge include vagueness, contradictions and incompleteness in the narrative guideline source, at least from the point of view of knowledge engineers or medical informaticians, who typically create the CIGs but do not possess the clinical knowledge and expertise of physicians or other clinicians. This leads us to yet another aspect of guideline knowledge modelling that makes it tedious and time-consuming, which is that knowledge engineers or medical informaticians need to collaborate closely with clinicians to validate the correctness and quality of their knowledge models (Latoszek-Berendsen et al., 2010).

1.5.4 Knowledge Execution

As the ultimate goal of CIGs is running them automatically, i.e. executing the knowledge they contain, there are various execution engines that accompany different CIG formalisms. Examples are the execution engines provided by the tools DeGel, GLEE and NewGuide for the CIG formalisms Asbru, GLIF3 and GUIDE respectively (Isern and Moreno, 2008). The function of these engines is basically to match the conditions, actions and other elements of CIG-contained knowledge with the patient data at hand, in order to assist clinicians with decision making and other clinical tasks.

1.5.5 Guideline-Oriented Clinical Decision Support

The main purpose of executing CIG knowledge is providing computerised clinical decision support (see also *1.5.1 Purpose and Desired Benefits*). An example of computerised clinical decision support is warning a physician by means of a pop-up message that their patient is allergic to the medication they are about to administer. This can be helpful sometimes

because clinicians can often be overwhelmed by the amount of information that they have to aggregate and process within a patient's case in order to reach diagnostic and treatment-related decisions, whereas a computer can aggregate and process larger amounts of information and thereby support, aid or assist clinicians with their decisions.

Clinical decision support systems were initially referred to as expert systems, but the notion of the computer replacing the expert physician was not so acceptable amongst many physicians, leading to a shift in perception of these systems during the last two decades from providing expertise to providing support. Also, care should be taken when designing clinical decision support systems to make sure that they do not disrupt the usual workflow of clinicians, take socio-technical aspects into account, are not stand-alone systems but rather integrated with EHRs, undergo sufficient management and maintenance, and intervene in clinical practice as simply as possible (Bates et al., 2003; Patel et al., 2009).

When the artificial intelligence provided by computerised clinical decision support systems is derived from guideline knowledge, one could also refer to this as 'guideline-oriented clinical decision support' (often also named 'guideline-*based* clinical decision support' in the literature). The strength of this particular kind of clinical decision support is that it relies on research evidence, ideally the latest in the field. It can also contribute to more patient centredness, e.g. through applications based on guideline knowledge that the patients work with themselves using their mobile phones (García Sáez et al., 2014).

1.6 COMPUTER-INTERPRETABLE GUIDELINES BASED ON STANDARD INFORMATION MODELS FOR ELECTRONIC HEALTH RECORDS

The exact research field of this thesis takes place within an intersection of all of the above, i.e. EHRs, clinical information modelling, health informatics standards, clinical practice guidelines and CIGs. More specifically, this thesis is about modelling and executing CIG knowledge using information models for EHR-based interoperability provided by openEHR (see *2 The Problem* for details of this thesis' exact research field).

2 THE PROBLEM

2.1 OPENEHR SPECIFICATIONS IN 2011

When this project started in 2011, the openEHR two-level modelling approach had been mature and its details had been worked out thoroughly. There had also been a clear picture of what an overall architecture of an openEHR-based EHR system should or could look like (The openEHR Foundation openEHR Architecture Overview, 2015). However, there had still not been any official openEHR specifications for modelling or executing CIGs and the details of creating openEHR-compliant CIGs, although within the focus of The openEHR Foundation and some researchers' work, had not been worked out fully yet (Barretto, 2005).

2.2 EXPECTED BENEFITS FROM SOLVING THE PROBLEM

Having CIGs that are based on interoperability standard specifications such as those by openEHR could lead to the following benefits:

- The shareability of a CIG's underlying patient data, due to the use of openEHR archetypes and a reference information model, would mean that the CIG itself becomes shareable with other systems supporting openEHR archetypes and that reference information model.

- That, in turn, means that one system could computerise certain guideline knowledge, share its resulting CIG with other openEHR-based systems and several openEHR-based systems could maintain this CIG together (similarly to the way in which archetypes are created, shared and maintained).

Being clinical decision support components, CIGs would only have to be created once in this way, and they could then be deployed in other openEHR-based systems directly for clinical decision support purposes (leading to 'the wheel' not having to be 'reinvented'). The systems using openEHR-based CIGs may notice improvements that they could make to the CIGs, carry out those improvements, and they could then share their updated CIG versions with any other systems deploying those CIGs.

This would be in contrast to the situation today, in which most health care organisations have their purely self-developed (or self-financed) clinical decision support systems, if at all, although their content could be similar to that of a neighbouring hospital's clinical decision support system, for example. This situation leads to multiple utilisation of resources for the same cause. Reducing this redundancy of efforts within different health care organisations

could lead to saving costs spent on developing clinical decision support and utilising the resulting new resources elsewhere in patient care.

2.3 STUDIES ADDRESSING THE PROBLEM

There has been some research work addressing openEHR-based CIGs. Chen et al. showed that it is possible to use openEHR archetypes to represent guideline-related patient data together with rules written in a rule language to represent guideline logic (Chen et al., 2009). Lezcano et al. also combined archetypes with a rule language to facilitate openEHR-based reasoning, and additionally used the Web Ontology Language (OWL) to represent archetype data (Lezcano et al., 2011). Marcos et al. used a combination of archetypes and the PROforma CIG formalism to propose a method for providing EHR-based clinical decision support with the interoperability advantage (Marcos et al., 2013).

Rector et al. established that to allow the independent development of patient data models (like archetypes), guideline models (like CIG formalisms) and concept models (like standard medical terminologies), the interfaces between those three different constituents of medical information systems have to be defined well (Rector et al., 2001).

2.4 EMERGENCE OF THE GUIDELINE DEFINITION LANGUAGE

During the course of this doctoral project, The openEHR Foundation endorsed a newly developed openEHR-specific CIG formalism – the Guideline Definition Language (GDL).

GDL is a rule language that uses openEHR archetypes as its basis for data required within guideline input (e.g. evaluating symptoms) as well as guideline output (e.g. generating alerts). Like the Archetype Definition Language (ADL), GDL also allows binding any data elements to terms from as many standard medical terminologies simultaneously as required. Due to its reliance on archetypes, GDL is a natural language-neutral formalism.

A GDL definition contains metadata (e.g. CIG authors, language, concept and description), definitions of bindings to elements from different archetypes, rule definitions including preconditions (with reference to the archetype bindings above), natural language translation definitions, medical terminology binding definitions and internal GDL definitions of all data elements, rule IDs and rule parts using so-called ‘GT codes’ (The openEHR Foundation Guideline Definition Language (GDL), 2015).

2.5 RESEARCH OPPORTUNITIES

Due to the limited amount of research addressing the modelling and automatic execution of guideline knowledge using the openEHR approach (see also *2.1 openEHR Specifications in*

2011) and the emergence of a new officially endorsed openEHR CIG formalism (see *2.4 Emergence of the Guideline Definition Language*), there is room for studying possibilities of openEHR-based guideline knowledge modelling and concrete applications of GDL as openEHR-based guideline knowledge execution. Furthermore, identified modelling techniques could serve as the basis for GDL implementations.

3 AIM, SCOPE AND RELEVANCE

3.1 AIM

To explore the openEHR approach in i) modelling knowledge from clinical practice guidelines and ii) automatically executing guideline knowledge via computer-interpretable guidelines.

3.2 EXCLUDED AREAS

This thesis excludes workflow aspects in the modelling and implementation of guidelines. We only stick to medical knowledge in guidelines and do not try to reflect any organisational aspects in our models and implementations, e.g. which actors carry out which parts of the guidelines, how different entities collaborate to achieve guideline recommendations or how resources are used within guideline execution.

3.3 RELEVANCE FOR HEALTH INFORMATICS

The results of this work could contribute to solving the problem of overwhelmingly stand-alone clinical decision support systems today. The vision in this field of research is that if computer-interpretable guidelines are based on interoperability specifications for patient data, then even the computerised guideline knowledge would become shareable across health care organisations (see also *2.2 Expected Benefits from Solving the Problem*).

3.4 RELEVANCE FOR HUMAN HEALTH

Through contributing to shareable, evidence-based and sustainable clinical decision support components, the results of this work could contribute to more effective patient care characterised by better clinical decision support, and to the release of new resources for patient care (see also *2.2 Expected Benefits from Solving the Problem*).

4 RESEARCH QUESTIONS

1. How can clinical practice guidelines be represented through openEHR concepts?

2. Is the openEHR Guideline Definition Language practicable for retrospectively checking compliance of archetype data instances with clinical practice guidelines?

3. Can the openEHR Guideline Definition Language be used to retrospectively check compliance of a large quantity of real patient data with clinical practice guidelines?

Research question 1 has been addressed in Study I, research question 2 in Study II and research question 3 in Study III and Study IV.

5 METHODS

5.1 STUDY DESIGN

This work followed an exploratory, observational study design, which either generated data through modelling techniques or collected epidemiological data, in order to subsequently descriptively analyse them. It either developed or applied new methods to pursue answers to the research questions posed, thereby trying to contribute approaches or solutions to the overall problem that had not been attempted anywhere else. One exception were the statistical analyses applied in the clinical study (Paper IV), which used a more established method (a logistic mixed effects model), but are not a part of the core health informatics methodology herein. Also, to validate the results obtained through developing or applying new methods, or to be able to interpret them more objectively, this work sometimes relied upon a comparison with more established methods.

The disadvantage of using an exploratory design is that it does not offer an exhaustive solution to the problem, but only provides a subset of all possible solutions. As an example, we could take research question 2: *Is the openEHR Guideline Definition Language practicable for retrospectively checking compliance of archetype data instances with clinical practice guidelines?* The answer we obtained to this question here (Paper II) may be solid enough to base further research, applications and policy on, but it is no absolute or definitive answer, as the study design did not allow for exhausting all scenarios and possible cases of using the Guideline Definition Language to do retrospective guideline compliance checking on archetyped data.

The advantage of the exploratory study design, however, is that it allows approaching the problem in a practical and sensible way, such that the answer may reasonably be taken to ascertain or disqualify certain phenomena. This is especially useful for answering a question of the type above, because the amount of experiments one could set up to account for all possible cases and scenarios is infinite. Additionally, this study design offers the advantage of enabling the pursuit of useful answers to interesting questions according to project constraints and using the resources at hand. More importantly, exploratory research design is characteristic of the young stages of a research area (Graziano and Raulin, 2007), which holds for openEHR-based guideline modelling and execution or, more generally, for guideline modelling and automatic execution based on standard information models.

As to observational study design, the main disadvantage occurs as a result of bias, especially bias due to the researcher's expectations. The advantage of observational design, on the other hand, is that it is well suitable for answering the kinds of research questions we have here, where the findings sought are either supposed to inform further research or give practical insights into the proposed solutions or clinical domain (Graziano and Raulin, 2007). When it

comes to conducting research using patient registry data, as we did in papers III and IV, observational design is generally the typical way of choice.

5.1.1 Compliance Checking as a Theme for Study Design

Throughout this dissertation, we used a very particular application of guideline modelling and automatic execution to guide our research: retrospective checking of compliance of patient data with guidelines. The aim of this thesis *to explore the openEHR approach in i) modelling knowledge from clinical practice guidelines and ii) automatically executing guideline knowledge via computer-interpretable guidelines* implies different alternatives for testing openEHR-based modelling and execution of guideline knowledge. We could have, for instance, chosen to deploy and evaluate a real-life clinical decision support system that executes guideline knowledge based on the openEHR approach. We went for this design theme of compliance checking as it provides a powerful possibility of testing the effectiveness of computerised guidelines without needing to go through the tedious and resource-intensive process of deploying a real-life decision support system or similar systems. The application of guideline compliance checking was merely dependent on technological resources in addition to clinical as well as statistical expertise needed for assessing the correctness of the compliance checks produced by automatic guideline executions on specific patient data, which we had available.

The terms compliance and adherence may correspond to different concepts to some clinicians, especially in the context of medication, as Gould and Mitty or Aronson have explained, for example (Gould and Mitty, 2010; Aronson, 2007). The term compliance is sometimes taken to have negative implications, such as following protocols or regulations blindly regardless of whether they are beneficial or not. Nevertheless, in this work we take the terms compliance and adherence to be synonymous and predominantly use compliance. The exception is Paper IV, where we use adherence as we felt it was more appropriate in addressing a clinical audience, which seemed to us to be more used to the term adherence.

5.1.2 Acute Stroke Care and Research as a Clinical Domain

Throughout this work, we used one clinical domain to explore our health informatics methodology in, which is the domain of acute stroke. Acute stroke came in such that our modelling (Paper I) and execution (papers II-IV) of openEHR-based CIGs used guideline knowledge related to acute stroke management. The execution of these acute stroke CIGs led to both an evaluation of GDL as such (papers II and III) and as a part of that evaluation, it led to clinically relevant findings that were a byproduct, so to speak, of evaluating GDL with real patient data (Paper IV).

This focus on one clinical domain brings with it the obvious limitation that acute stroke CIGs are not representative of all or any CIGs, since acute stroke guideline knowledge may be easier and less complex to model and execute than that of diabetes, for instance. It may also be the other way around. We took this step because it allowed us to spend enough time with one clinical domain and understand it thoroughly in addition to giving us comparable setups

across the four constituent studies. Not least, it was an application area where we had access to large datasets in the form of an international registry (papers III and IV).

We tackled this limitation alongside this doctoral work in other papers and through Master theses within other clinical domains, including atrial fibrillation, sepsis and septic shock, and Lynch syndrome (Chen et al., 2013; Kalliamvakos, 2013; Flores, 2015). We discuss these herein too.

5.2 MATERIALS

The following materials shaped this work.

5.2.1 European Guidelines for Acute Stroke Management

The European 'Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008' actually kick-started this doctoral work (European Stroke Organisation (ESO) Executive Committee and ESO Writing Committee, 2008). The first step of this research was namely transforming the recommendations in these paper-based and narrative guidelines into a representation that can act as an intermediate step between guideline content analysis and CIG formation.

While these guidelines deal with the whole picture of stroke management, including aspects such as education, prevention, organisational aspects and rehabilitation, we only worked with the recommendations related to the acute part of stroke care. These recommendations had also been complemented with an update to account for two new breakthroughs in acute stroke management (European Stroke Organisation, 2009), which we incorporated into our work as well.

We also took the first-ever European stroke guidelines from 2003 into account, which were the predecessors of the 2008 guidelines, as they played a role in our clinical research question (European Stroke Initiative Executive Committee and EUSI Writing Committee, 2003).

5.2.2 European Licence Contraindications for Intravenous Thrombolysis with Alteplase

Out of the European acute stroke recommendations from the guidelines above, those recommendations pertaining to a decisive acute stroke treatment - intravenous thrombolysis - evolved to gain central attention in our CIG modelling and execution. These recommendations, which are all in the form of contraindications to using that treatment, deserved special attention because they had also been issued as legally binding instructions in a licence label accompanying the licencing of alteplase, the medicine involved in intravenous thrombolysis, in Europe (European Medicines Agency, 2002).

The formulation of contraindications to alteplase use partly overlapped between the guidelines and licence label (or shortly 'label'), but also partly differed, which set the clinical

research question for Paper IV, where we measured compliance to both the label and guidelines as a way to evaluate GDL on a larger scale and produce clinical observations at the same time.

5.2.3 Calculation of a National Institutes of Health Stroke Scale Score

One part of acute stroke diagnostics that we decided to build an archetype and GDL rules for is a neurological score assessment that uses the National Institutes of Health Stroke Scale – NIHSS. Since the guideline documents above did not provide such details, but only that you have to make such an assessment at a certain point, for example, we retrieved the details of obtaining this score from the literature (NIH Stroke Scale International, 2007).

5.2.4 Neurologist Expertise

Having access to the expertise of some of the stroke specialists at the Karolinska University Hospital was an important resource to our work, both for validating the clinical aspects of our CIG representations and for comparing our experimental automatic compliance checks with manual compliance checks by expert humans (Paper II).

5.3 METHODS

The following methods formed this dissertation.

5.3.1 Knowledge Representation Model Inspired by Task-Network Models and openEHR

To model guideline knowledge based on core openEHR concepts while making use of established guideline modelling methodology, we developed a new method. Our method uses ideas from task-network models (see *1.5.2 CIG Formalisms*) and mixes them with `CARE_ENTRY` types from the openEHR reference information model (see *1.3.1 Types of Health Informatics Standards*). For the details see *6.1.1 Care Entry-Network Model*.

5.3.2 openEHR Archetypes Using the openEHR Reference Information Model

This dissertation utilises archetypes and a standard information model. Specifically, we use openEHR archetypes based on the openEHR reference information model.

openEHR archetypes are shareable models of clinical concepts, and they are ideally shaped through review processes that take place on local, national, regional as well as international levels. The openEHR reference information model provides data types and classes that are tailored to the needs of health care computing and can be used to build openEHR archetypes.

Since our research questions are all related to openEHR, applying openEHR's idea of two-level modelling through openEHR archetypes together with the openEHR reference information model was a natural choice.

openEHR archetypes can, by definition, be built using other information models too. This is an option we did not make use of because as things stand today, the vast majority of available archetypes use the openEHR reference information model and available tools support this information model best. Creating or using archetypes built upon uncommon information models would therefore have also been counterproductive in terms of reaching interoperability through archetypes (for more details on two-level modelling, openEHR archetypes, the openEHR reference information model and interoperability, see *1.3 Health Informatics Standards*).

5.3.3 GDL Rules

Rules written in the Guideline Definition Language (GDL) form a central construct of this thesis and, as with openEHR archetypes and the openEHR reference information model, came as the obvious method to choose given the openEHR focus of our research questions. GDL is namely the only existent formalism for authoring and automatically executing CIGs based on openEHR archetypes (for more details on GDL, see *2.4 Emergence of the Guideline Definition Language*).

5.3.4 Standard Medical Terminologies

Just like archetypes, GDL rules allow binding data to terms from standard medical terminologies. Where possible in this work, we bound data we used in GDL rules to terms from the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT), the International Classification of Diseases in its 10th edition (ICD-10) and Anatomical Therapeutic Chemical (ATC) standard terminologies.

SNOMED CT and ICD-10 were especially useful for coding diagnoses or clinical conditions related to thrombolysis contraindications, while ATC codes represented medication names or types. SNOMED CT was, in contrast to ICD-10 that is mostly specialised on diseases, also useful for finding terms corresponding to anything of relevance to the clinical world, e.g. oxygen saturation or a central venous catheter (you can find more on standard medical terminologies under *1.3.1.3 Standard Medical Terminologies*).

One distinct feature of GDL we made use of too was binding a single data element to multiple standard terms simultaneously. If, for example, a GDL rule looked for a recent diagnosis of duodenal ulcer in a patient, then we connected that diagnosis in GDL to both the ICD-10 and SNOMED CT terms for duodenal ulcer, K26 and 51868009 respectively.

5.3.5 Data Archetype Definition Language (dADL)

In our GDL experiment (Paper II) we used the Data Archetype Definition Language (dADL) to store patient data through archetypes. Our GDL rules were subsequently executed on these data.

dADL can simply be seen as a format for expressing concrete data instances of archetypes based on a certain information model. Typically, one dADL file would correspond to the data

of one patient coming from one particular archetype, e.g. a blood glucose archetype. That is the way dADL came to use in this project (Paper II).

Other formats and possibilities than dADL are available for storing archetyped patient data, such as XML, JSON, YAML, ODIN or 'traditional' relational databases. ODIN, for example, is the new version of dADL and more recommended according to the latest developments in the openEHR specifications (The openEHR Foundation Archetype Technology Overview, 2015). When we ran our GDL experiment in 2012 and 2013, dADL was a stable and established as well as feasible format to use for the purposes of our research. We used the dADL version specified under the Archetype Definition Language (ADL) 1.4 specifications and based on version 1.0.1 of the openEHR reference information model (The openEHR Foundation, 2008).

5.3.6 Comma-Separated Values (CSV) Data

Instead of relying on dADL, the technology we applied for our clinical registry-based study (papers III and IV) used Comma-Separated Values (CSV) files for storing archetype-based patient data. As described for dADL usage above, each CSV file we used was also based on data from one particular archetype, i.e. all data coming from a certain archetype (e.g. a blood pressure archetype) formed one CSV file. However, compared to the dADL solution, all patient data related to one archetype were also stored in that one CSV file instead of having one file per patient.

Every CSV file had a 'column' reserved for the patient's ID plus columns for archetype-specific data. Taking a blood pressure archetype as an example, the CSV file's structure was as follows: `ehrId;systolic;diastolic`. Note that `systolic` and `diastolic` are the exact names of the corresponding data elements within the blood pressure archetype we used.

The choice of CSV files here had performance advantages when running GDL rules on tens of thousands of patients (papers III and IV) compared to 49 patients (Paper II).

5.3.7 PROforma

PROforma is one of the most known and established guideline formalisms for authoring and automatically executing CIGs (see *1.5 Computer-Interpretable Guidelines* for more on PROforma). As a way of validating the CIG modelling and execution work we did in this project based on openEHR and GDL, we drew some comparisons with PROforma representations and executions of extracts from the same stroke knowledge. Wherever we drew comparisons with PROforma, we will mention these and what they suggested under Results.

5.3.8 Statistical Model

For statistically analysing the data in the registry-based study, we applied a logistic mixed effects model (Paper IV). This method was especially useful for determining our findings

regarding non-compliance with guidelines and contraindications from patient data of hierarchical structure, as our patients were clustered into different hospitals (one of our main clinical findings was about the relationship between hospital size and non-compliance with thrombolysis contraindications, see *6.2 Archetype-Based Clinical Research through Patient Data Registries*).

5.4 TOOLS

The following tools assisted us in this project.

- Visual Understanding Environment (VUE): an application developed by Tufts University which we used to visualise the knowledge representation model we invented.

- The international and Australian archetype repositories, i.e. the international and Australian instances of the Clinical Knowledge Manager (openEHR Clinical Knowledge Manager, 2015; NEHTA Clinical Knowledge Manager, 2015): We used these repositories to look for existing archetypes for clinical concepts we needed. These two repositories, amongst all repositories, seemed to contain the most mature archetypes and especially archetypes that had evolved over a long period of time.

- Ocean Archetype Editor[1]: When we did not find archetypes we needed in the repositories above or wanted to modify ones we found there, we used the free and open-sourced Archetype Editor.

- GDL Editor[2]: To author GDL rules, we used the free and open-sourced GDL Editor.

- CDS Workbench: To run GDL rules on patient data from archetypes, we used the CDS Workbench by Cambio Healthcare Systems.

- Safe Implementation of Treatments in Stroke (SITS) registry (SITS International, 2015): SITS is a prospective, multinational registry that has been storing structured patient data related to acute stroke treatment provided by stroke centres from across the world since 2002. It thus constituted a very powerful tool for doing clinical research.

- Java: We used the Java programming language (Java Development Kit 1.7) to produce random (test) patient data (Paper II).

[1] http://www.openehr.org/downloads/archetypeeditor/home

[2] http://sourceforge.net/projects/gdl-editor/

- Tallis[3]: Tallis includes a development environment for authoring CIGs in PROforma (see *5.3.7 PROforma*) and engine functionality for enacting (i.e. automatically executing) them both within Tallis and in a web browser.

5.5 DATA COLLECTION AND ANALYSIS

The following describes how materials, methods and tools described in this chapter helped *collect* and *analyse* data, in chronological order.

Structured recommendations from European stroke guidelines and contraindications for stroke thrombolysis were *collected* manually from their narratively written original sources.

The visual representation of stroke knowledge using openEHR and task-network model concepts was *collected* manually, using the tool Visual Understanding Environment to construct it.

The resulting representation was *analysed* manually aided by neurologist expertise. A part of this *analysis* was validating the results against a PROforma representation of an extract of the same stroke knowledge.

Following the emergence of the Guideline Definition Language (GDL), stroke representations from this project were now *collected* using GDL rules and archetypes through the GDL Editor and archetype repositories as well as the Archetype Editor.

The GDL technology was *analysed* by describing its components in detail, running GDL rules on a few test patient cases (*collected* by a Java program) in dADL format through the CDS Workbench and validating the results by neurologist expertise as well as against a PROforma enactment through Tallis.

The GDL technology was further *analysed* by running it through the CDS Workbench on more than 18,000 real patient cases *collected* from the SITS registry and mapped to an archetype-based CSV format.

Data *collected* from the SITS registry were additionally *analysed* statistically using a logistic mixed effects model to extract clinically relevant findings from them.

[3] http://www.cossac.org/tallis

5.6 ETHICAL ASPECTS

For exploring the representation of guideline knowledge using openEHR concepts (Paper I), there were no sensitive data of any sort involved, since this was a pure modelling undertaking. For producing test patient data in our GDL experiment (Paper II), we used an anonymised patient case to guide us in producing these mock data in a way that reflects real patient values to some extent; we asked this patient for her/his consent (through neurologist Tiago Prazeres Moreira, Karolinska University Hospital Solna) to view the data and his/her approval of the manuscript we sent out for publication. For the registry-based study (papers III and IV), we obtained ethical approval from the Central Ethical Review Board of the Stockholm County (EPN 2014/908-31/1) and from the SITS Scientific Committee.

6 RESULTS

6.1 ARCHETYPE-BASED GUIDELINE IMPLEMENTATION: FROM KNOWLEDGE MODELLING TO EXECUTION

6.1.1 Care Entry-Network Model

6.1.1.1 Functionality

Our new method of combining concepts from task-network models and openEHR `CARE_ENTRY` types forms the openEHR-based guideline modelling part (as opposed to automatic guideline execution) of this thesis work. This method uses openEHR `OBSERVATION`, `EVALUATION`, `INSTRUCTION` and `ACTION` types as its task types, which is why we decided to call it Care Entry-Network Model.

Starting with narrative guideline recommendations, an author of a knowledge representation according to our model classifies this knowledge into tasks and conditions between them, very much like the way task-network models are constructed. The main difference in our method is that it classifies the tasks into openEHR `CARE_ENTRY` types, i.e. `OBSERVATION`s, `EVALUATION`s, `INSTRUCTION`s and `ACTION`s. One thing to note is that `INSTRUCTION`s and `ACTION`s are merged into one task type (an Instruction/Action type). A further notable characteristic of our model is that it allows even conditions to be represented by a task type, but it restricts the choices to only one - the Evaluation type.

Another way tasks can be connected, aside from using an Evaluation type, is simply indicating that the next task or set of tasks are to follow using the notation *[next]*. When more than one task succeed a certain task through different conditions, these can further be designated with priorities using Arabic numbers or given equal priorities using *OR*. Finally, consists-of relationships enable constructing task hierarchies. The model assumes chronological order from left to right. Figure 3 shows an extract from our stroke guideline representation using this knowledge representation model.

The nodes in Figure 3 represent data from corresponding archetype instances. One could also think of the consists-of task hierarchies as a way of forming openEHR templates later on in the CIG development process. The conditions with arrows attached to them (‘acute stroke/TIA suspected’ and ‘complications’ in this extract) represent data from corresponding archetype instances as well, namely instances of `EVALUATION` archetypes, typically clinical assessment-related archetypes such as diagnosis, health risk or symptom assessment archetypes.

The idea with this is to ease the transition between narrative guidelines and CIGs that use archetyped clinical data.

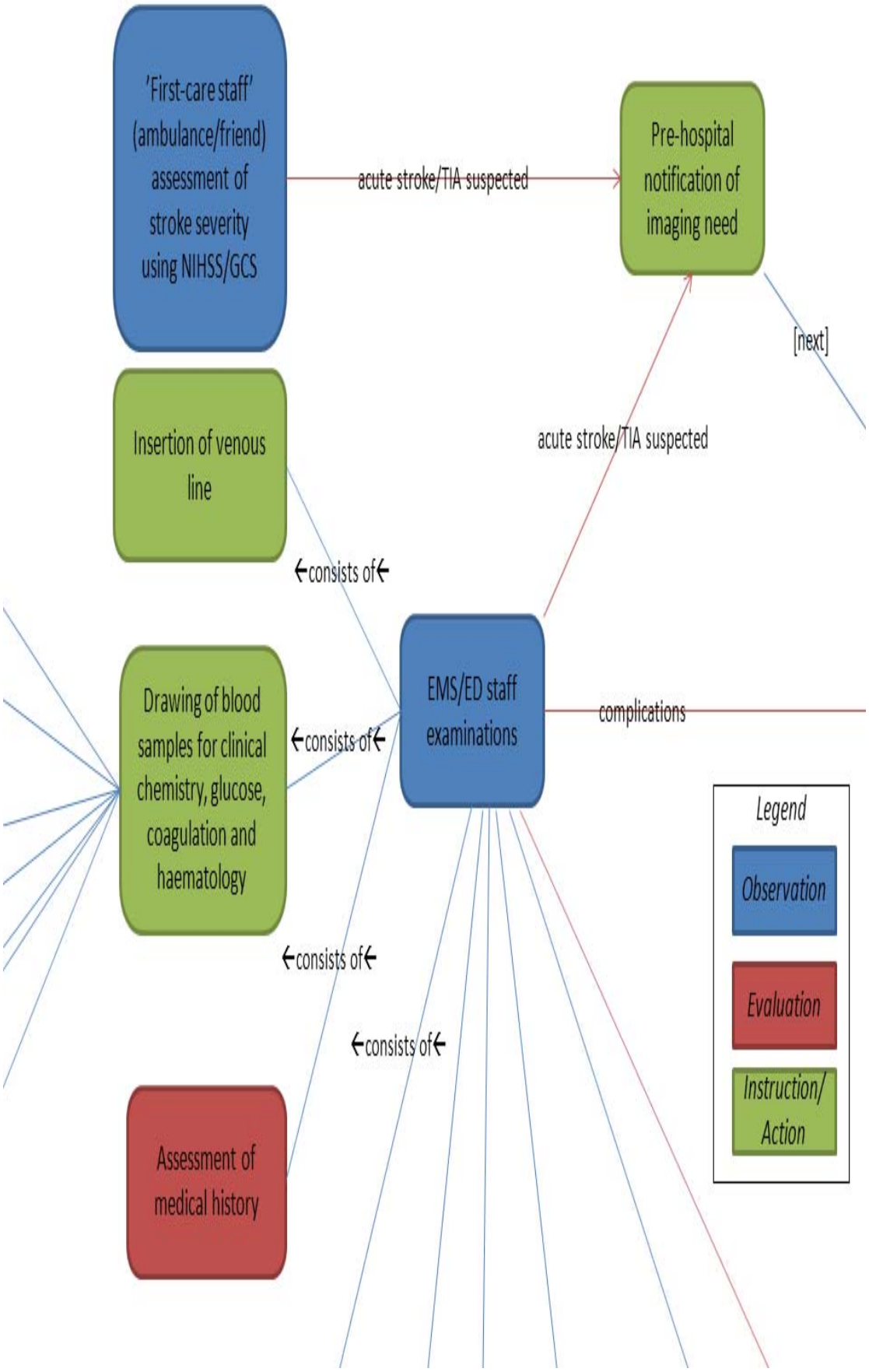

Figure 3. New method that combines concepts from task-network models and openEHR.

6.1.1.2 Evaluation

What follows here is an evaluation of the Care Entry-Network Model aided by our representation of European acute stroke guideline recommendations which we constructed with this method.

The following direct advantages emerge from using the Care Entry-Network Model:

- A representation of guideline content using the Care Entry-Network Model moves guideline knowledge one step closer to reaching a computer-interpretable format, as guideline recommendations get structured into tasks and relationships between them, instead of being described in narrative text.
- In addition to guideline knowledge being more structured than in a narrative format, the structure it gains is oriented towards openEHR data types, which facilitates a smoother transition to an openEHR-based implementation of guidelines.

Having said that, it is important to keep in mind that not all guidelines are published in a purely narrative format. Several guideline releases nowadays include flowcharts to present their knowledge more clearly or effectively (National Guideline Clearinghouse, 2015; National Institute for Health and Care Excellence, 2015). This thesis did not systematically compare the Care Entry-Network Model to flowcharts. It is, however, safe to state that the Care Entry-Network Model offers higher expressiveness for clinical knowledge than a flowchart, as flowcharts do not include elements related to the clinical investigation process, whereas the Care Entry-Network Model makes use of the clinical information models developed by openEHR in that respect (through making use of `CARE_ENTRY` classes, that is).

Another thing to keep in mind is that one of the most difficult parts of implementing computerised guideline knowledge when starting with a narrative guideline source involves a manual effort by the guideline modeller, who is often also referred to as a knowledge engineer in this context. The guideline modeller or knowledge engineer needs to work out, typically together with clinicians, how to transform narrative guideline content into a more structured format, irrespective of which model she chooses. Although there are tools to aid this first step in the knowledge computerisation process, which often rely on marking up narrative guideline text to identify different element types involved in guideline content (Hajizadeh et al., 2011), this step remains a complex undertaking that can require a lot of time and experience.

Now, moving on to the observations we made from constructing a representation of the European guidelines for acute stroke management, this is what we found (Paper I):

- The Care Entry-Network Model was a useful means of communicating the understanding of medical informaticians of a clinical process to a physician (or clinician).

- Being based on archetype classes (`CARE_ENTRY` types), the Care Entry-Network Model could help identify archetypes involved in guideline knowledge, which facilitates having the required repository of archetype data elements when implementing guidelines in an openEHR-based system.

- Providing a structured and chronological overview of the whole guideline process, the Care Entry-Network Model can help identify missing knowledge in guideline documents.

Regarding the first observation mentioned above (about the use of the model by medical informaticians to communicate their understanding of guideline content to clinicians), we believe that many other guideline representation models could achieve that too. In addition to the representation based on the Care Entry-Network Model, we presented neurologists at the Karolinska University Hospital Solna with a PROforma representation of extracts of the same guideline content. What physicians appreciated a lot about the PROforma representation was that they could run it step by step in a web browser.

This leads us to another characteristic of the Care Entry-Network Model: its instances cannot be run automatically, it is only a visualisation or an intermediate format between narrative guidelines and CIGs at this point.

6.1.2 GDL Experiment

Our experiment with GDL (Paper II) was the first-ever peer-reviewed study to evaluate GDL's functionality in checking compliance of patient data with guidelines automatically, and one of the first studies at all to use GDL. It produced the following findings:

- The GDL-related technology we used, consisting of GDL rules, openEHR archetypes, the openEHR reference information model, test patient cases in dADL and bindings to three different standard medical terminologies, reliably checked the compliance of patient data against contraindications for stroke thrombolysis and further recommendations from European stroke guidelines, as confirmed manually by a neurologist.

- Detailed descriptions of the technological components involved in our particular use case of GDL, i.e. in acute stroke management, in order to inform future research and implementations interested in using GDL.

- Descriptions of how GDL rules use openEHR archetypes in evaluating conditions and generating actions in the context of clinical decision support.

- Identification of archetypes and terminology codes (SNOMED CT and ICD-10 codes) needed within following acute stroke management recommendations from European guidelines and regulations. This additionally led to the creation of new archetypes (such as an NIHSS archetype) and modification of existing ones (such as the international problem/diagnosis archetype), which also influenced later international reviews of some of those new or modified archetypes.

- An overview of how GDL compares to other CIG formalisms such as Asbru, SAGE and PROforma (Paper II, Additional file 7).

6.1.3 GDL Application to Real Patient Data from a Large Sample

Applying GDL to the Safe Implementation of Treatments in Stroke (SITS) international stroke treatment registry showed the following (Paper III):

- The GDL-related technology we used (with a CSV database of archetype data instances instead of dADL when compared to Paper II) reliably checked the compliance of real data from 18,400 patient cases against contraindications for stroke thrombolysis, as confirmed by conventional data analysis from Paper IV (see *6.2 Archetype-Based Clinical Research through Patient Data Registries*).

- At the same time, this automatic compliance checking, being based on real and statistically representative patient data, yielded useful clinical findings to the stroke care and research communities (see *6.2 Archetype-Based Clinical Research through Patient Data Registries*).

6.2 ARCHETYPE-BASED CLINICAL RESEARCH THROUGH PATIENT DATA REGISTRIES

In contrast to the rest of this doctoral work, which produced findings within the field of health informatics (or medical informatics), the study in Paper IV generated clinical findings of use to stroke carers and researchers. These clinical findings were about compliance with guidelines and regulations concerning intravenous thrombolysis in Europe. The main results were that

- European stroke centres promptly complied with the new guideline release of 2008 and 2009, as indicated by lower proportions of compliance with outdated contraindications that had been updated in this release,

- the number of intravenously thrombolysed patients in the included European stroke centres nearly doubled from 6,354 in the years 2006 and 2007 to 12,046 in the years 2010 and 2011,

- the proportion of patients in non-compliance with the European label from 2002 (regulations that accompanied the licencing of alteplase for intravenous thrombolysis

in Europe) more than doubled from 23.6% in the years 2006 and 2007 to 51.1% in the years 2010 and 2011 and

- there is a clear association between hospital size and non-compliance with thrombolysis contraindications: the larger the hospital size, the higher the non-compliance.

SITS data analysis in this study (Paper IV) relied on conventional statistical software to calculate compliance proportions. When taking into account that the compliance proportions calculated by applying GDL to the same data completely matched those obtained by established software for such purposes (i.e. Paper III validated through Paper IV), and combining that with the fact that these findings were clinically useful (Paper IV), this also leads to an interesting finding from the point of view of health informatics research:

- Archetypes, together with GDL rules, can facilitate registry-based clinical research.

To the best of our awareness, this is the first work to generate clinical knowledge from a patient data registry through a technology based on openEHR archetypes.

6.3 CONSTITUENT PAPERS AT A GLANCE

The following summarises the research papers from this PhD work.

Paper I invents the Care Entry-Network Model for modelling guideline knowledge based on openEHR `CARE_ENTRY` types. First experiences indicate that this model is helpful in identifying needed archetypes within guideline processes and in preparing for guideline implementation in openEHR-based systems.

Paper II contains one of the first-ever applications of the Guideline Definition Language (GDL). It describes the technological artefacts involved in a GDL experiment which executes knowledge from European acute stroke guidelines. It also explains the main features of GDL, including through a comparison to other computer-interpretable guideline formalisms.

Paper III contains the first-ever work to generate new clinical knowledge from applying GDL to a patient data registry. It runs GDL rules on 18,400 patients from the Safe

Implementation of Treatments in Stroke (SITS) registry and describes the technological artefacts as well as methods involved in doing so.

Paper IV is the new clinical knowledge generated by Paper III and a complementary statistical analysis.

Figure 4 gives a further overview of the constituent papers.

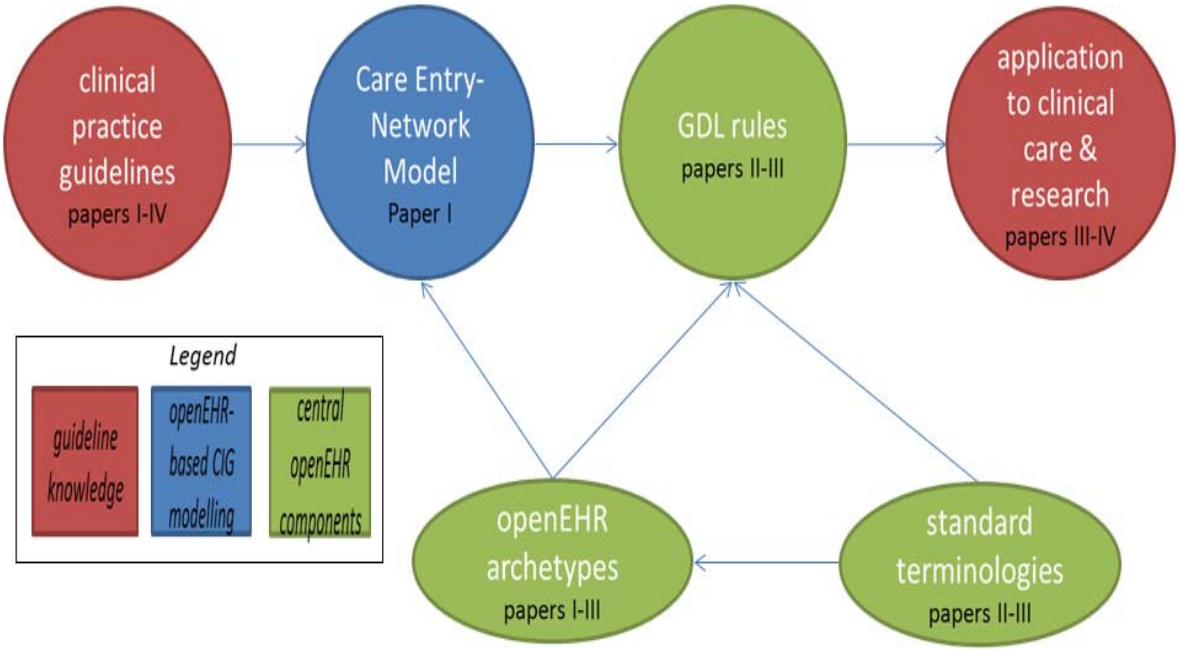

Figure 4. Contents of constituent papers. CIG: computer-interpretable guideline.

7 DISCUSSION

7.1 STRENGTHS, WEAKNESSES AND LIMITATIONS

7.1.1 Strengths

7.1.1.1 Contribution of New Method

The Care Entry-Network Model constitutes a new method for modelling knowledge from clinical practice guidelines for later use in openEHR-based systems. While other research groups have attempted to address the same problem, the Care Entry-Network Model probably represents a purer approach when it comes to letting archetypes drive the modelling, rather than deriving involved archetypes from guideline representations constructed using CIG formalisms or other methods (Marcos and Martínez-Salvador, 2011).

7.1.1.2 Application of New Method

The work presented here is amongst the first-ever efforts to apply, evaluate and report experiences with the Guideline Definition Language. Therewith, it is also amongst the first-ever efforts to execute computer-interpretable guidelines using only the openEHR specifications without components from any other standard specifications or CIG methodologies.

7.1.1.3 Real Clinical Results

We validated the feasibility of using openEHR archetypes and GDL for guideline compliance checking not only through an experiment, but also by applying this approach to real data from the SITS registry. This also led to real clinical results that benefited other fields than health informatics, e.g. stroke care and research.

7.1.2 Weaknesses

7.1.2.1 Assumption of Equivalence between Compliance Checking and Clinical Decision Support

We chose to test the effectiveness of GDL in achieving computerised guidelines using the function of retrospectively checking compliance in completed patient cases with guidelines (see *5.1.1 Compliance Checking as a Theme for Study Design*). While the primary goal of computerised guidelines is providing computerised clinical decision support, we assumed that GDL would be applied in exactly the same way for that use case as for compliance checking, and that our results thus are an indication of the general effectiveness of using GDL. This assumption, however, is yet to be proven with studies from real-life implementations of GDL within clinical decision support systems.

7.1.2.2 Assumption of Applicability to Any openEHR-Based System

Real-life EHRs that are based on the openEHR specifications all have certain aspects in common, e.g. using archetypes, using a reference information model or using an archetype-based query language for retrieving patient data. However, as the preceding sentence already suggests, *a* reference information model does not necessarily mean openEHR's reference model, which was the basis of our work. This and other variations between different openEHR-based systems could compromise our assumption that our results are applicable to any openEHR-based system.

7.1.3 Limitations

7.1.3.1 Acute Stroke Focus

For purposes of mastering the clinical domain we worked with and consistence, we only modelled and executed guideline knowledge from the acute stroke domain within this doctoral project (see also *5.1.2 Acute Stroke Care and Research as a Clinical Domain*). We have, however, conducted GDL-related research within other clinical domains too (see *7.4 GDL Research: Status Quo*). Nevertheless, one emerging topic in CIG research is tackling comorbidities, the existence of multiple conditions in one patient, in computerised guidelines, which we have not done here (Abidi, 2011).

7.1.3.2 No Workflow Aspects

We defined the scope for this thesis as not including the workflow dimension of patient management (see *3.2 Excluded Areas*). This is also a topic of interest within CIG research (Ferrante et al., 2013).

One thing worth noting here is that the Care Entry-Network Model does consider workflow to some extent, by considering the chronology of tasks in the guideline process (see also *6.1.1 Care Entry-Network Model*). However, this is no comprehensive representation of workflow and more components would be needed to reflect more workflow details.

7.2 WHICH KNOWLEDGE MODELLING METHOD SHOULD ONE USE BEFORE GDL IMPLEMENTATION?

In order to come up with the required rules to be authored using GDL and archetypes, it may be a good idea to model the guideline process first, as is the case within software development and engineering in general, i.e. there are typically modelling phases before implementation, e.g. class diagrams prior to object-oriented programming (Fowler, 2004). The modelling facilitates bringing structure into the original guideline content and breaking guideline recommendations down into entities from which necessary GDL rules can become more visible.

There are several options that could be used for guideline knowledge modelling prior to implementation, the most obvious of which from the point of view of this thesis is the Care Entry-Network Model. The direct advantage of the Care Entry-Network Model is that its tasks are archetypes, so by merely looking at its nodes, the archetypes needed for GDL rules become clear, in addition to further `EVALUATION` archetypes represented by some of the conditions in the Care Entry-Network Model (e.g. ‘suspected transient ischaemic attack’). The rest of the conditions would correspond to either the GDL conditions themselves (e.g. ‘blood glucose > 22.2 mmol/L’) or openEHR templates (consists-of relationships in the Care Entry-Network Model).

Another option would be using business process modelling, e.g. the Business Process Modelling Notation (BPMN) (Ly et al., 2015). This would provide an effective way of visualising the guideline process through the various constructs provided by BPMN. On the other hand, a BPMN representation would also typically include workflow aspects, which would add some ‘noise’ to the needed GDL rules and thereby make the implementation requirements less obvious, since GDL itself is not designed to support workflow functions at this point.

A third option would be using graphical development environments of CIG formalisms, e.g. PROforma’s Tallis Composer, GLIF3’s GLIF Editor or Protégé (Sutton and Fox, 2003; Wang et al., 2004; Gennari et al., 2003). The advantage is that these are established tools for modelling and implementing guideline knowledge, with lots of functionality to support exactly that purpose. The immediate disadvantage, however, is that such tools are mostly oriented towards supporting the development of CIGs using a very particular formalism, e.g. PROforma or GLIF3, rather than GDL.

Flowcharts would be a further option that is rather simple in its approach, having only actions and yes/no-type conditions in their most basic form, yet possibly very effective because any developer of CIGs would be able to relate to them as they are universally known to software engineers, system developers and most laymen as well (Anani, 2014). Thereby, practically anybody who intends to author GDL rules would have a model they know how to deal with. Additionally, flowcharts might not even have to be constructed from scratch to represent guideline knowledge, since many guidelines nowadays are published with accompanying flowcharts (National Guideline Clearinghouse, 2015; National Institute for Health and Care Excellence, 2015).

Finally, one could attempt to author GDL rules directly upon reading narrative guideline text, which is not to recommend, e.g. for software quality and maintainability as well as patient safety reasons.

7.3 IS THE REAL CHALLENGE SYSTEMATISING KNOWLEDGE TRANSFER FROM PRIMARY GUIDELINE SOURCES?

As mentioned in *1.5.3 Knowledge Modelling*, guideline publications in their released format often contain their knowledge in narrative text form and this leads to complicating the process of reaching computerised guidelines. Although many guideline documents contain a condensed version of their recommendations in lists with bullet points or the like, knowledge engineers often face the difficulties of dealing with vagueness, incompleteness, and contradictions, at least from their point of view, not being fully knowledgeable of the clinical domain at hand. An example of vagueness is using the word 'recent', which leaves a knowledge engineer wondering how to quantify that. An example of incompleteness is not knowing which recommendation should be carried out first, i.e. not knowing the chronology of things. An example of contradictions is having two different diastolic blood pressure thresholds to consider in conjunction with a medication administration, which come up in two separate sections of the guideline document (maybe because these two sections were written by two or more different authors).

These difficulties often necessitate a tight collaboration between medical informaticians and clinicians, which is tedious and time-consuming.

One approach to tackle these issues is assessing the implementability of guidelines while they are still being authored before even releasing them, e.g. using tools like the GuideLine Implementability Appraisal (GLIA) (Shiffman et al., 2005; Freixa et al., 2015). Furthermore, guideline authoring is suggested to be carried out by a team of clinicians and knowledge engineers, rather than only clinicians or only physicians (Latoszek-Berendsen, 2010).

7.4 GDL RESEARCH: STATUS QUO

Beside this thesis, some other research has been conducted on the Guideline Definition Language. There was one study which showed that it was possible to use GDL to check the compliance of thousands of patients from a regional EHR system with European guidelines for the management of atrial fibrillation, with the results also indicating that deploying a clinical decision support system in that region could increase guideline compliance. This study was similar to our clinical study (papers III and IV) in that it was based on compliance checking, but differed in that it used EHR data instead of registry data (Chen et al., 2013).

Also, a few studies have explored the feasibility of using GDL for implementing guideline knowledge from different clinical domains. These included GDL implementations in the areas of sepsis and septic shock, and Lynch syndrome. These two studies also used a compliance-checking setup, and both produced positive results in terms of GDL's ability to execute the guideline knowledge in those clinical domains (Kalliamvakos, 2013; Flores, 2015).

Since GDL is a relatively new formalism (first released in 2013), not much has been done to compare it to other CIG formalisms yet. Paper II's Additional file 7 gives an idea of the main strengths of GDL compared to several other CIG formalisms, which include the ability to bind data to as many standard medical terminologies as required, the ability to support as many natural languages as required without the need to maintain translations within the rules themselves, and the thorough interoperability focus.

7.5 DO EHR STANDARDS AND PATIENT DATA REGISTRIES STAND IN CONFLICT WITH ONE ANOTHER?

Two methods that this thesis combines in Paper III – standards for electronic health records and patient data registries – actually share a mutual goal, which is enabling effective querying of patient data for research, statistical reporting and other purposes. Beside wanting to facilitate interoperability between EHRs, EHR standard specifications also aim to create effective EHRs from which patient data can be retrieved extensively according to fine-grained search criteria, not least for secondary purposes. As for patient data registries, retrieving patient data for research, statistical reporting and quality assurance is the primary purpose.

This is, however, not the first effort to make this combination. There have been several other examples. One group proposes integrating an openEHR-based system for childhood immunisation with quality registries across Pakistan, in order to enable interoperability between different registries as well as between registries and other applications such as smartphone apps (Liu et al., 2013). Another group uses openEHR-based information modelling in order to improve data management within the development of a national cardiac registry in New Zealand, and to integrate this registry into a bigger national framework of health information systems (Atalag et al., 2015). A third group uses the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) to standardise question and answer sets for rare disease registries and thus enable the reusability of registry structures (Richesson et al., 2010).

What the above studies have in common is that they attempt to introduce structure into a set of heterogeneously constructed systems in a world where not all EHR and registry systems have been built from scratch according to an EHR or interoperability standard. If the concept of EHR standards is to succeed widely and highly effective querying of patient data is to become possible within and across EHRs, then the need for patient data registries may gradually decrease.

7.6 DIRECTIONS FOR FUTURE WORK

As mentioned in Results (under *6.1.1 Care Entry-Network Model*), instances of the Care Entry-Network Model cannot be run automatically. One thing to work on in the future could

be to investigate whether the current form of this model is systematic enough to be able to generate GDL rules from it automatically, and if not, to gather requirements for missing elements. One could imagine having a development environment that is connected to archetype repositories, so that modellers could indicate the exact archetypes and archetype elements they have in mind within the guideline process, and for the resulting representation to be compiled and mapped to GDL rules or other artefacts.

As for future work with GDL, research will be needed to evaluate GDL deployment within real-life clinical decision support systems. This could give a good indication of the value of using GDL to different stakeholders in health care. Also, the more guidelines from different clinical domains are represented and executed using GDL, the clearer the requirements will get regarding potential enhancements the language and the tools around it may need. Furthermore, it would be useful to include GDL in upcoming systematic reviews of CIG formalisms.

When it comes to guidelines and transferring their recommendations to computer-interpretable formats, it might be more decisive to find efficient ways of extracting structured recommendations from narrative text than improving the CIG formalisms as such. Once the authoring of CIGs is underway, there are also some important challenges to solve by authoring environments, e.g. allowing for collaborative authoring or making the modelling outcome less dependent on the user (Shah et al., 2012; Khodambashi et al., 2015).

When guideline-oriented clinical decision support systems are deployed, e.g. to assist with checking thrombolysis contraindications like in our GDL use case here, then comparative analyses between using clinical decision support as an intervention versus not having it will be interesting. The comparisons can be based on different variables such as whether or not the contraindications are noticed by physicians or the time it takes to notice contraindications (Sun and Chan, 2015).

Finally, studies on conducting clinical research using different openEHR-based systems would constitute a future research direction too, as generating new clinical knowledge from openEHR-compliant systems is still in its early stages and could be a useful complement to other typical openEHR-related research efforts, which tend to focus only on the technological aspects of openEHR usage.

8 CONCLUSIONS

This work explored possibilities of modelling and automatically executing knowledge contained in clinical practice guidelines by means of the openEHR approach for interoperability between electronic health records (EHRs). For openEHR-based guideline modelling, we developed the Care Entry-Network Model. For openEHR-based execution of computer-interpretable guidelines (CIGs), we applied the Guideline Definition Language (GDL). We used a study design based on guideline compliance checking and acute stroke management, and applied central openEHR methods such as archetypes and a reference information model.

The Care Entry-Network Model proved useful in identifying archetypes contained in guideline recommendations and in providing a basis for a later implementation of guideline knowledge in an openEHR-based system. Applying GDL within retrospectively checking compliance of patient cases with European acute stroke guidelines i) led to establishing that GDL was practicable for creating and running CIGs using archetyped data, ii) gave a detailed picture of what a GDL technology could look like and iii) generated new clinical knowledge through real patient data from the Safe Implementation of Treatments in Stroke (SITS) registry.

If decision makers in a health care setting decide to build their EHRs according to the openEHR specifications, then our findings indicate to them that it is possible to achieve evidence-based guideline-oriented functionality using archetypes together with GDL rules. In the long run, this combination of archetypes and GDL rules may prove increasingly rewarding, if more and more organisations adopt this methodology as well, since both archetypes and GDL rules are highly shareable and well maintainable components.

As for the implications of this work for the research world, it suggests solutions for modelling and executing guideline knowledge using the openEHR approach, but ‘leaves the floor open’ for testing other approaches to modelling and enacting openEHR-based CIGs as well as evaluating GDL at the point of clinical decision making. Finally, this dissertation paves the way for conducting more clinical research using data from openEHR-compliant EHRs or patient data registries.

9 MAIN MESSAGES

This PhD work provides evidence that there are ways to model and computerise clinical practice guidelines based on the openEHR approach; both experimental evidence and evidence from real clinical data. Thus, it lays the foundations for further research that either tries to evaluate the methodologies herein further, especially at the point of clinical decision making, or explores other ways of utilising openEHR or similar standard specifications within the domain of computer-interpretable guidelines.

9.1 WHAT WAS KNOWN BEFORE THIS DISSERTATION

- Standard specifications for electronic health records, such as the openEHR specifications, aim to encompass methods for computing patient data based on knowledge from clinical practice guidelines, but this part of specifications has not reached the same level of maturity as other aspects such as information modelling for patient data storage and retrieval purposes.
- Patient data registries are valuable research tools, but they often lack an automatic (electronic) connection to data from electronic health records, and if they contain it, the connection is often customised to one particular electronic health record system.

9.2 WHAT HAPPENED DURING THIS DISSERTATION

- The Guideline Definition Language (GDL) was developed for automatically executing guideline content on data from openEHR archetypes.

9.3 WHAT THIS DISSERTATION ADDS

- It offers a method for modelling guideline knowledge based on openEHR concepts, particularly using `CARE_ENTRY` types, namely `OBSERVATION`s, `EVALUATION`s, `INSTRUCTION`s and `ACTION`s.
- It is one of the first works to evaluate openEHR's Guideline Definition Language, which it does both experimentally and using real data of thousands of European stroke patients.
- It is one of the first works to conduct registry-based research using the openEHR approach, therewith helping pave the way towards registry data that are beneficial to a wider community of researchers.

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