An Approach for Managing Clinical Trial Applications Using Semantic Information Models

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Abstract. The management of clinical trial applications by public authorities is a complex process involving several regulations, actors, and IT systems. In this paper we present a modeling approach based on semantic information models that supports this process. In particular, the approach can be used for the generation of user-centric visualizations, performance and compliance analyses and the distribution of the contained knowledge within an organization and to third parties. The approach has been developed together with AGES PharmMed and applied to their core processes.

Keywords: Clinical trials, process management, semantic information, visualization.

1 Introduction

The preservation of a high standard of public health is today one of the major challenges of the industrialized countries. This involves both the efficient use of public resources for all types of health services as well as the provision of regulations that foster the development of new medical treatments and products cf. [1]. The development of new methods and new drugs in particular is a long, costly and risky process primarily conducted by pharmaceutical companies [2]. The translation of recent discoveries in basic biomedical research such as in human genomics, stem cell biology, molecular biology or immunology into knowledge that ultimately affects clinical practice and human health requires *clinical research* [3]. Thereby, new understandings of disease mechanisms that are gained in the laboratory are translated into methods for diagnosis, therapy, and prevention. In the course of *clinical trials* these methods are then tested in humans. The results are translated into clinical practice and health decision making, thus leading to the potential improvement of human health care [3].

In the heavily regulated pharmaceutical industry it is thus essential that the involved parties cooperate effectively to ensure both a high quality of service and regulatory compliance [4]. The application for clinical trials has to be approved by *public authorities*. Thereby formal, pre-clinical, and clinical aspects

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are evaluated. In parallel, ethics committees assess the ethical impact of the prospective trial, the pre-clinical and clinical aspects and the standard of care. The basis for all these tasks are a number of national and European legal regulations. After the clinical trial phase, the licensing applications may either be submitted on a national level, in the course of a mutual recognition procedure (MRP) if a substance is already approved in one member country, by a decentralised procedure (DCP) for gaining approval in several countries in parallel or, for selected substances, via a central procedure by the European Medicines Agency (EMEA). During the stage of clinical trial evaluation there is usually a tight interaction between the applicant and the public authorities. During these tasks several national and European IT systems and databases are accessed to exchange information with authorities in other EU countries. Based on the legal regulations set time frames have to be kept for informing the applicant of the acceptance or rejection of the application.

In the following we will describe a modeling approach for the administration of clinical trial applications on the side of public authorities that has been developed together with AGES PharmMed[1]. In this context, a combination of meta modeling and semantic modeling techniques were used for three purposes: a. to create user-centric visualizations for managing the complexity of the processes, b. to support management in the analysis of the performance and compliance of their processes, c. to make the knowledge contained in the processes accessible to other stakeholders.

The remainder of the paper is structured as follows: In section two we will outline the foundations used for our modeling approach. Section three presents the modeling approach and the meta model. In section four the concrete scenario of managing clinical trials at AGES PharmMed and the application of the modeling approach are described. The paper is concluded in section four by giving an outlook on future work.

2 Foundations

This section gives a brief introduction to the fields of meta modeling and the relation of semantic business process modeling and semantic information models.

2.1 Meta Modeling

Today it can be chosen from a large variety of different modeling methods and corresponding modeling languages, each with its particular advantages and pitfalls. Besides the selection of a single modeling language it is also possible to

[1] AGES PharmMed and the the Federal Office for Safety in Health Care (BASG), the Austrian Competent Authority, went operative on January 2, 2006 following a reorganization and out-sourcing from the Federal Ministery for Health. Legal responsibilities of the BASG center around issues pertinent to drug development and licensing. The purpose of AGES PharmMed, which is fully owned by the Republic of Austria is to support the BASG by providing services, personnel and location.

create a new domain or purpose specific language, modify an existing language to meet particular needs or use a combination of these options. For our approach we will therefore revert to the concepts and terminology of *meta modeling*.

In this terminology modeling methods are divided into a modeling technique and mechanisms and algorithms [5] (see figure 1). The modeling technique comprises a modeling language and a modeling procedure. The modeling language is used to describe the models and is itself split into syntax, semantics, and notation. The semantics of the modeling language contain a semantic schema and a mapping of the syntax of the modeling language to the schema. The notation is separated from the syntax of the modeling language and thus allows for an independent modification of the visual representation [6]. The modeling procedure defines the way how to apply the modeling language. Mechanisms and algorithms are used by the modeling procedure. A meta model can now be viewed as a model of a modeling language [7]. Meta models may also be graphically represented themselves and can thus provide a means to discuss the concepts of a modeling language also with non-technical users.

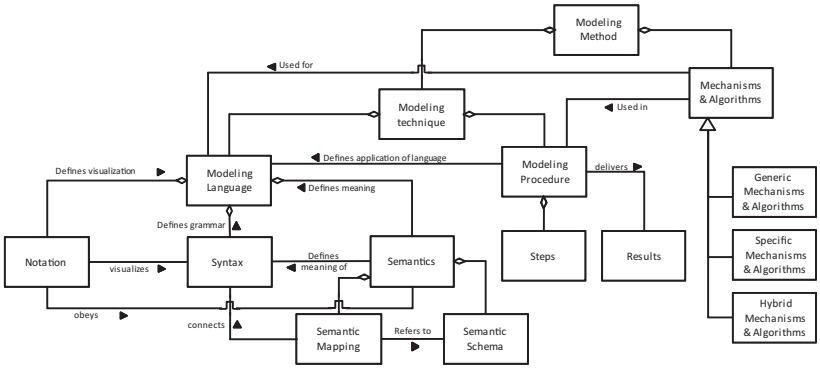

Fig. 1. Components of Modeling Methods [5]

2.2 Semantic Business Process Modeling and Semantic Information Models

The use of business process modeling can today be regarded as the defacto standard approach for analyzing complex organizational relationships and enabling IT-based management. Several modeling languages are available for this purpose. In general, it can be differentiated between two types of languages: On the one side modeling languages that are explicitly directed towards business processes such as event driven process chains [8], Adonis [9] or BPMN [10]. And on the other side modeling languages that are also suitable for business process modeling but that have not originally been conceived for this application such as UML activity diagrams [11] or Petri nets [12].

Recent attempts have been made to investigate how the *inherent semantics* of the elements, i.e. the inner meaning of the elements can be made explicit [13].

Thereby, the information contained in the description of the model elements shall be made processable by machines. In several publications this approach is denoted as *semantic business process modeling* (SBPM) e.g. [14,15]. Through SBPM several benefits may be gained: By annotating or lifting model elements with concepts from a formal semantic schema, functionalities such as semantic similarity measures and transformations between models [15], automated re-use of process fragments [14], semantic service discovery [16] or auto-completion during the creation of the models may be realized [14]. Similar results for measuring syntactic, linguistic, and structural similarity can be achieved through the transformation of business process models to a formal semantic schema [12].

Besides business process management, model annotation has also been used for other types of models, e.g. interaction and workflow models [17]. Additionally, semantic annotation may also be applied on the level of meta models [14], for the assignment of graphical notations [6] or for mechanisms and algorithms. We will therefore denote the combinations of traditional models with formal semantic schemata through annotation as *semantic information models*. The application of these approaches to real-world scenarios has so far only been described for very small cases [18]. It is therefore of high interest to apply these methods to practical scenarios. When introducing these methods to practice a central issue is to adequately balance technological opportunities and business benefits. Therefore we used modified parts of existing approaches together with new functionalities as described in the following.

3 Design of Semantic Information Models for Managing Clinical Trial Applications by a Competent Authority

The management of clinical trials on the side of public authorities is a complex issue involving several actors and IT systems. Additionally, a number of national and international legal constraints and regulations have to be taken into account. These are not invariant but are subject to frequent changes based on advancements in scientific methods and new organizational requirements. Derived from these regulations is the importance of time constraints and the appropriate planning of available resources. For these purposes we derived a modeling framework using semantic information models.

3.1 Setup of the Modeling Framework

In the first step it had to be decided which types of models should be included in the framework (see figure 2). As the management of clinical trials is basically a complex sequence of activities, the use of business process models seemed obvious. Therefore, Adonis as an established process modeling language was chosen based on its intuitive notation and extensive configuration options [9]. Several extensions were used compared to the pure process modeling configuration: *swimlanes* to represent the interaction between human actors and IT systems, *simulation elements* to allow for stochastic simulations of the duration time and capacity analyses, and *IT resource elements* to depict concrete

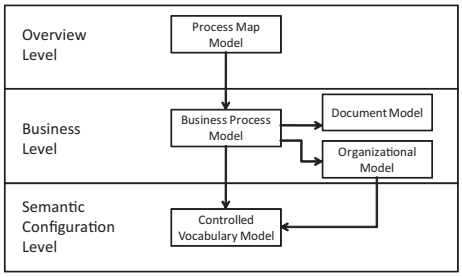

Fig. 2. Modeling Framework for Managing Clinical Trials using Semantic Information Models

IT applications during the process flow. For the representation of organizational structures a model type including *actors*, *role definitions* and *organizational units* was added. To be able to document the relation to legal regulations a document model was used and linkages from the activity elements of the business process model were defined.

To take advantage of some of the benefits arising from semantic annotation a *controlled vocabulary model* completes the modeling framework. It contains *terms* and relations to express *is broader* relationships between terms. To keep the semantic models manageable also by standard users further semantic relations are currently not included. The controlled vocabulary model is linked both to activites of business processes as well as role elements in the organizational model. By using *view definition elements* in the business process and the organizational model term instances may be selected for each instance. All model types were defined in the form of meta models and linked to each other (see figure 3). The meta model was then implemented using the Adonis meta modeling platform[2].

3.2 User-Centric Semantic Visualizations

A particular advantage of using meta modeling techniques together with semantic information models can be yielded in regard to the visualization of the models [6]. Through using the information contained in the models to influence their visualization, additional insights into the structure and relationships of a model can be gained. In our approach the visualization of elements in the process models and the organizational models can be modified based on the view definition elements and the semantic annotations through terms in the sense of *semantic visualization* [6]. By selecting terms in the view definition element other elements that are annotated with the same or related terms can be highlighted. This allows to visualize semantic relationships in the model that could otherwise not be investigated at first sight. Especially for very large models containing huge numbers of elements this functionality directly supports model analyses.

[2] Adonis is a commerical product by BOC AG. A free community edition is available at http://www.adonis-community.com/

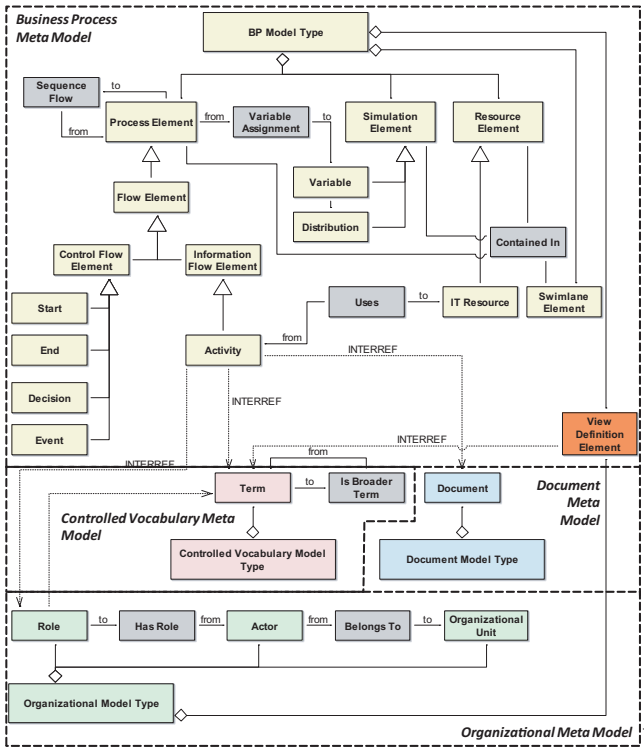

Fig. 3. Excerpt of the used Meta Model

3.3 Performance and Compliance of Processes

As the compliance to legal regulations and time constraints is of particular concern for the management of clinical trial applications, special attention was given to this subject. Based on the formal definition of the model syntax by meta models several types of analyses and simulations can be applied. Examples include the evaluation of durations and cycle times of process paths, capacity analyses for the planning of what-if scenarios or the analysis of interactions with IT systems during different process stages. Based on the linkage with document models activities relevant to certain changes of legal regulations can be directly identified and adapted if necessary. Again, the use of semantic annotations by using the controlled vocabulary model type can additionally support these analyses by integrating user-specific information. It is thus e.g. possible to annotate certain process activities with terms defining their priority in case of legal changes.

3.4 Knowledge Distribution

Due to the numerous actors and stakeholders involved in the processing of applications for clinical trials the efficient and specific distribution of knowledge

marks an important aspect. On the one side the existing staff as well as new employees of the public authority require personalized information about their embedding in the overall process structure. On the other side also third parties such as other public authorities, pharmaceutical companies or quality auditors may demand information about the processes. By reverting to the formal representation of the meta models and models transformations to other formats, e.g. HTML, word-processors or spreadsheets can be immediately realized. With the help of the semantic annotation also visualizations that are customized to a specific user group are possible. An example is the highlighting of activities in a large process that are related to a certain overall subject such as the filing of documents.

4 Management of Clinical Trial Applications at AGES PharmMed

In the following we will describe how the approach of semantic information models has been applied to the management of clinical trial applications at the Austrian public service authority AGES PharmMed.

4.1 Function and Responsibilities of AGES PharmMed

The Austrian medicines and medical devices agency (PharmMed) area of activity of AGES provides service responsibilities related to the life-cycle of medicinal products and devices. AGES PharmMed is concerned with eight tasks: (a) the approval of pharmaceuticals; (b) pharmacovigilance, i.e. the systematic logging of new adverse reactions; (c) the monitoring of the market of medicincal products; (d) the inspection of pharmaceutical companies; (e) haemovigilance, i.e. the monitoring of blood donations and transfusions; (f) the provision of scientific advice for pharmaceutical companies; (g) the official medicines control laboratory (OMCL); and (h) the official international representation of Austria in several pharmaceutical bodies.

4.2 Focus Area: Registration and Approval of Clinical Trials

The management of clinical trial applications is subject to several legal regulations. The European Clinical Trials Directive that is applicable to all EU member countries aims to harmonize clinical research practice within the EU and align Europe with international standards in the following way [19]: The role of central and local ethics committes is clearly defined. A central ethics committee should provide a single opinion for a country. The parallel submission of clinical trial applications to a central ethics committee and the country's competent authority has to be put in place. Both ethics committees and competent authorities at the country level should give an opinion on the trial within 60 days from the receipt of the application. As the the duration of the regulatory approval process has been supposed to directly affect the competitive position of a country in clinical research this time schedule is today of particular concern [19]. Additional

challenges that have to be met by government agencies involved in the administration of clinical research are [3]: to provide mechanisms whereby regulatory information can be accessed and understood by both investigators and the general public; to evaluate and improve standards in clinical trials that maintain an appropriate level of privacy while ensuring enough freedom for research; and the standardization of information systems in the health care area, in particular the development of standards to facilitate the collection and sharing of information in clinical research. Furthermore, constant adaptations of national and international procedures require a high degree of flexibility. An example are the recent developments in regard to a *voluntary harmonization procedure* that aims for an optimization of multi-national clinical trials applications [20].

4.3 Application of Modeling Approach

At AGES PharmMed the following steps were taken to apply the modeling approach. At first, the main processes related to the administration of clinical trial applications were identified. These were depicted using the process map model type to provide a first overview (see figure 4).

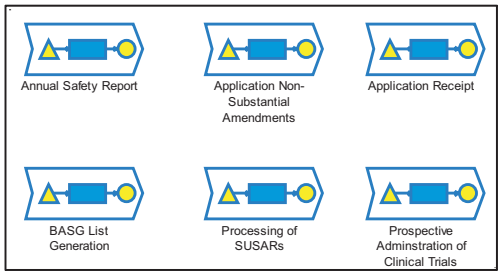

Fig. 4. Excerpt of the Process Map Model

In a second step, each of the processes has been detailed - for an overview of the main process see figure 5. For each process the involved organizational units and IT systems have been assessed. For the administration of clinical trials four main entities have been identified at AGES PharmMed: the evaluators and management staff of the department for science and information at AGES PharmMed, the ethics committees or institutional review boards (IRB), PharmMed service units such as mailpoint or finance, the Eudra-CT system, and the national clinical trials database (CTN). Eudra-CT is a European database of all clinical trials since May 2004[3]. It provides unique identifiers (Eudra-CT numbers) to track clinical trials all over Europe and log their status. The CTN provides the same service on a national level. These four main entities have been modeled using the swimlane element.

[3] https://eudract.emea.europa.eu/

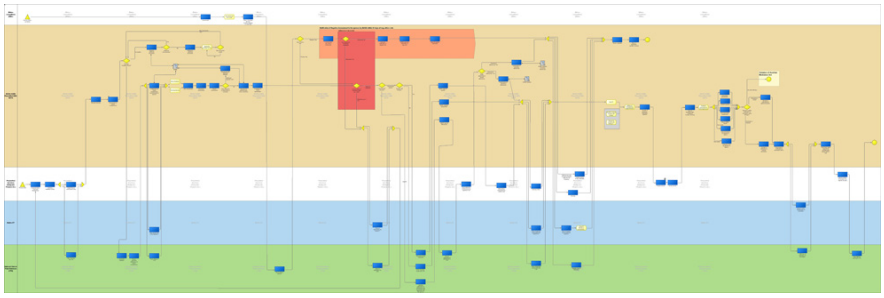

Fig. 5. Prospective Main Process for the Future Management of Clinical Trials

As shown in figure 6 the use of swimlanes directly allows to model parallel flows and task responsibilities for several actors. Especially the interaction with different IT systems can be clearly shown. For activities that are related to legal regulations links to elements of the document model have been created. From the document elements references to electronic documents and websites were stored to allow for a direct access when analyzing the process. After the modeling of the processes a number of terms were declared using the controlled vocabulary

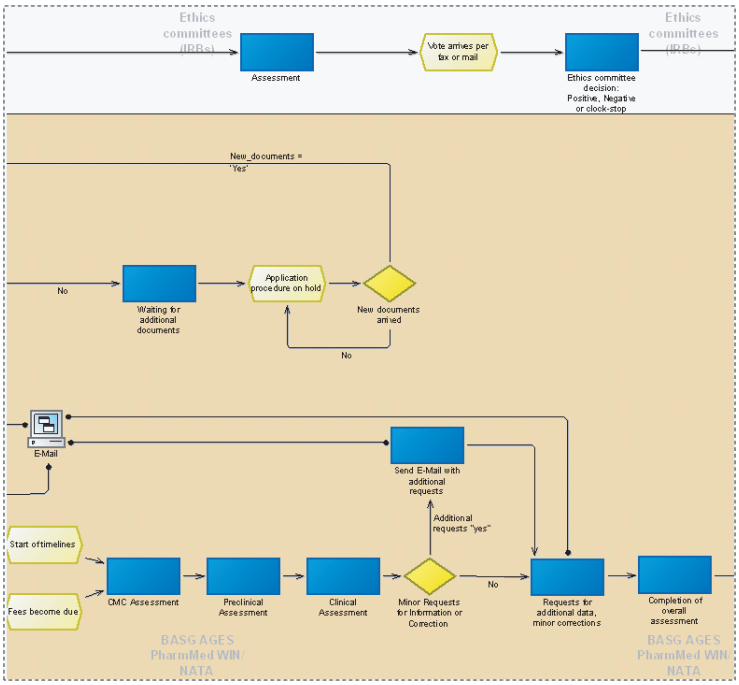

Fig. 6. Excerpt of the Prospective Main Process from Figure 5 for Managing Clinical Trial Applications at AGES PharmMed

model. The activities related to these terms were annotated by adding references to these terms.

The models were completed by organizational models to specify the involved actors and their roles. Where applicable, the activities in the process models were linked to the according role elements. After the phase of modeling, additional process data was acquired based on the models. Due to the formal definiton of the models on the Adonis plattform, transformation functionalities to spreadsheet applications could be provided. The spreadsheets were distributed to the involved actors in the process together with user-group specific process visualizations (see figure 7). Thereby, attributes such as execution and waiting times were recorded for several process executions. Together with existing data about the number of applications analyses and simulations of the cycle times for selected process paths could then be conducted. Due to confidentiality these results are not included here. From the models on the Adonis platform other distribution formats such as HTML-pages were generated and made available for involved parties.

4.4 Evaluation of the Approach

Although the application of the approach is currently limited to one organization first results can be reported. Based on the annotation of the process models user-centric visualizations could be created. These supported both the management

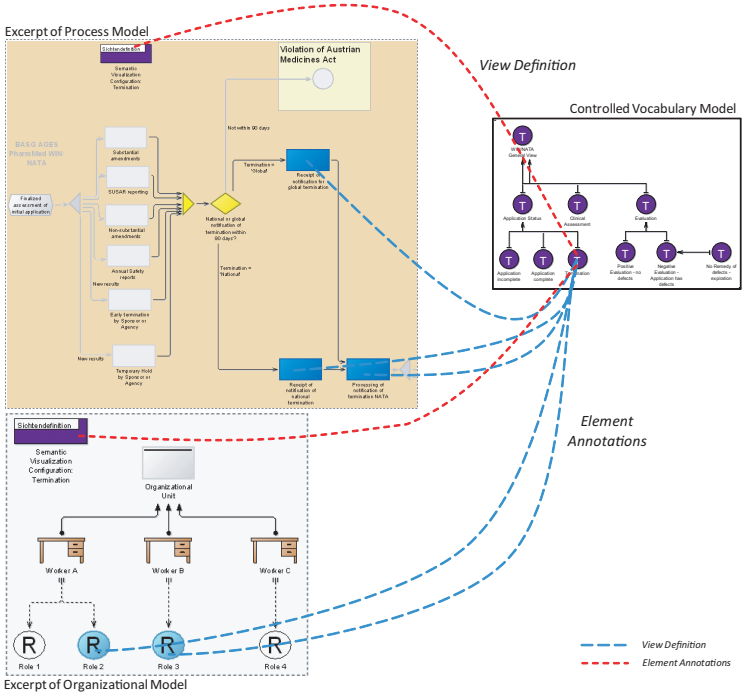

Fig. 7. Example for a Semantic Visualization for higlighting process parts

staff of AGES PharmMed in analyzing specific parts and relationships of complex processes and helped staff involved in the process executions to better understand their embedding in the overall structure. Furthermore, the possibility to analyze the duration times of the processes directly allowed to check process parts for the compliance to legal regulations. In addition, a first basis for the management of resources along the processes was established. Through the clear depiction of the currently involved IT systems requirements for the future IT support could be formulated and candidates of activities for additional automation identified.

By distributing the process models and their visualizations to the management staff and the workforce of AGES PharmMed as well as to external stakeholders the knowledge about the application processes could be easily made available. Thereby precise feedback on possible process optimizations and future interfaces to other departments and involved parties could be given. A particular advantage was also the availability of intuitive process descriptions for newly hired personnel.

5 Conclusion and Future Work

With the presented approach it could be shown how semantic information models can be used for real-world scenarios. The approach is estimated to be directly applicable to public authorities working in health care management of other EU countries. Future work will include the derivation of a reference process for the administration of clinical trials in the EU and the further evaluation of the approach.

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