Identifying Pattern in Clinical Guidelines

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In Dankbarkeit an meine Eltern,

Brigitte und Friedrich.

Abstract

This master's thesis is embedded in the Asgaard Project, which concentrates on developing methods and programs for authoring, verifying and executing clinical protocols. The goal of this thesis was to identify relevant pattern in clinical guidelines.

First of all, it was necessary to detect guidelines which were suitable for the further work. For this reason, miscellaneous medical and technical criteria had to be defined, which the guidelines had to meet. After the selection of 10 guidelines, it was possible to start with the major task – the analysis. For the detection of recurring pattern the domain of text linguistics was taken. These detected pattern were classified and specified in detail. Afterwards, one group of these detected pattern was chosen, which was suitable for the implementation in Asbru. These chosen pattern were implemented in Asbru and macros for the Guideline Markup Tool (GMT) were developed subsequently.

The major objective of this thesis was to provide a detailed analysis of the process which leads to the generation of pattern in clinical guidelines. Beginning with the selection of the guidelines, the identification of pattern, the implementation of pattern in Asbru until the generation of macros in GMT – all necessary steps of the development of pattern were completely specified and explained within this thesis.

Kurzfassung

Diese Diplomarbeit ist Teil des Asgaard Projektes, welches sich mit der Entwicklung von Methoden und Programmen zur Erstellung, Überprüfung und Ausführung von medizinischen Behandlungsplänen (bzw. clinical Protocols) beschäftigt. Das Ziel dieser Diplomarbeit war es relevante Pattern in klinischen Guidelines zu identifizieren.

Als erstes war es notwendig klinischen Guidelines (bzw. klinischen Leitlinien) zu finden, welche sich für die bevorstehende Arbeit eignen. Hierzu wurden verschiedene medizinische und technische Kriterien definiert, welchen die Guidelines entsprechen mussten. Nachdem eine Anzahl von 10 Guidelines gefunden war, konnte die eigentliche Analysearbeit beginnen. Dabei wurden die Guidelines auf wiederkehrende Muster (bzw. Pattern) untersucht. Als Ansatz für diese Mustersuche wurde der sehr allgemeine Ansatz der Textanalyse (bzw. Textlinguistik) gewählt. Diese entdeckten Muster wurden klassifiziert und im Detail beschrieben. Weiters wurde aus diesen entdeckten Mustern eine Gruppe ausgewählt, welche sich für die Implementierung in die Sprache Asbru eignet. Diese gewählten Pattern wurden in Asbru übersetzt und in einem nächsten Schritt wurden daraus Macros für das Guideline markup Tool (GMT) entwickelt.

Das Ergebnis dieser Arbeit ist eine detaillierte Analyse des Ableitungs- bzw. Entwicklungsprozesses von Pattern aus klinischen Guidelines. Alle Schritte, von der Auswahl der zugrunde liegenden Guidelines, der Identifizierung der Pattern, der Implementierung in Asbru bis hin zur Entwicklung von Macros im GMT, werden ausführlich beschrieben und erklärt.

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Acknowledgements

First of all, I would like to thank my supervisor Silvia Miksch, who really did a great job in supporting me in this thesis. Thanks for encouraging me to choose this topic, also acknowledging that for me – especially in the beginning – it was quite difficult to get an orientation in the domain of medical application. But with her positive attitude it was a pleasure to take one hurdle after the other.

I also wish to thank Peter Votruba, one member of the Asgaard Group, for explaining me the Guideline Markup Tool and answering all my questions and supporting me whenever I contacted him.

Special thank deserves to my friend Elmar for the motivation and help during the last years, especially the last six months and for the early revision of this thesis.

1 Introduction

This chapter gives a short introduction to the underlying motivation and problem characteristics including the application domain. Furthermore, it contains an overview of both the contents and the structure of this thesis.

1.1 Motivation

A major concept in this thesis is the concept of clinical guidelines. Clinical guidelines were introduced to standardize treatment methods of physicians. Guidelines embody each step of a treatment of a certain disease and mostly they are written as a plain document.

The Asgaard Project[1] ([Shahar et al., 1998]) was initiated to develop "a task-specific framework for the application and critiquing of time-oriented clinical guidelines". Within the Asgaard Project, a language and several methods and tools for performing design and execution of clinical guidelines were developed. The representation language for guidelines is called Asbru[2] (see section 3.1.1) and supports the representation of skeletal plans. Also a visualisation tool was created, which is called AsbruView (see section 3.2.2).

The demand for this thesis arose, after the completion of the development of the Guideline Markup Tool (GMT) (see section 3.2.1) by Peter Votruba ([Votruba, 2003b]). The GMT is a tool for supporting the translation task of guidelines from their plain text representation into their target Asbru representation. After this translation task, the Asbru representation can further be used by physicians in AsbruView. At that time, when developing GMT, also a macro file for facilitating the authoring task was developed. But the development of this macro file was not based on analysing any clinical guidelines.

The aim of this thesis is to detect pattern in a set of clinical guidelines, which first was chosen in an analysing process. The last task is the transformation task from the pattern into the macro for the GMT.

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[1] Most of the names in the Asgaard Project are based on names from Norse mythology. Asgaard respectively, was the home and citadel of the gods.

[2] Asbru (also known as Bifrost) is based on Norse mythology and is the rainbow bridge which leads to Asgaard.

1.2 Structure of this Thesis

This thesis is structured in three parts, which are “Problem Analysis”, “Design and Implementation” and “Conclusion”.

The first part gives an overview of the basic concepts used in this thesis and provides general definition for these concepts. It explains a convention used in this thesis and gives a rational for using some words. Furthermore, the first part contains information about the State of the Art of the application domain and introduces some guideline modelling methods, where Asbru is part of and some guideline modelling tools with the Guideline Markup Tool, which is a basic concept in this thesis.

The second part is the central part and presents the work I have done in this thesis. It presents the way from searching clinical guidelines, their analysis, the definition of pattern and their detection in guidelines until the implementation of some selected pattern in Asbru, for creating Macros for the GMT.

The third part finishes the thesis and gives my conclusion about the work in this domain and summarizes the results of this work.

Additionally, Appendices A to F provide several documents, which give additional information and may be used for future work.

Part I

Problem Analysis

2 Basic Concepts

The purpose of this chapter is the definition of frequently used terms in this thesis. It explains a certain convention of using some terms and gives a rational for using these words.

2.1 Pattern vs. Patterns

The idea of patterns, as they are established in the domain of computer science, is originally conceived of Christopher Alexander, who introduced pattern on the basis of the architectural domain. The following common definitions of pattern are taken from [URL#24] and from Christopher Alexander's book "The Pattern Language" [Alexander et al., 1977]:

> "PATTERN: A pattern is a careful description of a perennial solution to a recurring problem within a building context, describing one of the configurations which brings life to a building.
>
> Each pattern describes a problem which occurs over and over again in our environment, and then describes the core of the solution to that problem, in such a way that you can use this solution a million times over, without ever doing it the same way twice."

In computer science, patterns are recognized as a powerful theoretical framework, which can help to solve problems or provide general solutions for problems.

Basically, the terms "pattern" and "patterns" stand for the singular and plural form of the word. Especially for this thesis, I introduce a certain convention of using these two terms. This convention is based on a further differentiation between these two terms which concerns the meaning.

In this thesis, pattern are only used in the original meaning of the term, which can be characterised as something like a sample. Pattern is also used in the plural form of the term.

Contrary, the term patterns is used for are a more complex form of a pattern. Patterns can be seen as templates or macros. The term patterns is used interchangeably with template of macro in this thesis.

To link these two central terms it can be said, that the aim of this thesis is the detection of pattern in clinical guidelines and the development of patterns for the Guideline Markup Tool.

2.2 Guidelines and Protocols

In this thesis, terms in combination with the word guideline frequently occur. Definitions for these terms – guidelines, clinical guidelines, protocols, clinical protocols, and clinical practice guidelines – are presented in the following paragraphs:

Guideline: In [Field and Lohr, 1990] guidelines are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances", and guidelines "are validated policy statements representing best clinical practice. Used to support standardized patient care." In [Miksch, 1999, p. 210] a further definition for guideline is given. A guideline can be defined as “a method, that identifies actions, that are to be performed and that specify conditions that govern when it is appropriate to perform them”.

Clinical Guidelines: In [Miksch et al., 1997b, p. 2] clinical guidelines are defined as “a set of schematic plans for management of patients who have a particular clinical condition”. The aim of clinical guidelines is to support physicians and clinical staff in their treatment decisions for patients.

Protocols: Protocols are defined in [CBO, 2004] as "local tools that set out specifically what should happen, when and by whom in the care process. They can be seen as the local definition of a particular care process derived from a more discretionary guideline. They are in essence tools that assist in quality improvement and reducing inequalities. Protocols reflect local circumstances, and variation will due to the differing types of local provision."

Clinical Protocols: Clinical protocols are defined in [Seyfang and Miksch, 2002, p. 1] “as a more detailed version of a clinical guideline referring to a certain class of therapeutic interventions”. In the glossary of Open Clinical [URL#1] clinical protocols are “a standard set of tasks that define precisely how classes of patients should be managed or treated”.

Clinical Practice Guidelines: A definition for clinical practice guidelines is given at [URL#1], where they are defined as “validated policy statements representing best clinical practice. Used to support standardised patient care”.

For the process of analysis only clinical guidelines were taken in this thesis. They form the basis of the detected patterns for the GMT. The terms clinical guidelines and guidelines are used interchangeably.

3 State of the Art

This chapter gives an introduction to relevant modelling methods and modelling tools of guidelines. It describes several languages, with focus on the plan representation language Asbru. Additionally, some guideline modelling tools will be presented.

3.1 Guideline Modelling Methods

This section gives an introduction to modelling concepts of guidelines. At first, it describes the language Asbru and then it presents an overview of further guideline modelling methods. Finally, a short comparison between Asbru and the other described modelling methods will be given.

3.1.1 The Plan Representation Language Asbru

The language Asbru has been developed within the *Asgaard Project* by Silvia Miksch together with Yuval Shahar and Peter Johnson ([Miksch et al., 1997a, p. 1], [Miksch et al., 1997b, p. 1] and is characterised as follows:

> "Asbru: A task-specific, intention-based, and time-oriented language for representing skeletal plans."

The definition provides various expressions which are worth to be explained.

task-specific: Asbru is comparable to other programming languages because of its huge amount of non-terminal symbols. However, Asbru features a lot of *task-specific* parts and can not be seen as a general-purpose language.

intention-based: In [Bacchus and Kabanza, 1996] intentions are viewed as "temporally extended goals" at various abstraction levels. In [Miksch et al., 1997b, p. 4] "intentions are temporal patterns of actions or states, to be maintained, achieved, or avoided". The meaning of *intention-based* concerning Asbru is that the designer has a strong focus on goals (intentions) of a guideline, during and after the execution of a plan.

time-oriented: Asbru places strong emphasis on the temporal aspect of plans. The concept of *time annotations*[3] offers possibilities to deal with these requirements.

skeletal plans: [Friedland and Iwasaki, 1985] define skeletal plans as plan schemata at various levels of detail that capture the essence of the procedure, but leave room for execution-time flexibility in the achievement of particular goals. Generally, skeletal plans are qualified to model guidelines.

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[3] see [Miksch et a., 1997b]: section 3.2.2, page 4

Because of the importance of Asbru in this thesis, a short introduction of the main features – *Preferences, Intentions, Conditions, Effects and Plan Body* – will be given now.

Preferences are plan parameters which restrict the plan selection and consequently the desired goal and behaviour of the plan. Examples for such preferences are strategy (e.g., aggressive, normal), utility (e.g., minimize the cost or inconvenience), etc.

Intentions are high-level goals which should be achieved, maintained of avoided by a plan during its execution. Asbru knows four categories of intentions such as intermediate state, intermediate action, overall state pattern and overall action pattern.

Conditions are described in [Miksch et al., 1997b], as temporal patterns, sampled at a specified frequency, that need to hold a particular plan steps to induce a particular state transition of the plan instance. In other words, conditions describe the state of a patient (each plan instance represents a patient) and the state diagram (see Figure 3.1) as mentioned below, shows the mapping between the patient (plan instance) and its possible states.

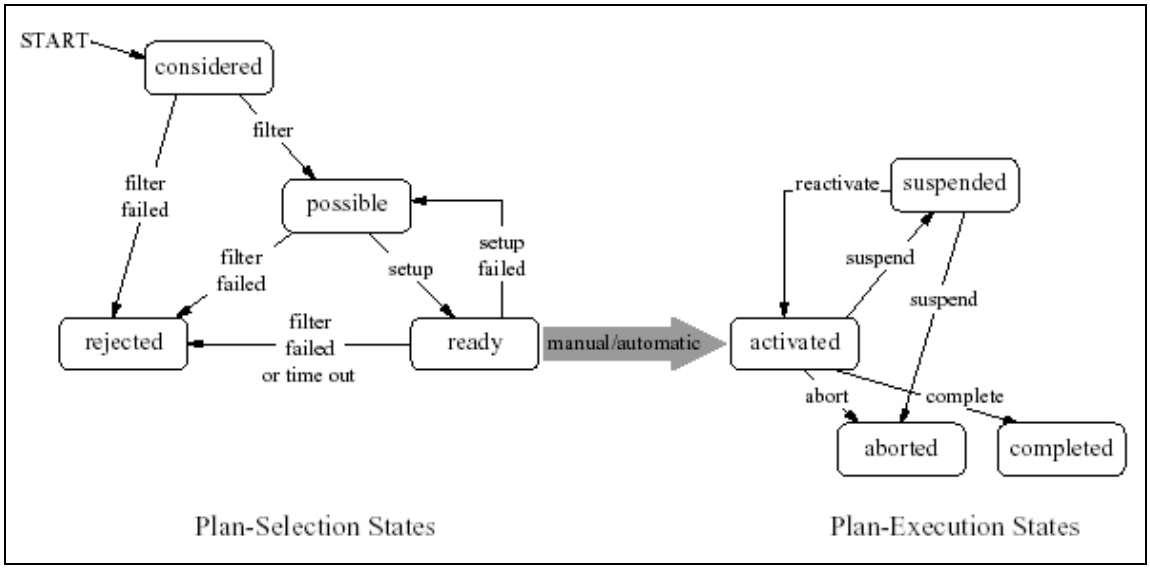

Figure 3.1: Plan States and Conditions for Asbru plans (from [Seyfang et al., 2002, p. 73]).

Effects can be seen as the achievement of a plan in terms of functional relationships (possibilities are exact formulas or describing trends) between plan arguments and measurable parameters. Moreover, effects have a likelihood annotation.

In Asbru a *Plan Body* (resp. Actions) may consist of a set of plan steps (subplans) which can be executed in different ways. These execution types (resp. plan types) are sequential, parallel, any-order, and unordered. In chapter 7 some of these plan types will be described more detailed.

As stated before, Asbru is a powerful modelling language. A detailed analysis of all features is therefore out of scope. At this place it should be mentioned that Asbru is an XML based language, which will be important in a later section in this thesis. More information can be drawn from several, existing papers and the *Asbru Reference Manual* [Seyfang et al., 2002].

3.1.2 Further Approaches

Besides Asbru, there are several other guideline modelling methods. This chapter gives a short introduction to these concepts. At the end of the chapter, a comparison between the different approaches will be carried out.

It should also be mentioned, that most of the information which will be presented in the following paragraphs are drawn from http://www.openclinical.org (resp. URL#1).

3.1.2.1 Arden Syntax

The Arden Syntax was developed by "a group at the Arden Homestead in Harriman, New York State in 1990 and is maintained by the Arden Syntax Special Interest Group of the Clinical Decision Support Technical Committee of HL74" [URL#2].

On [URL#3] the Arden Syntax for Medical Logic Systems is described as "a system, which encodes medical knowledge in knowledge based form as *Medical Logic Modules* (MLMs)". Furthermore, Arden Syntax is a *rule-based* modelling language.

A MLM can be seen as a rule, which contains enough logic to get a single medical decision. A plan or a protocol consists of a set of MLMs. MLMs are primarily used for generating clinical alerts and reminders, interpretations, diagnoses and so on. Slots within three categories – maintenance, library and knowledge – form the general structure of a MLM.

maintenance:
title:
CT study with contrast in patient with renal failure;;
filename:
astm_ct_contrast;;
version:
1.00;;
institution:
ASTM E31.15; SMS;;
author:
Harm Scherpbier, M.D.;;
specialist:
;;
date:
1995-09-11;;
validation:
testing;;

Figure 3.2: Part of a MLM (from [URL#14]).

[4] Health Level Seven

In Figure 3.2, maintenance information with its element – *title, filename, version, institution, author, specialist, date, validation* – is shown. A detailed description of the different elements and further information of Arden Syntax is given in the *Arden Syntax for Medical Logic Systems* (published by Health Level Seven, Inc) and at the *Arden Syntax Web Site*: http://cslxinfmtcs.csmc.edu/hl7/arden/ .

3.1.2.2 EON

The EON architecture was developed at the Stanford Medical Informatics group, USA. EON is composed of a set of components which "represent independent, reusable software modules that developers can assemble to build systems that solve tasks related to the administration of protocol-directed therapy" [Musen et al., 1996, p. 2].

The EON guideline model is called the *Dharma* model. The *Dharma* model defines the guideline knowledge structures, such as eligibility criteria, abstraction definitions, guideline algorithm, and decision models. During the modelling process, conditional goals are associated with guidelines and subguidelines; a set of scenarios, action steps, decisions, branches, synchronisation nodes connected by a "followed-by" relation are used, which form the guideline algorithm. This guideline algorithm is comparable to PRODIGY (see section 3.1.2.7), which is a further modelling method.

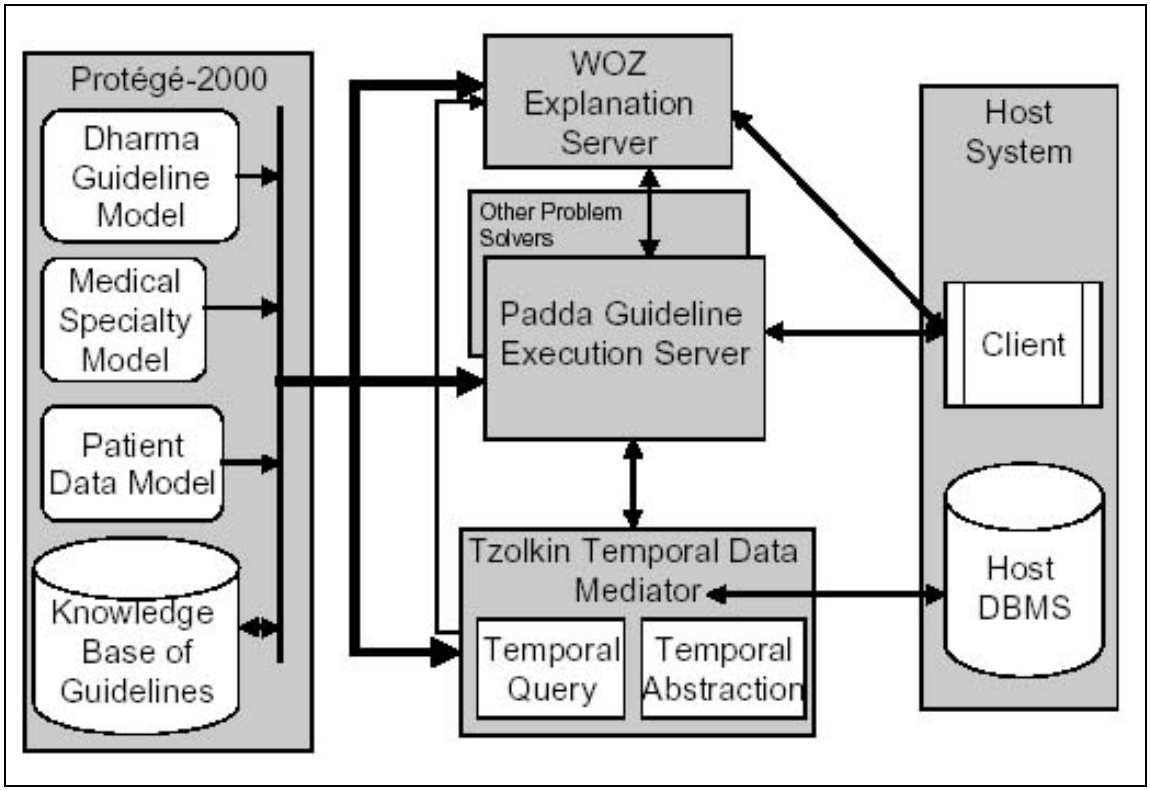

Figure 3.3: Architecture of EON guideline applications (from [Tu et al., 2001, p. 281])

Figure 3.3 shows the EON architecture with its combination of models and software components. Figure 3.3 depicts tree main parts of the architecture. The first part is a *Host System*. The second part "contains a set of middleware servers that perform the

computation necessary to support specific tasks in guideline-based patient care" [Tu et al., 2001, p. 1] and the third part is the *Protégé-2000* (see section 3.2.6) knowledge-engineering environment – containing the Dharma Guideline Model. More information about the EON architecture can be found in [Tu et al., 2001].

3.1.2.3 GLARE

GLARE has been developed at the Dipartimento di Informatica, Università del Piemonte Orientale, Alessandria, Italy, in co-operation with the Laboratorio di Informatica Clinica, Azienda Ospedaliera San Giovanni Battista, Torino, Italy.

GLARE can be described as a domain-independent system to perform acquisition, representation and execution of clinical guidelines. The term "GLARE" is an acronym for the main tasks and is short for *GuideLine Acquisition, Representation and Execution*.

The GLARE system is based on a modular architecture. In Figure 3.4, the main parts of GLARE – the acquisition tool and the execution tool – are shown.

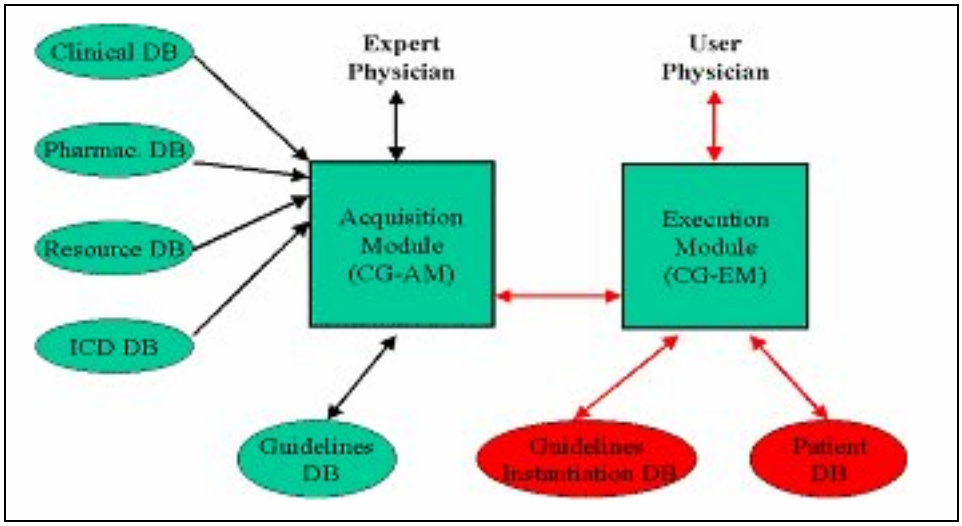

Figure 3.4: GLARE architecture (from [URL#6])

However, GLARE is a representation language, too. The purpose of designing the GLARE representation language was "to achieve a balance between expressiveness and complexity" [URL#6]. The language is made up of a set of primitives, which are easy to understand and consist of two types of actions. These types are *plans* (i.e. composite actions, hierarchically decomposable in their sub-actions) and *atomic actions* (i.e. queries or decisions). Due to the order of execution, actions are linked together by different control relations. These relations can express a sequence, an alternative or a repetition.

3.1.2.4 GLIF

GLIF was developed by the InterMed Collaboratory, which includes Stanford Medical Informatics, Harvard University, McGill University and Columbia University, USA.

GLIF stands for *Guideline Interchange Format* and GLIF consists of an object-oriented model and the corresponding text syntax. In [Ohno-Machado et al., 1998, p. 357] the GLIF model is described as "an object-oriented representation that consists of a set of classes for guideline entities, attributes for those classes, and data types for the attribute values. The GLIF syntax specifies the format of the test file that contains the encoding."

In Figure 3.5 the object-oriented approach with its classes, which are arranged in a hierarchy, is shown. Each class has its own attributes as well as the attributes it inherits from the class above.

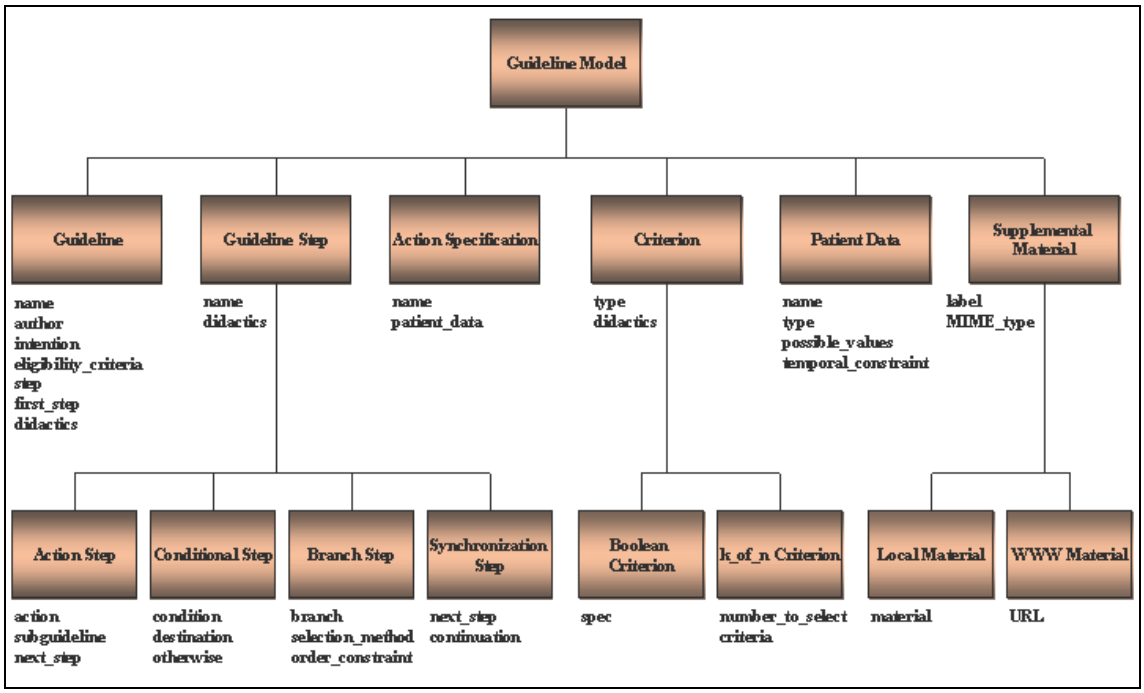

Figure 3.5: GLIF classes and attributes (from [Ohno-Machado et al., 1998, p. 364]).

Up to now, several versions have been released from GLIF. A guideline modelled in GLIF2 results in a flowchart of structured steps. These steps are *action steps* and various types of *decision steps*. Several steps lead to a structured construct, which again can have attributes. However, these attributes are defined as text strings which can not be parsed in GLIF2. This is a major drawback for computer-based execution.

Furthermore, GLIF provides the object-oriented expression language *GELLO*, which is used to specify decision and eligibility criteria.

GLIF3 is the current version. It improves GLIF2 by introducing new constructs, allowing a more formal definition of the GLIF2 constructs and supporting computer-based execution. More information about the evolution of GLIF can be drawn from [Plege et al., 2000].

3.1.2.5 GUIDE

The guideline model GUIDE has been developed at Pavia University, Italy.

GUIDE is based on Petri Nets[5]. The Pavia Team has enriched the concept of Petri Nets with the result of an "improved modelling of time, data and hierarchies. GUIDE, uses the underlying Petri Net formalism to be able to support the representation of sequential, parallel and iterative logic flows" [URL#8].

In other words, GUIDE is a state-based formalism with the aim of modelling complex concurrent processes in healthcare. GUIDE also facilitates the management of patient care workflow, by integrating clinical tasks specified in guidelines with organisational models.

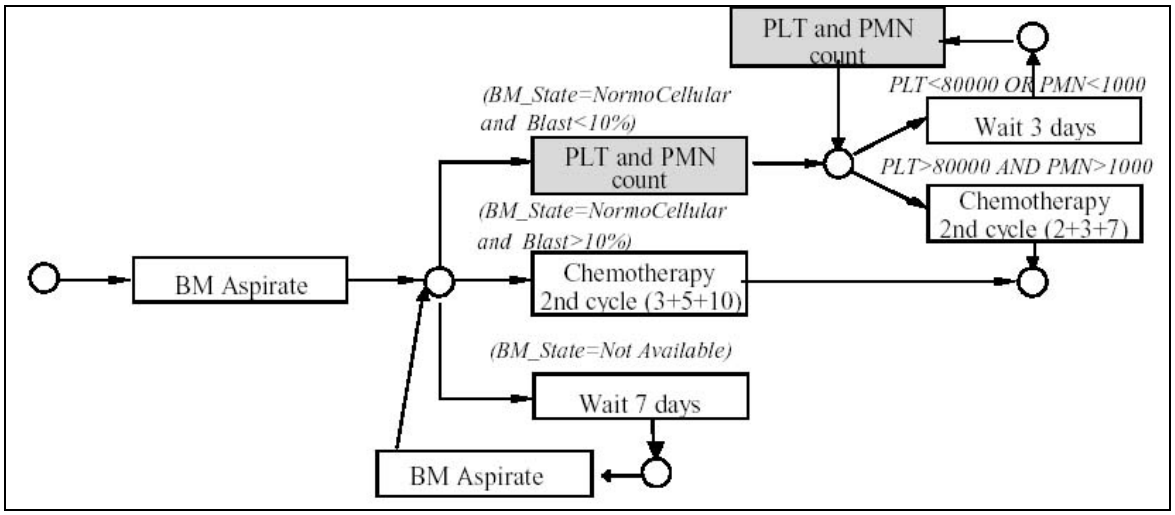

Figure 3.6: The Petri Net of a formalized guideline (from [Dazzi et al., 1997, p.3]).

Figure 3.6 shows the guideline for Acute Myeloid Leukemia (AML) in the formalism of a Petri Net.

In order to receive the Petri Net representation, in [Dazzi et al., 1997] two steps are necessary. First, the guideline is translated into a formal representation. For this task, the EON (see section 3.1.2.2) model is used. Then, a second translation process takes place where the formalized guideline results in the Petri Net.

3.1.2.6 Prestige

Prestige was an international project with the aim of "an installed and sustainable healthcare telematics infrastructure that supports dissemination and application of research based and consensus based guidelines, that in turn supports best practice for routine clinical care" [Gordon et al., 1999, p. 1].

[5] Petri Nets are a rigorous formalism for modelling concurrent processes, invented by Carl Adam Petri in the 1960s.

Prestige provides the *Prestige Conceptual Guideline Model*, which is an "explicite, declarative representation format in knowledge bases" [Gordon et al., 1997, p. 1]. The purpose of the *Prestige Conceptual Guideline Model* is to support the use of guidelines by describing all the information needed. In order to reach this goal, Prestige needs the ability to represent knowledge about various medical domains (such as diagnoses, therapies and symptoms), patients, carers, corporations and staff.

The knowledge provided by Prestige can be separated into two major sub-areas. The first area includes general healthcare knowledge, the second area specifies clinical protocols.

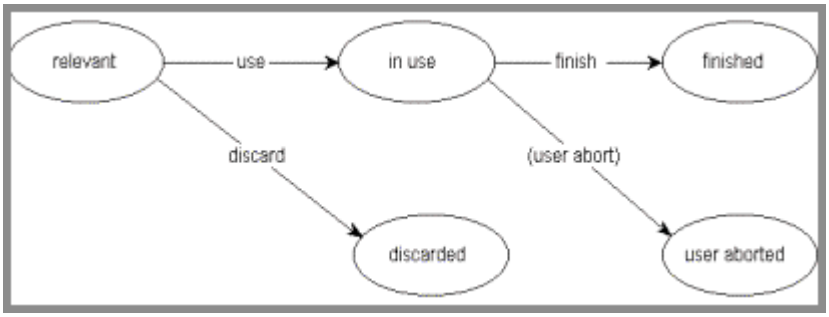

Figure 3.7: Part of the Prestige guideline model: component states (from [URL#9]).

Figure 3.7 shows a part of the Prestige Conceptual Guideline Model with the possible component states of knowledge.

Two guideline authoring tools, GAUDI (Guideline Authoring and Dissemination Tool) and GLEAM (Guideline Editing and Authoring Module), which implement the Prestige Conceptual Guideline Model, have been built.

3.1.2.7 Prodigy

PRODIGY is short for "*P*rescribing *R*ati*O*nally with *D*ecision-support *I*n General-practice stud*Y*" [Johnson et al., 2000, p. 1] and was developed at New Castle University, UK.

PRODIGY can be described as "a guideline-based decision-support system" [Johnson et al., 2000, p. 1] and is suitable for "managing patients with chronic diseases such as asthma and hypertension" [Johnson et al., 2000, p. 1].

The basis of the decision process is a structured guideline, consisting of a set of possible choices. The set of choices is available to physicians, and enables them to meet one decision after the other. Referring to input data, Prodigy is very robust.

Regarding Figure 3.8, the *PRODIGY Guidance Browser* is shown. On [URL#15], a link to the demonstration of the *PRODIGY Guidance Browser* and the *Web Browser Instruction Manual* is accessible. The Browser is divided into two sections. In the left part, the structure – with the set of choices – is represented and the decision process can be tracked. The right part is the information section, which shows the *Guidance Texts*, *Information Display* and the *Advice Texts*.

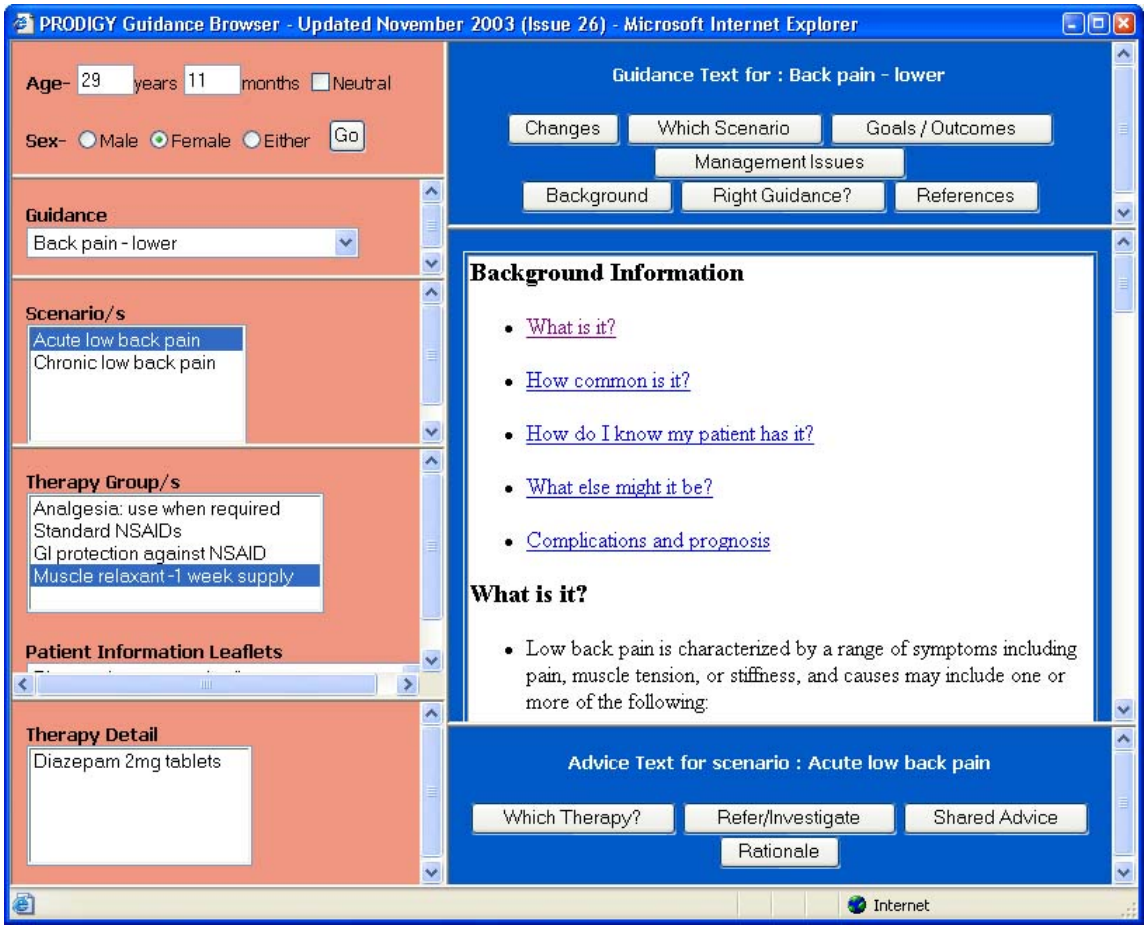

Figure 3.8: Prodigy Guidance Browser

On this place, http://www.prodigy.nhs.uk/ is recommended for further information.

3.1.2.8 PROforma

The PROforma tool was developed at Cancer Research, UK. In [Bury et al., 2000, p. 12] and [URL#11], PROforma is defined as "a formal knowledge representation language designed to capture the content and structure of a clinical guideline in a form that can be interpreted by a computer".

According to [Bury et al., 2000, p. 17], the PROforma technology can be considered as a kind of *logic programming system* and as well as an *object-oriented system*. Considering PROforma as a modelling method, the concept of an object-oriented system is crucial.

A guideline, modelled in PROforma consists of a set of tasks[6] and a set of data items and the values of the data items are accessible to the tasks.

[6] In PROforma, tasks are „encapsulated procedures for achieving particular goals" [Bury et al., 2000, p. 17].

The *Task-based ontology* is the key feature and there are four different task-types. In Figure 3.9 the task ontology with its types - decisions, actions, plans and enquiries – is shown.

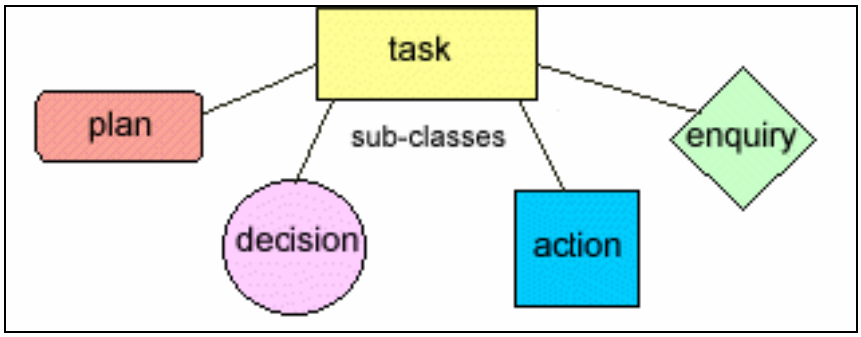

Figure 3.9: The PROforma task ontology (from [Bury et al., 2000, p. 17]).

Decisions are choice points and are defined through options (resp. *Candidates*) between which the choice has to result and a *Choice mode* which can be single[7] or multiple[8].

Actions are defined through procedures. Procedures can be specified in *free text*[9] or *SQL statements*.

Enquiries include a set of *sources*, which are needed to execute a procedure.

Plans consist of tasks (resp. *components*) and possible *constraints* – scheduling, abort or termination constraints – which specify the plan more exactly.

The PROforma software is composed of the *graphical editor* and the *engine* (an execution environment). The *graphical editor* is needed to author guidelines. The *engine* executes the guideline specification and is used for verification and testing the toolset, too.

Currently, two authoring tools – *Arezzo* and *Tallis* – have been created for the modelling language PROforma.

[7] single: only one candidate may be chosen

[8] multiple: many candidates may be chosen

[9] Operations to be performed by a human agent are specified in free text.

3.1.3 Comparison: Asbru vs. other Modelling Languages

Notably, there exist differences in central concepts of the introduced modelling languages. Referring to representation formalisms and computational techniques almost every modelling language features a different approach. The Arden Syntax follows a rule-based concept, whereas PROforma is logic-based. Furthermore, Prodigy is network-based and GUIDE is based on Petri Nets. Asbru with its task-specific, intention-based, and time-oriented concepts is a new approach. Therefore, it is difficult to compare Asbru with the modelling languages, mentioned before.

Finally, it can be said, that [URL#13] provides full documentation on a comparison study carried out in 2001 to compare six computer-interpretable guideline models (Asbru, EON, GLIF, GUIDE, PRODIGY and PROforma).

3.2 Guideline Modelling Tools

This section gives an introduction to modelling tools guidelines. It describes the Guideline Markup Tool and then it presents an overview of AsbruView, GEM-Cutter, Stepper, DeGeL and Protégé-2000. Concluding, a short comparison between the Guideline Markup Tool and the other described modelling tools will be given.

3.2.1 The Guideline Markup Tool (GMT)

The abbreviation *GMT* stands for *Guideline Markup Tool* ([Votruba et al., 2003a, p. 1], [Votruba et al., 2004, p. 1]). GMT was developed at the Vienna University of Technology, Austria within the Asgaard-Group.

The motivation to develop GMT was, that Asbru (see section 3.1.1) became rather complex and the need for a special tool to support the translation task from guidelines in free-text files (HTML or XML) to a machine-readable formal representation arose. The solution to these needs was GMT. The aims of this markup tool are described in [Votruba et al., 2004] as follows:

- The support of the translation of clinical guidelines into a guideline modelling language such as Asbru.
- The maintenance of the connection between the original guideline and its formal representation.

In order to work with GMT, the operator must have a thorough understanding in clinical guidelines and a guideline modelling language. Therefore, GMT is primarily intended for knowledge engineers.

The GMT user interface window is divided into three sections which can be seen in Figure 4.4. The right window of the upper part shows the HTML or XML text file. The Asbru XML file (resp. the *Asbru XML tree*) is displayed on the left side of the upper window. The smaller part of this, gives a more detailed view of the selected element and its attributes. The bottom part is the macro-part where the user can select between available macros and insert these into the *Asbru XML tree*.

In chapter 8, the Macro-Part of GMT will be described more precisely.

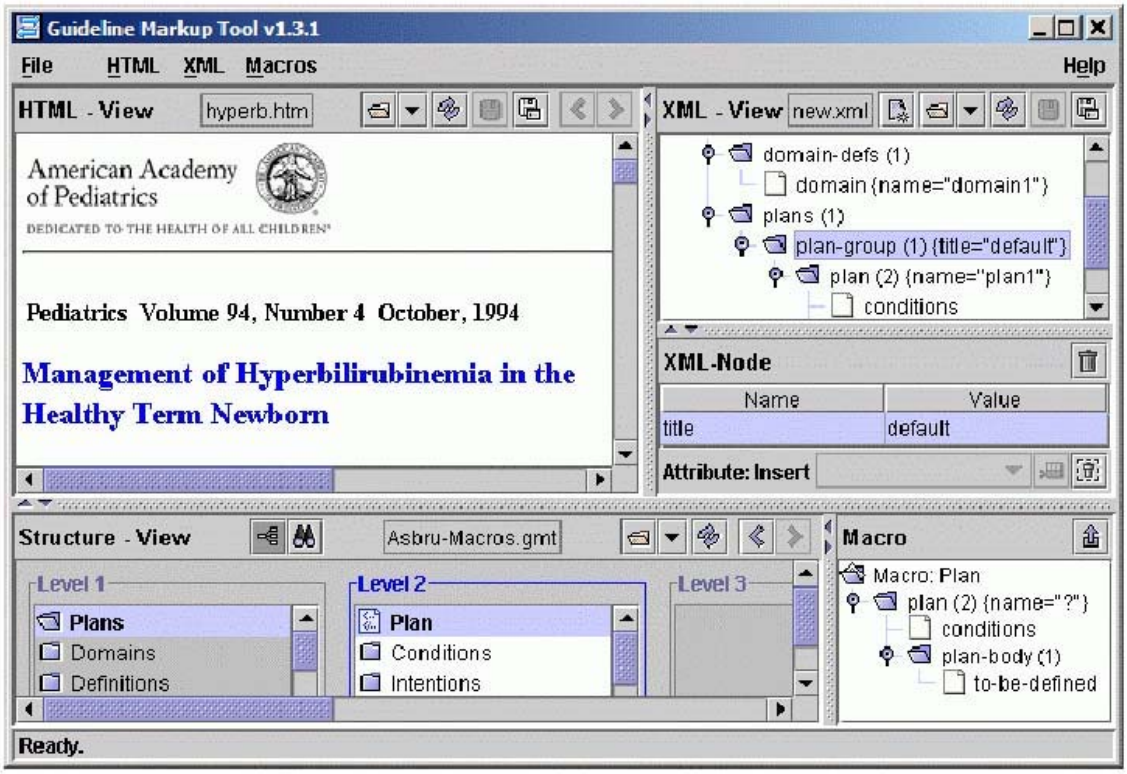

Figure 3.10: User Interface Window of GMT (from [Votruba et al., 2003a, p. 4]).

Later in this thesis – when describing GEM-Cutter, Stepper and DeGeL - it will be shown, that user interfaces of the other tools have similarities with the user interface of GMT.

There are two main advantages of GMT. First, GMT supports the *translation task* with its design. Second, the new features *Links* and *Macros* are implemented.

The *Link Feature* enables the reconstruction of the translation process from the textual guideline to the formal representation at a later time.

Macros are objects which combine several Asbru elements with their attributes. The Macro-Part is useful *to facilitate creating and extending Asbru XML files* [Votruba, 2003b, p. 21] in an easier way.

It will be shown in chapter 8, that detected patterns in guidelines will be authored in Asbru to be taken over in the GMT macro tool, in order to provide useful common design patterns. Furthermore, an example of an implemented macro will be given.

In the following sections of this chapter further guideline tools will be introduced. At this place it should be stated, that only Stepper (see section 3.2.4) has the possibility of links, but none of the other tools described below provides features, comparable to the *Link Feature* and the *Macro Feature*.

3.2.2 AsbruView

Like the guideline modelling language Asbru, AsbruView has also been developed at the Vienna University of Technology, Austria within the *Asgaard Project*.

As mentioned, Asbru is a powerful and complex language and with its *LISP-like* syntax it is extremely difficult to read for the medical domain experts. Out of this reason, AsbruView has been created aiming to provide access to a plan representation language for physicians and medical staff.

In [Kosara and Miksch, 2001, p. 1, AsbruView is defined as *a Visualization and User Interface for Time-Oriented*[10]*, Skeletal Plans*[11]. In addition, in [Kosara and Miksch, 2001] and [Miksch et al., 1998] the requirements which AsbruView meets are given. In this thesis there will be only a short overview of the Asbru parts (resp. views) and their functionality.

To meet the requirements of AsbruView, concepts like *graphical metaphors*[12] and *glyphs*[13] are embedded in the different parts – Topological View, Temporal View and SOPOView - of AsbruView.

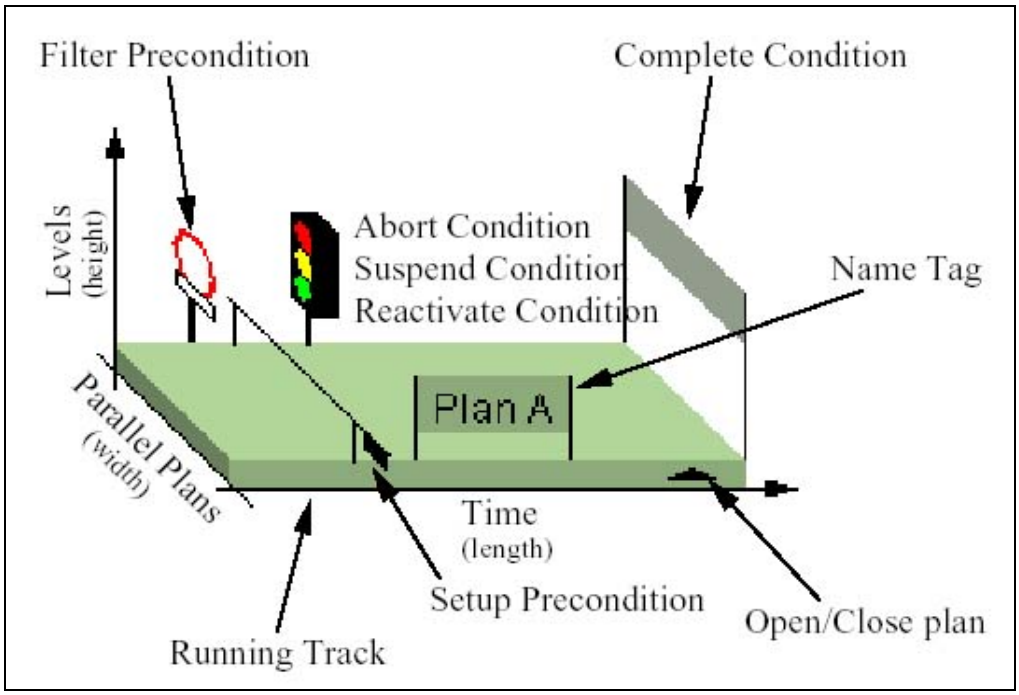

Figure 3.11: Anatomy of an AsbruView Plan in Topological View (form [Kosara and Miksch, 2001. p. 7]).

[10] For definition of time-oriented see section 4.1.1

[11] For definition of skeletal-plans see section 4.1.1

[12] In [Kosara and Miksch, 2001], graphical metaphors are described as signs from (more or less) daily life to communicate the various components of Asbru.

[13] Glyphs *are graphical objects whose features reflect values, and therefore change their shape or size according to them*. [Kosara and Miksch, 2001]

The Topological View mainly displays the relationships between plans, without a precise time scale [Kosara and Miksch, 2001, p. 7]. The concept of *graphical metaphors* is introduced in the Topological View. The most important feature is the running track ("Plan A" in Figure 3.11), which represents the plan. Additionally, this view also displays the conditions which have to be defined. Metaphors like the *traffic control* are used.

Secondly, AsbruView contains a Temporal View. This view is based on the concept of *LifeLines*[14] and tries to present the temporal dimension of plans and conditions.

Among the parts of the temporal View in Figure 3.12, one part is the *Time Annotation*[15] where the concept of *glyphs* can be found. *Glyphs* have been designed especially for AsbruView and capture all the (uncertain and possibly undefined) parts of a *Time Annotation*. For further description of glyphs see [Kosara and Miksch, 2001].

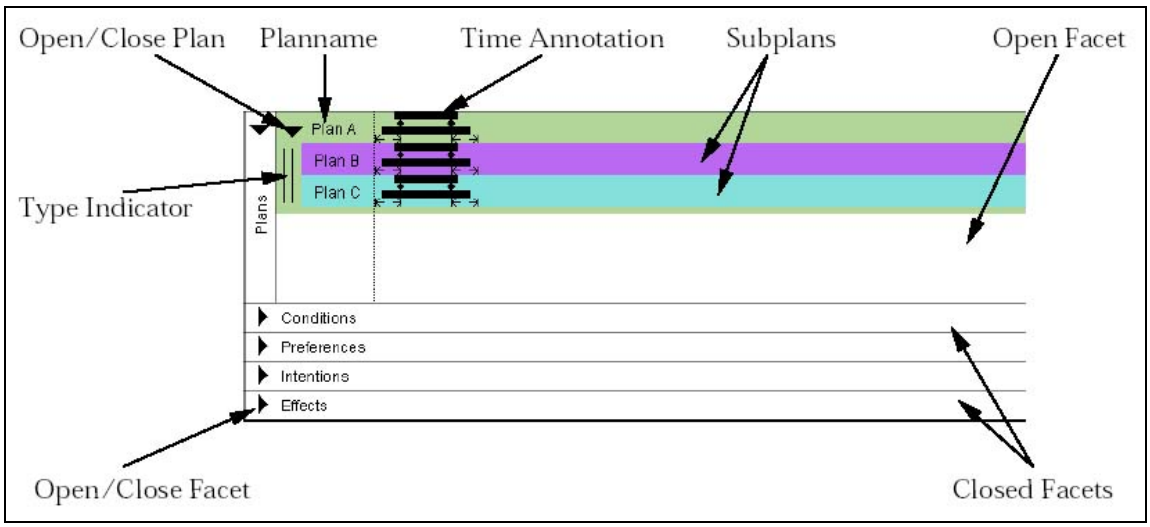

Figure 3.12: Anatomy of a plan in Temporal View (form [Kosara and Miksch, 2001, p. 12]).

The third view is the SOPOView. *SOPO* stands for *Sets Of Possible Occurrences*. The SOPOView is a graphical view to support the graphical propagation of temporal constraints.

3.2.3 GEM and GEM-Cutter

GEM stands for *Guideline Elements Model* and has been developed at Yale University, USA. With GEM a solution for the increasing demand of extracting knowledge from practice guidelines was provided.

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[14] For further information on LifeLines, [Plaisant et al., 1996] is recommended.

[15] *Time Annotations specify the complex temporal aspects of plans. It specifies four points in time relevant to a reference point: The earliest starting shift (ESS), latest starting shift (LSS), earliest finishing shift (EFS) and latest finishing shift (LFS). Two durations can also be defines: The minimum duration (MinDu) and maximum duration (MaxDu).* [Kosara and Miksch, 2001]

The purpose of GEM is to translate guidelines written in natural language to a "standard compute interpretable format and to ease the implementation of the guidelines through a markup process that does not require programming knowledge" [URL#5].

Modelling in GEM results in a xml-based guideline document model. As shown in Figure 3.13, the GEM model "can be depicted as a directed graph with Guideline Document as the root" [Shiffman et al., 2000, p. 490]. The most important concepts in the first level of the GEM hierarchy are identity, developer, purpose, intended audience, method of development, target population, knowledge components, testing, and review plan. Each of these elements again can have one or more additional levels of guideline constructs. In order to get full information about the detailed model of the knowledge components hierarchy, [Shiffman et al., 2000] is recommended.

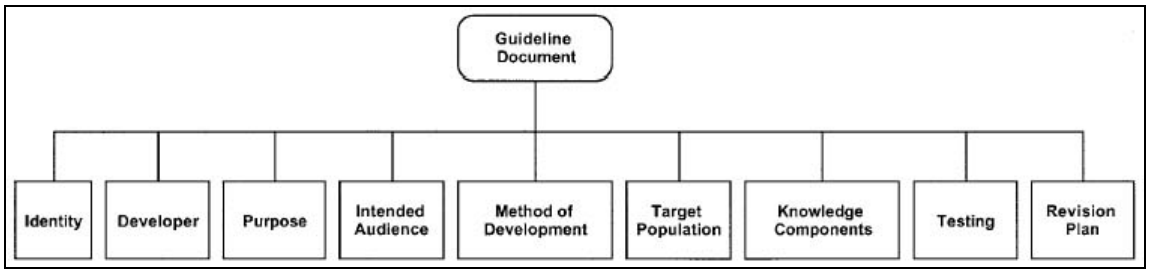

Figure 3.13: High-level concepts in the Guideline Elements Model (from [Shiffman et al., 2000, p. 491]).

The aim of GEM is the use of the model throughout the entire *guideline lifecycle*[16] and the encoding of these guidelines information.

GEM is a very successful model and will become standard "E2210-02, a document model for clinical practice guidelines".

With GEM also GEM-Cutter has been developed. GEM-Cutter is a modelling tool for facilitating markup of clinical guidelines.

For every person who is interested in GEM-Cutter, it is free for download at:

http://ycmi.med.yale.edu/GEM/GEM_%20cutter/gem_cutter.htm

Worth to be mentioned, that GEM-Cutter and GMT show several similarities. One target of both tools is to facilitate authoring clinical guidelines. Both tools support XML-editing.

Referring to the user interface of GEM-Cutter (see Figure 3.14) and GMT (see Figure 3.10), a view of the *original text file* (the guideline text) and a view of the *XML tree file* is provided. Additionally, both possess a UI part in which the elements used are described and can be manipulated.

[16] Referring to [URL#5], the lifecycle of a guideline contains development, dissemination, implementation, and maintenance.

It should also be mentioned, that if the operator uses GEM-Cutter in guideline modelling he will require "specific knowledge in the target guideline modelling language (in this case GEM)" [Votruba et al., 2004, p. 2].

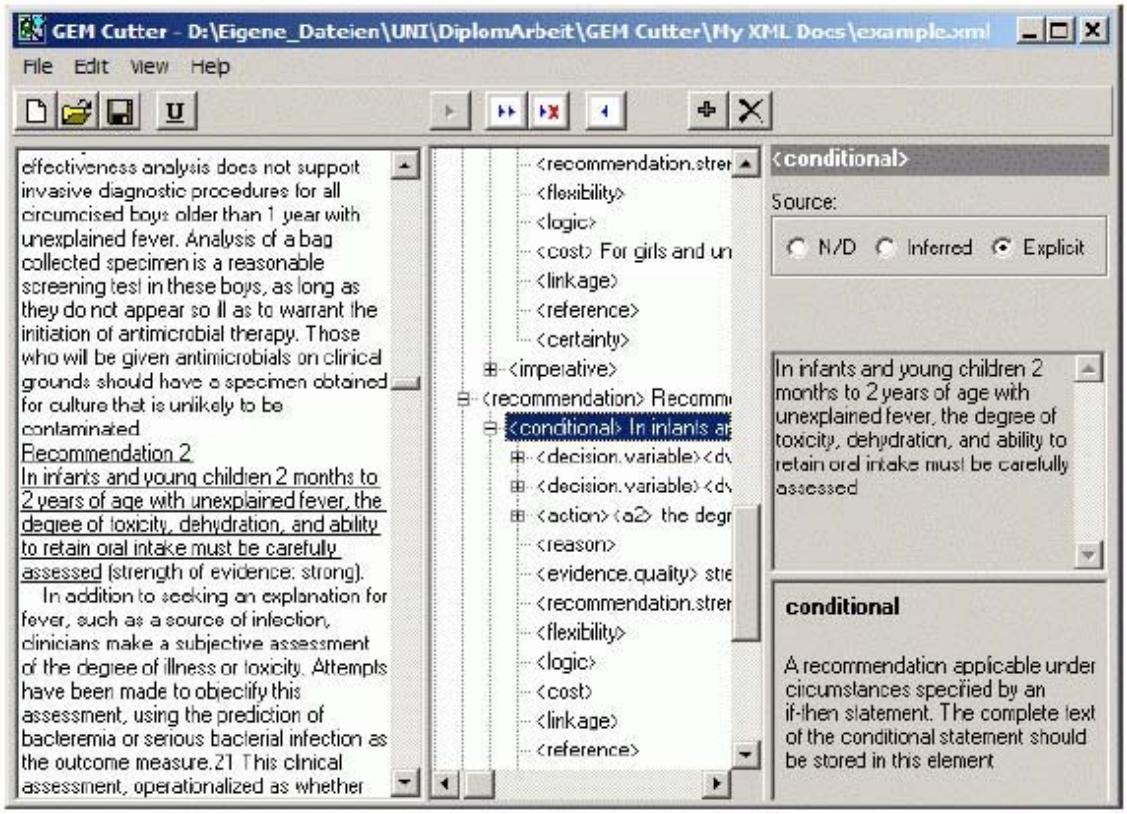

Figure 3.14: User Interface window of GEM-Cutter (from [Votruba, 2003b, p. 16]).

For further more details about GEM-Cutter, see the *GEM-Cutter Manual* [Polvani et al., 2000].

3.2.4 Stepper

The Stepper has been developed at University of Economics in Prague, Czech Republic by Vojtech Svátek and Marek Rùžièka.

[Svátek and Rùžièka, 2003, p. 2] describes the Stepper as "a methodology and software tool supporting the step-by-step formalisation process" of medical guidelines.

The term *formalisation process* (resp. the *Step-By-Step-Approach*) is the main concept of the Stepper and can be divided into *four steps*:

- Step 0 – viewing source document
- Step 1 – Assigning Knowledge Blocks
- Step 2+ - Knowledge block transformations
- Final Step – Export

An explanation would be too detailed and the *Stepper Documentation*[17] is recommended for further information.

In summary, it can be said, that the *Step-By-Step-Approach* is the transition from a plain text document containing knowledge to an operational representation.

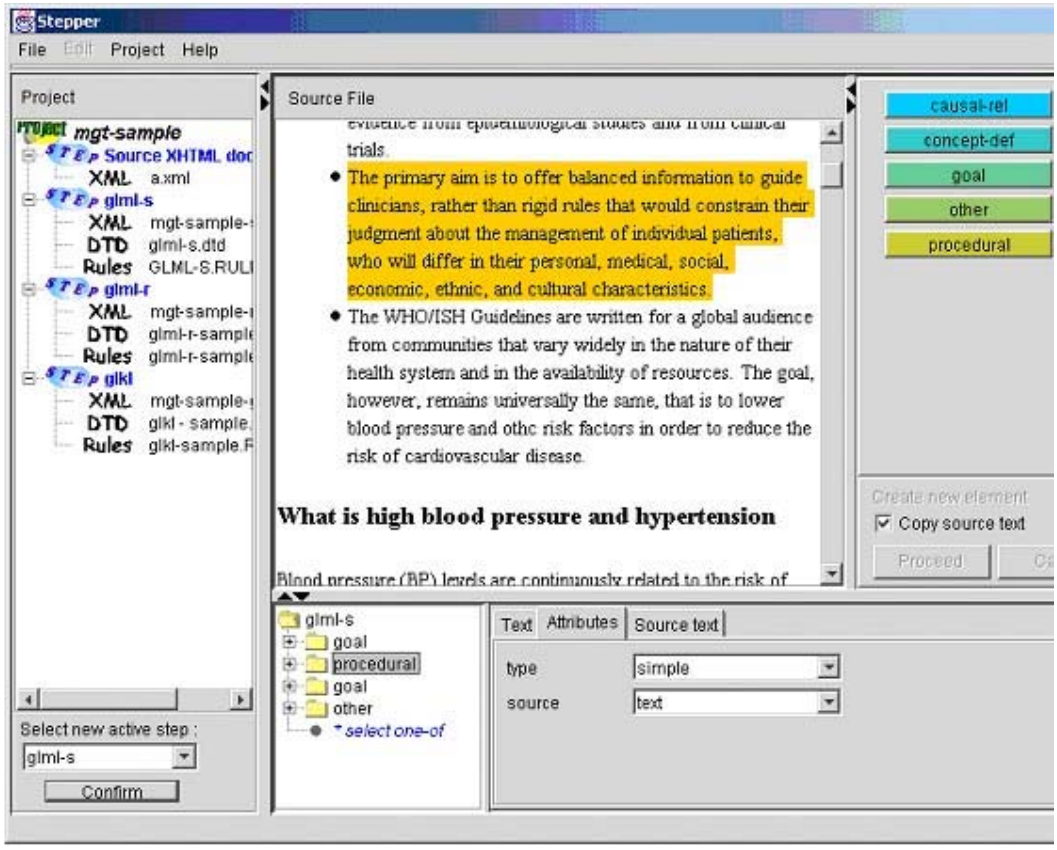

Figure 3.15: User Interface window of Stepper (from [URL#16])

Because of Steppers similarity to GMT and GEM-Cutter a brief description of the User Interface is given.

The user interface window is divided into tree parts (see Figure 3.15). The left side shows the *Project tree*. The right side shows one specific part of the *formalization process*. To show one specific part means, that it shows only *one Step* of the *formalization process* at once. Furthermore, the right side is divides into a section for the *source document* (upper part) and a section for the *destination document* (lower part).

The *destination file* (or document) becomes automatically generated during the *formalization process*. After the end of the "first step", the "second step" starts and the former *destination document* becomes the *source file* and the *transformation process* starts again. This process will be repeated until completion of all necessary steps.

[17] [URL#16]: http://euromise.vse.cz/stepper/aplikace_stepper/stepper_documentation.doc

It is remarkable, that Stepper provides a *Rule Editor*, where the user can define the transformation rules which enable the automation of large parts of the transformation process.

In conclusion, Stepper is a fairly new project and tested in the domain of cardiology.

3.2.5 DeGeL

In [Shahar et al., 2003, p. 122] the *Digital Electronic Guideline Library (DeGeL)* is defined as "a Hybrid, Multiple-Ontology Framework for Specification and Retrieval of Clinical Guidelines". Furthermore, [Shahar et al., 2003, p. 122] characterises DeGeL as a "Web-based, modular, distributed architecture, which facilitates gradual conversion of clinical guidelines from text to a formal representation in a chosen guideline ontology".

In the description given above, the term distributed architecture represents the set of tools which DeGeL combines. To achieve its aims DeGeL provides all necessary tools for storage, authoring, retrieval and application of clinical guidelines.

The second characterising term in the definition is the *hybrid meta-ontology*. Hybrid stands for *multiple* and the *hybrid meta-ontology* of DeGeL includes elements which can be found in all guideline ontologies, for example semantic classification, and domain knowledge.

The DeGel's HelpManual[18] comprises the *Guideline Uploading interface*, the *Uruz Interface* (editing tool), the *Vaidurya* (search and retrieval tool) and the *Axis Builder Interface* as the main tools.

For this thesis, the most interesting tool of DeGeL is the *Uruz Interface,* which will be specified hereafter.

The aim of Uruz is, "to handle conversion of the clinical guidelines from textual format (or creating de-novo Clinical guidelines) into semi-structured representation in accordance with the hybrid ontology developed for use in the clinical digital library" [URL#17].

Comparing the user interface of Uruz in Figure 3.16 with the user interface of Stepper in Figure 3.15, both user interfaces are divided in several parts. Each user interface has a window for the original source and the working source. The application flow of the conversion process of Uruz and Stepper is similar and demands knowledge from different experts.

[18] [URL#17]: http://medinfo.ise.bgu.ac.il/DeGeL2/HelpManual/Home.htm

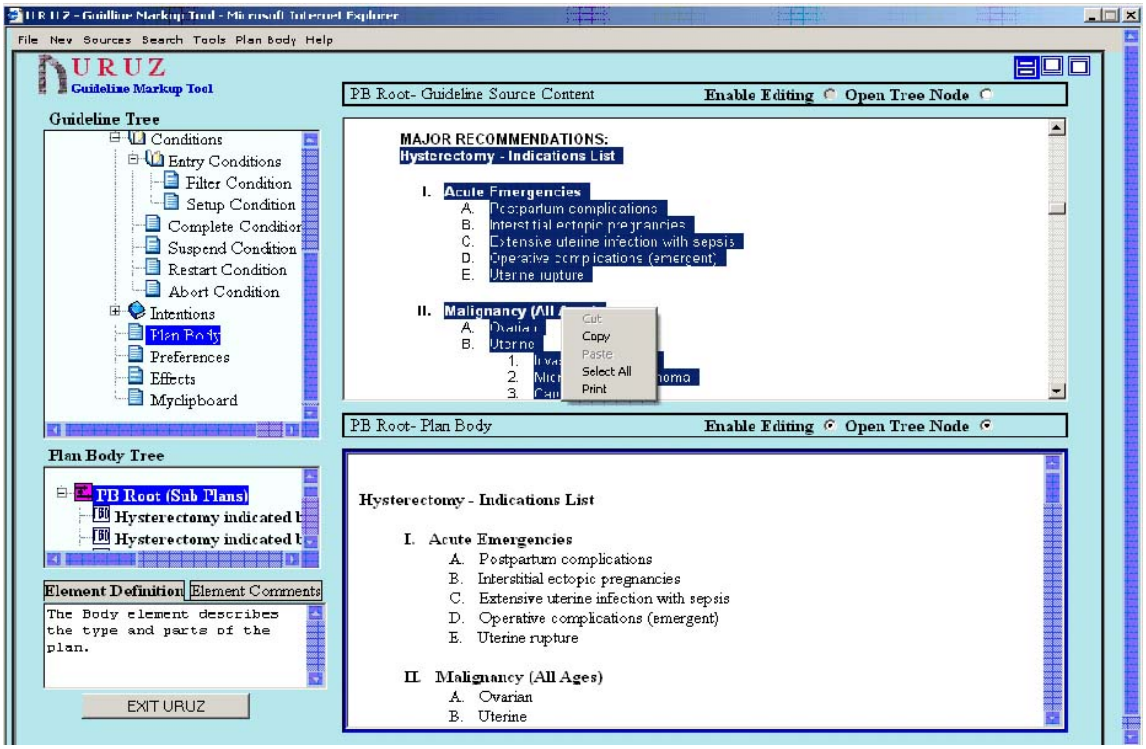

Figure 3.16: User Interface window of Uruz (from [URL#17]).

The application flow of Uruz works as follows: First, the guideline is converted to a *semantically semi-structured*[19] text and to a *semi-formal language*[20] by a medical expert. Second, the guideline will be transformed into a *fully formal representation*[21] by a knowledge engineer.

3.2.6 Protégé-2000

Protégé-2000 has been developed by Stanford Medical Informatics (SMI), USA. In [URL#12], Protégé-2000 is described as an "extensible, platform-independent environment for creating and editing ontologies and knowledge bases".

In other words, Protégé-2000 is a

- A knowledge-base editing tool which supports: constructing a domain ontology; designing customized knowledge-acquisition forms; entering domain knowledge.
- A platform which can be extended with graphical widgets for tables, diagrams, animation components to access other knowledge-based systems embedded applications;

[19] Semi-structured text uses the semantic roles of the formal language

[20] Semi-formal representation includes control structures and single-action specifications

[21] Fully structured, formal, machine-comprehensible language (e.g., Asbru or GLIF)

- A library which other applications can use to access and display knowledge bases.

Furthermore, in Protégé-2000 it is possible to show guidelines, which are written in GLIF, PRODIGY or PROforma.

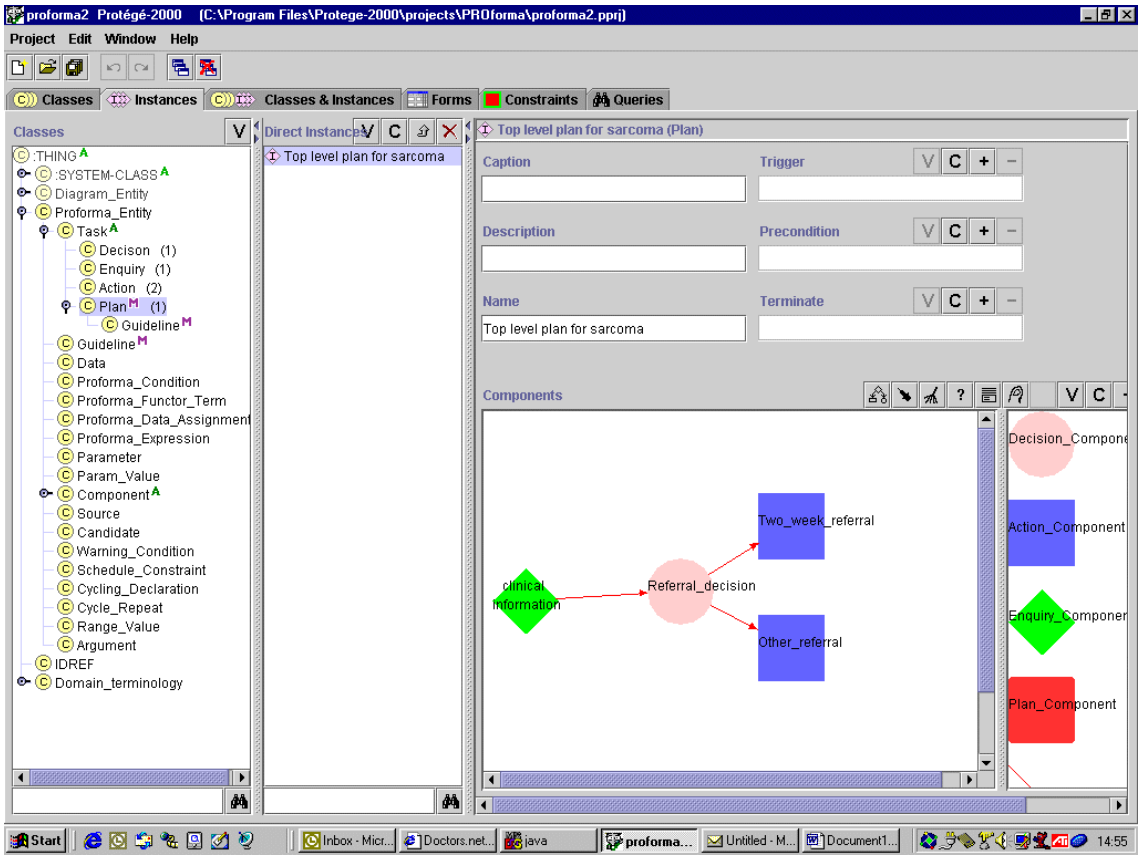

Figure 3.17: PROforma Guideline modelled in Protégé (from [URL#12]).

As it can be seen from Figure 3.17, the Protégé-2000 user interface is basically divided into three parts. The left part displays the class hierarchy as a tree. The middle part shows the list of instances for the just selected class and the right part provides a form for the selected instance.

It is remarkable, that Protégé2000 is an open-source, Java tool. For further information, the web site of Protégé-2000, http://protege.stanford.edu/ is recommended.

3.2.7 Comparison: GMT vs. other Tools

In order to compare the various modelling tools mentioned in this thesis, task orientation of the specific tools can be used. There are two groups. These are the authoring tools and the visualisation tools.

Among the visualisation tools are Asbru (see section 3.1.1) and PROforma (see section 3.1.2.8). The main advantage of the concept of visualisation is the presentation of complex data contents in an understandable way. Asbru is the only tool, which is specially intended to support physicians. All other presented tools additionally require a knowledge engineer. According to [Bury et al., 2000] a main requirement in developing PROforma was to use a concept that is intuitive for clinical user.

Regarding the authoring tools, a further distinction can be made. Here, authoring tools for supporting the formal-representation and authoring tools for modelling guidelines from scratch can be distinguished.

In the first group – tools for supporting the formal-representation – are GMT (see section 3.2.1), GEM-Cutter (see section 3.2.3), Stepper (see section 3.2.4) and DeGeL (see section 3.2.5).

All these tools start their translation processes and tasks with a plain text document containing knowledge. Due to the fact, that GEM-Cutter and GMT are XML-based tools, both support computer processing of the guideline information and both facilitate the markup process. However, GMT additionally provides the Link-Feature and the Macro-Feature. Stepper and DeGeL are tools, which are quite similar in their application flow. Both tools feature a translation process, which is separated into steps processed sequentially (resp. step-by-step). This application flow distinguishes Stepper and DeGeL from GMT and GEM-Cutter.

Finally, there are tools for supporting the authoring of clinical guidelines from scratch. One such tool is Protégé-2000 (see section 3.2.6). It provides a development environment, which supports modelling guidelines in GLIF, PRODIGY and PROforma. Furthermore, during the development of the modelling languages PROforma and Prestige, tools for authoring guidelines from scratch arose. Arezzo and Tallis are part of the PROforma technology and have the challenge to author, create and visualise guidelines. GAUDI and GLEAM belong to Prestige and their main task is also authoring guidelines.

Part II

Design and Implementation

4 The Guideline Selection Approach

The goal of this chapter is to receive a selection of representative guidelines for further work in this thesis. To fulfil this goal it is necessary to define some criteria – overall, medical, and technical – which are described in the following sections in detail. Furthermore the selection process itself and the results of the analysis are part of this chapter.

4.1 Criteria for Guidelines

4.1.1 The Overall Criterion

The basis of the guideline selection approach form the guidelines from the database of the National Guideline Clearinghouse (NGC). NGC provides more than 1000 guidelines where guidelines are represented in a brief and a complete summary. However, these summaries are already structured in a definite type which is the reason why these summaries do not fit in the following analysis. Out of this reason, an overall criterion has been defined which determines, that a guideline has to be available in *full plain text*.

4.1.2 The Medical Criteria

To start analyzing guidelines, it is necessary to choose several criteria in order to get only a small selection of a vast quantity of guidelines provided by NGC. Several medical criteria were defined to receive adequate guidelines. The following sections describe the medical criteria – Guideline Categories, Quality, Intended User and Clinical Specialities.

4.1.2.1 Guideline Category

The criteria guideline category is the core of a guideline. There exist various guideline categories, like diagnosis, evaluation, management, rehabilitation, treatment to name only a few. For this thesis, the guideline categories *Management*[22] and *Treatment*[23] were chosen.

4.1.2.2 Quality

Concerning the quality criterion of guidelines, it has been determined that guidelines should be evidence-based. Furthermore, guidelines should not be older than 5 years.

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[22] Guideline category management: "A guideline whose scope integrates diagnosis, treatment, and monitoring or follow-up" [URL#19].

[23] Guideline category treatment: "A guideline that recommends procedures or practices that are intended to relieve physical or mental illness or injury" [URL#19].

At NGC, the evidence-based nature of guidelines is represented using two selection possibilities. These are the "Methods Used to Assess the Quality and Strength of the Evidence" and the "Methods Used to Analyze the Evidence".

The first one, the "Methods Used to Assess the Quality and Strength of the Evidence" classifies the methods used by the guideline developer to determine what relative importance to give the evidence they obtain.

The second one, the "Methods Used to Analyze the Evidence" classifies the methods used by the guideline developer to evaluate the data in the evidence they obtain.

Appendix A shows the complete search details for the guidelines and provides information about the methods to meet the evidence-based character of the quality criterion.

4.1.2.3 Intended User

The intended user classifies the groups intended to use the guideline. It can be said, that all professions which are related to the health domain are possible users of guidelines. For this thesis, the intended users –Physicians, Nurses, Patients and Students – had been shortlisted. *Physicians* and *Nurses* were chosen, because for patients and students no guidelines which correspond to other medical criteria were available.

4.1.2.4 Clinical Speciality

Due to the many possibilities of clinical specialities but no specific knowledge in any clinical domain, the choice was a result of personal interest. Therefore, *Oncology* and *Radiation Oncology* were chosen.

4.1.3 The Technical Criteria

Having chosen guidelines in line with the medical criteria, it is necessary to choose several technical criteria to start with the analysis itself. For this purpose, modularity, structure, temporal dimension and intentions were defined as technical criteria. The next step was studying the chosen guidelines for the selected technical criteria.

4.1.3.1 Modularity

It can be assumed, that every guideline is composed in a kind of modularity.

The term modularity describes the property of an entity which can be decomposed into a set of smaller units.

Modularity in texts (resp. guidelines) is shown in the textual arrangement. These textual arrangements are mostly reflected in the paragraphs of texts.

The purpose of the analysis was, to detect modularity, and if possible, to classify the detected modularity.

4.1.3.2 Structure

Structure is the second technical criterion. Structural criteria enable the detection of text modules like tables, lists and algorithms.

Due to the evidence-based quality criteria, it has been expected that there are many such text modules.

4.1.3.3 Temporal Dimension

The criteria of temporal dimension should detect sections in guidelines, describing tasks (resp. methods of treatments) which concern a longer period of time. Due to the chosen guideline categories – Management and Treatment – it can be expected that temporal dimension will occur frequently. The aim of the following analyse is the verification of this expectation.

4.1.3.4 Intentions

Intentions are the last technical criterion. This criterion is not mandatory. This implies that it cannot be expected to find intentions in every guideline. The meaning of intentions is to find sections in guidelines which explicitly mention goals of medical treatment or management.

4.2 Choice of Guidelines

4.2.1 Guideline Base

According to the medical criteria, eighteen guidelines were selected. Except one, all of these guidelines are available in full plain text at different resources and thus they fulfil the overall criterion (see section 4.1.1). Appendix C provides links to the full plain text resource of each guideline.

4.2.2 Chosen Guidelines

Referring to the medical criteria of clinical speciality, all guidelines are embedded in the domain of oncology which means that the titles of the guidelines are about different kinds of cancer, chemotherapy and different therapeutic treatments.

On regarding the titles of the guidelines, nine of the eighteen guidelines cover different topics of lung cancer, which also meet the overall criterion (see section 4.1.1). Additionally, to these nine guidelines, one guideline about general treatment of cancer patients was chosen.

Recapitulating it can be said, that the close relationship of some guideline titles was the main criterion for choosing these ten guidelines, which form the guideline base for all following analysis.

4.3 Way of the Analysis

The purpose of the analysis is to provide answers to the following questions:

- Do the defined technical criteria – Modularity, Structure, Temporal Dimension and Intention – occur in guidelines?
- How often do these technical criteria occur in guidelines?
- Is it possible to detect special types or schemes of technical criteria?

Additionally for each technical criterion and type or scheme detected, an example will be presented and described in this thesis.

The analysing process itself was carried out as follows: Each guideline was read with regard to the technical criteria. During this examination, the important sections were marked and notes were taken parallelly.

Appendix C, which comprises the extracted information of each guideline in terms of

- The link to the available full text
- The guideline's length
- The type of modularity
- The number of structure elements in consideration of the guideline's length
- The occurrence of temporal dimension
- The occurrence of intentions

summarises the analysis.

4.4 Result of the Analysis

The following paragraphs present the result of the guideline analysis in detail and give examples of each technical criterion – Modularity, Structure, Temporal Dimension and Intentions.

4.4.1 Length of Guideline

It has to be mentioned, that the guideline's length was no selection criterion, but it turned out to be an important aspect in analyzing the guidelines. Referring to the guideline's length when classifying technical criteria – especially with the structure elements (see section 4.4.3) – it is possible to obtain comparability of guidelines.

In order to get an objective partition of the guidelines with respect to the length of the guideline, the concept of the Box Plot[24] was used.

[24] "A Box Plot, also known as a box and whisker diagram, is a basic graphing tool that displays centering, spread, and distribution of a continuous data set. It provides a 5 point summary of the data." [URL#20]

Box Plot 1 of Appendix D shows all steps of the calculation process in receiving a classification of the guideline's length in detail. The result of this process are three intervals. These intervals lead to the following classification:

- Interval 1: [1.5, 12[⇒ Short Guideline
- Interval 2: [12, 19] ⇒ Medium Guideline
- Interval 3:]19, 29.5] ⇒ Long Guideline

Grouping the guidelines according to this classification scheme shows that the guideline base consists of 2 short, 2 long and 6 medium guidelines. Which guideline forms part of which interval can be seen in Appendix C or Appendix D.

4.4.2 Modularity

As already mentioned in the general description of the criterion in section 4.1.3.1, every guideline is composed of a kind of modularity, which can be agreed upon after the analysis. Three different types of modularity were identified, which are presented in the following three sections. For each modularity type, an example is given which contains a description of the modularity and the module structure of an example guideline. Additionally, Appendix E provides the corresponding text sections, to get a better comprehension of each modularity type presented.

4.4.2.1 Modularity – Type 1

This type represents the simplest type of modularity. The textual arrangements of the guidelines are structured in paragraphs. All these paragraphs are clearly separated by content and independent by each other. The guidelines 1, 3, 5, 6, 9 and 10[25] are examples for this kind of modularity.

Table 4.1: Example Type 1

GL 1: Chemotherapeutic management of stage IV non-small cell lung cancer.
Description of the Modularity:
The guideline is structured in 11 questions, where each paragraph is concerned with one question and gives full answer to this question. Finally, the paragraph ends with special recommendations of the discussed paragraph content.
Module Structure:
Question 1: Are There Identifiable Prognostic Factors That Should Be Used When Selecting Patients For Systemic Chemotherapy? + Recommendation 1

[25] Appendix C shows the corresponding guidelines to the given numbers.

Question 2:	What Is the Evidence That Platinum-Based Chemotherapy Improves Survival? + Recommendation 2
… etc.	
Question 11:	What Are The Outcome Expectations and Adverse Effects Seen With Chemotherapy and How Do They Compare With the Natural History? + Recommendation 11

4.4.2.2 Modularity – Type 2

The next type, type 2 is based on type 1. Guidelines composed in modularity of type 2 are basically structured in two main parts. Each of these parts again consists of paragraphs, which are clearly separated by content and independent by each other. Type 2 can be found in the guidelines 2, 7 and 8.

Table 4.2: Example Type 2

GL 8: Treatment of stage II non-small cell lung cancer.			
Description of the Modularity:			
The basic subdivisions of the guideline are the two different types of stage II non-small cell lung cancer. Each of these types comprises again independent paragraphs.			
Module Structure:			
First Type:	(T1-2N1M0) Treatment Guidelines Stage II NSCLC		
		Intraoperative Management: Sleeve Resection v. Pneumonectomy	
			+ Recommendation
		… etc.	
Second Type:	(T3N0M0) Treatment Guidelines Stage II NSCLC		
		CT Assessment of Stage II (T3 [Chest Wall]) NSCLC	
			+ Recommendation
		… etc.	

4.4.2.3 Modularity – Type 3

Type 3 is also based on type 1, and consists of clearly separated and independent paragraphs. However, again, each paragraph consists of several sections and the sections of the different paragraphs have almost the same titles.

Table 4.3: Example Type 3

GL 4: Presentations of lung cancer with special treatment considerations.	
Description of the Modularity:	
Each paragraph in guideline 4 deals with a particular form of lung cancer. The sequence of the paragraphs again is a not crucial factor. The characteristic of type 3 is that each paragraph is structured in similar subparts, like a definition, workup, treatment, patient selection or recommendation.	
Module Structure:	
Paragraph 1	Pancoast Tumors
	Definition
	Workup
	Treatment
	Recommendations
Paragraph 2	T4N0,1M0 Tumors
	Patient Selection and Workup
	Outcomes After Surgery
	Recommendations
… etc.	
Paragraph 8	Isolated Adrenal Metastasis
	Patient Selection and Treatment Results
	Recommendations

4.4.3 Structure

As supposed in section 4.1.3.2, it was possible to find structural elements, such as lists (see Table 4.4), tables (see Table 4.5), and algorithms in each guideline. Additionally, two types of list elements – the numeration and the enumeration – were detected. Table 4.4 shows both of these types.

Table 4.4: Structure element: List

GL 1: Chemotherapeutic management of stage IV non-small cell lung cancer. Page 240, second column, first paragraph: Appendix
The enumeration:
… age and lung cancer, antineoplastic agents, combined; carcinoma, non-small cell lung; carcinoma, non-small cell lung/drug therapy; carcinoma, non-small cell lung/therapy; chemotherapy; clinical trials; combination chemotherapy; duration of therapy; lung neoplasms; lung neoplasms/drug therapy; lung neoplasms/therapy; outcomes; performance status and lung cancer; prognosis and non-small cell lung cancer; quality of life and lung cancer; randomized trials; sex and lung cancer; stage IV non-small cell lung cancer; weight loss and lung cancer.

GL 8: Treatment of stage II non-small cell lung cancer. Page 194, second column, first paragraph.
The numeration:
… (1) patients are more likely to complete the prescribed course of therapy; (2) chemotherapy will have a greater effect on the primary tumor while ist blood supply is still intact; (3) occult distant diseases will be treated sonner; and (4) surgical resection may be easier once the tumor has decreased in size.

Table 4.5: Structure element: Table

GL 8: Treatment of stage II non-small cell lung cancer. Page 203.

Table 1—*Subsets of Stage IIIA (N2)**

Subset	Description
$IIIA_1$	Incidental nodal metastases found on final pathologic examination of the resection specimen
$IIIA_2$	Nodal (single station) metastases recognized intraoperatively
$IIIA_3$	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
$IIIA_4$	Bulky or fixed multistation N2 disease

*Adapted from Ruckdeschel.[2]

The maximum number of structural elements in one guideline was thirteen. In order to get a kind of classification and a possibility to compare the guidelines to each other in more detail, the occurrence of structural elements of each guideline was relativised to the guideline's length. The resulting ratio, structural element per page, was the basis of

the Box Plot 2 in Appendix D. The following classification scheme was the result of the calculation process:

- Interval 1: [0, 0.214[⇒ Small number of structural elements
- Interval 2: [0.216, 0.6] ⇒ Medium number of structural elements
- Interval 3:]0.6, 1.179] ⇒ Large number of structural elements

Appendix C provides the information, which guideline is part of which interval.

Before starting analysing guidelines, the author of this thesis had expected various algorithm elements. However, the result of the analysis was different from the expectation. Except in one guideline, no algorithm elements were found in the eighteen guidelines from the detailed search (see section 4.2.1). Due to the main criteria from section 4.2.2, this guideline was not taken into consideration for further analysis.

4.4.4 Temporal Dimension

The technical criterion temporal dimension was found in each guideline. However, it has to be said, that the number of the occurrence of this criterion was lower than expected when choosing treatment and management as guideline category (see section 4.1.3.3). Definitely, one reason for this marginal occurrence of temporal dimension is the evidence-based character of the chosen guidelines.

It has to be stated, that there are many temporal statements in each guideline. However, most of them refer to a definite point of time. Such temporal statements do not correspond to the character of a temporal dimension (see section 4.1.3.3) and consequently, these statements are not suitable for temporal dimensions.

The maximum number of temporal dimension in one guideline is 5. Due to this low number the existence of temporal dimensions (see Appendix C) is only recorded with Yes or No. Another result of the analysis was that two types – the Simple and the Complex one – of temporal dimension were detected.

4.4.4.1 Type 1 – The simple Temporal Dimension

The simple type of temporal dimension can be characterized as an ordinary sequence of actions. Table 4.6 shows an example of the simple type.

Table 4.6: An example of simple Temporal Dimension

GL 1: Chemotherapeutic Management of Stage IV Non-small Cell Lung Cancer. Page 234, second column, third paragraph.
The proportion of patients receiving second-line therapy following disease progression after receiving first-line platinum-based therapy has not been well-described but is generally < 50%.

4.4.4.2 Type 2 – The complex Temporal Dimension

It can be said, that the complex type of temporal dimensions is made up of a nested structure of several actions.

Such examples of complex temporal dimensions in guidelines are shown in Table 4.7.

Table 4.7: Two examples of complex Temporal Dimensions

GL 5: Small cell lung cancer. Page 263, first column, first paragraph.
… oral etoposide for 14 days combined with carboplatin on day 1 every 28 days; abbreviated chemotherapy with CAV in full doses followed 3 weeks later by chemotherapy with cisplatin …

GL 9: Treatment of stage IIIA non-small cell lung cancer. Page 212, first column, second paragraph.
… three radiotherapy fractions were delivered per day in a continuous schedule (7 days rather than 5 days per week) over 12 days to a total dose of 50.4 Gy or 54 Gy.

4.4.5 Intention

As already supposed in section 4.1.3.4, it was not possible to detect intentions in each guideline. Two guidelines (guideline 5 and 7) did not show intentions. Furthermore, it was difficult to detect them. In case of intentions (see Table 4.8 for examples of Intentions), they were only detected in a sub-sentence.

Table 4.8: Examples of Intentions

GL 1: Chemotherapeutic management of stage IV non-small cell lung cancer. Page 227, first column, first paragraph.
… , cure remains the goal in fit patients, …

GL 3: Lung cancer. Palliative care. Page 286, first column, paragraph: Recommendations for Pain Control.
… pain can be relieved safely and effectively.

The maximum value of intentions in one guideline is 6 times. Due to this low number of occurrence and the fact that Intentions were not mandatory, Appendix C provides only the information of the existence of intentions in guidelines with Yes or No.

5 The Pattern Approach

In this chapter the detection of general text pattern will be discussed. A text pattern can be defined as a "recognizable part" in almost all texts with no relationship to the content.

The analysis can be performed by two different approaches. The first approach is the analysis of the structure of the text. The goal of this approach is to find the smallest possible structure pattern. The second approach focuses on simple text elements. The goal of this approach is to identify single recurring element pattern.

5.1 Possible Design Pattern in Texts

This section is based on the knowledge of text linguistics[26] and [URL#21] provides knowledge about the structure of texts and elements in texts. In the following sections, the basic distinction between the structure of a text and elements in texts is also the differentiation between the possible text pattern.

5.1.1 The Structure of a text

The structure of a text consists of different text parts. These text parts have a certain relationship to each other. These two constituents of the structure of a text – the text parts and their respective relationship – will be described.

5.1.1.1 The Text Component

The different parts of a text can be seen as the text components. Text components are parts which are relatively independent in terms of thematic and semantic. There exist different types of text components which can be classified in chapter, section and paragraph.

- Chapter: A Chapter can consist of sections and paragraphs.
- Section: A Section is the term used for the level between the chapter and the paragraph.
- Paragraph: A Paragraph is placed behind the section and is the smallest unit of the text components.

[26] In [Carstens, 2003, p. 23] text linguistics is defined as follows: "text linguistics is "… devoted to describing how texts are created and understood" and in doing this it studies the "… defining properties of texts – what constitutes their textuality or texture …".

5.1.1.2 The Arrangement of a Text

The arrangement of a text shows the relationship between the single text components (see section 5.1.1.1). The complexity of a text is the most important criterion for the arrangement of a text. Complex texts are often arranged in multiple hierarchical levels. In contrary, simple texts only consist of a flat structure with only a few levels. These levels – Hierarchical and Flat – correspond to the text components – Chapter, Section and Paragraph.

5.1.1.3 Identified design pattern in texts

To get an appropriate text pattern for the structure of a text, the basic description of the text components was used. According to these definitions, the *Paragraph* was identified as a possible text pattern, because it is the smallest unit and all other text components can be reduced to it.

5.1.2 Text Elements

For text elements, two different kinds of elements are possible. The first class of elements consists of sentences or sequences of sentences. An appropriate example for this class is a special formatted text. The second class of text elements contains special text elements such as lists and tables.

Due to the fact, that this is only a general approach of detecting pattern, it is difficult to specify exact element pattern.

Therefore, the next two sections only give general introduction in formatted text and list and table elements. The final definition of pattern will be done in chapter 6, where clinical guidelines are the basis for text analysis.

5.1.2.1 Formatted Texts

Formatted texts are special sequences of sentences or only parts of a sentence, which are characterized by a particular syntax or semantic. Each kind of text provides its own formatted text constructs and therefore it is very difficult to identify a general pattern for formatted texts. In section 6.3, formatted text pattern are presented for the text class of clinical guidelines

5.1.2.2 Lists and Tables

A further classification of text elements are lists and tables. Such elements can be found in almost every text. These elements are also extremely important in scientific papers, such as guidelines. List and table elements are qualified for presenting facts, scientific results and achievements in an appropriate way.

6 Detected Pattern in Guidelines

In both chapters, 5 and 6, the detection of pattern is the main objective. However, in opposition to the introduced pattern in chapter 5, which refer to texts in general and are universally valid, the following pattern in chapter 6 apply to a specific text class – clinical guidelines – and are only significant for this special class.

In the following sections, the detected pattern in guidelines – Structure, Temporal and Element pattern – are presented.

6.1 Structure Pattern

The structure pattern is the most important one. As already mentioned in section 4.1.3.1, where the technical criterion of modularity is described and also mentioned in section 4.4, where the results of the guideline analysis are presented, it can be stated, that each guideline is based on a specific structure. The types of modularity described in section 4.4.2 exactly correspond to the structure types detected in guidelines. Therefore, the types 1, 2 and 3 of modularity were used for the derived structure pattern which are presented as follows. Characteristics of all types can be found in section 4.4.2. Detailed text examples for each modularity type (resp. pattern type) are given in Appendix E.

Figure 6.1: Pattern 1: Modularity Type 1 - "The Independent Structure"

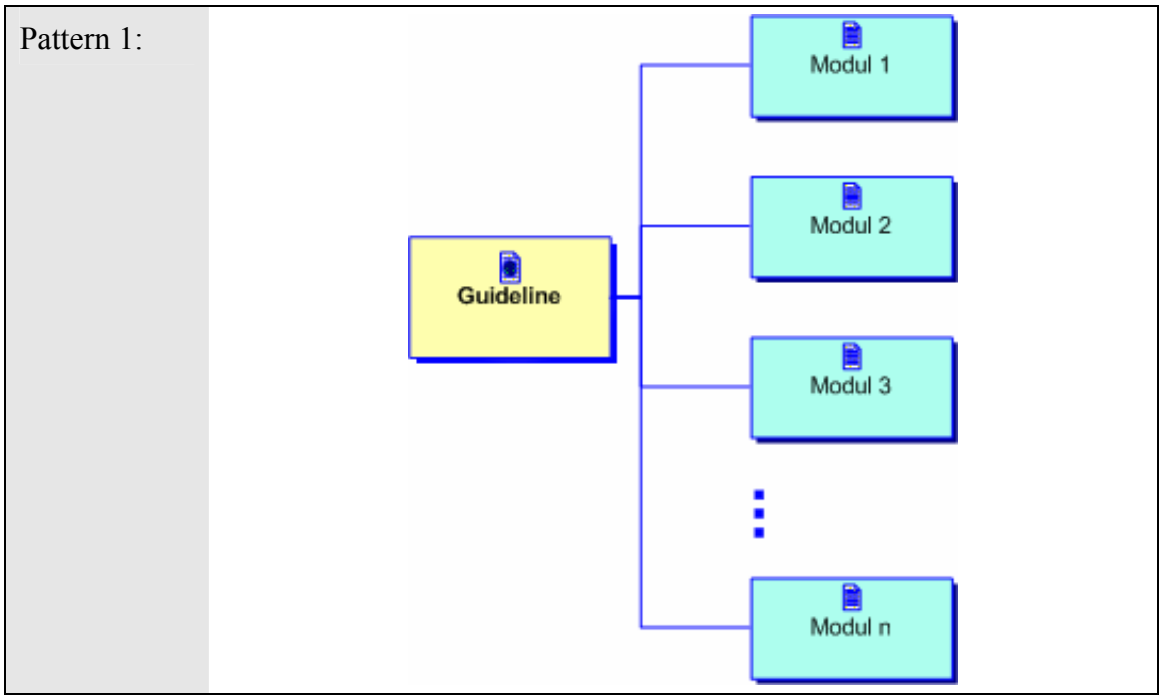


Figure 6.2: Pattern 2: Modularity Type 2 - "The XOR Structure"

Pattern 2:

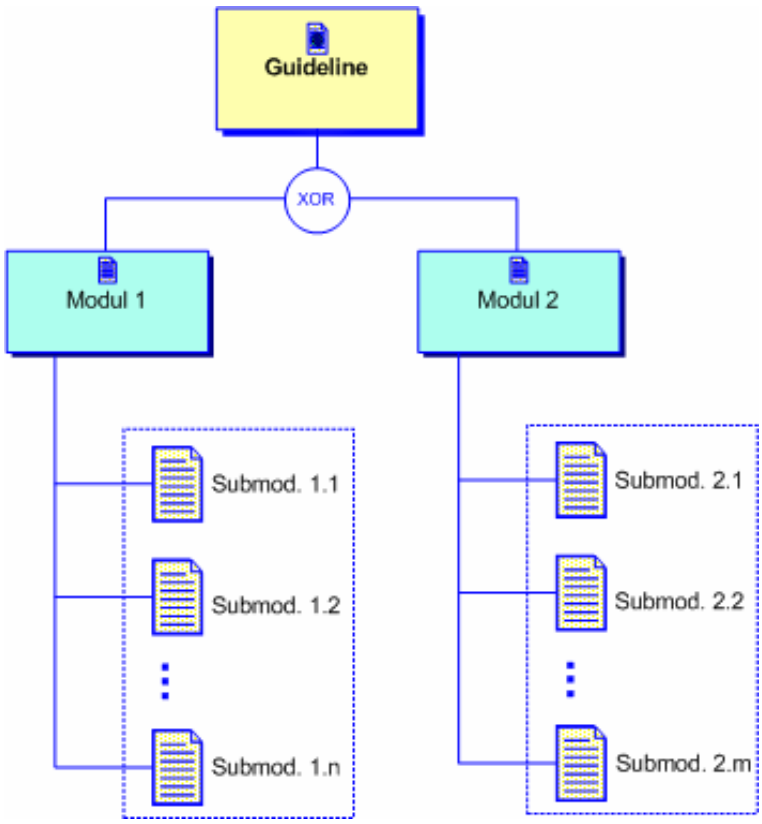
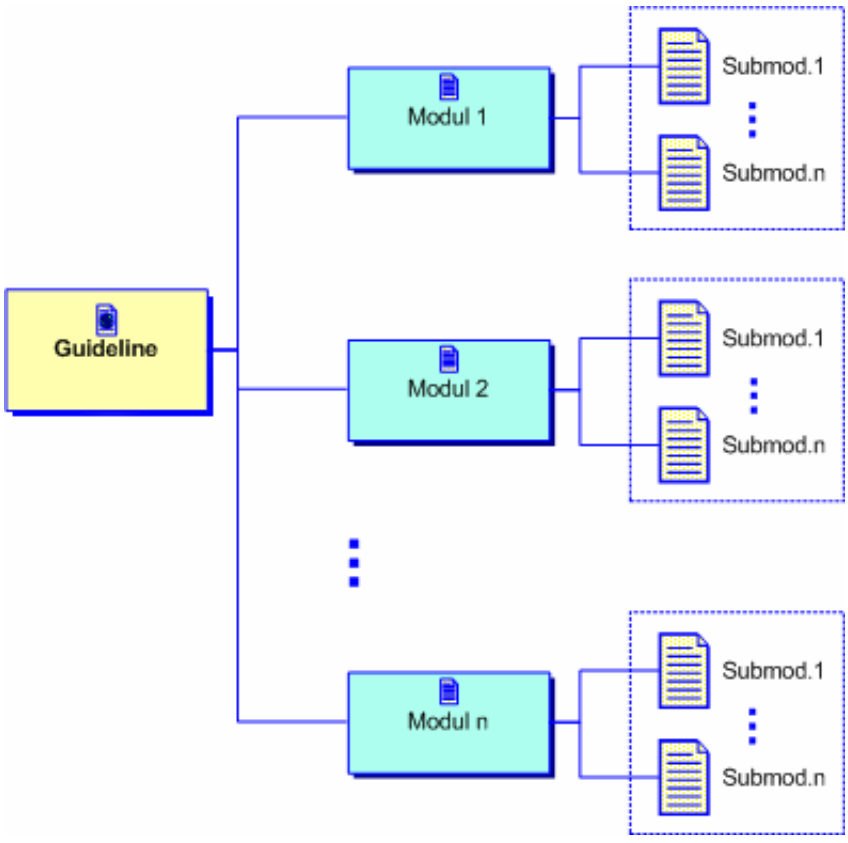


Figure 6.3: Pattern 3: Modularity Type 3 - "The Recurring Structure"

Pattern 3:



6.2 Temporal Pattern

Temporal information in clinical guidelines is very important. Due to the scientific character of clinical guidelines, they often present clinical trials and statements which include temporal data. It was possible to distinguish between single temporal statements and temporal statements concerning activities.

Pattern 4 from Figure 6.4 presents single temporal statements which frequently occur in the examined guidelines.

Figure 6.4: Pattern 4: "The Temporal Statement"

Pattern 4:	
Example: GL 1, page 229, first and second column	… The medina survival time of patients receiving BSC was *3.6 months* (range, *2.4 to 4.9 months*) in these 10 trials, providing a benchmark for survival in patients with untreated, advanced NSCLC. The median survival time of the treated patients was *6.5 months* (range, *4.7 to 8.5 months*). … … The end point analyzed was the number of deaths at *3-month intervals* up to *18 months*. There was a significant reduction in mortality for up to *6 months* for chemotherapy vs BSC. …

In the following two Tables, pattern for temporal activities are shown. These activities embody temporal dimensions, as they were described in section 4.1.3.3. Two different types of temporal activities were identified. The first type of temporal activity consists of several, simple actions arranged in a sequence. The second type of temporal activity also consists of several actions, however, one of these actions may again consist of one or more actions. Therefore, this temporal activity is classified as complex temporal activity. These two temporal activity types correspond to the two detected types of temporal dimension described in section 4.4.4. In Figure 6.5 and Figure 6.6 the two deduced pattern are presented. Appropriate text examples for the two pattern are given in section 4.4.4.1 and 4.4.4.2.

Figure 6.5: Pattern 5: Temporal Dimension Type 1 – "The Simple Temporal Activity"

Pattern 5:	

Figure 6.6: Pattern 6: Temporal Dimension Type 2 – "The Complex Temporal Activity"

Pattern 6:

6.3 Element Pattern

Besides the structure and temporal pattern in guidelines mentioned above, also element pattern were detected. These deduced element pattern refer to frequently used text sequences and text instruments in guidelines with the aim of

- structuring the text.
- presenting facts, scientific results, or achievements.
- using preformatted sequences of text, sentences or words.

The following abbreviations are used in the element pattern figures:

- LE … List Element
- AT … Attribute
- V … Value

6.3.1 Headlines

Headlines were the first detected elements. Headlines are also possibilities for structuring the text and make it better readable.

It depends on the content and on the author of a guideline where headlines are placed in a text (resp. in a guideline). Due to these two unpredictable factors, it is only possible to define a possible layout pattern for headlines. Figure 6.7 shows such a headline pattern, which provides different hierarchical levels.

Figure 6.7: Pattern 7 – "The Headlinepattern"

Pattern 7:

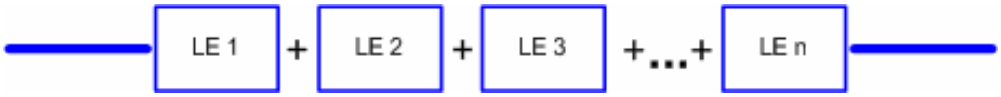
6.3.2 Lists and Tables

As mentioned in the introducing description of element pattern, pattern for presenting facts, scientific results or achievements were detected. Lists and tables were such elements.

Within list elements it was possible to distinguish between the enumeration list (see Figure 6.8 with Pattern 8) and the numeration list (see Figure 6.9 with Pattern 9), which are the same list types as in section 4.4.3. Examples for the two list types are also given in section 4.4.3.

Figure 6.8: Pattern 8 – "The Enumeration-List"

Pattern 8:



LE … List Element

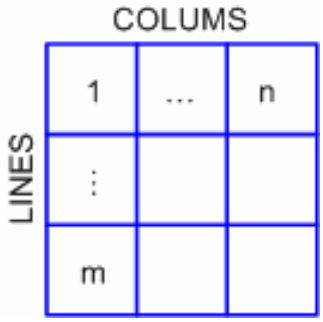
Figure 6.9: Pattern 9 – "The Numeration-List"

Pattern 9:

Table elements are extremely useful elements in scientific papers to present detailed facts. But almost each used table differs from each other, which shows the dynamic character of the table element. It is only useful to reduce tables to its two components – Columns and Lines – which are the parts of Pattern 10 in Figure 6.10.

Figure 6.10: Pattern 10 – "The Table"

Pattern 10:



6.3.3 Formatted Text

The last class of element pattern detected in guidelines were formatted texts. As already described in section 5.1.2.1, formatted texts are special sequences of sentences or only parts or a sentence. In the following sections, the detected formatted text pattern in guidelines are presented. For each formatted text element, the pattern and an example is given.

6.3.3.1 Formatted text with a programming character

Two structures with a programming character were detected. The first formatted text pattern, which was deduced form the guidelines is shown in Figure 6.11, is similar to the well-known IF-Then relationship. In Figure 6.12 the second derived pattern is shown, and it describes a specific relationship between two terms. The first term (the attribute) always receives a suitable character. In programming this is known as the Attribute-Value combination.

Figure 6.11: Pattern 11 – "The IF-Then Pattern"

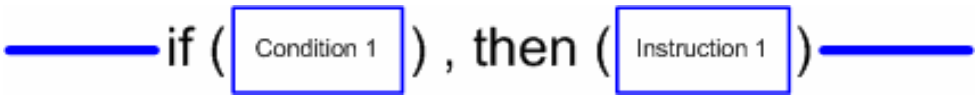
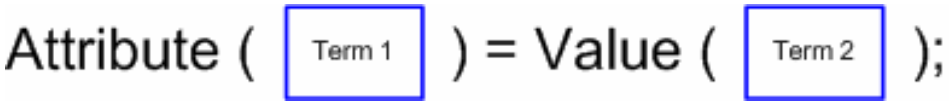
Pattern 11:	
Example: GL6 (p. 177)	If the lesion was < 1.0 cm and the margin was visible, complete response was achieved in 98% of cases.

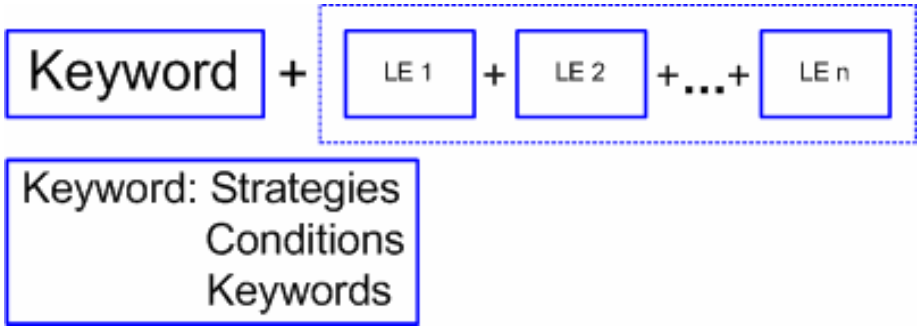
Figure 6.12: Pattern 12 – "The Attribute-Value Pattern"

Pattern 12:	
Example: GL6 (p. 177)	Level of evidence, poor; benefit, moderate; grade of recommendation, C

6.3.3.2 Formatted text in combination with a list

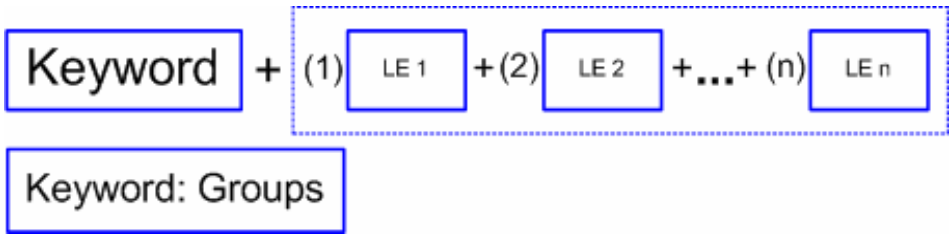
This following detected text elements are a combination of a formatted text and list pattern. The formatted text component is a special keyword (such as strategies, conditions, categories or keywords) and this special keyword is always followed by a list pattern as defined above, which can either be the "Enumeration-List" (see Figure 6.8) or the "Numeration-List" (see Figure 6.9). Due to this two possibilities in list elements, two pattern were defined, which are presented in Figure 6.13 and Figure 6.14 with its different formatted text occurrences.

Figure 6.13: Pattern 13 – "The Text+Enumeration-List Pattern"

Pattern 13:	

Example:	
Strategies (GL3, p.294)	… used various strategies. These include breathing control, activity pacing, relaxation techniques, and psychosocial support, …
Conditions (GL3, p.296)	… conditions such as COPD, cardiac failure, loss of lung tissue, etc.
Keywords (GL6, p.176)	Key words: carcinoma in situ; cryotherypy; interventional bronchoscopy; lasers

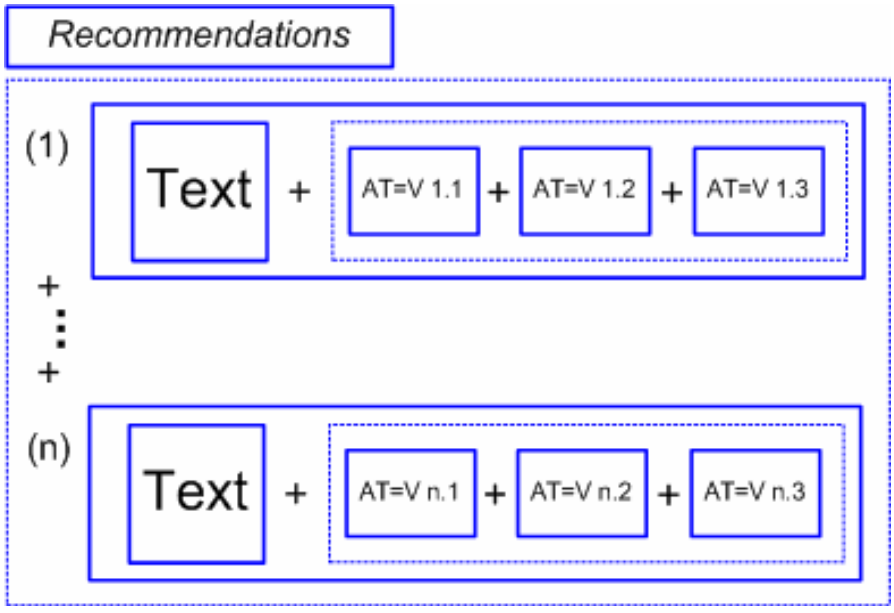
Figure 6.14: Pattern 14 – "The Text+Numeration-List Pattern"

Pattern 14:	
Example: Groups (GL5, p. 260)	… groups: (1) cisplatin vs no cisplatin (1 trial); (2) etoposide (without cisplatin) vs no etoposide (17 trials); (3) cisplatin/etoposide vs no cisplatin/etoposide (9 trials); and (4) cisplatin/etoposide vs etoposide (9 trials).

6.3.3.3 Compositions of Element Pattern

The third class of detected pattern in guidelines are compositions of formatted text elements and different pattern, which were already introduced in the section of Element Pattern. In Figure 6.15 to 6.17 the derived composition pattern are introduced.

Figure 6.15: Pattern 15 – "The Recommendation"

Pattern 15:	

Pattern used:	**Pattern 7: The Headlinepattern** Headline = Recommendations; Recommendations **Pattern 9: The Numeration-List** LE 1 ⇒ (Text + Enumeration-List 1); LE 2 ⇒ (Text + Enumeration-List 2); LE n ⇒ (Text + Enumeration-List n) **Pattern 12: The Attribute-Value Pattern** Term 1 = Attribute (AT) and Term 2 = Value (V) ⇒ AT=V **Pattern 8: The Enumeration-List** LE 1 ⇒ AT=V 1; LE 2 ⇒ AT=V 2; LE 3 ⇒ AT=V 3
Example: GL6 (p. 177)	*Recommendations* 1. For Patients with early superficial squamous cell carcinoma who are not surgical candidates, PDT should be considered as a treatment option. Level of evidence, fair; benefit, moderate; grade of recommendation, B 2. For Patients with early superficial squamous cell carcinoma who are surgical candidates, the use of PDT appears to be a promising treatment, but more experience is needed to compare PDT to surgical outcomes. Level of evidence, poor; benefit, none/negative; grade of recommendation, I

Figure 6.16: Pattern 16 – "The Definition"

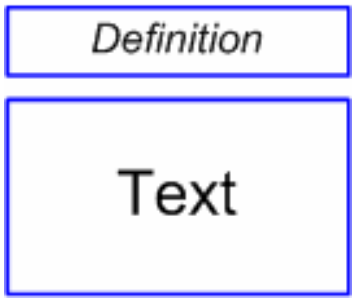
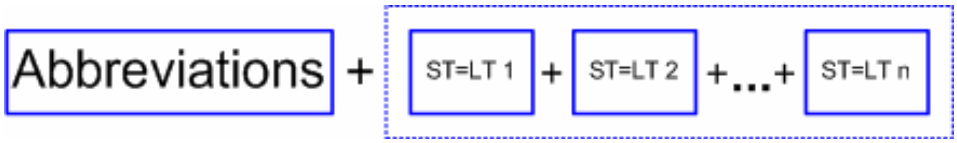
Pattern 16:	
Pattern used:	**Pattern 7: The Headlinepattern** Headline = Definition
Example: GL4 (p. 251)	*Definition* A metachronous second focus of lung cancer is easily defined as a second primary lung cancer when the two tumors are different histologic types. When …

Figure 6.17: Pattern 17 – "The Abbreviation List"

Pattern17: Pattern used:	 **Pattern 12: Attribute-Value Pattern** Term 1 = Short Term (ST) and Term 2 = Long Term (LT) ⇒ ST=LT **Pattern 13: Text+Enumeration-List Pattern** Keyword = Abbreviation; Abbreviations LE 1 ⇒ ST=LT 1; LE 2 ⇒ ST=LT 2; LE n ⇒ ST=LT n
Example: GL8 (p. 188)	Abbreviations: CI = confidence interval; LCSG = Lung Cancer Study Group; NSCLC = non-small cell lung cancer

6.3.3.4 Special case of formatted text

Finally, a special kind of text element was detected. Due to the content based character of this text element, it was only detectable within the context of the guidelines. Because of the recurrence of these elements a separate pattern was introduced. The technical criterion of intentions in section 4.1.3.4 corresponds to “The Intentions-Pattern”, which is shown in Figure 6.18.

Figure 6.18: Pattern 18 – "The Intentions-Pattern"

Pattern 18:	

7 Selected Pattern to develop Macros (Patterns)

The purpose of this chapter is to match the detected pattern from the general pattern approach (see chapter 5) and the specific detected pattern in guidelines (see chapter 6). The aim is to select some pattern, which are suitable for the implementation in the guideline modelling method Asbru (see section 3.1.1) and further usage as Macros (resp. patterns) in the guideline modelling tool GMT (see section 3.2.1).

For the exemplary implementation in Asbru and creation of macros for GMT respectively, the structure pattern from section 6.1 were chosen. The following sections present the process of obtaining macros of these detected structure pattern, which are:

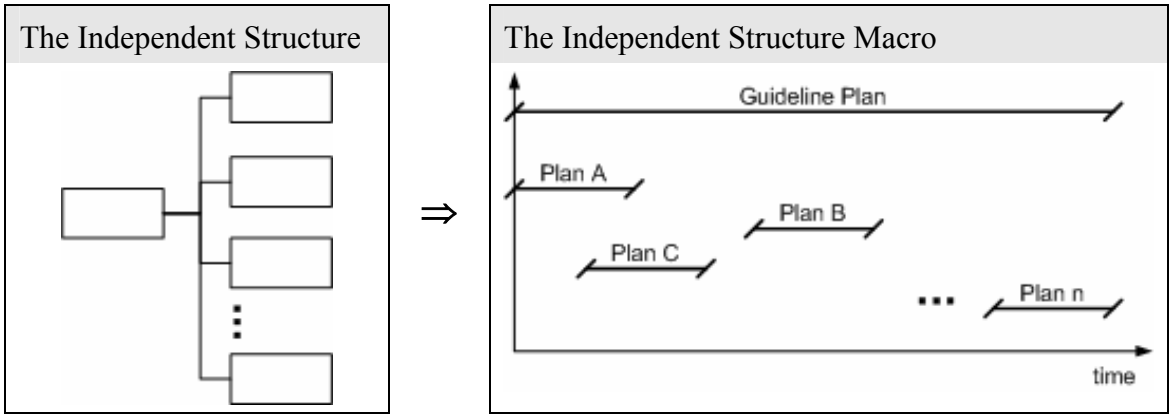
- The Independent Structure (Pattern 1 from Figure 6.1)
- The XOR Structure (Pattern 2 from Figure 6.2)
- The Recurring Structure (Pattern 3 from Figure 6.3)

Each of these three structure elements results in a specific Asbru plan type, which were shortly introduced in section 3.1.1, where the plan representation language Asbru was presented and which will be each explained in more detail when introducing the macros in the following sections. At this place it should be stated, that all Asbru specific information in the following sections is based on the *Asbru Reference Manual* [Seyfang et al., 2002].

7.1 The Independent Structure Macro

The independent structure pattern leads to the *Independent Structure Macro*. Figure 7.1 shows a schematic presentation of the basic pattern structure and the resulting plan scheme – the unordered plan – in Asbru.

Figure 7.1: Schematic presentation of the "Independent Structure Macro".



An unordered plan consists of a parent plan and several plans of its children. During the execution of an unordered plan, there is no ordering between the single steps. The children's plans may overlap or not, and each of them may start and end whenever appropriate. However, it is to consider that each of the children's plans starts after the start of the parent plan and the parent plan finishes not before the last of the children is finished.

In Figure 7.1 it can be seen, that the independent structure macro consists of a parent plan, which is the guideline itself and several plans of its children. The execution phase of the subplans (resp. children's plans) shows no ordering between the single execution steps. If all children's plans are executed, the parent plan is completed.

7.2 The XOR Structure Macro

The second macro which will be implemented is the *XOR Structure Macro* which is based on the XOR structure pattern. The best practice to receive an XOR structure in Asbru is the any-order plan. The decision with which plan the execution phases starts is done in the pre-selection phase. In the pre-selection phase the plans are not synchronized. The plan which first passes the pre-selection phase is executed. Passing the pre-selection phase means to reach the plan state "activated" of the execution phase.

Figure 7.2: Schematic presentation of the "XOR Structure Macro".

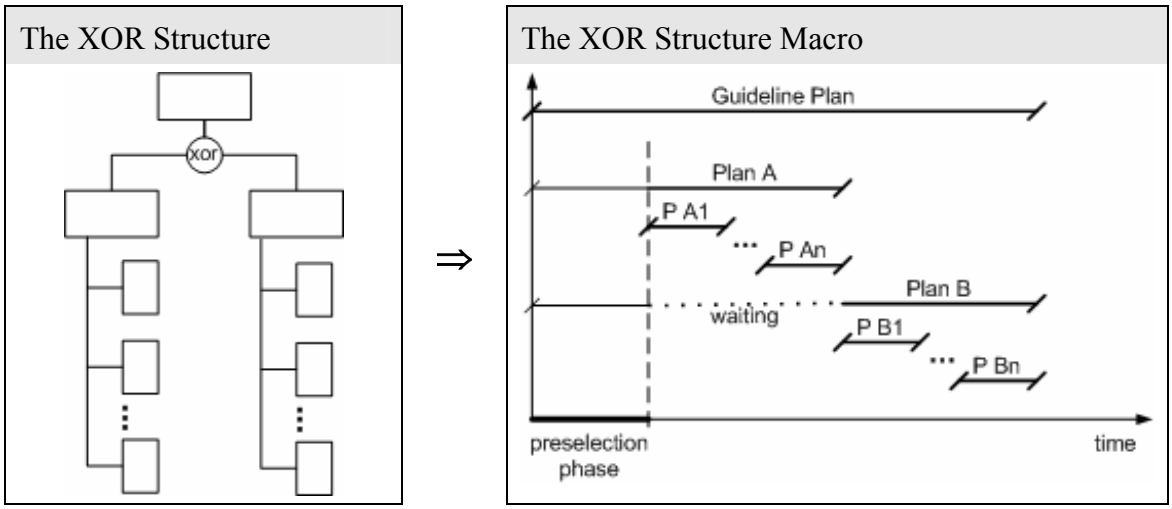


Figure 7.2 shows the structure of the XOR structure macro with its Asbru plan representation. It consists of a parent plan (the Guideline Plan) and two children's plans (Plan A and Plan B). Each of the two children's plans again consists of several children's plans with a number from 1 to n.

This children's children relation embodies the independent structure macro with its unordered plan execution.

The parent children relation is a XOR structure which is achieved through the any-order plan. The decision which plan is executed first is taken in the pre-selection phase. While

executing one child plan, the other one is waiting. If the two children's plans are executed, the parent plan is completed.

7.3 The Recurring Structure Macro

The third macro is the *Recurring Structure Macro* and is based on the recurring structure pattern. The respective Asbru plan for this macro is not as easy to detect, as for the already introduced macros. By splitting the recurring structure in two independent structures (resp. plans), the Asbru plan structures can easier be detected.

Figure 7.3: Schematic presentation of the "Recurring Structure Macro".

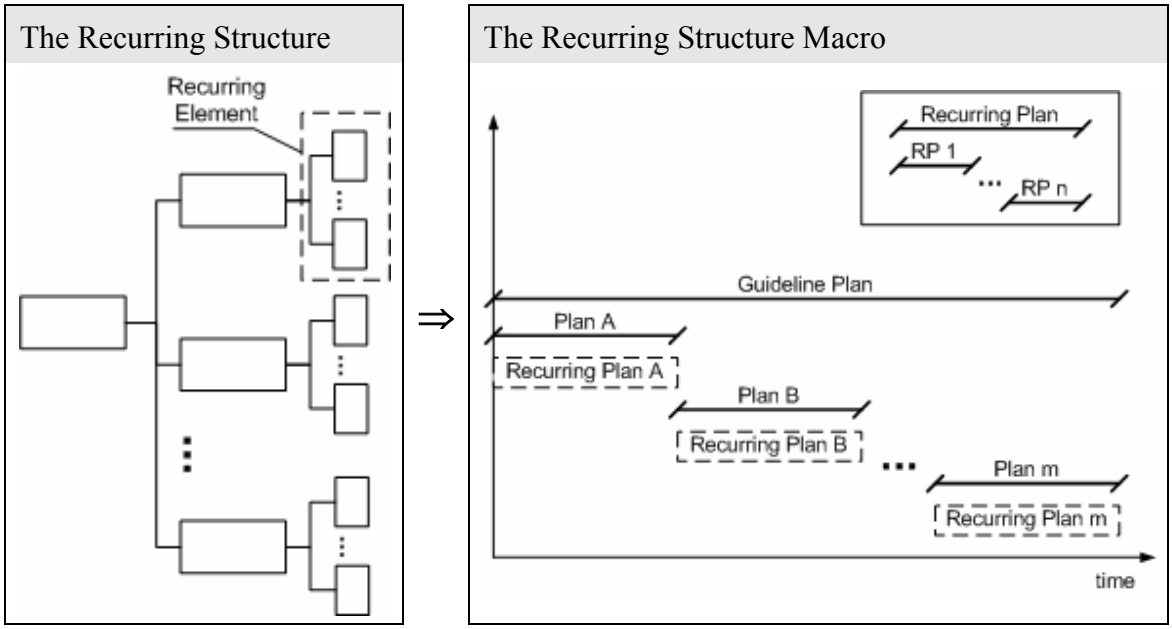


Figure 7.3 shows the underlying structure of the macro. It consists of two separate plans – the Recurring Plan and the Guideline Plan.

The recurring plan is a parent plan with several children's plans. The execution process of the children is again made with the unordered plan structure and is based on the independent structure macro from section 7.1.

The actual plan of the guideline consists of a parent plan (Plan Guideline) and also children's plans (Plan A to Plan m). The Asbru plan structure of this parent children relationship can also be traced back to the independent structure macro. The recurring plan element occurs as a child of the children's plans.

In conclusion, it can be said that the recurring structure macro is implemented through a nested structure of the independent structure macro.

8 GMT Macros

A macro can be defined as a structure of XML elements that are often placed together. XML elements are used, because Asbru (as described in section 3.1.1) is a XML based language. Using macros in GMT means, that the XML elements of these macros are transformed to the target XML language, which Asbru is.

To get an executable macro file for the GMT, it is furthermore necessary to specify a specific Document Type Definition (DTD) for this implementation process. This defined DTD can be seen as the GMT macros language.

In the following sections below, the relationship between the DTD, the macro elements and the target Asbru elements are explained in more detail and one example of an executable macro file – The Independent Structure Macro – is presented. Finally, for testing the functionality of the macros, one complete structure of a guideline was authored in GMT.

Appendix F presents the complete source code of the DTD. Furthermore, the complete source code of the three implemented macros – the Independent, the XOR and the Recurring Structure Macro – with their Asbru elements and the representation in the GMT's macro preview are given. Additionally, Appendix F provides the XML view of the structure of GL 1: "Chemotherapeutic management of stage IV non-small cell lung cancer", which was authored in GMT by using the independent structure macro file.

8.1 The Macro File

As mentioned, the DTD contains all available elements, which can be used to author a macro. The root element of a macro file is the <gmt-macros> element. Elements of the next macro level are <macros-def> and <structure-def> which specify the structure of a macro file. Figure 8.1 shows these two parts – the macros definition part and the structure definition part.

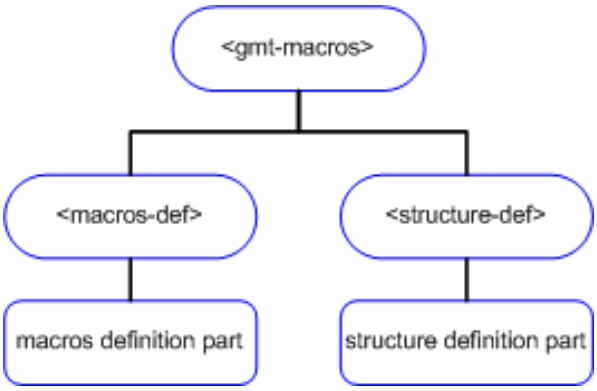


Figure 8.1: Structure of a macro file.

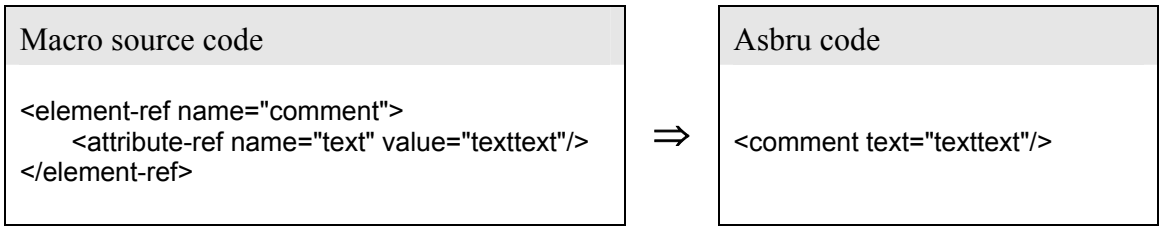
8.1.1 The Macros Definition Part

The macros definition part of a macro file may provide several macros. The definition of each macro starts after a <macro> tag and consists of a unique name and an optional description. The content of a macro, the Asbru element respectively, is composed of two elements:

- <element-ref> specifies the target Asbru element.
- <attribute-ref> defines the attribute and its value of the Asbru element already enclosed in the <element-ref> tag.

It can be said, that these two macro elements produce an Asbru element. Figure 8.2 shows the starting macro's source code and the resulting target Asbru code.

Figure 8.2: Transformation from macro-code to Asbru code.



The <attribute-ref> may have different values which are described through special character combinations[27]. The following descriptions of the character combinations used in this thesis are taken from [URL#23], the *HTML documentation of "macros-commented.dtd"*.

- %INPUT% - The user is asked for a value. If he cancels the input, the attribute won't be inserted.
- %DATE% - Will be replaced with the current date.
- %TIME% - Will be replaced with the current time.
- %USER% - Will be replaced with the current user. Currently "GMT-User" only is available.

On [URL#23] all text-macros supported by GMT are given.

Furthermore, GMT provides an additional feature for authoring macros – the variable-macro. The advantage of such variables is that an attribute's value, which occurs more frequent needs only be defined once. GMT provides two variable types:

- Local variable: Only defined for the macro, which is just inserted. Possible characters to define the variable's name are [a-z, 0-9] and it has to be located between two $-symbols. Example: $local1$

[27] These character combinations are again special text-macros for attributes in GMT.

- Global variable: Remains defined until the XML-file, which is just processed, is reloaded. Possible characters to define the variable's name are [A-Z, 0-9] and it has to be located between two $-symbols. Example: $GLOBAL1$

All introduced value types of the <attribute-ref> and the variable-macro were used in the macro example of the independent structure, which will be provided below.

8.1.2 The Structure Definition Part

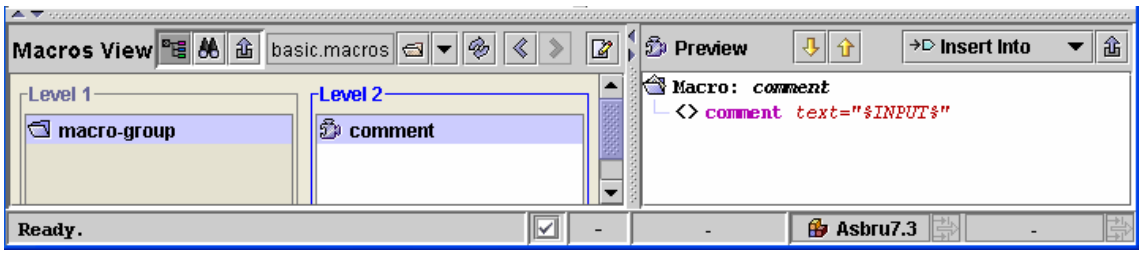
The structure definition part defines the structure of the macro in the GMT's macros view. The macros view in GMT is separated in different levels, which can be seen in Figure 8.3.

Figure 8.3: Structure Definition

Macro code of the Structure Definition Part

```
<structure-def>
    <group description="name of the macro-group" name="macro-group">
        <macro-ref name="comment"/>
    </group>
</structure-def>
```

Macros View in GMT



In our purpose, Level 1 provides the different macro groups of which one macro file consists. Level 2 gives the macro's name and in the Preview, the target XML code or optionally the GMT's macros preview is presented.

Having defined all requirements for a GMT macro file – the macros language in the macros.dtd file (see Appendix F) and the structure of the macros file – the macro implementation process may begin.

In the following section, the implementation of the Independent Structure Macro is shown and explained in detail. For the following implementation process all Asbru specific information was taken from the *Asbru Reference Manual* [Seyfang et al., 2002] and [URL#22] which provides the HTML documentation for the Asbru 7.3 DTD.

8.2 Example: The Independent Structure Macro

The independent structure macro was chosen, because it is the less complex macro file and all specialties in the macros definition part mentioned occur. In this section only selected parts of the macro file are shown and explained. The whole source code of the independent structure macro file as well as the two other macro files– the XOR structure and the recurring structure macro file – are shown in Appendix F.

The macro definition part of the independent structure macro file consists of five macros. One macro contains the independent structure itself and the other macros comprise useful element sequences to expand the underlying independent structure to the required structure from a certain guideline.

For each macro introduced in the following pages the source code of the macro file and two previews – the plain source and the tree view – of the GMT's Macro View are given. The plain source preview presents the Asbru representation of a macro.

Macro "library-info"

This "library-info" macro (Figure 8.4) is part of each of the three macro files implemented. Loading a plain Asbru file in GMT, it consists already of a <plan-library> and a <plans> tag. With the "library-info" macro it is possible to insert additional information about the Asbru plan which will be authored. In this macro file the GMT's text-macros (see section 8.1.1) %INPUT%, %DATE%, %TIME% and %USER% were used.

Figure 8.4: "library-info" - macro file, plain source and tree view.

Macro File

```
<macro name="library-info">
    <element-ref name="library-info">
        <attribute-ref name="title"
                       value="%INPUT%"/>
        <attribute-ref name="version" value="1"/>
        <element-ref name="administrative-data">
            <attribute-ref name="creation-date"
                           value="%DATE%, %TIME%"/>
            <attribute-ref name="original-author"
                           value="%USER%"/>
        </element-ref>
    </element-ref>
</macro>
```

Preview: plain source

```
Macro: library-info
<library-info title="%INPUT%"
              version="1">
  <administrative-data
    creation-date="%DATE%,
                   %TIME%"
    original-author="%USER%"/>
</library-info>
```

Preview: tree view

```
Macro: library-info
<> library-info (1) title="$INPUT$" version="1"
   <> administrative-data creation-date="$DATE$, $TIME$" original-author="$USER$"
```

Macro “independent_structure”

The “independent_structure” macro embodies the independent structure with its Asbru plan representation, which was introduced in section 7.1. This macro again uses the %INPUT% text-macro for defining the name of the parent plan. Also the variable-macro with a local variable was used. The local variable is set for the name of the first child (<plan-schema name="$unorderedplan1$"/>) inserted with this macro. The name assigned for the first child will also be placed for the name of the first child’s plan (<plan name="$unorderedplan1$"/>).

Figure 8.5: "independent_structure" - macro file, plain source and tree view.

Macro File

```
<macro name="independent_structure">
    <element-ref name="plan-group">
        <element-ref name="plan">
            <attribute-ref name="name"
                    value="%INPUT%guideline_plan"/>
            <element-ref name="plan-body">
                <element-ref name="subplans">
                    <attribute-ref name="type"
                                value="unordered"/>
                    <element-ref name="wait-for">
                        <element-ref name="all"/>
                    </element-ref>
                    <element-ref name="plan-activation">
                      <element-ref name="plan-schema">
                            <attribute-ref name="name"
                            value="$unorderedplan1$"/>
                       </element-ref>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
        <element-ref name="plan">
            <attribute-ref name="name"
                        value="$unorderedplan1$"/>
        </element-ref>
    </element-ref>
</macro>
```

Preview: plain source

```
Macro: independent_structure
<plan-group>
   <plan name=
         "%INPUT%guideline_plan">
      <plan-body>
         <subplans
                  type="unordered">
            <wait-for>
               <all/>
            </wait-for>
            <plan-activation>
               <plan-schema name=
                  "$unorderedplan1$"/>
            </plan-activation>
         </subplans>
      </plan-body>
   </plan>
   <plan name="$unorderedplan1$"/>
</plan-group>
```

Preview: tree view

```
Macro: independent_structure
 <> plan-group (2)
   <> plan (1) name="$INPUT$guideline_plan"
      <> plan-body (1)
         <> subplans (2) type="unordered"
            <> wait-for (1)
               <> all
            <> plan-activation (1)
               <> plan-schema name="$unorderedplan1$"
   <> plan name="$unorderedplan1$"
```

Macro “single_plan-activation”

With this macro, it is possible to activate a further plan in the parent plan of the “independent_structure” macro.

Figure 8.6: "single_plan-activation" - macro file, plain source and tree view.

Macro File

```
<macro name="single_plan-activation">
    <element-ref name="plan-activation">
        <element-ref name="plan-schema">
            <attribute-ref name="name"
                           value="%INPUT%plan"/>
        </element-ref>
    </element-ref>
</macro>
```

Preview: plain source

```
Macro: single_plan-activation
<plan-activation>
   <plan-schema
         name="%INPUT%plan"/>
</plan-activation>
```

Preview: tree view

```
Macro: single_plan-activation
<> plan-activation (1)
   <> plan-schema name="$INPUT$plan"
```

Macro “single_plan”

Having inserted a further child into the independent structure with the “single_plan-activation” macro, it is necessary to create a plan for this child. This can be done with the “single_plan” macro.

Figure 8.7: "single_plan" - macro file, plain source and tree view.

Macro File

```
<macro name="single_plan">
    <element-ref name="plan">
        <attribute-ref name="name"
                       value="%INPUT%plan n"/>
    </element-ref>
</macro>
```

Preview: plain source

```
Macro: single_plan
<plan name="%INPUT%plan n"/>
```

Preview: tree view

```
Macro: single_plan
<> plan name="$INPUT$plan n"
```

Macro “comment”

The “comment” macro is also contained in each of the three macro files implemented. It is a frequent used Asbru element and useful for commenting the authoring task.

Figure 8.8: "comment" - macro file, plain source and tree view.

Macro File	Preview: plain source
<macro name="comment"> <element-ref name="comment"> <attribute-ref name="text" value="%INPUT%"/> </element-ref> </macro>	**Macro: comment** <comment text="%INPUT%"/>
Preview: tree view	
Macro: comment <> comment text="$INPUT$"	

Part III

Conclusion

9 Conclusion

The aim of this thesis was the creation of patterns for the support of the authoring task of the Guideline Markup Tool. These patterns should not only be based on a logical combination of Asbru tags but also on medical knowledge which was constituted in clinical guidelines.

The first task in this thesis was the selection and the analysis of guidelines. In a further step the detection of pattern in guidelines and the implementation of these pattern in Asbru were made, and finally the exemplary creation of macros for the GMT was executed. All these tasks were necessary to achieve the target of this thesis and are presented in detail.

During the analysis, some important findings were made. One finding was that clinical guidelines were not as qualified for this work as it had been expected before. Clinical guidelines are authored at a very high level of abstraction. Furthermore, the evidence-based character of the guidelines had an impact on the results of the analysis. We assume that these two facts – the high level of abstraction and the evidence-based character – are one reason why only few temporal dimensions and intentions were detected during the analysing process. Additionally, we were also very surprised that there were almost no procedural algorithms in the guidelines.

Among others these two facts were the reason for the quite abstract approach of text linguistics to detect pattern and not the approach of software pattern which was taken in consideration at the beginning. The consequence of this text linguistic approach was the detection of only few pattern on a very high level.

Taking this results into account, it can be stated, that clinical protocols would provide a more appropriate basis for the research of pattern because of their more detailed and procedural character. The analysis of clinical protocols for pattern could be an approach for further research in this domain in the future.

Additionally, to this professional lesson learned, also personal cognitions arose during the work for this thesis.

Although I had no relation to the medical domain before this master's thesis it was surprising that research in the field of clinical guidelines was not as difficult as expected before, which is, for my opinion, due to the high level of abstraction of the clinical guidelines.

Recapitulating the work done during the last five months, there were many ups and downs, but ultimately I can say, that I have learned a lot during this time.

Part IV

Appendix

Appendix A

Search Criteria

Criteria	Selection
Guideline Categories:	Management, Treatment
Intended Users:	Nurses, Physicians
Clinical Speciality:	Oncology, Radiation Oncology
Methods Used to Assess the Quality and Strength of the Evidence:	Weighting According to a Rating Scheme (Scheme Given)[28]
Methods Used to Analyze the Evidence:	Systematic Review with Evidence Tables[29]
Publication Date(s):	2003, 2002, 2001, 2000, 1999
Sort Order:	Relevance

In the specific guidelines, rating schemes and methods to analyze the evidence of guidelines are only rarely mentioned. However, National Guideline Clearinghouse (NGC) provides a complete summary of each guideline, containing particular information about the analyzing methods and rating schemes used. Furthermore, the homepage of NGC, www.guideline.gov (URL#18), offers additional information about guidelines and is recommended at this place.

[28] Weighting according to a rating scheme: "This method consists of using a system that assigns a weighted value (e.g., levels or grades) to distinguish high from low quality research studies and/or strong from weak bodies of evidence. Systems have been developed for studies/evidence pertaining to therapy, prevention, diagnosis, prognosis and harm" [URL#19].

[29] Systematic review with evidence tables: "A systematic review that utilizes a tabular compilation of the data from individual studies" [URL#19].

Appendix B

Search Result

"American Gastroenterological Association medical position statement on management of oropharyngeal dysphagia." American Gastroenterological Association - Medical Specialty Society. 1998 Jul 24 (reviewed 2001). 3 pages. NGC:002293

"American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma." American Society of Clinical Oncology - Medical Specialty Society. 2002 Sep 1. 19 pages. NGC:002593

"An evidence-based analysis of the effect of busulfan, hydroxyurea, interferon, and allogeneic bone marrow transplantation in treating the chronic phase of chronic myeloid leukemia." American Society of Hematology - Medical Specialty Society. 1999 Sep 1. 20 pages. NGC:001589

GL 1: "Chemotherapeutic management of stage IV non-small cell lung cancer."[30] American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 18 pages. NGC:002875

GL 2: "Follow-up and surveillance of the lung cancer patient following curative-intent therapy." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 12 pages. NGC:002878

"Guidelines of care for primary cutaneous melanoma." American Academy of Dermatology - Medical Specialty Society. 2001 Mar. 8 pages. NGC:001967

GL 3: "Lung cancer. Palliative care." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 28 pages. NGC:002879

"Management of hepatitis C: 2002." National Institutes of Health (NIH) Consensus Development Panel on Management of Hepatitis C - Independent Expert Panel. 1997 Mar (revised 2002 Aug 26). 44 pages. NGC:002642

GL 10: "Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology." American Society of Clinical Oncology - Medical Specialty Society. 2000 Nov 3. 20 pages. NGC:001982

"Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology." American Society of Clinical Oncology - Medical Specialty Society. 2000 Nov 3. 31 pages. NGC:001986

[30] Guideline titles, which are numerated and formatted in this colour represent a chosen guideline.

GL 4: "Presentations of lung cancer with special treatment considerations." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 15 pages. NGC:002876

GL 5: "Small cell lung cancer." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 13 pages. NGC:002877

"Systemic adjuvant therapy for patients at high risk for recurrent melanoma." Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]. 1998 May 27 (updated 2002 Nov). 32 pages. NGC:002761

GL 6: "Treatment of early stage non-small cell lung cancer." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 5 pages. NGC:002870

GL 7: "Treatment of stage I non-small cell lung carcinoma." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 7 pages. NGC:002871

GL 8: "Treatment of stage II non-small cell lung cancer." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 14 pages. NGC:002872

GL 9: "Treatment of stage IIIA non-small cell lung cancer." American College of Chest Physicians - Medical Specialty Society. 2003 Jan. 19 pages. NGC:002873

"Use of epoetin in patients with cancer: evidence-based clinical practice guidelines of the American Society of Clinical Oncology and the American Society of Hematology." American Society of Clinical Oncology - Medical Specialty Society American Society of Hematology - Medical Specialty Society. 2002 Apr 18. 25 pages. NGC:002768

Appendix C

Results of the Analysis

GL 1 Chemotherapeutic management of stage IV non-small cell lung cancer.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/226S.pdf
Guideline's Length	Medium Guideline (18 pages)
Technical Criteria	
Modularity:	Type 1
Structure:	Interval 2
Lists: Tables: Algorithms:	4 8 None
Temp. Dimension:	Yes
Intention:	Yes

GL 2 Follow-up and surveillance of the lung cancer patient following curative-intent therapy.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/272S.pdf
Guideline's Length	Medium Guideline (12 pages)
Technical Criteria	
Modularity:	Type 2
Structure:	Interval 2
Lists: Tables: Algorithms:	3 4 None
Temp. Dimension:	Yes
Intention:	Yes

GL 3 Lung cancer. Palliative care.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/284S.pdf
Guideline's Length	Long Guideline (28 pages)
Technical Criteria	
Modularity:	Type 1
Structure:	Interval 2
Lists: Tables: Algorithms:	3 3 None
Temp. Dimension:	Yes
Intention:	Yes

GL 4 Presentations of lung cancer with special treatment considerations.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/244S.pdf
Guideline's Length **Technical Criteria**	Medium Guideline (15 pages)
Modularity:	Type 3
Structure:	Interval 1
Lists: Tables: Algorithms:	1 2 None
Temp. Dimension:	Yes
Intention:	Yes

GL 5 Small cell lung cancer.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/259S.pdf
Guideline's Length **Technical Criteria**	Medium Guideline (13 pages)
Modularity:	Type 1
Structure:	Interval 2
Lists: Tables: Algorithms:	4 3 None
Temp. Dimension:	Yes
Intention:	No

GL 6 Treatment of early stage non-small cell lung cancer.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/176S.pdf
Guideline's Length **Technical Criteria**	Short Guideline (5 pages)
Modularity:	Type 1
Structure:	Interval 3
Lists: Tables: Algorithms:	4 None None
Temp. Dimension:	Yes
Intention:	No

GL 7 Treatment of stage I non-small cell lung carcinoma.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/181S.pdf
Guideline's Length **Technical Criteria**	Short Guideline (7 pages)
Modularity:	Type 2
Structure:	Interval 2
Lists: Tables: Algorithms:	2 None None
Temp. Dimension:	Yes
Intention:	Yes

GL 8 Treatment of stage II non-small cell lung cancer.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/188S.pdf
Guideline's Length **Technical Criteria**	Medium Guideline (14 pages)
Modularity:	Type 2
Structure:	Interval 2
Lists: Tables: Algorithms:	2 6 None
Temp. Dimension:	Yes
Intention:	Yes

GL 9 Treatment of stage IIIA non-small cell lung cancer.

Link to Full Text:	http://www.chestjournal.org/cgi/reprint/123/1_suppl/202S.pdf
Guideline's Length **Technical Criteria**	Medium Guideline (19 pages)
Modularity:	Type 1
Structure:	Interval 3
Lists: Tables: Algorithms:	7 6 None
Temp. Dimension:	Yes
Intention:	Yes

GL 10 Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology.

Link to Full Text:	http://www.jco.org/cgi/reprint/19/5/1519.pdf
Guideline's Length	Long Guideline (20 pages)
Technical Criteria	
Modularity:	Type 1
Structure:	Interval 1
Lists: Tables: Algorithms:	1 2 None
Temp. Dimension:	Yes
Intention:	Yes

Appendix D

Box Plot 1: Length of Guidelines

Dataset of the number of pages of the guidelines:

5	7	12	13	14	15	18	19	20	28

" The 5 number summary":

Minimum[31]	5
Maximum[32]	28
First Quartile[33] (Q1)	12
Third Quartile[34] (Q3)	19
Median[35] (M)	14,5

The inner quartile range[36] (IQR):	19 – 12 = 7

Calculating the ends of the whiskers:

IQR x 1,5	10.5
Left whisker	12 – 10.5 = 1.5
Right whisker	19 + 10.5 = 29.5

[31] The Minimum is the smallest value in the data set.

[32] The Maximum is the largest value in the data set.

[33] The First Quartile is the 25th quartile. It is where 25% of the data fall below it.

[34] The Third Quartile is the 75th quartile. It is where 25% of the data is above it.

[35] The Median is a measure of the center. It is the point where 50% of the data is above and 50% below it.

[36] The inner quartile range (IQR) is the distance between the Third Quartile and the First Quartile (Q3 – Q1).

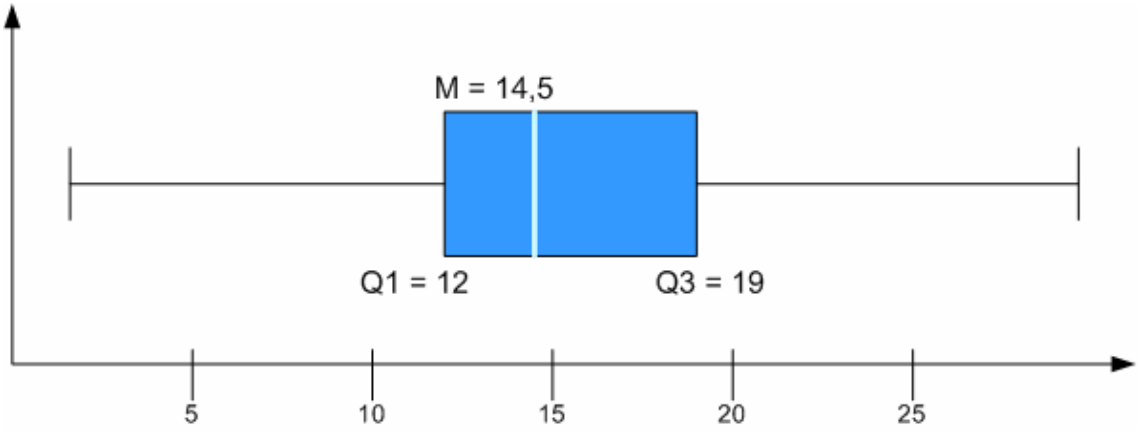


Figure D1: Box Plot diagram of the Length of Guidelines

As it can be seen in the Box Plot diagram in Figure D1, it results in three ranges. These three ranges – the left whisker range, the IQR and the right whisker range – were used for classifying the length of the guidelines. The following three intervals were deducted from the Box Plot diagram and taken for further analysis in section 4.4.1:

- Interval 1: [1.5, 12[
- Interval 2: [12, 19]
- Interval 3:]19, 29.5]

Classification of the guidelines according to the intervals:

Intervals	Guidelines	Number of guidelines in each interval
[1.5, 12[	GL 6, 7	2
[12, 19]	GL 1, 2, 4, 5, 8, 9	6
]19, 29.5]	GL 3, 10	2

Box Plot 2: Structural Elements

Dataset of the Structural Elements:

Guideline	Structural Elements	Number of Pages	Ratio (Struct. Elements / Pages)
GL 1	12	18	0.6
GL 2	7	12	0.583
GL 3	6	28	0.214
GL 4	3	15	0.2
GL 5	7	13	0.583
GL 6	4	5	0.8
GL 7	2	7	0.258
GL 8	8	14	0.571
GL 9	13	19	0.684
GL 10	3	20	0.15

The Ratio column contains the relevant data for finding "The 5 number summary" and drawing the Box Plot diagram.

"The 5 number summary":

Minimum	0.15
Maximum	0.8
First Quartile (Q1)	0.214
Third Quartile (Q3)	0.6
Median (M)	0.577

The inner quartile range (IQR):	0.6 – 0.214 = 0.386

Calculating the ends of the whiskers:

IQR x 1,5	0.579
Left whisker	0
Right whisker	0.6 + 0.579 = 1.179

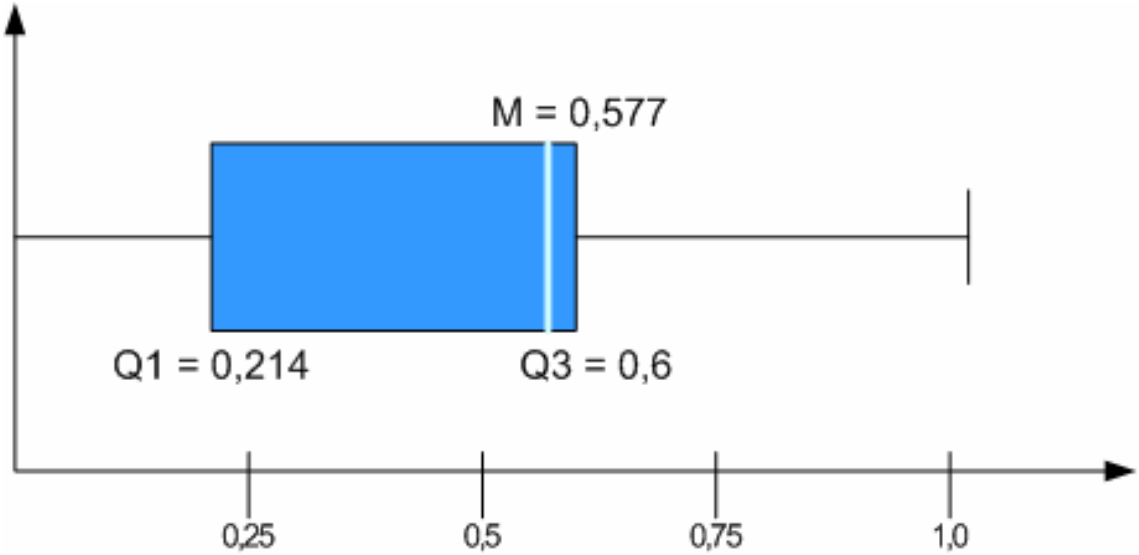


Figure D2: Box Plot diagram of Structure Elements

As mentioned already in Box Plot 1, a Box Plot diagram results in three ranges – the left whisker range, the IQR and the right whisker range. The Box Plot in Figure D2 was used to deduct intervals for the Structural Elements. The following three intervals were defined and used for further analysis in section 4.4.3:

- Interval 1: [0, 0.214[
- Interval 2: [0.216, 0.6]
- Interval 3:]0.6, 1.179]

Classification of the guidelines according to the intervals:

Intervals	Guidelines	Number of guidelines in each interval
[0, 0.214[	GL 4, 10	2
[0.214, 0.6]	GL 1, 2, 3, 5, 7, 8	6
]0.6, 1.179]	GL 6, 9	2

Appendix E

Text sections of Modularity Type 1

GL 1: Chemotherapeutic management of stage IV non-small cell lung cancer.	
Module Structure:	
Question 1:	ARE THERE IDENTIFIABLE PROGNOSTIC FACTORS THAT SHOULD BE USED WHEN SELECTING PATIENTS FOR SYSTEMIC CHEMOTHERAPY?
	The prognosis of patients with advanced NSCLC is poor. Most large phase III trials have shown a median survival time of 8 to 10 months and a 1-year survival rate of 30 to 35%.[2] Given the consistent improvement in the survival of patients who have been treated with chemotherapy over those receiving supportive care alone, clinicians struggle to stratify these patients into different prognostic groups. One would like to identify those patients who are the most likely to benefit from aggressive chemotherapy and to tolerate its side effects, and to identify another group of patients who are unlikely to obtain any meaningful advantage from such therapy. Ideally, prognostic groups could help to stratify patients in order to apply different approaches or levels of aggression. This also could allow an appropriate focus on quality of life (QOL) as a major end point. Individual patient characteristics seem to influence survival in patients with advanced NSCLC. The most important factor across all studies is performance status (PS). Patients with stage IV NSCLC who are compromised by their disease have poorer survival compared to patients who are less compromised. Two commonly used PS scales are shown in Table 1. At least 10 trials evaluating prognostic factors in patients with advanced NSCLC have clearly identified PS at the time of diagnosis to be a powerful predictor of survival.[4–13] In a landmark analysis of 893 patients with stage IV NSCLC, Finkelstein et al[7] documented the impact that PS had on survival. In that study, the 1-year survival rate was 36% for PS level 0 patients, 16% for PS level 1 patients, and 9% for PS level 2 patients ($p < 0.001$).

Pretreatment weight loss is generally regarded as a negative prognostic factor,[4,5,7,9] but not all trials have reliably corroborated this.[6,8,10,13] The sex of NSCLC patients also has been described as an important prognostic variable, with most trials suggesting improved survival for women.[6–8,12,13] Differences in survival based on patient sex have generally been small, usually ≤ 1 to 2 months.

Age may be a predictor of survival, with some studies suggesting that elderly patients with advanced NSCLC have poor outcomes.[4,10,13] Other studies looking at this variable have failed to confirm this or have suggested that older patients have a similar or even superior survival.[6–9,11,12] In a retrospective review,[14] no difference in survival was seen for patients < 40 years of age compared with a matched group of patients who were > 50 years of age. Therefore, it is difficult to say that age is a reliable independent prognostic factor for these patients.

A large Eastern Cooperative Oncology Group (ECOG) trial[13] in the United States (ECOG 5592) showed that QOL scores, as measured by the functional assessment of cancer therapy-lung cancer (FACT-L), were important predictive factors. This study also showed that the absence of change in cough or hoarseness, the absence of bone pain, the absence of other symptoms from metastases, and the absence of anorexia were all independent favorable prognostic factors. Another retrospective study[16] showed pain level to correlate inversely with survival. QOL, however, was not a predictive factor in this analysis.

Pretreatment stage, even among those patients with advanced NSCLC is prognostic, with stage IIIB patients generally having a better survival rate than those with overt metastatic or stage IV disease.[3,17] The total number of metastatic sites may influence the prognosis.[4–10,12,13] Several nonrandomized trials[6] have suggested that patients with a solitary site of metastasis may have superior outcomes and that more aggressive therapy (including surgical resection of the primary tumor and metastatic site) may provide up to 20 to 30% of patients with long-term survival. Studies also have suggested that specific sites of metastatic disease may change the prognosis in patients with advanced NSCLC. Specifically, patients with disease confined to the lungs may have superior outcomes. Those with brain metastases may have poorer outcomes,[4] but this conclusion is controversial.[18,19] The presence of bone or liver metastases has been found to confer a poor prognosis in the retrospective analysis mentioned previously.[15]

Histologic subtype does not reliably provide prognostic importance in patients with advanced NSCLC, despite the different clinical manifestations of adenocarcinoma compared to squamous histology.[4–6,10,11] Normal levels of serum lactate dehydrogenase, high levels of albumin, and low levels of alkaline phosphatase all have, however, been associated with a better prognosis in patients with advanced NSCLC.[6,13,20]

The expression of neuroendocrine markers may predict survival in patients with NSCLC. In one study,[21] responding patients with two or more positive markers survived longer. Another study[22] found that tumors containing > 50% positively staining cells were associated with shorter survival times. Currently, neuroendocrine markers cannot be used to reliably predict survival in patients with advanced NSCLC.

Perhaps the most important prognostic factor, and the one most clearly proven in randomized trials, is whether patients receive chemotherapy.[23–32] Numerous randomized trials and several meta-analyses have confirmed an improvement in the median survival time of 6 to 8 weeks, translating to a 10% improvement in the 1-year survival rate for those advanced NSCLC patients who are receiving platinum-based chemotherapy.

Recommendation 1

1. When selecting patients for systemic chemotherapy, PS at the time of diagnosis should be used because it is a consistent prognostic factor for survival. Patients with a PS of ECOG level 0 or 1 should be offered chemotherapy. Level of evidence, good; benefit, substantial; grade of recommendation, **A**
2. Data are not yet sufficient to routinely recommend chemotherapy to patients with a PS of ECOG level 2. Level of evidence, poor; benefit, small/weak; grade of recommendation, I
3. Patients with a PS of ECOG level 3 or 4 should not receive chemotherapy. Level of evidence, fair; benefit, moderate; grade of recommendation, B
4. Other patient-related factors (*eg*, gender, age, sites of metastases, and histology) have not been consistent prognostic factors for survival. Level of evidence, poor; benefit, small/weak; grade of recommendation, I

Question 2:	WHAT IS THE EVIDENCE THAT PLATINUM-BASED CHEMOTHERAPY IMPROVES SURVIVAL?

Ten randomized clinical trials have been published[23–32] comparing platinum-based chemotherapy to best supportive care (BSC) [Table 2]. It should be noted that BSC in these trials included aggressive symptom management (*eg*, antitussive agents, supplemental oxygen, and nonnarcotic and narcotic analgesic agents) as well as palliative radiotherapy when indicated. In all 10 trials, the median survival time of the treated patients was numerically superior to that of patients receiving BSC. The median survival time of patients receiving BSC was 3.6 months (range, 2.4 to 4.9 months) in these 10 trials, providing a benchmark for survival in patients with untreated, advanced NSCLC. The median survival time of the treated patients was 6.5 months (range, 4.7 to 8.5 months). The numeric survival advantage seen in all 10 trials was statistically significant in 6 of these trials.

Four meta-analyses[33–36] have been published examining the effect of treatment vs BSC in patients with advanced NSCLC. The studies have differed in how trials were selected for review, in the number of trials included, in the use of group or individual patient data in the analysis, and in the statistical methodology used (Table 3). Despite this, these four meta-analyses were consistent in their conclusions. The majority of trials included in these four studies used cisplatin-based regimens. Souquet et al[33] included seven trials, of which six were cisplatin-based.

The end point analyzed was the number of deaths at 3-month intervals up to 18 months. There was a significant reduction in mortality for up to 6 months for chemotherapy vs BSC. The odds ratio (OR) at 6 months was approximately 0.6 in favor of chemotherapy. Grilli et al[34] analyzed six trials (of which five were cisplatin-based) in terms of relative risk (RR). The overall RR for death for chemotherapy vs BSC was 0.76 (95% confidence interval [CI], 0.66 to 0.87). Marino et al[35] included eight trials (of which six were cisplatin-based) and determined the individual and pooled odd ratios for death at 6 months. The OR for death was 0.44 (95% CI, 0.32 to 0.50) in favor of chemotherapy. The Non-Small Cell Lung Cancer Collaborative Group used individual patient

data from 11 randomized trials (of which 8 were cisplatin-based).[36] The other three trials used long-term alkylating agents or vinca alkaloids and etoposide. Although a survival advantage for chemotherapy was documented over BSC, there was a difference between cisplatin-based trials and non-cisplatin-based trials. In fact, the long-term administration of alkylating agents actually had a negative impact on survival compared to BSC. When evaluating trials employing only cisplatin-based regimens, there was a 27% reduction in the risk of death (hazard ratio, 0.73; 95% CI, 0.63 to 0.85; $p < 0.0001$) with chemotherapy vs BSC (Fig 1).

Table 4 summarizes the recommendations from several guidelines addressing this issue. As can be seen, the organizations represent national as well as international societies from the United States, Canada, and Europe. The guidelines are either evidence-based or consensus guidelines and represent an analysis of the cisplatin-based literature. All of these organizations recommend chemotherapy in patients with advanced stage IV NSCLC.

It is difficult to portray to patients the magnitude of the survival effect in this setting. Table 2 shows the differences in median survival times in trials comparing platinum-based regimens to BSC. Stage IV NSCLC still is a disease with a steeply downsloping survival curve, making median survival a less meaningful end point. In general, investigators in this area have focused on the 1-year survival percentage. To evaluate this end point, the last four trials[31,32,37,38] published in which the 1-year survival percentage was reported and that included a BSC control were analyzed. Fig 2 shows the percentage of patients who are alive at 1 year as well as the absolute number of patients who are alive in the United States, comparing BSC to chemotherapy. The data suggest a doubling of the 1-year survival rate and approximately 10,000 more patients surviving beyond 1 year as a result of chemotherapy.

In conclusion, the evidence from both randomized clinical trials and four separate meta-analyses support the fact that platinum-based chemotherapy improves survival in patients with advanced stage IV NSCLC.

Recommendation 2

Patients with a good PS (*ie*, ECOG level 0 or 1) should be considered for a platinum-based chemotherapy regimen based on the survival advantage provided over BSC. Level of evidence, good; benefit, substantial; grade of recommendation, A

… etc.

Question 11: WHAT ARE THE OUTCOME EXPECTATIONS AND ADVERSE EFFECTS SEEN WITH CHEMOTHERAPY AND HOW DO THEY COMPARE WITH THE NATURAL HISTORY?

The natural history of untreated stage IV NSCLC is best documented in the randomized trials of chemotherapy vs BSC (Tables 2 and 5). The impact that chemotherapy has on survival is significant and has been discussed in the previous sections. When QOL has been examined, patients receiving chemotherapy report better scores compared to patients receiving only BSC,[31,32,39] supporting the contention that the disease is worse than the treatment. The expectations regarding survival and toxicity when using modern chemotherapy regimens are shown in Table 8. The trials shown in Table 8 predominantly include patients with good PS with stage IV disease who have been studied in large phase III trials that have been published in peer-reviewed journals. Only platinum-based regimens are described as those regimens represent the standard of care in patients with good PS and stage IV NSCLC. As is shown in Table 8, the median survival time and the 1-year survival rate expectations are 8.0 to 9.9 months and 30 to 43%, respectively. The major toxicities are hematologic, with neutropenia being the predominant adverse effect. Despite this, the clinical consequences of severe neutropenia (*ie*, sepsis) occur in < 10% of patients, and the treatment-related death rates in these studies ranged from 0 to 4%. Severe anemia occurs in 7 to 30% of patients. Severe thrombocytopenia varies depending on the regimen used as well as on the dose and schedule of the agents in the regimen. However, bleeding complications are unusual. Nonhematologic toxicity consists mainly of nausea/vomiting, fatigue, and alopecia. In the more recent trials employing modern antiemetic regimens or using carboplatin rather than cisplatin, the rates of severe nausea/vomiting range from 7 to 20%. The toxicity profiles of single agents are somewhat less than those of combination regimens and can be found in the individual references provided. It should also be noted that the risk of toxicity increases in patients with PS 2.[92]

Recommendation 11

Combination platinum-based chemotherapy can be administered safely with acceptable and manageable toxicity profiles in patients with good PS who have stage IV NSCLC. Level of evidence, good; benefit, substantial; grade of recommendation, A

Text sections of Modularity Type 2

GL 8: Treatment of stage II non-small cell lung cancer.		
Module Structure:		
First Type:	TREATMENT GUIDELINES STAGE II NSCLC (T1-2N1M0)	
		Intraoperative Management: Sleeve Resection vs Pneumonectomy
		No randomized trials comparing sleeve lobectomy with pneumonectomy have been reported in the literature. The data available consist of retrospective reviews of the outcomes in patients treated with sleeve lobectomy and compared with matched or unmatched control subjects treated with pneumonectomy. Gaissert and colleagues[17] at the Massachusetts General Hospital reviewed their experience with 72 consecutive patients treated with sleeve lobectomy for NSCLC. They compared the results in this cohort to an unmatched group of patients undergoing pneumonectomy for lung cancer between 1986 and 1990. The actuarial survival at 5 years was 42% for the patients undergoing sleeve lobectomy and 44% for patients undergoing pneumonectomy. Local recurrence occurred in 14% of the patients undergoing sleeve lobectomy, while the local recurrence was not reported for the unmatched pneumonectomy cohort. The majority of the local recurrences occurred in the mediastinum. There was a higher mortality (9% vs 4%) and major complication rate (16% vs 11%) among patients undergoing pneumonectomy. In a retrospective review of 29 patients undergoing sleeve lobectomy for lung cancer and compared with a matched cohort of patients undergoing pneumonectomy, Yoshino et al[18] found no difference in the 3-year disease-free survival between the two groups. In addition, local recurrence occurred in 1 of 15 patients undergoing sleeve lobectomy with N1 disease and in 2 of 11 patients undergoing pneumonectomy with N1 disease. Operative mortality (6.9% vs 0%) and complication rates (24.1% vs 13.7%) were significantly higher, respectively ($p < 0.05$), in the group undergoing pneumonectomy compared to patients undergoing sleeve lobectomy.

Okada et al[19] compared the outcomes after sleeve lobectomy and pneumonectomy for patients with NSCLC distributed according to their nodal involvement status. Between June 1984 and December 1998, 151 patients underwent sleeve lobectomy while 60 patients underwent pneumonectomy. A matched group of 60 patients undergoing sleeve lobectomy was compared with the patients undergoing pneumonectomy. The operative mortality rate was 0% in the sleeve lobectomy group and 2% in the pneumonectomy group. Local recurrence developed in five patients (8%) after sleeve lobectomy and six patients (10%) after pneumonectomy. Patients undergoing sleeve lobectomy had a significantly longer 5-year survival (48%) than patients undergoing pneumonectomy (29%). While these studies are limited by their retrospective method and small numbers of patients, the authors agree with the conclusions of these articles that sleeve lobectomy is preferred over pneumonectomy whenever a complete pathologic resection can be obtained using bronchoplastic techniques.

Recommendation

1. For patients with N1 lymph node metastases in whom a complete resection can be achieved with either technique, sleeve lobectomy is recommended over pneumonectomy. Level of evidence, poor; benefit, moderate; grade of recommendation, C

… etc.

Second Type:

TREATMENT GUIDELINES STAGE II NSCLC (T3N0M0)

CT Assessment of Stage II (T3 [Chest Wall]) NSCLC

The ability of chest CT to predict the presence of chest wall invasion by a lung tumor adjacent to the chest wall has been investigated by Ratto et al[36] in a study involving 112 patients. They determined that the presence of a chest wall mass protruding through the ribs on CT was the most sensitive predictor of chest wall invasion, while a ratio of length of chest wall contact/tumor diameter of ≤ 0.5 was the best predictor of the absence of chest wall invasion. Other studies have reported similar findings.[37,38] Radiographic signs on chest CT other than a mass protruding thorough the ribs of the chest wall or gross rib destruction are not sufficiently accurate to make a diagnosis of chest wall invasion by a tumor adjacent to or abutting the chest wall. MRI has not generally been shown to provide any advantage over CT in detecting involvement of the lateral chest wall by an adjacent lung tumor.[39]

	Recommendation
	8. For patients with lung tumors that abut or are adjacent to the chest wall based on chest CT (clinical T3 [chest wall] NSCLC), the presence or absence of chest wall invasion should not be assumed based on CT findings alone but should be confirmed by surgical exploration. Level of evidence, poor; benefit, moderate; grade of recommendation, C.
… etc.	

Text sections of Modularity Type 3

GL 4: Presentations of lung cancer with special treatment considerations.	
Module Structure:	
Paragraph 1	PANCOAST TUMORS
	Definition Lung cancers that occur in the apex of the chest and invade apical chest wall structures are called *superior sulcus tumors* or *Pancoast tumors*. The classic description of such patients involves a syndrome of pain radiating down the arm as a manifestation of brachial plexus involvement. With improvements in radiographic techniques, earlier diagnosis, and a more detailed understanding of the anatomy, a tumor can be classified as a Pancoast tumor if it invades any of the structures at the apex of the chest, including the most superior ribs or periostium, the lower nerve roots of the brachial plexus, the sympathetic chain near the apex of the chest, or the subclavian vessels. These tumors are now divided into anterior, middle, and posterior compartment tumors depending on the location of the chest wall involvement in relation to the insertions of the anterior and middle scalene muscles on the first rib.[7] A syndrome of pain radiating down the arm is no longer a prerequisite for an apical tumor to be designated a Pancoast tumor.
	Workup There are no data that specifically address the reliability of the clinical examination in patients with Pancoast tumors with regard to the presence of distant metastases. In the absence of data to the contrary, the panel thought that Pancoast tumors should be treated like most other resectable lung cancers, meaning that imaging tests for distant metastases are not routinely necessary in the presence of a negative clinical evaluation. There is also no evidence regarding the reliability of CT or positron emission tomography (PET) scans for mediastinal node involvement specifically in patients with Pancoast tumors. The consensus of the panel was that, in the face of normal-sized lymph nodes by CT, mediastinoscopy should be performed, although a negative PET scan in the mediastinum may obviate this.

In addition, mediastinoscopy should be performed in the presence of enlarged or PET-positive lymph nodes. The argument for this approach to intrathoracic staging is that it is consistent with the general recommendation for accurate staging before initiation of a major intervention, such as resection, and consistent with data demonstrating that N2,3 node involvement is a major negative prognostic factor.

No firm recommendation can be made about whether mediastinoscopy should be done before or after preoperative therapy. An MRI demonstrates involvement of apical chest wall structures better than a CT scan,[8] but CT provides more information about the presence of nodal enlargement, and pulmonary, hepatic, and adrenal metastases. Therefore, both a chest CT and an MRI are indicated to assess the resectability of a Pancoast tumor.

Treatment

The classic approach to curative treatment of Pancoast tumors has been preoperative radiotherapy followed by surgical resection. This dates back to an experience published in 1961 by Shaw et al,[9] in which 12 of 18 patients treated with this approach were still alive at the time the paper was written. However, the follow-up was < 2 years in 90% of the patients.[9] Alternatives are treatment with radiation alone, preoperative chemoradiotherapy and resection, or chemoradiotherapy without resection.

Treatment with radiation alone has achieved good palliation of pain in approximately 75% of patients.[10] In general, very few patients treated with radiation alone are long-term survivors (approximately 5%).[11] However, many of these series have included patients with advanced stage tumors. Among studies that have involved primarily patients who had a reasonable chance of cure, the average median survival time was 16 months, and the average 5-year survival was 20% (range 15–23%).[10,12–14]

Treatment with preoperative radiation and resection has resulted in an average median survival time of 22 months and a 5-year survival of 27%.[11] In these series, approximately one third of patients underwent an incomplete (R_1 or R_2) resection, and approximately one third of the resections involved only a limited resection of the affected lobe of the lung.[11] Retrospective analysis has found that a complete resection with negative margins (R_0) and a pulmonary resection involving at least a lobectomy are major factors associated with better survival.[15] Furthermore, N2,3 lymph node involvement is a major negative prognostic factor and should generally be considered a contraindication to surgery.[11] Patients with vertebral body or subclavian vessel involvement have traditionally been considered to be unresect-

	able, but it appears that, with improved surgical approaches to these structures, a few experienced centers have been able to achieve reasonable survival in such patients.[16,17] The presence of Horner syndrome is also associated with poor survival.[11] A large phase II study of preoperative chemoradiotherapy in patients with Pancoast tumors has shown a complete resection rate of 92% and a good 2-year survival rate compared with historical controls of radiotherapy followed by surgery.[18] Furthermore, local recurrences were seen in only 33% of those patients with a recurrence, whereas in series involving preoperative radiotherapy alone, the majority of recurrences involved the tumor bed. These data, in combination with the data for non-Pancoast stage III NSCLC, suggest that preoperative chemoradiotherapy is a significant improvement over preoperative radiotherapy, particularly in light of the fact that there are insufficient numbers of patients with Pancoast tumors to complete a randomized comparison. Other published guidelines have recommended that patients with Pancoast tumors should be evaluated by a thoracic surgeon.[3] If there is no evidence of mediastinal node involvement[1] or extensive local invasion,[5] patients should undergo resection in combination with radiotherapy or chemoradiotherapy.[1,4,5] Patients with inoperable Pancoast tumors should be treated with radiotherapy.[2] The latter two recommendations were rated grade B, whereas the strengths of the other statements were rated grade C. Thus other guidelines have reached the same conclusions as this ACCP document, although the recommendations in those other documents have been less detailed and more vaguely worded. In summary, the available data suggests that the best survival is achieved by preoperative chemoradiotherapy followed by surgical resection in carefully selected patients. Preoperative radiotherapy followed by surgical resection is a reasonable alternative. Involvement of subclavian vessels or the vertebral column is associated with poor survival after resection. However, a few centers have gained experience with improved surgical approaches to these structures and have reported reasonable survival rates after resection. Involvement of mediastinal nodes is associated with poor survival after resection. At the time of resection, it is important to carry out a complete resection, which should involve at least a lobectomy. There is no data on how unresectable, yet potentially curable, patients with Pancoast tumors should be treated. However, extrapolation from the data for non-Pancoast stage III NSCLC suggests that chemoradiotherapy is the best approach. For patients in whom cure is not believed possible, radiotherapy offers good palliation of pain.

	Recommendations: Pancoast tumor 1. For patients with a Pancoast tumor, a tissue diagnosis should be obtained prior to the initiation of therapy. Level of evidence, poor; benefit, substantial; grade of recommendation, C 2. Patients with a Pancoast tumor without evidence of mediastinal node involvement or distant metastases should be evaluated by an experienced thoracic surgeon for potential resection. Level of evidence, fair; benefit, substantial; grade of recommendation, B 3. Patients with a Pancoast tumor being considered for resection should undergo evaluation with an MRI of the thoracic inlet and brachial plexus, in addition to a CT of the chest. Level of evidence, fair; benefit, substantial; grade of recommendation, B 4. Resection of patients with a Pancoast tumor with involvement of the subclavian vessels or the vertebral column should not be routinely undertaken (outside of specialized centers). Level of evidence, poor; benefit, moderate; grade of recommendation, D 5. Patients with a Pancoast tumor being considered for curative resection should undergo a cervical mediastinoscopy. Involvement of mediastinal nodes represents a contraindication to resection. Level of evidence, good; benefit, substantial; grade of recommendation, A 6. Patients with a potentially resectable, nonmetastatic Pancoast tumor (and good performance status) should undergo preoperative chemoradiotherapy prior to resection. A reasonable alternative for such patients is preoperative radiotherapy. Level of evidence, fair; benefit, moderate; grade of recommendation, B 7. At the time of resection of a Pancoast tumor, every effort should be made to achieve a complete resection. Level of evidence, good; benefit, substantial; grade of recommendation, A 8. Resection of a Pancoast tumor should consist of a lobectomy (instead of a wedge), as well as removal of the involved chest wall structures. Level of evidence, fair; benefit, moderate; grade of recommendation, B 9. For patients with a Pancoast tumor, postoperative radiotherapy is not recommended, in either completely or incompletely resected patients, because of lack of a demonstrated survival benefit. Level of evidence, poor; benefit, none; grade of recommendation, D 10. Patients with a good performance status and an unresectable but nonmetastatic Pancoast tumor should be considered for combination

	chemotherapy and radiotherapy with intent to cure. Level of evidence, poor; benefit, moderate; grade of recommendation, C 11. Palliative radiotherapy should be considered in patients who are not candidates for treatment with curative intent (*ie*, surgery, chemoradiotherapy etc.). Level of evidence, fair; benefit, moderate; grade of recommendation, B
Paragraph 2	T4No,1Mo Tumors
	Patient Selection and Workup Most patients with involvement of T4 structures have mediastinal node involvement as well. These patients should be treated with chemoradiotherapy, as is generally recommended for patients with stage IIIB NSCLC. However, selected patients with T4 involvement, but without mediastinal node involvement, can be viewed as candidates for surgery. Although many reports have demonstrated the technical feasibility of resection of T4 structures, fewer series have provided long-term survival data. The largest experience of resection for T4 involvement involved carinal resections, usually together with a right pneumonectomy (327 patients in whom long-term survival data were reported).[19] A moderate experience is available with left atrial involvement (85 patients), and a smaller experience has been reported with involvement of the superior vena cava (40 patients).[19] The fact that so few patients have been reported with long-term survival statistics underscores the fact that patients who are candidates for a surgical approach are extremely rare and highly selected. A mediastinoscopy should be performed even if a CT suggests no N2,3 involvement in patients with T4 tumors being considered for a surgical approach. This argument is based on the fact that CT evaluation of the mediastinum in central tumors has a high false negative rate. Furthermore, the operative mortality and the poor survival of T4N2,3M0 patients argues that surgical resection be undertaken only in carefully selected patients. For patients who are being considered for carinal resection, it may be best to perform mediastinoscopy at the same time as resection, in order to prevent scarring and therefore lack of mobility of the airways at the time of reconstruction.

Outcomes After Surgery

In a fairly large series from Japan involving an aggressive approach to T4 tumors, approximately one third of patients were able to undergo complete (R_0) resection, one third a microscopically incomplete resection (R_1), and one third a grossly incomplete resection (R_2).[20] The 5-year survival rates for these groups were 22%, 18%, and 0%, respectively.[20] No data are available regarding how often a resection can actually be carried out among patients with involvement of specific T4 structures.

The data regarding the outcome after resection in patients with carinal involvement shows an average 5-year survival of 26%. However, the survival comes at a price of an average operative mortality of 18% (range 7–29%). It should be noted, however, that the survival statistics have included all operative deaths as well. The fact that the best reported 5-year survival (42%) comes from the largest series,[21] which also reported an operative mortality of only 7%, can be interpreted to suggest that such resections should be undertaken only in experienced centers. Survival data for resections involving other T4 structures have involved fewer patients, making interpretation of the data difficult (Table 1). The survival of patients with left atrial involvement has been poor. In general, however, the survival of patients with involvement of other T4 structures has been similar to that reported for patients with carinal involvement.

Patients with involvement of T4 structures should be very carefully selected before undertaking surgical resection, because of the limited survival and the high mortality. This means that these patients should have a high likelihood of being able to tolerate a major operation from a general medical standpoint. This also means that the evaluations to rule out either mediastinal or extrathoracic metastases should be especially thorough and that the threshold for pursuing subtle abnormalities seen on imaging tests should be low.

Preoperative chemotherapy or chemoradiotherapy in patients with T4 tumors has been reported in several trials. A 5-year survival of 20% was reported among all patients in the largest trial (57 patients; 62% of whom underwent complete resection).[22] These results are encouraging, given that 60% of the patients entered in the study had T4N2M0 tumors by careful surgical staging. By comparison, 5-year survival results for chemoradiotherapy without surgery in patients with stage IIIA,B tumors have been approximately 9% and 14% in large randomized trials involving sequential or concurrent chemoradio-

	therapy, respectively.[23] However, these latter series have included both stage IIIA and IIIB patients and have not reported data separately or reported any data specifically in patients with T4N0,1M0 tumors. A retrospective analysis of the Southwest Oncology Group experience suggested that patients with T4N0,1M0 tumors benefited from preoperative chemoradiotherapy and surgery compared with treatment with chemoradiotherapy alone (2-year survival of 64% vs 33%).[24]
	Recommendations: T4N0,1M0 tumors 12. Patients with a clinical T4N0,1M0 NSCLC should be carefully evaluated (with imaging studies) for distant metastatic disease prior to considering surgical resection. Level of evidence, fair; benefit, substantial; grade of recommendation, B 13. Resection of T4N0,1M0 tumors in selected patients may result in better survival than chemoradiotherapy without resection. Level of evidence, poor; benefit, moderate; grade of recommendation, C 14. Mediastinoscopy should be done prior to surgical resection of patients with clinical T4N0,1M0 tumors. Level of evidence, fair; benefit, substantial; grade of recommendation, B
… etc.	
Paragraph 8	ISOLATED ADRENAL METASTASIS
	Patient Selection and Treatment Results Highly selected patients have been reported who have undergone resection of an adrenal metastasis from NSCLC with intent to cure. The overall 5-year survival for these patients has been 10 to 23%.[47,55,56] Survival after resection of the primary and the adrenal metastasis appears to be good primarily in patients without nodal involvement.[47,56] Other factors such as the histologic type, synchronous vs metachronous presentation, and ipsilateral vs contralateral location do not have prognostic value in the limited number of reported patients who underwent this treatment.[47,55,56]

	Recommendations: Isolated Adrenal Metastasis 32. Patients with an isolated adrenal metastasis from NSCLC should be considered for a curative approach. Level of evidence, poor; benefit, substantial; grade of recommendation, C 33. For patients with an isolated adrenal metastasis being considered for curative therapy, a careful search for other distant metastases should be carried out with imaging tests. Level of evidence, poor; benefit, substantial; grade of recommendation, C 34. For patients with a synchronous presentation of an isolated adrenal metastasis and a resectable primary lung cancer, mediastinoscopy should be done to rule out N2,3 involvement prior to resection. Level of evidence, poor; benefit, substantial; grade of recommendation, C 35. For carefully selected patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection of an isolated adrenal metastasis from NSCLC should be undertaken (as well as resection of the primary tumor). Level of evidence, poor; benefit, moderate; grade of recommendation, C 36. For patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection of an isolated adrenal metastasis should be undertaken. Level of evidence, poor; benefit, moderate; grade of recommendation, C

Appendix F

The macros.dtd

On this place, [URL#23] is recommended. It provides a HTML documentation of all elements used in the macros.dtd.

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GMT-LINK_EXT)+>
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        description CDATA #IMPLIED
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| GMT-LINK | GMT-LINK_EXT)*>
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separator | label)+>
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        name CDATA #REQUIRED
        label CDATA #IMPLIED
        description CDATA #IMPLIED
>
<!ELEMENT single-element-ref EMPTY>
<!ATTLIST single-element-ref
        name NMTOKEN #REQUIRED
        description CDATA #IMPLIED
        standalone (true | false) "true"
>
<!ELEMENT separator EMPTY>
<!ELEMENT label EMPTY>
<!ATTLIST label
        text CDATA #REQUIRED
>
```

The Independent Structure Macro

The following pages contain the complete source code of the independent structure macro file. The macro definition part consists of five macros. The "independent_structure" macro itself contains the independent structure and the other four macros comprise useful element sequences to expand the "independent_structure" macro. These macros were already introduced in section 8.2 when presenting the independent structure macro file as an example. But for completeness the preview of the plain source and the GMT's preview tree of all macros is provided in the following pages.

Source Code and Preview – plain source

Macro File: source code	Preview: plain source
<?xml version="1.0" encoding="UTF-8"?> <!-- edited with XMLSPY v2004 rel. 3 U (http://www.xmlspy.com) by Moser (Moser Ltd.) --> <!DOCTYPE gmt-macros SYSTEM "macros.dtd"> <gmt-macros> <macros-def> <macros-group description="macros to build an independent structure"> <macro name="library-info"> <element-ref name="library-info"> <attribute-ref name="title" value="%INPUT%"/> <attribute-ref name="version" value="1"/> <element-ref name="administrative-data"> <attribute-ref name="creation-date" value="%DATE%, %TIME%"/> <attribute-ref name="original-author" value="%USER%"/> </element-ref> </element-ref> </macro>	**Macro: library-info** <library-info title="%INPUT%" version="1"> <administrative-data creation-date="%DATE%, %TIME%" original-author="%USER%"/> </library-info>
<macro name="independent_structure"> <element-ref name="plan-group"> <element-ref name="plan"> <attribute-ref name="name" value="%INPUT%guideline_plan"/>	**Macro: independent_structure** <plan-group> <plan name= "%INPUT%guideline_plan">

```
            <element-ref name="plan-body">
                <element-ref name="subplans">
                    <attribute-ref name="type" value="unordered"/>
                    <element-ref name="wait-for">
                        <element-ref name="all"/>
                    </element-ref>
                    <element-ref name="plan-activation">
                        <element-ref name="plan-schema">
                            <attribute-ref name="name"
                                           value="$unorderedplan1$"/>
                        </element-ref>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
        <element-ref name="plan">
            <attribute-ref name="name" value="$unorderedplan1$"/>
        </element-ref>
    </element-ref>
</macro>
```

```
    <plan-body>
      <subplans
               type="unordered">
        <wait-for>
          <all/>
        </wait-for>
        <plan-activation>
          <plan-schema name=
            "$unorderedplan1$"/>
        </plan-activation>
      </subplans>
    </plan-body>
  </plan>


  <plan name="$unorderedplan1$"/>
</plan-group>
```

```
<macro name="single_plan-activation">
    <element-ref name="plan-activation">
        <element-ref name="plan-schema">
            <attribute-ref name="name" value="%INPUT%plan"/>
        </element-ref>
    </element-ref>
</macro>
<macro name="single_plan">
    <element-ref name="plan">
        <attribute-ref name="name" value="%INPUT%plan n"/>
    </element-ref>
</macro>
<macro name="comment">
    <element-ref name="comment">
        <attribute-ref name="text" value="%INPUT%"/>
```

Macro: single_plan-activation

```
<plan-activation>
  <plan-schema name="%INPUT%plan"/>
</plan-activation>
```

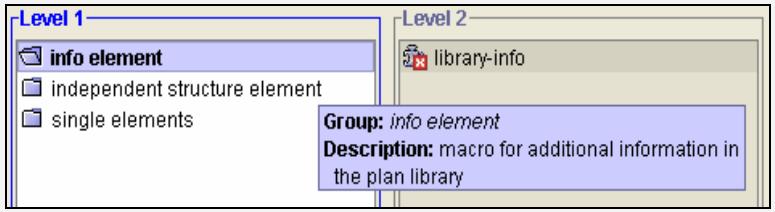
Macro: single_plan

```
<plan name="%INPUT%plan n"/>
```

Macro: comment

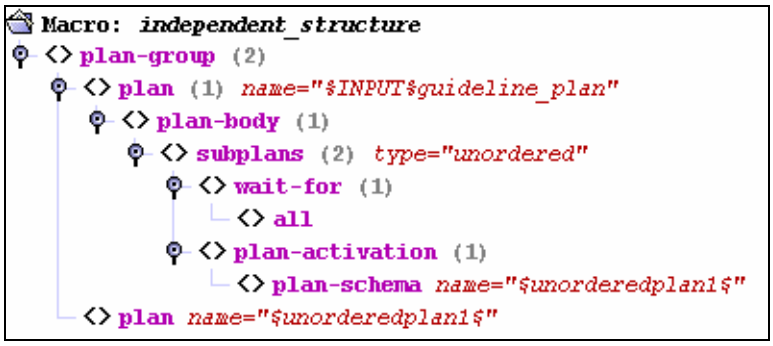
```
<comment text="%INPUT%"/>
```

```
                </element-ref>
            </macro>
        </macros-group>
    </macros-def>
    <structure-def>
        <group description="macro for additional information in the plan library"
                name="info element">
            <macro-ref name="library-info"/>
        </group>
        <group description="macro for the independent structure"
                name="independent structure element">
            <macro-ref name="independent_structure"/>
        </group>
        <group description="macro for single plan elements" name="single elements">
            <macro-ref name="single_plan-activation"/>
            <macro-ref name="single_plan"/>
            <macro-ref name="comment"/>
        </group>
    </structure-def>
</gmt-macros>
```

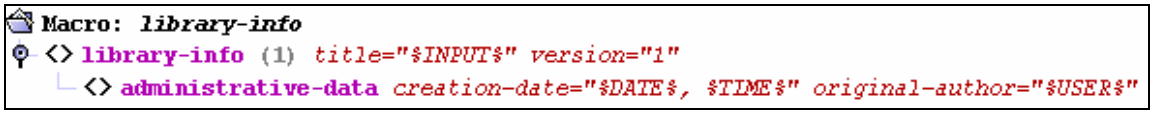


Preview – tree view

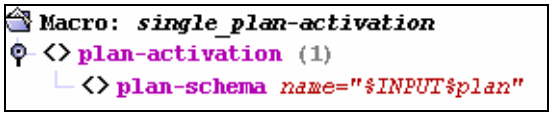
Macro “independent_structure”



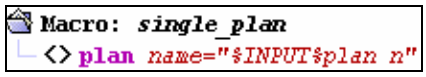
Macro “library-info”



Macro “single_plan-activation”



Macro “single_plan”



Macro “comment”

The XOR Structure Macro

The following pages contain the complete source code of the XOR structure macro file. The macro definition part of the XOR structure macro file consists of five macros. The "xor_structure" macro itself contains the XOR structure and the other four macros comprise useful element sequences to expand the "xor_structure" macro. For all macros the preview of the plain source is given and subsequent to the source code, the GMT's preview tree is given for the "xor_structure" macro.

Source Code and Preview – plain source

Macro File	Preview: plain source
<?xml version="1.0" encoding="UTF-8"?> <!-- edited with XMLSPY v2004 rel. 3 U (http://www.xmlspy.com) by Moser (Moser Ltd.) --> <!DOCTYPE gmt-macros SYSTEM "macros.dtd"> <gmt-macros> <macros-def> <macros-group description="macros to build a xor structure"> <macro name="library-info"> <element-ref name="library-info"> <attribute-ref name="title" value="%INPUT%"/> <attribute-ref name="version" value="1"/> <element-ref name="administrative-data"> <attribute-ref name="creation-date" value="%DATE%, %TIME%"/> <attribute-ref name="original-author" value="%USER%"/> </element-ref> </element-ref> </macro>	**Macro: library-info** <library-info title="%INPUT%" version="1"> <administrative-data creation-date="%DATE%, %TIME%" original-author="%USER%"/> </library-info>
<macro name="xor_structure"> <element-ref name="plan-group"> <element-ref name="plan"> <attribute-ref name="name" value="%INPUT%guideline_plan"/>	**Macro: xor_structure_macro** <plan-group> <plan name="%INPUT%guideline_plan"> <plan-body>

```
        <element-ref name="plan-body">
            <element-ref name="subplans">
                <attribute-ref name="type" value="any-order"/>
                <element-ref name="wait-for">
                    <element-ref name="all"/>
                </element-ref>
                <element-ref name="plan-activation">
                    <element-ref name="plan-schema">
                        <attribute-ref name="name" value="$plan1$"/>
                    </element-ref>
                </element-ref>
                <element-ref name="plan-activation">
                    <element-ref name="plan-schema">
                        <attribute-ref name="name" value="$plan2$"/>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
    </element-ref>
    <element-ref name="plan">
        <attribute-ref name="name" value="$plan1$"/>
        <element-ref name="plan-body">
            <element-ref name="subplans">
                <attribute-ref name="type" value="unordered"/>
                <element-ref name="wait-for">
                    <element-ref name="all"/>
                </element-ref>
                <element-ref name="plan-activation">
                    <element-ref name="plan-schema">
                        <attribute-ref name="name"
                                value="$unorderedplan1of1$"/>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
```

```
<subplans type="any-order">
  <wait-for>
    <all/>
  </wait-for>
  <plan-activation>
    <plan-schema name="$plan1$"/>
  </plan-activation>
  <plan-activation>
    <plan-schema name="$plan2$"/>
  </plan-activation>
</subplans>
</plan-body>
</plan>
```

```
<plan name="$plan1$">
  <plan-body>
    <subplans type="unordered">
      <wait-for>
        <all/>
      </wait-for>
      <plan-activation>
        <plan-schema name="$unorderedplan1of1$"/>
      </plan-activation>
    </subplans>
  </plan-body>
</plan>
```

```
        </element-ref>
        <element-ref name="plan">
            <attribute-ref name="name" value="$unorderedplan1of1$"/>
        </element-ref>
        <element-ref name="plan">
            <attribute-ref name="name" value="$plan2$"/>
            <element-ref name="plan-body">
                <element-ref name="subplans">
                    <attribute-ref name="type" value="unordered"/>
                    <element-ref name="wait-for">
                        <element-ref name="all"/>
                    </element-ref>
                    <element-ref name="plan-activation">
                        <element-ref name="plan-schema">
                            <attribute-ref name="name"
                                           value="$unorderedplan1of2$"/>
                        </element-ref>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
        <element-ref name="plan">
            <attribute-ref name="name" value="$unorderedplan1of2$"/>
        </element-ref>
    </element-ref>
</macro>
```

```
<plan name="$unorderedplan1of1$"/>

<plan name="$plan2$">
   <plan-body>
      <subplans type="unordered">
         <wait-for>
            <all/>
         </wait-for>
         <plan-activation>
            <plan-schema name="$unorderedplan1of2$"/>
         </plan-activation>
      </subplans>
   </plan-body>
</plan>

   <plan name="$unorderedplan1of2$"/>
</plan-group>
```

```
<macro name="single_plan-activation">
    <element-ref name="plan-activation">
        <element-ref name="plan-schema">
            <attribute-ref name="name" value="%INPUT%plan n"/>
        </element-ref>
    </element-ref>
</macro>
```

Macro: single_plan-activation

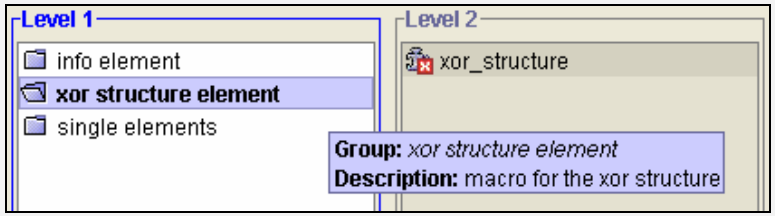
```
<plan-activation>
   <plan-schema name="%INPUT%plan"/>
</plan-activation>
```

```
            <macro name="single_plan">
                <element-ref name="plan">
                    <attribute-ref name="name" value="%INPUT%plan n"/>
                </element-ref>
            </macro>
            <macro name="comment">
                <element-ref name="comment">
                    <attribute-ref name="text" value="%INPUT%"/>
                </element-ref>
            </macro>
        </macros-group>
    </macros-def>
```

Macro: single_plan
<plan name="%INPUT%plan n"/>

Macro: comment
<comment text="%INPUT%"/>

```
    <structure-def>
        <group description="macro for additional information in the plan library"
                name="info element">
            <macro-ref name="library-info"/>
        </group>
        <group description="macro for the xor structure" name="xor structure element">
            <macro-ref name="xor_structure"/>
        </group>
        <group description="macro for single plan elements" name="single elements">
            <macro-ref name="single_plan-activation"/>
            <macro-ref name="single_plan"/>
            <macro-ref name="comment"/>
        </group>
    </structure-def>
</gmt-macros>
```



Preview – tree view

Macro “xor_structure”

The Recurring Structure Macro

The following pages contain the complete source code of the recurring structure macro file. The macro definition part consists of six macros. The "recurring_structure" macro itself contains the recurring plan and the guideline plan, where the recurring plan occurs. The other five macros comprise useful element sequences to expand the "recurring_structure" macro. For all macros the preview of the plain source is given. The "single_plan_incl_activation-part" macro has not yet been introduced. Therefore, this macro will be shown together with the "recurring_structure" macro in tree view subsequently.

Source Code and Preview – plain source

Macro File	Preview: plain source
<?xml version="1.0" encoding="UTF-8"?> <!-- edited with XMLSPY v2004 rel. 3 U (http://www.xmlspy.com) by Moser (Moser Ltd.) --> <!DOCTYPE gmt-macros SYSTEM "macros.dtd"> <gmt-macros> <macros-def> <macros-group description="macros to build a recurring structure"> <macro name="library-info"> <element-ref name="library-info"> <attribute-ref name="title" value="%INPUT%"/> <attribute-ref name="version" value="1"/> <element-ref name="administrative-data"> <attribute-ref name="creation-date" value="%DATE%, %TIME%"/> <attribute-ref name="original-author" value="%USER%"/> </element-ref> </element-ref> </macro>	**Macro: library-info** <library-info title="%INPUT%" version="1"> <administrative-data creation-date="%DATE%, %TIME%" original-author="%USER%"/> </library-info>
<macro name="recurring_structure"> <element-ref name="plan-group"> <element-ref name="plan"> <attribute-ref name="name" value="$RECURRINGPLANNAME$"/>	**Macro: recurring_structure** <plan-group> <plan name="$RECURRINGPLANNAME$"> <plan-body>

```
        <element-ref name="plan-body">
            <element-ref name="subplans">
                <attribute-ref name="type" value="unordered"/>
                <element-ref name="wait-for">
                    <element-ref name="all"/>
                </element-ref>
                <element-ref name="plan-activation">
                    <element-ref name="plan-schema">
                        <attribute-ref name="name"
                                value="$recurringplan1$"/>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
    </element-ref>
    <element-ref name="plan">
        <attribute-ref name="name" value="$recurringplan1$"/>
    </element-ref>
    <element-ref name="plan">
        <attribute-ref name="name" value="%INPUT%guideline_plan"/>
        <element-ref name="plan-body">
            <element-ref name="subplans">
                <attribute-ref name="type" value="unordered"/>
                <element-ref name="wait-for">
                    <element-ref name="all"/>
                </element-ref>
                <element-ref name="plan-activation">
                    <element-ref name="plan-schema">
                        <attribute-ref name="name"
                                value="$unorderedplan1$"/>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
    </element-ref>
```

```
            <subplans type="unordered">
                <wait-for>
                    <all/>
                </wait-for>
                <plan-activation>
                    <plan-schema name="$recurringplan1$"/>
                </plan-activation>
            </subplans>
        </plan-body>
    </plan>

    <plan name="$recurringplan1$"/>
    <plan name="%INPUT%guideline_plan">
        <plan-body>
            <subplans type="unordered">
                <wait-for>
                    <all/>
                </wait-for>
                <plan-activation>
                    <plan-schema name="$unorderedplan1$"/>
                </plan-activation>
            </subplans>
        </plan-body>
    </plan>
```

```
        <element-ref name="plan">
            <attribute-ref name="name" value="$unorderedplan1$"/>
            <element-ref name="plan-body">
                <element-ref name="plan-activation">
                    <element-ref name="plan-schema">
                        <attribute-ref name="name"
                                value="$RECURRINGPLANNAME$"/>
                    </element-ref>
                </element-ref>
            </element-ref>
        </element-ref>
    </macro>
```

```
<plan name="$unorderedplan1$">
  <plan-body>
    <plan-activation>
      <plan-schema
          name="$RECURRINGPLANNAME$"/>
    </plan-activation>
  </plan-body>
</plan>
</plan-group>
```

```
<macro name="single_plan-activation">
    <element-ref name="plan-activation">
        <element-ref name="plan-schema">
            <attribute-ref name="name" value="%INPUT%plan n"/>
        </element-ref>
    </element-ref>
</macro>
```

Macro: single_plan-activation

```
<plan-activation>
  <plan-schema name="%INPUT%plan"/>
</plan-activation>
```

```
<macro name="single_plan">
    <element-ref name="plan">
        <attribute-ref name="name" value="%INPUT%plan n"/>
    </element-ref>
</macro>
```

Macro: single_plan

```
<plan name="%INPUT%plan n"/>
```

```
<macro name="single_plan_incl_activation-part">
    <element-ref name="plan">
        <attribute-ref name="name" value="%INPUT%plan n"/>
        <element-ref name="plan-body">
            <element-ref name="plan-activation">
                <element-ref name="plan-schema">
                    <attribute-ref name="name"
                            value="$RECURRINGPLANNAME$"/>
                </element-ref>
```

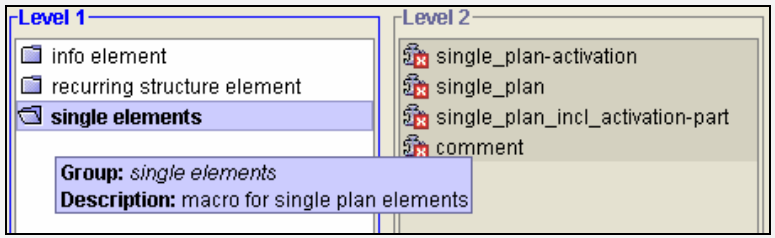
Macro: single_plan_incl_activation-part

```
<plan name="%INPUT%plan n">
  <plan-body>
    <plan-activation>
      <plan-schema
          name="$RECURRINGPLANNAME$"/>
    </plan-activation>
  </plan-body>
</plan>
```

```
                    </element-ref>
                </element-ref>
            </element-ref>
        </macro>
        <macro name="comment">
            <element-ref name="comment">
                <attribute-ref name="text" value="%INPUT%"/>
            </element-ref>
        </macro>
    </macros-group>
</macros-def>
```

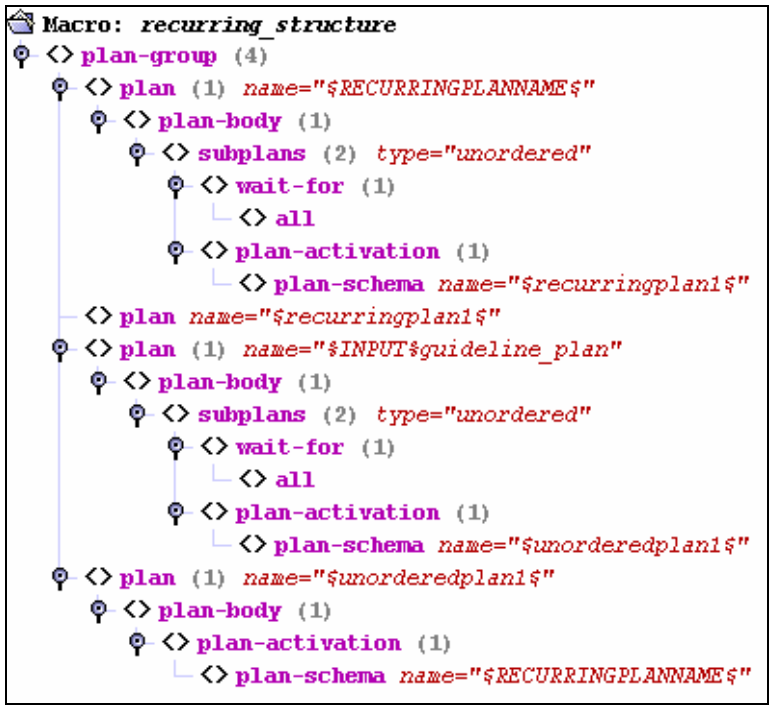
Macro: comment
<comment text="%INPUT%"/>

```
<structure-def>
    <group description="macro for additional information in the plan library"
           name="info element">
        <macro-ref name="library-info"/>
    </group>
    <group description="macro for the recurring structure"
           name="recurring structure element">
        <macro-ref name="recurring_structure"/>
    </group>
    <group description="macro for single plan elements" name="single elements">
        <macro-ref name="single_plan-activation"/>
        <macro-ref name="single_plan"/>
        <macro-ref name="single_plan_incl_activation-part"/>
        <macro-ref name="comment"/>
    </group>
</structure-def>
</gmt-macros>
```

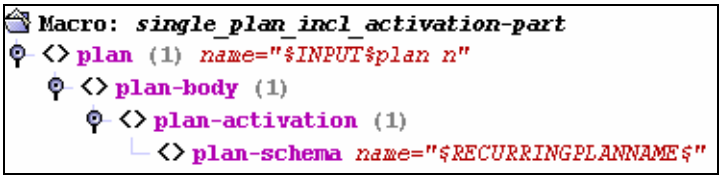


Preview – tree view

Macro “recurring_structure”

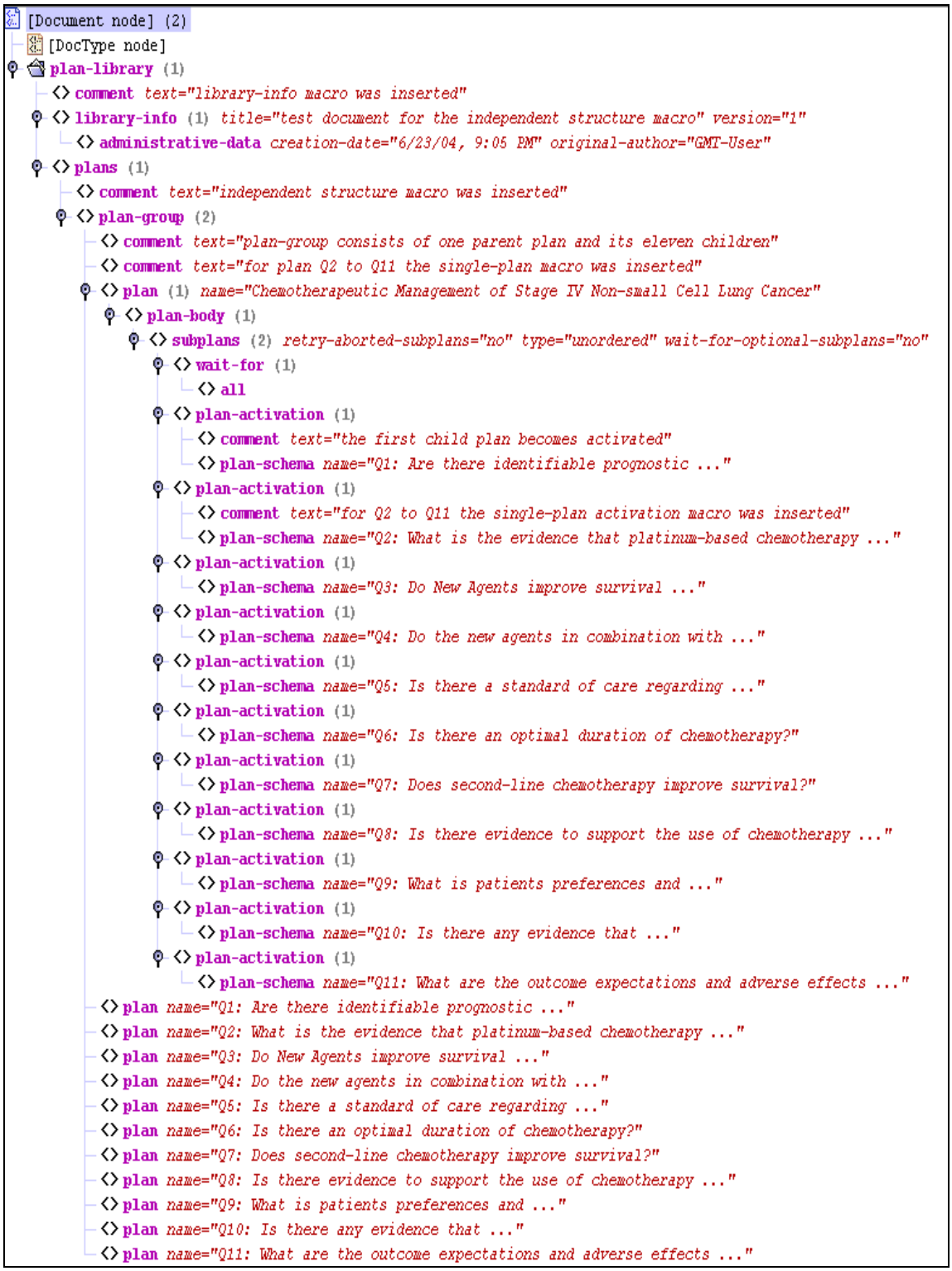


Macro “single_plan_incl_activation-part”



Structure of GL 1

The following Figure shows the structure of GL 1: Chemotherapeutic Management of Stage IV Non-small Cell Lung Cancer, authored in GMT by using the macros from the independent structure macro file.



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[Gordon et al., 1997]: Colin Gordon, Ian Herbert, Peter Johnson, Peter Nicklin, Philip Reeves. *Telematics for Clinical Guidelines: A Conceptual Modelling Approach*. Proceedings of MIE'97, 1997.

[Johnson et al., 2000]: Peter D. Johnson, Samson W. Tu, Nick Booth, Bob Sugden, Ian N. Purves. *Using Scenarios in Chronic Disease Management Guidelines for Primary Care*. In: Proc. AMIA Annual Symposium, 2000.

[Kosara and Miksch, 2001]: Robert Kosara, and Silvia Miksch. *Metaphors of Movement: A Visualization and User Interface for Time-Oriented, Skeletal Plans*. Artificial Intelligence in Medicine, Special Issue: Information Visualization in Medicine, pp. 111-131, 22(2), 2001.

[Miksch et al., 1997a]: Silvia Miksch, Yuval Shahar, Werner Horn, Christian Popow, Franz Paky, and Peter Johnson. *Time-Oriented Skeletal Plans: Support to Design and Execution*. In: S. Steel, R. Alami (eds.), Recent Advances in AI Planning – Fourth European Conference on Planning ECP '97 (EWSP'97), Springer, Lecture Notes in Artificial Intelligence (LNAI), Toulouse, France. 1997.

[Miksch et al., 1997b]: Silvia Miksch, Yuval Shahar, and Peter Johnson. *Asbru: A Task-Specific, Intention-Based, and Time-Oriented Language for Representing Skeletal Plans*. In: E. Motta, F. v. Harmelen, C.Pierret-Golbreich, I. Filby, N. Wijngaards (eds.), Proceedings of the 7th Workshop on Knowledge Engineering: Methods & Languages (KEML-97). Milton Keynes, UK, Open University. 1997.

[Miksch et al., 1998]: Silvia Miksch, Robert Kosara, Yuval Shahar, and Peter Johnson. *AsbruView: Visualization of Time-Oriented, Skeletal Plans*. Proceedings of the 4th International Conference on Artificial Intelligence Planning Systems 1998 (AIPS-98). Carnegie Mellon University, AAAI Press. 1998.

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