

Aus der  
Klinik für Pädiatrische Onkologie und Hämatologie  
Universitätsklinikum des Saarlandes  
Homburg/Saar  
Direktor: Prof. Dr. med. Graf

---

***Utilization of IT for Clinical Study Master-  
Protocol generation***

***Umsetzung eines Masterprotokolls  
für Klinische Studien in einer IT-Software***

DISSERTATION

ZUR ERLANGUNG DES GRADES EINES DOKTORS DER MEDIZIN

DER MEDIZINISCHEN FAKULTÄT

DER UNIVERSITÄT DES SAARLANDES

2016

vorgelegt von **Andreas Glatz**

geboren am **04.10.1988** in Fürth

# Danksagung

An dieser Stelle möchte ich mich bei all denjenigen bedanken, die mich während der Anfertigung dieser Dissertationsarbeit unterstützt und motiviert haben.

Mein ganz besondere Dank gilt meinem Doktorvater Herrn Prof. Dr. med. Norbert Graf für das interessante Thema, zahlreiche wertvolle Diskussionen und Anregungen sowie die materielle Unterstützung dieser Arbeit. Prof Graf war für mich jederzeit ansprechbar und Korrekturen und Hilfestellungen erfolgten stets zeitnah in einer sehr positiven Arbeitsatmosphäre.

Daneben gilt mein Dank auch der ObTiMA-Entwicklergruppe, Herrn Holger Stenzhorn, Herrn Stefan Theobald, Herrn Thomas Hemprich und Frau Dr. Yvonne Braun. Die Kollegen haben mir zahlreiche wichtige Hinweise zur Programm-erstellung gegeben und mich mit dem notwendigen technischen Support zur Integration des MasterProtocol-Creators in ObTiMA unterstützt. Ich bedanke mich weiterhin für den stets angenehmen und kollegialen Umgang sowie die vielen engagierten Diskussionen.

## Table of Contents

1	Summary.....	5
1.1	Zusammenfassung.....	5
1.2	Summary.....	6
2	Introduction .....	8
2.1	Evolution of Study Protocols .....	9
2.2	Necessity of Study Protocols.....	12
2.3	Potential Issues with Study Protocols.....	14
2.4	Guidelines .....	16
2.4.1	Trial Registration.....	16
2.4.2	Trial funding - Horizon 2020 .....	17
2.4.3	Most widely used Guidelines .....	18
2.4.3.1	ICH GCP Guideline .....	18
2.4.3.2	EQUATOR .....	19
2.4.3.2.1	CONSORT Statement.....	19
2.4.3.2.2	SPIRIT .....	20
2.4.3.2.3	TIDieR.....	20
2.4.3.3	CDISC .....	21
2.4.4	SIOPE Template.....	24
2.4.5	Current IT Tools supporting Protocol Creation .....	25
2.4.5.1	CT Toolkit.....	25
2.4.5.2	The Trial Protocol Tool.....	26
2.4.5.3	CDISC Protocol Wizard Demonstration Tool.....	28
2.4.5.4	The CONSORT based writing Tool .....	29
2.4.5.5	SWOG Protocol Reviewing System .....	31
2.4.5.6	Miscellaneous Tool .....	33

2.5	Conclusion: Current Situation.....	34
2.6	Aims and Objectives.....	35
3	Materials and Methods.....	36
3.1	Input into Design .....	36
3.1.1	Protocol Template.....	36
3.1.2	Legal Framework.....	36
3.1.3	ObTiMA .....	37
3.1.4	Design, Development and Program Structure .....	38
3.2	Infrastructure .....	39
3.2.1	Programm Environment.....	39
3.2.2	Server Software.....	39
3.3	Development Environment .....	41
3.4	Program Architecture .....	42
3.4.1	Spring Framework .....	42
3.4.2	Hibernate Framework .....	43
3.5	Paragraphs.....	43
3.6	Generation and Printout of the Study Protocol .....	46
3.7	Additional Libraries used by the Program.....	47
3.8	Software Licenses.....	47
4	Results .....	49
4.1	MasterProtocol-Wizard.....	51
4.1.1	Wizard Structure .....	51
4.1.2	Wizard Steps .....	52
4.2	MasterProtocol-Editor.....	55
4.2.1	Editor Structure.....	55
4.2.1.1	Paragraph Section .....	56

4.2.1.2	Editor Space.....	56
4.2.1.3	Help Section.....	58
4.2.2	Paragraphs.....	58
4.2.2.1	Types of Paragraphs.....	58
4.2.2.1.1	Type Text-Paragraph.....	58
4.2.2.1.2	Type Resources-Paragraph.....	60
4.2.2.1.3	Type Personnel-Paragraph.....	62
4.2.2.1.4	Type Table of Contents-Paragraph.....	70
4.2.2.1.5	Type Amendment-Paragraph.....	72
4.2.2.2	Folders.....	75
4.2.2.3	Customizing the Protocol.....	76
4.2.2.3.1	Move and delete Paragraph.....	76
4.2.2.3.2	Create new Paragraph.....	77
4.2.2.3.3	Edit Paragraph Settings.....	78
4.2.2.3.4	Create new Folders.....	79
4.2.3	Internationalization.....	79
4.2.4	Overview over Paragraphs in various Languages.....	81
4.2.5	PDF Export.....	83
4.2.6	Editor Settings.....	84
4.2.6.1	General.....	84
4.2.6.2	Language.....	85
4.2.6.3	Editor.....	85
4.2.6.4	PDF Style.....	87
4.2.6.4.1	Page Style.....	87
4.2.6.4.2	Header/Footer.....	88
4.3	MasterProtocol-Helpcenter.....	89

5	Discussion.....	90
5.1	Solution .....	90
5.2	Programm Advantages.....	94
5.3	Comparison to other Programs available .....	95
5.4	Limitations .....	97
5.5	Perspectives.....	98
6	Appendix.....	99
6.1	References.....	99
6.2	List of Tables.....	108
6.3	List of Figures.....	109
6.4	SIOPE-TEMPLATE .....	111

# 1 Summary

## 1.1 Zusammenfassung

Voraussetzung für eine valide klinische Studie sind umfassende, lückenlose, schriftlich niedergelegte Rahmenbedingungen. Bedingt durch die Vielzahl experimenteller, ethischer und juristischer Anforderungen genügen viele Studienprotokolle den GCP (**G**ood **C**linical **P**ractice) Mindestanforderungen nicht.

Im Rahmen dieser Arbeit konnten alle Erfordernisse zur Generierung eines Studienprotokolls entsprechend den Mindestanforderungen der GCP erstmals vollständig in Software übertragen werden. Die Software basiert auf dem SIOPE (**E**uropean **S**ociety of **P**ediatric **O**ncology) Template. Es lässt sich sehr einfach an individuelle Benutzeranforderungen und verschiedene Gebiete klinischer Forschung anpassen. Die Software unterstützt sowohl Single- wie auch Multicenter-Studien und ist in der Lage, mehrsprachige Protokolle zu generieren. Durch eine fehlertolerante, grafische Benutzeroberfläche und umfangreiche Hilfe-Funktionen können auch unerfahrene Anwender perfekte Studienprotokolle erstellen. Das

Programm ist Web-basiert, es ermöglicht simultanen Zugriff mehrerer Anwender und alle Daten stehen den autorisierten Benutzern sofort zur Verfügung. Das fertige Protokoll ist online verfügbar und kann als PDF ausgedruckt werden. Anwenderseitig ist lediglich ein Laptop/PC, ein handelsüblicher Web Browser und Internetzugang erforderlich.

Ein besonderes Augenmerk wurde auf Datensicherheit, Zugriffskontrolle und Audit Trail gelegt, welche lückenlos gewährleistet sind. Die Software ist in ObTiMA (**O**ntology **b**ased **T**rial **M**anagement **A**pplication) integriert.

## 1.2 Summary

Only a complete and very comprehensive protocol enables a valid clinical study. Due to the highly diverse experimental, ethical and legal requirements many protocols do not meet the GCP (**G**ood **C**linical **P**ractice) standard.

Through this work all requirements could completely be mapped in software for the first time. The program is based on the SIOPE (**E**uropean **S**ociety of **P**ediatric **O**ncology) template and it is also easily extendible and adaptable to any other area of clinical research. The software supports single- and multicenter studies and generates multilingual protocols. Even inexperienced users can generate a perfect study protocol guided by a failure preventing graphical user interface and a highly elaborated help system. The program is web based and supports simultaneous use by multiple persons. All data entered are immediately available for all authorized users and the protocol can be printed out at any location. There is no installation or maintenance work on the part of user required, just a PC or laptop, internet access and a common web browser is necessary for protocol generation.

Access and version control, personnel data protection and audit trail are seamlessly ensured. The software is integrated in ObTiMA (**O**ntology **b**ased **T**rial **M**anagement **A**pplication).





## 2 Introduction

Clinical studies are conducted to generate evidence-based data to support drug development up to market approval and thus establish new therapies. The legal environment has rapidly evolved throughout the recent decades and today there are plenty of statutory provisions worldwide implemented. Study design, execution and documentation are subjects to these detailed regulations. Although a certain degree of standardization has been reached, there are still differences with regard to national legislation. The situation is less confusing within the EU as there are EU Directives dealing with this topic.

Basis of any study is a protocol that defines any detail of the clinical trial. This reaches from objectives through execution and evaluation to documentation. To meet this objective, many details must be addressed. Among those there are purpose and ethology, organization, trial population, personnel involved, schedule for monitoring, evaluation criteria, data integrity, safety of individuals affected and many more. In addition there might be a need for multilingual protocols and in single and multi-center trials one unique set of data and version control must be ensured. In addition amendments of protocols need to be handled according to GCP (Good Clinical Practice) criteria.

It is also important to remember that statutory requirements must be complied in detail. Even minor deviations might lead to invalid or doubtful study results. In addition, there are plenty of highly sensitive personal data that must be protected against misuse. As of today, all these requirements are mainly met by very comprehensive and elaborated paper based documentation. Despite of all efforts, a lack of consistency or gaps in the protocols led to unnecessary high cost or even repetition of a complete study.

## 2.1 Evolution of Study Protocols

The current state of the art study protocols are very extensive and highly elaborated. They represent a comprehensive and precise instruction of the study and all study related matters. This is required to ensure reproducibility and integrity of the trial results. The current format has only evolved since a few decades.

The first medical studies were performed without any systematic planning and results were achieved by chance. One of these very early studies was performed in 1537 by the French surgeon Ambroise Paré. He treated wounded soldiers with boiling oil, which was the “gold standard” at this time. When he ran out of oil he utilized a mixture of egg yolk, rose oil and turpentine to cover the open wounds. Healing was much faster and issues as infects and others were significantly reduced compared to the previous treatment [1].

It took approximately another hundred years until natural science in the today sense started to evolve and systematic investigations became more and more applied to problem solving. The first known “clinical study” was performed in 1747 by James Lind. He was a physician in the British Royal Navy and is today known as the discoverer of the scorbutic therapy. On the sailing vessel HMS Salisbury he was confronted with 12 sailors being ill with scurvy. Each two of them received well defined but different kind of food. Based on this trial he draw the conclusion that oranges and citrons are the most effective scurvy therapy [2].

It took another hundred years until understanding of clinical studies and natural science methods evolved to a degree that some elements of current standard occurred in trials. First time placebo controlled, randomized double blind studies were applied in the beginning of the 19<sup>th</sup> century to generate medical data [3].

However, at this time there have not been any rules and regulations with regard to safe and human study execution. The first ethical codex addressing this issue, the Berlin Codex, was set up in the year 1900. It was initiated by press publication of several inhuman studies. Much later, the more comprehensive “Reichsrundschreiben 1931” replaced the Berlin Codex [4]. All this progress was lost during the

Second World War [5] and detainees, disabled people and prisoners of war have been misused for medical experiments [6].

Triggered by these shocking incidents the first worldwide recognized codex was issued in 1947. It was included in the verdicts against National Socialist physicians in the Nuremberg Trials [7]. This Codex comprised of 10 paragraphs codifying human rights and voluntary study participation. It gave priority to physical and psychological integrity over all other considerations [8]. A closer look reveals close links to the “Reichsrundschreiben 1931” [5].

Based on the Nuremberg Codex the Helsinki Declaration was issued by the World Medical Association in 1964. The Helsinki Declaration is much more detailed than its predecessors. In addition to the human rights, guidelines are included concerning risk assessments, minimal scientific requirements, necessity of a research protocol, vote of an Ethical Committee, the patient information, the “Informed Consent” and some more [9]. This guideline is still accepted all over the Western Hemisphere and many other rules and regulations refer to it [10]. The World Medical Association has regularly updated the Helsinki Declaration and the last version was issued at the 64<sup>th</sup> WMA General Assembly in Fortaleza, Brazil, in October 2013.

The FDA<sup>1</sup> conducted the first transcription of this guideline into a national law, the “National Research Act”, in 1974. Among others, this was triggered by the thalidomide scandal [11].

In context with the international harmonization of rules, regulations and guidelines among the USA, Australia, Japan and Europe, the ICH GCP Guideline [12] (International **C**onference on **H**armonisation **G**ood **C**linical **P**ractice) was issued in 1996 [13]. Unlike the Declaration of Helsinki, the ICH GCP Guideline gives a clear and detailed guidance on preparation, execution and documentation of a study. A list of requirements concerning a study protocol is given in chapter 6. It is important to keep in mind that ICH GCP and the Helsinki Declaration are guidelines only, which represent “current state of research”, but they are no legally binding jurisdiction. Thus, the guidelines need to be transposed into national law. For the

---

<sup>1</sup> U.S. Food and Drug Administration

European Union this was done by the EU Directives 2001/20/EG (Clinical Trials Directive) [14] and 2005/28/EC (Good Clinical Practice Directive) [15]. In accordance to the EU regulations, these directives were implemented in German law by the 12<sup>th</sup> novel of the German Drug Law (“Arzneimittelgesetz”, [16]) and the GCP-Decree (“Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen“, [17]), [18], ([19], pp. 13-17).

All international Pharmaceutical Companies build on the ICH GCP Guideline that is overlapping more than 90% with national laws in US, Europe and Japan ([19], p. 39).

## 2.2 Necessity of Study Protocols

Regarding the necessity of study protocols within the European Union, one has to differentiate between two types of studies. The first type is the Clinical Study, the other is the Non-Interventional Study. Definitions of both are given in the 2001/20/EG Clinical Trials Directive.

*“Clinical Trial’: Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.” ( [14], Article 2(a))*

*“Non-Interventional Trial’: a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.” ( [14], Article 2(b))*

A study protocol is only mandatory for clinical trials. The initiator of the study must set it up and it must cover many different subjects. Mandatory subjects are goals and objectives, methodology, study population, inclusion and exclusion criteria, risk assessment, statistical methods, conflicts of interest and others. The final protocol must be complete and comprehensive to give precise instructions for execution and evaluation of a study. Sponsors and scientists must find a detailed guidance how to act. Participants, the Ethical Committee and the Review Boards must have the opportunity to unequivocally understand any aspect of the study and there must be

no room for individual interpretation. A precise description is a prerequisite for reproducibility of the trial and traceability of study conclusions by the reviewer.

There are more reasons for this requirement. A precise and detailed protocol avoids amendments of the finalized and approved document. If anything needs to be modified or supplemented at this stage or if a CRF (Case Report Form) requires additional data, the protocol must be updated and dependent on the impact of the change it might need re-approval by the supervising authorities ( [17], §10 Nachträgliche Änderungen). Finally, unidentified elements or gaps might jeopardize the entire study results.<sup>2</sup>

The required content of a study protocol has been specified first time by just one single paragraph in Article 22 of the Declaration of Helsinki. Today it is required by Article 2(a) of the Directive 2001/20/EG (Clinical Trials Directive) of the European Union. However, in this Directive still there is only a brief definition, leaving the applicants some room for interpretation:

*„‘Protocol’: a document that describes the objective(s), design, methodology, statistical considerations and organization of a trial. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments.“ ( [14], Article 2(h))*

Meanwhile there are many other documents and guidelines available, which give additional guidance concerning protocols. Among these there is chapter 6 of the ICH GCP Guideline, which is a very valuable supplementation of the Declaration of Helsinki. This will be described in chapter 2.4.3 Most widely used Guidelines.

In order to initiate a clinical study, the protocol must be completed. Only based on the protocol and some supporting documents the study can be endorsed by the supervising agency and an ethical committee ( [17], §7 Antragstellung).

---

<sup>2</sup> Details see Chapter 2.3 Potential Issues with Study Protocols

## 2.3 Potential Issues with Study Protocols

Study protocols are not only required to register and execute clinical trials, but they affect the scientific validity of published reports as well. Since many details need to be taken into account and there is a lack of clarity with some guidelines, rather frequently insufficient protocols have been used. There are many research papers and review articles dealing with this issue. To identify potential discrepancies with regard to protocols and published study results, experienced scientists have reviewed publications. With a high proportion of clinical trials, a bias has been identified between the protocol, the reporting and execution of the clinical study. There have not been just one but several critical points causing issues [20], [21], [22], [23].

The following example, taken from a study performed by Julie Pildal et al. "Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study", illustrates this statement. The authors reviewed 102 clinical studies, which have been approved in 1994/95 by the Ethical Committee of Copenhagen and Frederiksberg [24].

Objective of the review was the comparison of trial protocols and corresponding publications with regard to an adequate allocation concealment of randomized clinical trials. Depending on the evaluation criteria deviations have been identified with 83 to 96 out of the 102 studies. Only 15 to 20 gave a distinct description of the allocation concealment. In addition there have been discrepancies between the protocols and the publications. In the majority of all cases, these discrepancies were either not or at least not sufficiently explained.

The authors concluded that these studies overestimated the treatment effect by 20 to 30%:

*„Our results make it reasonable to assume that the empirical surveys, which show a 20-30% exaggeration of the treatment effect for trial publications with unclear or inadequate allocation concealment, included some trials with*

*allocation concealment that was adequately carried out but insufficiently reported.” [24]*

Although the reviewed studies have been initiated in 1994/95, there is no doubt that issues continue until today. Tammy Hoffmann et al. reviewed 137 publications dated from 2009 with regard to the description of the applied interventions. Only 39% of these met the criteria of an adequate description. Root causes might have been vague guidelines or lacking protocol information. The protocol constituents have been either badly or not defined at all. Based on these facts the authors draw another conclusion:

*„ If trial reports do not have a sufficient description of interventions, other researchers cannot build on the findings, and clinicians and patients cannot reliably implement useful interventions. Improvement will require action by funders, researchers and publishers, aided by long term repositories of materials linked to publications.” [25]*

Inadequate descriptions of protocol items have been confirmed by another recent review. There were failures found regarding the patient-reported outcome and these could be traced back to the fact, that the patient-reported outcome assessment guidelines were inconsistent and difficult to access [26].

Even reporting deficiencies, which seem to be negligible, should not be underestimated. If “ghost writers” are utilized but not revealed, it cannot be excluded that a conflict of interest affects transparency and significance of the study. An investigation, performed in 2007, indicated that these problems occurred in a significant number of studies sponsored by Pharmaceutical Industry [27].

All these issues are even more severe as they do not only affect a single study but might lead to wrong information appearing in scientific literature available to healthcare professionals [28].



In accordance to EQUATOR network (**E**nhancing the **Q**UAlity and **T**ransparency **O**f health **R**esearch)<sup>3</sup> the identified problems are summarized in a paper published in BMC Med in 2010 [29] giving the following list:

- *Non-reporting or delayed reporting of entire studies*
- *Incomplete reporting of the study in relation to study findings*
- *The omission of crucial information in the description of research methods and interventions*
- *Omissions or misinterpretation of results in abstracts*
- *Inadequate or distorted reporting of harms*
- *Confusing or misleading presentations of results, data and graphs*

## **2.4 Guidelines**

During the recent years, many guidelines and protocol templates have been published to improve quality of study protocols. These documents list items, propose concrete protocol structure and give guidance to authors how to set up a state of the art protocol.

### **2.4.1 Trial Registration**

The Declaration of Helsinki requires official registration of any clinical trial with a study register. Within EU it is stipulated by the Directive 2001/20/EC that any clinical study being performed within the EU must be registered in the EudraCT (**E**uropean **U**nion **D**rug **R**egulating **A**uthorities **C**linical **T**rials) database [30]. This registration is mandatory and without a clinical study should not be carried out. In addition to EudraCT there are several other organizations available for registration. Among those there are the WHO (**W**orld **H**ealth **O**rganization) and the U.S. FDA (**F**ood and **D**rug **A**dministration of the USA).

There are many very valid reasons for study registration. Scientists and patients can easily get an overview over current research and the publication bias is significantly

---

<sup>3</sup> Description see Chapter 2.4.3.2 EQUATOR

reduced. Studies with unexpected or undesirable outcome cannot be excluded from publication [31], they must be made public. As important, the registration enforces standardization and compliance to the ethical standards. This is effectuated by the „minimal dataset“ required to register the study/protocol with a study register. The minimal dataset required for EudraCT registration is defined in the document “CT 5.2 EudraCT core data set” [32]. However it is important to know, that this data set covers minimal standards only. It is not sufficient to set up a protocol just based on the above referenced document. To generate a complete and comprehensive study protocol it is essential to consider additional guidelines.

#### **2.4.2 Trial funding - Horizon 2020**

A basic study data set is not only required for trial registration but it is a prerequisite for any financial support of public and private sponsors. One of the most impactful funding programs is Horizon 2020 [33]. This largest subsidiary program of the European Union is intended to promote science and innovation with 80 billion Euro in the period 2014 to 2020.

In order to get access to this program the applicant must provide comprehensive documentation with regard to objectives, methodology and financials of a clinical trial. In September 2015, a template has been issued „*Template for essential information to be provided for proposals including clinical trials / studies / investigations*“ [34], which precisely stipulates the requested data. Many of these are identical with those required for study registration.

*„For each clinical study performed within the scope of the proposal, information on the issues listed below should be provided, compiled into one single document per proposal based on this template. Each section must be shortly and concisely described. In case one or more issues do not apply to a particular study, please briefly explain/justify.“* [34]

### **2.4.3 Most widely used Guidelines**

Meanwhile there are plenty of guidelines available. Many organizations and enterprises have issued proprietary guidelines [35], [36], [37], [38], [39], [40], [41]. There are many common elements among these guidelines but there are significant differences as well. Some of the guidelines are incomplete, and several important items are not included at all. Another widespread deficiency is missing explanation in relation to guideline development and evidence of items is not always given [42]. There are some state of the art frequently used and international accepted guidelines available. These are described below.


#### **2.4.3.1 ICH GCP Guideline**

The ICH GCP (International **C**ommittee on **H**armonization of **G**ood **C**linical **P**ractice) Guideline was developed by an international work group and it is accepted by the USA, Australia, Japan and the EU. In paragraph 6 of this guideline 16 chapters are given concerning mandatory subjects of a study protocol. The subject of each of the chapters is precisely stipulated. The guideline sets a standard for patient protection and data integrity ([19], p. 39). The 16 chapters are as follows:

1. General Information
2. Background Information
3. Trial Objectives and Purpose
4. Trial Design
5. Selection and Withdrawal of Subjects
6. Treatment of Subjects
7. Assessment of Efficacy
8. Assessment of Safety
9. Statistics
10. Direct Access to Source Data/Documents
11. Quality Control and Quality Assurance
12. Ethics
13. Data Handling and Record Keeping
14. Financing and Insurance
15. Publication Policy
16. Supplements

### 2.4.3.2 EQUATOR

The EQUATOR (Enhancing the **QUAL**ity and **TR**ansparency **Of** Health **R**esearch) network was founded in 2008. It represents an initiative of international scientists with exceptional expertise concerning test methodology, reporting and publication. Objective of the network is improvement of scientific reporting by promotion of highly precise and transparent guidelines. To set a standard, many of the existing guidelines were reviewed and prototypes were selected [29]. Some of the best in class guidelines are given in Figure 1. These and some more are accessible at the EQUATOR network website [43]. As the work continues it is recommended to repeatedly access the website.



<u>Randomised trials</u>	<u>CONSORT</u>	<u>Extensions</u>	<u>Other</u>
<u>Observational studies</u>	<u>STROBE</u>	<u>Extensions</u>	<u>Other</u>
<u>Systematic reviews</u>	<u>PRISMA</u>	<u>Extensions</u>	<u>Other</u>
<u>Case reports</u>	<u>CARE</u>		<u>Other</u>
<u>Qualitative research</u>	<u>SRQR</u>	<u>COREQ</u>	<u>Other</u>
<u>Diagnostic / prognostic studies</u>	<u>STARD</u>	<u>TRIPOD</u>	<u>Other</u>
<u>Quality improvement studies</u>	<u>SQUIRE</u>		<u>Other</u>
<u>Economic evaluations</u>	<u>CHEERS</u>		<u>Other</u>
<u>Animal pre-clinical studies</u>	<u>ARRIVE</u>		<u>Other</u>
<u>Study protocols</u>	<u>SPIRIT</u>	<u>PRISMA-P</u>	<u>Other</u>

Figure 1: Best in Class Guidelines, recommended by EQUATOR [43]

The most relevant EQUATOR recommendations concerning randomized clinical trials are presented in the next three chapters.

#### 2.4.3.2.1 CONSORT Statement

The CONSORT Statement (**C**onsolidated **S**tandards **o**f **R**eporting **T**rials, [44]) is frequently utilized and widely accepted [45]. This guideline was published first time

in 1996 [46]. Since then it was continuously improved and new revisions were released in 2001 [47] and 2010 [45]. Essence of the CONSORT Statement is a set of minimal requirements concerning reporting and publication of randomized clinical trials. The current version provides a checklist with 25 items and a flow chart. This checklist can be downloaded from the CONSORT Statement website and there are detailed explanations and examples given. It was proven that utilization of the CONSORT checklist significantly enhances quality of trial reports [48]. However, there is still a need for improvements. Despite the CONSORT Statement there are still gaps and deficiencies in a significant number of reports. It can be assumed that the CONSORT Statement was not used or has not been fully understood or misinterpreted by the authors [49].

#### **2.4.3.2.2 SPIRIT**

The SPIRIT (**S**tandard **P**rotocol **I**tems: **R**ecommendations for **I**nterventional **T**rials, [50]) initiative was founded in 2007 and the first result was published in 2013. This guideline is applicable for study protocols of randomized clinical trials and it consists of 33 items [51]. These items define the minimal protocol standard and they were selected based on expert interviews [52]. Several of these items have been taken over word by word from the CONSORT 2010 Statement [53]. By analogy with the CONSORT Statement, explanations are provided for each item and examples are given [54].

#### **2.4.3.2.3 TIDieR**

Despite SPIRIT and CONSORT Statement, interventions in protocols and reports are often poorly described. To improve this issue the TIDieR (**T**emplate for **I**ntervention **D**escription and **R**eplication) was published in 2014. It includes a 33 items list which should be used in extension to the CONSORT and SPIRIT checklists. The TIDieR documents can be downloaded from the Equator Network homepage [55], [56].

### 2.4.3.3 CDISC

The CDISC (**C**linical **D**ata **I**nterchange **S**tandards **C**onsortium) is a global non-profit organization. This organization aims to establish platform independent electronic data models to record, transmit and publish clinical study data [57].

The CDISC has released several data models concerning electronic storage and data transfer in the XML<sup>4</sup> format. The FDA accepts these standards and study data can be submitted in this format [58].

One of the models developed by the CDISC is the **O**perational **D**ata **M**odel (ODM). The first version was issued in 1999. CRFs (**C**ase **R**eport **F**orms) were the focus of this edition. Since then some data fields have been attached to enable electronic storage of clinical study protocols but this still does not cover the complete protocol.

*“ODM constructs for value sets, form sections and study events may also provide guidance for developers of electronic data capture system and contribute to better data structure compatibility across studies. The current ODM version 1.3.2 has limited support for capturing full protocol and study registration data but supports case report form representation well (in the design phase and with patient-level data). These limitations exist mainly because this was not the original use case for creating the standard.” [59]*

In 2012 the CDISC published a model, specific for study protocols, called the CDISC **P**rotocol **R**epresentation **M**odel (PRM). It was developed with assistance of the **E**uropean **M**edicines **A**gency (EMA) and the FDA and it was designed to support study protocol generation and trial registration. This model covers all essential items of a study protocol. All over all there are 300 items included, among those there are “Trial Objective”, „Phase“, and “Subject Age”.

The model is intended to provide a standardized dataset, which can be screened electronically. Like the ODM, data fields are not filled with running text but with

---

<sup>4</sup> XML (Extensible Markup Language): Computer language, which supports storage of hierarchical structured data

keywords. The item “degree of blind” for example is just filled with “double-blind”, “single-blind” or “not-blind”.

As Figure 2 demonstrates, there is a significant difference between a “traditional” study protocol in the upper part and the CDISC Protocol Representation Model in the lower part of the figure. In the CDISC model there are just keywords left, which otherwise would be hidden in the text [60].

A Document Example:  
Structuring Information by “Meta” Information

**3.1. Summary of Study Design**  
This is a prospective, randomized, **double-blind**, double-dummy, placebo controlled, forced-titration, multicenter, **parallel group trial**. **Stage I or II hypertensive patients, age 18 years of age or older**, who meet all other inclusion and exclusion criteria and successfully complete the placebo run-in period will be randomized at the site level.

**Configuration**
**Population disease description**
**Degree of blind**

**Subject age description**

Source: Kristin O'Connor

A Document Example:  
Structuring Information by “Meta” Information

“Meta” Information about Content	Content
Subject age description	Age 18 years of age or older
Configuration	Parallel group trial
Population disease description	Stage I or II hypertensive patients
Degree of blind	Double-blind

**Much More Useful!**

**Figure 2: Difference between a traditional Study Protocol and the CDISC Protocol Representation Model [60]**

The single items of the model are correlated by the UML diagram ([61], p. 496). An excerpt of the UML diagram is shown in Figure 3. The items are framed by squares and the lines indicate the correlations among these. The following example is given to better understand the basics of the UML model. The red box „Study Conduct Sub-Domain::StudySite“, for example, symbolizes a study site. The other boxes represent many other study data, among these there is the postal address of the study site “Study Conduct Sub-Domain::StudySiteContact“. The study site and its postal address are correlated. Therefore they are linked by the red line. As there is no direct correlation of the study site with other items (frames) in the diagram, they are not connected by a line.

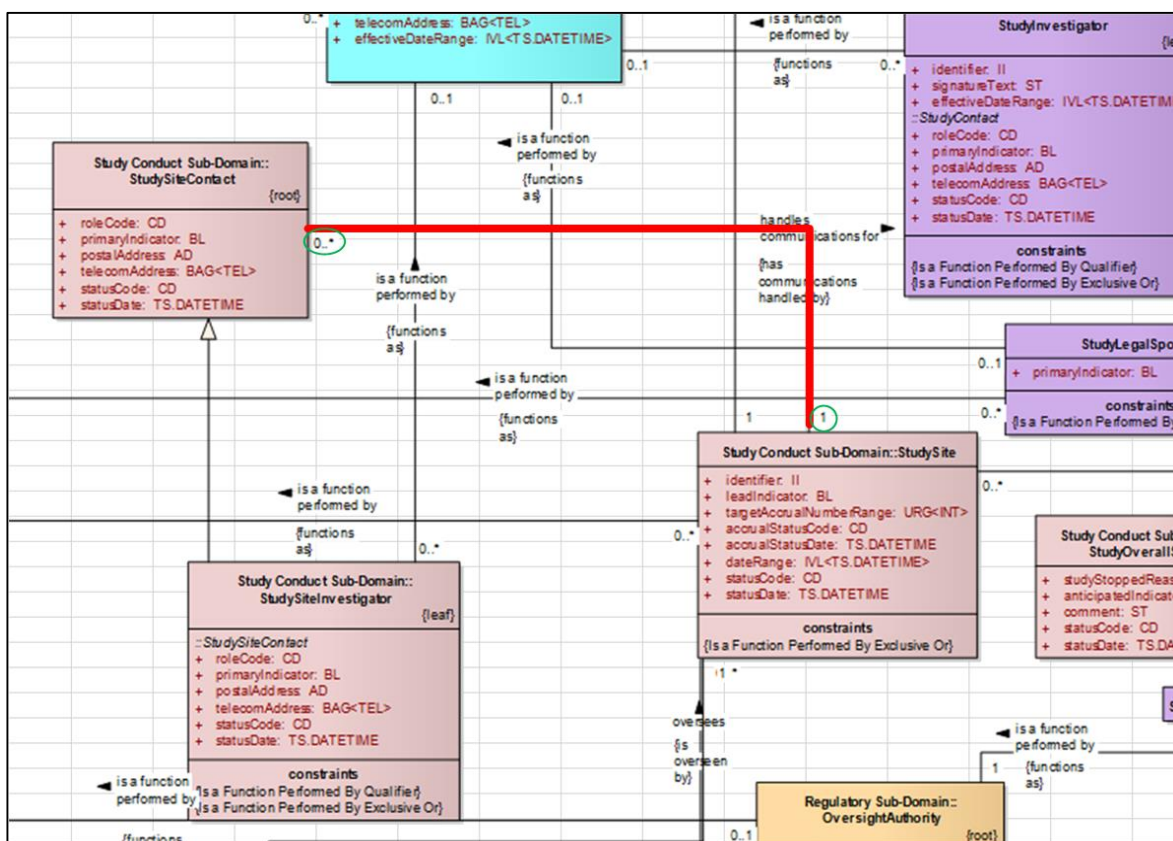


Figure 3: UML Diagram of the Protocol Representation Model [103]

However, as pointed out by the authors, this concept “was found to be too technical for ready use by certain target audiences” [60]. To simplify the concept, a word document has been issued focusing on the 30 most important items of a study protocol. It is very similar to the table, given in the lower part of Figure 2 and it



neglects the interactions among the items. Once the simplified template is populated with the study data, the document represents the key information of a clinical study [60].

#### **2.4.4 SIOPE Template**

In addition to the generic guidelines, which are applicable to all studies, it can be beneficial to have more specific guidelines which are tailor-made for a distinct field of research. This is specifically valid for studies concerning pediatric oncology. There are few patients only in different pediatric cancers and therefore it is difficult to obtain funding for this research as there is little pay back in this orphan drug area. To increase efficiency, reduce cost and bureaucratic hurdle a specific template was proposed for pediatric oncology. This template was developed by a cooperation of SIOPE (**E**uropean **S**ociety of **P**ediatric **O**ncology) and the ENCCA (**E**uropean **N**etwork of **C**ancer in **C**hildren and **A**dolescents). The template [41] is designed in accordance to the ICH GCP Guideline and the EU Clinical Trials Directive (2001/20/EC) and it entails all items necessary for clinical trials. Requirements for each item are thoroughly explained supporting a protocol author to achieve a perfect result. In addition data structure and format of a protocol are proposed as well. These advantages should not be underestimated as it facilitates the work of authors and prevents gaps in protocols. Therefore the creators of the SIOPE template explicitly point out that modification of the protocol format should be kept to a minimum [62].

## 2.4.5 Current IT Tools supporting Protocol Creation

### 2.4.5.1 CT Toolkit

A first attempt of IT support for study development and protocol generation is the „Clinical Trials Toolkit“ [63] published by the UK National Institute of Health Research.

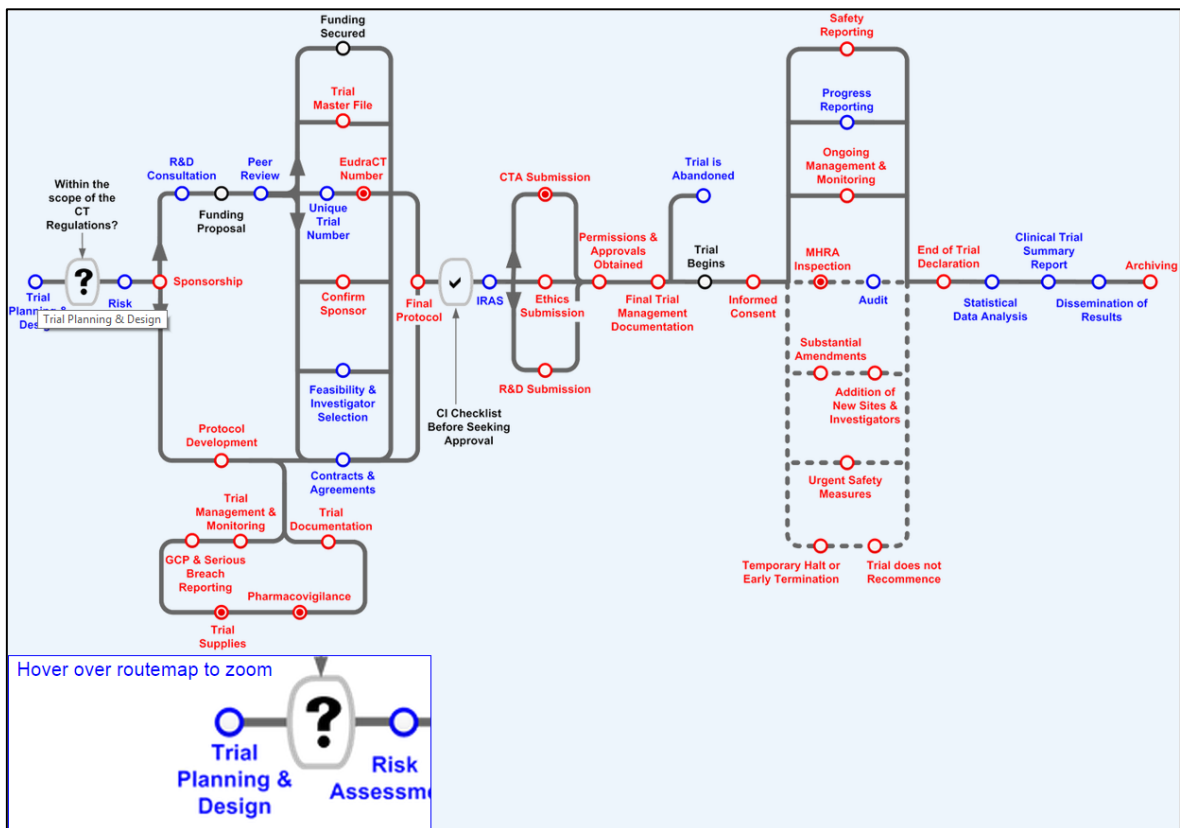


Figure 4: Clinical Trials Toolkit Interface [100]

The web based toolkit provides a route map (Figure 4) and explanations are given for all steps from design through execution to archiving of clinical studies. On the webpage of the National Institute for Health Research a user can click with the mouse on each station of the route map and he will be linked to another page providing detailed explanations and further readings. In the station Protocol Development for example, a user is referred to the SPIRIT Statement. However he is left alone with the transcription of the guideline to the protocol. The arrangement of the single stations in the route map matches the chronological order of a clinical trial.

The toolkit differentiates between legally mandatory steps (red) and those which represent Good Practice (blue). The filled out circles indicate steps applicable to a clinical study, whereas empty circles are required for all types of studies. The toolkit is designed in accordance to the European Guidelines with special emphasis on the UK regulations.

#### **2.4.5.2 The Trial Protocol Tool**

Another attempt to simplify protocol generation has been published in 2006 by Shaun Treweek et al [64]. This tool, developed on behalf of the Practihc (**P**ragmatic **R**andomized **C**ontrolled **T**rials in **H**ealth**C**are) [65] was aimed to support inexperienced scientists located in low and middle income countries to generate comprehensive study protocols.

The tool was issued as Microsoft Windows HTML help system, which is utilized for the Windows help since Windows 95. It is structured in six sections. It explains all essential aspects of a study and provides some protocol templates.

Within each section, there are short paragraphs explaining the key features required; examples of suggested text and pointers to additional information including further readings and internet resources are given. Among those, there is the Consort Statement as well. However, there is no reference made to the EU regulations and the tool has not been updated since 2006. This is why more recent legislative developments of relevance are not addressed and some of the links point to obsolete documentation.

The trial protocol tool can be downloaded from the Practihc website and it can be executed offline. The user interface of the Trial Protocol Tool is displayed in Figure 5. At the left hand side of the screen there are all available subjects listed and on the right hand side there is the corresponding content.

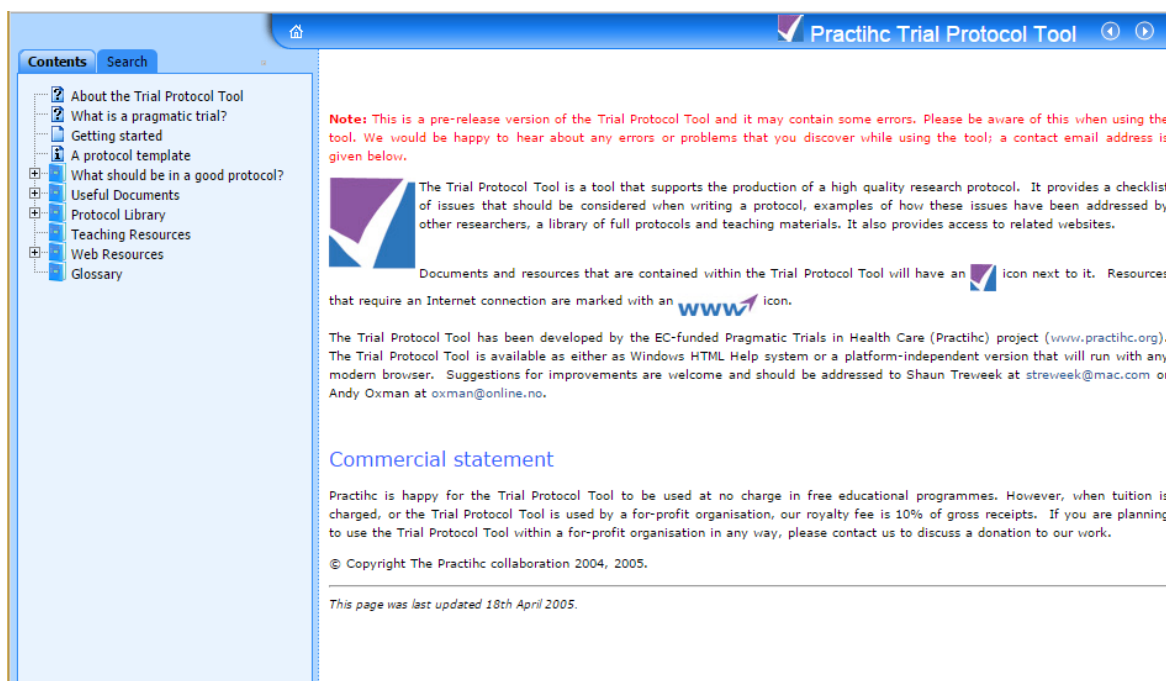


Figure 5: User Interface of the Trial Protocol Tool

### 2.4.5.3 CDISC Protocol Wizard Demonstration Tool

As mentioned in chapter 2.4.3.3 CDISC, a digital assistance tool has been published by the CDISC. The initially rather complicated concept of the PRM was reduced to a 30 item Word template. Alternatively to the Word template CDISC offers a web tool on its homepage [66]. Figure 6 displays the user interface.

The screenshot shows a web-based form titled "Enter your Protocol Title". At the top is a text input field for the title. Below this is a section titled "General Information" with a dropdown arrow. This section contains several fields: "Protocol Identification Number" (text input), "Sponsor" (text input), "Phase" (dropdown menu with "Choose an Item" selected), "Indication" (text input), "Multicenter" (radio buttons for "Yes" and "No"), and "Planned Countries" (a text input field above a dropdown menu with "Choose an Item" selected, and an "Add Planned Country" button). Below the "General Information" section are four expandable sections: "Trial Objective and Purpose", "Trial Design", "Selection of Subjects", and "Statistics", each with a right-pointing triangle icon. At the bottom of the form are four buttons: "Save as PDF", "Save as SDTM", "Clear", and "Exit".

Figure 6: Web Tool of CDISC for the PRM [101]

A user can insert all required items into the provided input boxes and thereafter a PDF can be printed (Figure 7). This contains the key information of a study protocol [60].

General Information	
Protocol Identification Number	0370582934
Sponsor	Random Sponsor
Phase	I/II
Indication	Test
Multicenter	
Planned Country	Germany
	Egypt
Trial Objective and Purpose	
Trial Purpose Summary	
Primary Objective	

Figure 7: PDF Printout of the CDISC Toolkit [101]

#### 2.4.5.4 The CONSORT based writing Tool

IT support has the potential to significantly improve quality of study reports. This was shown by a study conducted by Caroline Barnes et al. They split up the method chapter of a study report into six domains: „Trial Design“, „Randomization“, „Blinding“, „Participants“, „Interventions“, and „Outcomes“ [67]. Thereafter they asked less experienced individuals to write a report based on executed study protocols. For three of the six domains there were online tools available, the others were not supported. The online tools offered lists of essential content in accordance to the CONSORT-Statement and in addition there were examples provided for each domain.

**Blinding (PT)**

**If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how**

➔ Please state who was blinded to treatment assignments and if so how

- Study participant
- Healthcare provider(s)
- Data collectors
- Outcome adjudicator(s)
- Data analysts
- Others

Not applicable \_\_\_\_\_

Information not available \_\_\_\_\_

Examples. "Whereas patients and physicians allocated to the intervention group were aware of the allocated arm, outcome assessors and data analysts were kept blinded to the allocation."

**Figure 8: Online Tool for “Blinding” Domain [67]**

Figure 8 displays the online tool for the domain “Blinding”. Very surprisingly, there has not only been a highly significant difference between the supported and non-supported domains, but quality and completeness of the supported domains have even been superior to the original publications.

*“Overall, the global completeness of reporting scores for the sections written without the writing aid tool did not significantly differ from those of the published manuscripts, [...]. In contrast, the global score for completeness of reporting scores for the sections written with the writing aid tool were higher than those of the publications [...].” [67].*

This tool was exclusively written for this study and it only covered six domains. It was never extended to a complete set and it is not suitable to generate complete protocols.

### 2.4.5.5 SWOG Protocol Reviewing System

A working group led by Chunhua Wen et al. developed a tool for members of the SWOG (Southwest Oncology Group) [68]. This tool is web based and can be accessed simultaneously by several scientists. It provides a simple web editor and enables commenting of previously highlighted passages. The tool comprises the following modules [69]:

- Electronic protocol management with version control
- Collaborative annotation and group discussion support
- Online protocol editing support by a rich-text web editor
- Group and shared workspace awareness support

The user interface of the tool is given Figure 9. On the left hand side of the screen there are the chapters given and on the right hand side there is the word editor.

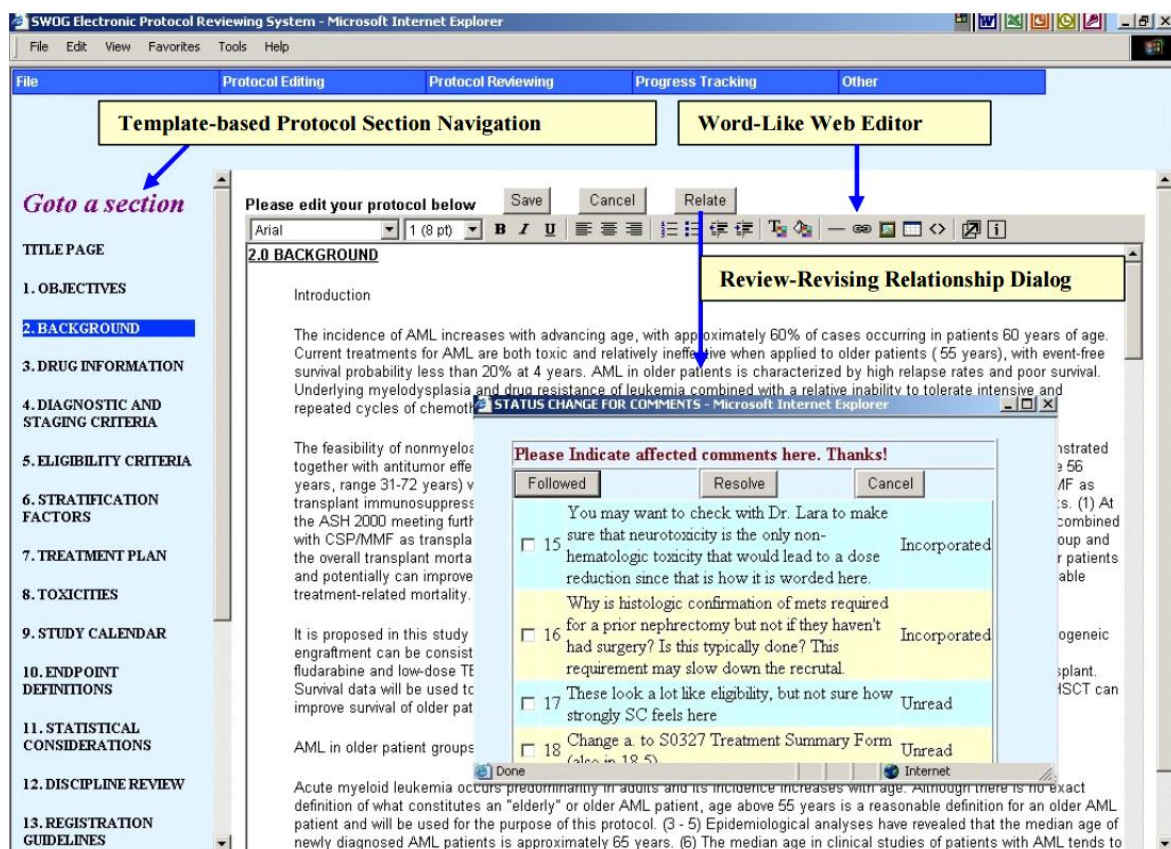


Figure 9: SWOG Protocol Reviewing System User Interface



Guiding principle for program development was the “Participatory design”. This innovative approach involved users into all stages of program development and resulted in a significantly improved usability of the program. Among others there is one major improvement concerning the review process. Traditionally emails were utilized to communicate comments and necessary protocol modifications. This was rather time consuming as big data packages had to be shared. In addition a seamless version control was difficult to achieve in case of parallel work of several scientists. After having identified this issue a web based program architecture was chosen and all participants got read/write access to one central master document.

A screen shot of the SWOG Protocol Reviewing System is given in Figure 10. On the right hand side there is the current document. Highlighted in yellow there are the comments of other users. At the left hand side there is the discussion history, displaying authors and some comments [70].

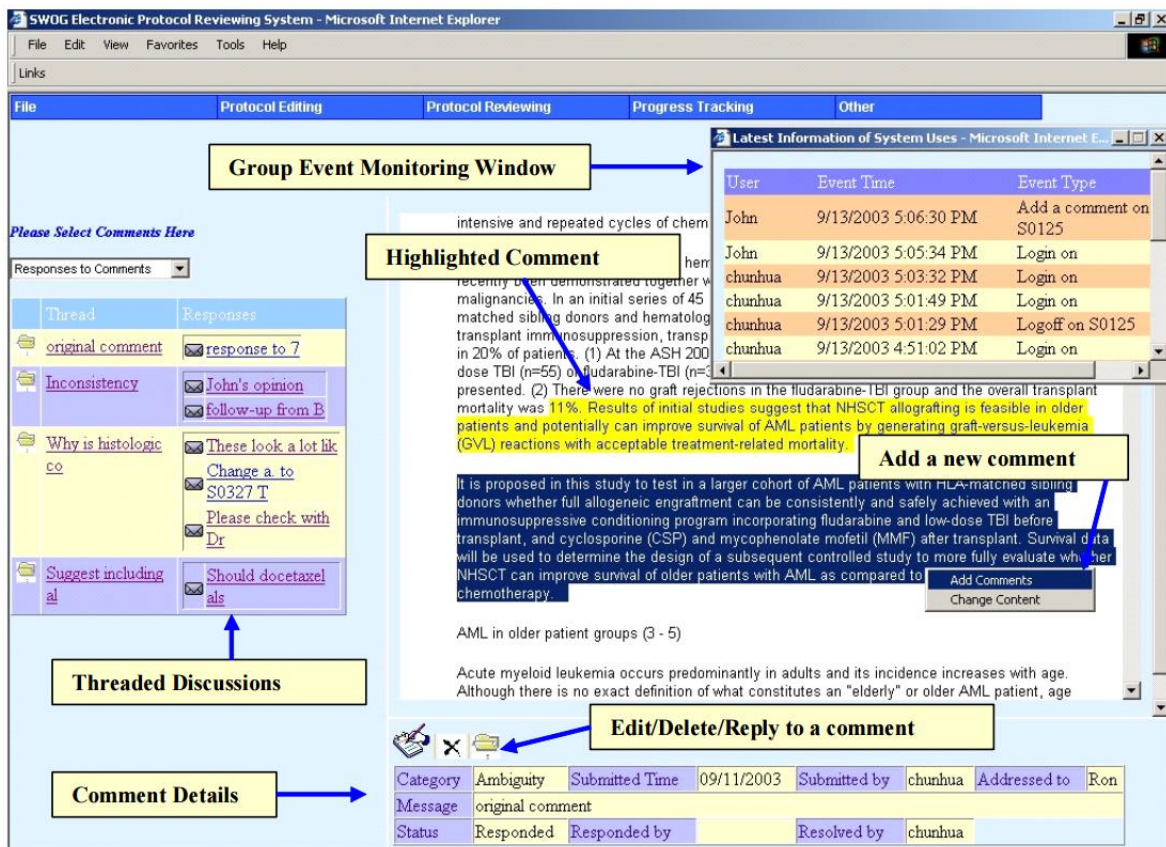


Figure 10: SWOG Protocol Reviewing System

In 2005 Chunhua Weng published an article „*Why it is hard to Support Group Work in Distributed Healthcare Organizations: Empirical Knowledge of the Social-Technical Gap*“. This paper describes the program development over a two years period and it includes user feedback. Many users appreciated the review mode. Others criticized an increased workload for authors as a lot of comments must be reviewed by all individuals involved.

*“Is it helpful to look at other people’s comments? It is sort of a double-edged sword. By looking at other people’s comments, you may see how other people phrase a comment in a better way so that you can learn. However, I cannot stop myself from looking at other people’s comments; therefore, I have to spend more than double the time on the system. I cannot get my job done in the limited time. Also, not every comment applies to me.” [71]*

Another point of criticism concerned the transcription from the electronic protocol to a paper-based document. Since there were no templates or other formatting aids given, formatting of the protocol depended on the authors. Thus quite frequently various sections of the protocols differed with regard to format. The limited features of the simple word processor contributed to this issue. All over all, the program offered very limited flexibility, it increased the workload for some authors and it never could find a wider use as it became not publicly accessible [71].

#### **2.4.5.6 Miscellaneous Tool**

A number of tools intended to support scientists with regard to protocol generation have been developed around the year 2000. Among those there are the „Design a Trial“ [72], “EON” [73], “DeGel” [74] and the TrialWiz [75]. Each of these programs is focused on specific aspects but does not support a complete protocol. The “Trial Protocol Tool“ (2.4.5.2 The Trial Protocol Tool) for example provides a knowledge database, others as EON can be utilized to convert a given paper based protocol into a computer readable format. Most of the tools seem to have disappeared, the remaining are obsolete from a technical point of view.

## **2.5 Conclusion: Current Situation**

As explicated in the previous chapters, a valid study protocol is the cornerstone of clinical research. It is mandatory from the ethical and scientific point of view but it is a legal obligation as well. A thorough execution of a valid study protocol ensures significance of study results, whereas failures in a protocol or failures during execution will jeopardize the complete study. Despite the high importance of protocol integrity it has been disclosed by research that many protocols and corresponding studies do not meet the required standards. That is why many efforts have been made to improve the situation. EQUATOR and other initiatives have been launched and plenty of checklists have been generated. Recent research has shown that this has positively impacted quality of protocols and studies, however there are still gaps. The confusing large number of guidelines and checklists already available and the ongoing work to extend these and generate new proprietary guidelines, give a clear evidence of limitation of traditional tools in this highly complex matter.

As described above there are just a few tools, which provide help for protocol generation and none of these tools support preparation of a complete protocol. Some databases such as the CT Toolkit and the Trial Protocol Tool provide comprehensive information but a user is left alone with regard to wording and format of the protocol.

Other tools such as the CDISC Protocol Wizard Demonstration Tool provides an online input mask, based on the 30 most important study protocol items. At the end of the process, a PDF listing of these items can be printed out. This is a good summary, but it cannot substitute an executable study protocol.

The SWOG Protocol Reviewing System provides a simple editor and a sophisticated review system. However user guidance, an elaborated help system and background information are missing, printout format is not defined and some users regard this program as confusingly complex.

## **2.6 Aims and Objectives**

As the current situation is not very satisfactory, it should be explored if there is an opportunity to support protocol generation by means of a comprehensive IT tool. A failure tolerant IT tool should support compilation of protocol subjects and printout of a complete ready to use study protocol.

To identify a suitable basis, applicable regulations, guidelines, protocol templates and other supporting materials should be reviewed.

Since legal requirements might change, it was important to design a modular program structure easily to adopt and extend. To eliminate any misinterpretation, it was required as well to incorporate background information for protocol authors. In addition it should be explored, if parallel and multicenter work can be supported without jeopardizing data protection and version control.

The completed protocol should immediately be available in the standard PDF format via online transfer at any location.

Finally, cost containment should be applied with regard to the utilized software.

Ultimate goal of this dissertation was the creation of a low cost failure preventing IT solution to support even inexperienced scientists to prepare a state of the art study protocol.

## **3 Materials and Methods**

### **3.1 Input into Design**

#### **3.1.1 Protocol Template**

To establish a solid foundation for software development various protocol templates were reviewed. Finally the SIOPE template was chosen, as it offers several advantages. As described in chapter 2.4.4 the SIOPE template is very well elaborated and covers all items required by chapter 6 of the ICH GCP Guideline. In addition, this template takes European regulations into consideration which is not the case with these issued by the US Institutes of Health and other organizations.

Another advantage of the SIOPE template is the clear structure and high degree of standardization among the different pages. Despite this, the pages are designed in a way that adaptations to a specific study can easily be done and a concrete page format is given.

One example of the high degree of user friendliness of the SIOPE template is the included chapter “Trial Records”. In the very most cases the text provided in this chapter can be used as proposed and only minor changes must be applied. This design and the high degree of standardization simplifies the transcription into an IT solution.

The SIOPE protocol has been developed for pediatric oncology but it is applicable for any trials concerning Investigational Medicinal Products (IMP). The software design has followed a modular approach. Therefore, it is feasible at any time to extend the program and offer additional sets of templates if SIOPE does not completely satisfy the needs.

#### **3.1.2 Legal Framework**

To fully understand the legal provisions relating to templates and to avoid any pitfalls, significant work has been performed. Many discussions and interviews with experienced physicians and scientists were made, having had many years of

experience in regard to study design and execution. Very valuable information has been gained through these interviews and has been implemented into software design. In supplementation of these interviews, protocols of valid and approved studies have been analyzed and as a matter of course all applicable regulations have been checked. These are the ICH GCP Guideline, the EU Directives 2001/20/EG (Clinical Trials Directive), the 2005/28/EC (Good Clinical Practice Directive) and the corresponding German Regulations, the German Drug Law (Arzneimittelgesetz), the Medical Device Directive (Medizinproduktgesetz) and the Decree concerning Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for human Use (Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen).

The correct understanding of the legal framework was validated by experienced colleagues of the research team of the Saarland University (Saarbrücken/Homburg).

### **3.1.3 ObTiMA**

To design and code a new piece of software from the very scratch is extremely demanding and time consuming. It is much more economical to utilize an already existing environment. A first evaluation revealed the ObTiMA (**O**ntology-**b**ased **T**rial **M**anagement **A**pplication, [76]) study administration program as ideal platform to build on.

ObTiMA is a highly innovative very flexible study administration program. It supports study design, data administration and supervision of clinical studies. It provides the capability to link a study to patients, investigators and organizations. In addition it offers the opportunity to process CRFs (**C**ase **R**eport **F**orms), Bio-Databases (pathological laboratory data) and it is capable to automatically handle and distribute adverse event reports. Even more there are mechanisms in place to ensure personal data protection and anonymization in accordance to the applicable regulations. Finally ObTiMA offers a mature and very well tested environment and

due to its modular design and the very well defined interfaces it seemed to be an ideal platform to build on.

For this reason the MasterProtocol-Creator was not developed as a standalone program, but as extension of ObTiMA. Many of the required study data as personnel, investigators and organizations are available in ObTiMA and can be taken over by the MasterProtocol-Creator avoiding redundant data entry. In addition some of the established safety features as user administration and access management of ObTiMA can be utilized as well.

#### **3.1.4 Design, Development and Program Structure**

Guiding principle for program design were easy learnability and ergonomic use. This was achieved by a graphical user interface. These characteristics and the adherence to legal requirements have been validated at any time of software development through feedback from experienced clinical physicians. In addition to this, an early version of the program was presented in the frame of the Second Summer School in Computational Oncology 2013. Highly valuable input and improvement ideas have been received from the experts and have been taken into consideration during further program evolution. Another source of information has been the University internal ObTiMA developer's conferences. A close cooperation with the ObTiMA developers enabled a seamless integration of the MasterProtocol-Creator into the ObTiMA program.

## 3.2 Infrastructure

The MasterProtocol-Creator has been written as a web server client application [77]. All software, data and resources are located on the server and the user (client) just needs a simple PC or Laptop equipped with a common web browser. The only additional requirement is permanent web access to the ObTiMA server. This design always ensures utilization of the latest program version and minimizes local resources in terms of hardware, software and program updates. Another benefit is minimization of cost. No software package needs to be purchased and installed by an untrained user and no complex and expensive hardware needs to be kept. Finally study data are highly sensitive information. The program design enables highest level of data protection and seamless data access control.

As explained above, requirements for the user are negligible, but the program design is rather demanding with regard to hard- and software of the server.

### 3.2.1 Programm Environment

During development and testing, the MasterProtocol-Creator was executed on a virtual server<sup>5</sup>. The virtual server runs the operation system Ubuntu 15.10 [78] and it was executed on a main frame in the computing center of the Saarland University. 16 GB ram and 16 GB hard disc were allocated to the virtual server. Depending on the number of users and the frequency of access it is recommended to execute the finalized software package on a non-virtual, dedicated machine.

### 3.2.2 Server Software

To execute ObTiMA and the MasterProtocol-Creator, various software components have to be available on the server.

**Web server:** The web server has been an Apache-Tomcat web server, version 8 [79]. This program is open source and provides the vast majority of the standards required by the Java Enterprise Edition ( [80], p. 4 ff). Therefore it includes a Servlet-

---

<sup>5</sup> Virtual server: Is an artificial computer system emulated by a main frame. A main frame can run several virtual servers simultaneously.



Container ([81], p. 1 ff), which interprets and runs ObTiMA and the MasterProtocol-Creator. Apache-Tomcat is published under the Apache License Version 2 and can be freely used without jeopardizing intellectual property. The server machine was accessible through port 8123 via Http protocol [82]. Data transfer was encrypted utilizing the TLS protocol [83].

**Database:** The data have been processed by means of the PostgreSQL data base software which supports the majority of the SQL (**Structured Query Language**) standards ([84], p. 1 ff). To ensure data protection, the database is only accessible by programs running on the server. There is no direct access feasible from the web except utilizing ObTiMA and the MasterProtocol-Creator. PostgreSQL has been selected to minimize cost, as it is open source and the PostgreSQL License authorizes private and commercial usage as well without any royalties. PostgreSQL has some significant advantages with regard to data integrity. This is achieved by the ACID (Atomic, Consistent, Isolated, Durable) concept. Which basically means that a new set of data will not be transferred into the database before the transmission is finalized. Incomplete set of data will be dispatched. This procedure prevents a corruption of the database ([84], p.164 ff).

**Java Runtime Environment:** The MasterProtocol-Creator, ObTiMA and the Apache Tomcat web server are written in Java. Java and Java based programs were selected as this computer language has several advantages. Most significant, Java enables object orientated programming. Each Java program consists of single independent modules called „objects“. Once objects have been programmed they can be used repeatedly on various steps in the program. This reduces program coding, shortens the source code, simplifies bug fixing and increases readability of the program code. This language can be freely utilized without license cost as well. Because of its advantages Java is one of the most commonly used languages and there are plenty of libraries and programming tools available. These significantly reduce efforts of program writing. Finally there is a huge community which can be approached in case support is needed. The established Java code is a byte code ([85], pp. 52 - 57), thus it cannot be processed by the common operating systems. In order to execute the Java code an operating system specific Java runtime

environment is required. This software is freely available as well and to execute a Java program, it will be translated into binary code first by the runtime environment. As there are runtime environments available for various operating systems, Java programs are easily portable and platform independent. The runtime environment chosen for ObTiMA and the MasterProtocol-Editor has been Java Version 8 [86].

The interactions between the software components described above are visualized in Figure 11.

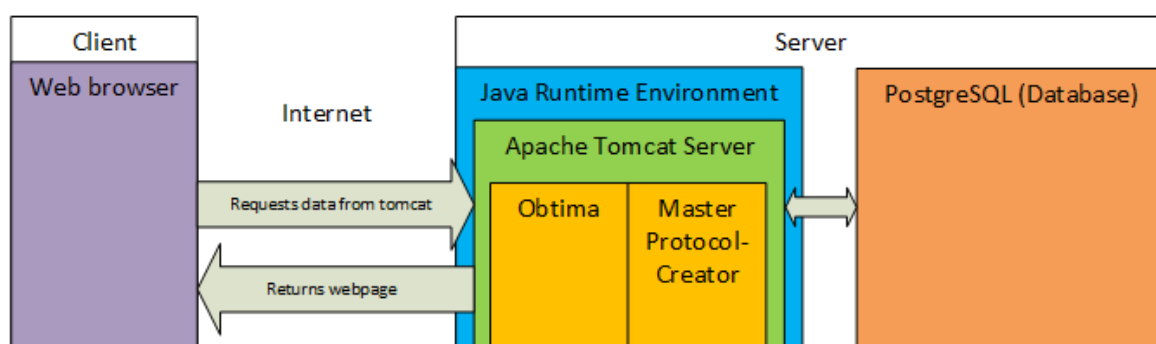


Figure 11: Software Environment of the MasterProtocol-Creator

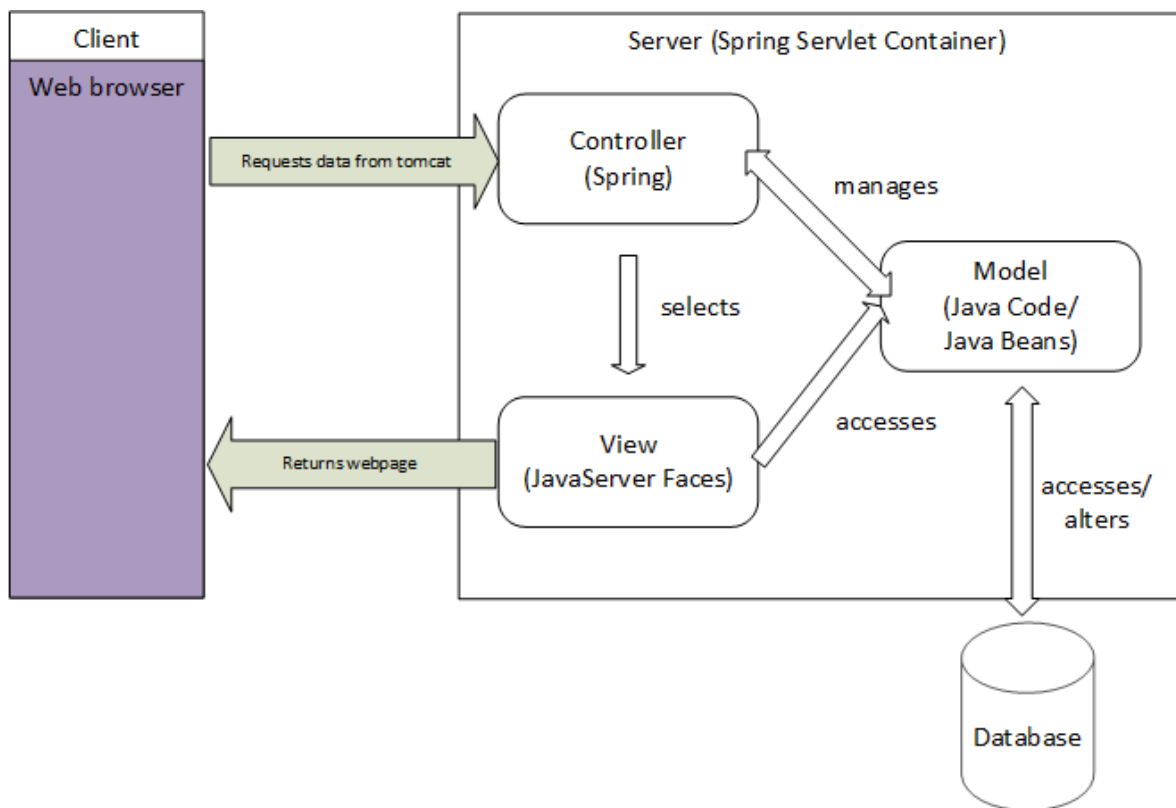
### 3.3 Development Environment

The MasterProtocol-Creator was written in the Java development environment Eclipse [87], Java EE developer Version 4.5. To become independent from the web, a local Tomcat server was installed on the laptop utilized for programming and test runs. After finalizing and bug fixing, the program modules were uploaded to the web accessible space of Apache Subversion Server by the Tortoise SVN client [88]. Following this process the new modules of the MasterProtocol-Creator were merged with the latest ObTiMA version and a copy was stored in the Apache Tomcat execution folder. This enabled immediate access for other ObTiMA users to support a multi user testing. In addition to Eclipse, Photoshop Version 5 and Paint.net were used to create icons and images for the MasterProtocol-Creator. Wizard Help Texts and Quick Guides were written with Microsoft Word.

## 3.4 Program Architecture

### 3.4.1 Spring Framework

As described above, the program was written in Java. To extend functionality and further reduce programming efforts, the Spring Framework was used. This bears several significant advantages. One of these, the Dependency Injection automatically assigns previous user defined resources and objects. The administration runs in the background without involvement of the programmer ( [89], pp. 37 - 38).



**Figure 12: Model View Controller Concept**

Another frequently used Spring Framework feature is the Model-View-Controller Concept illustrated in Figure 12. This concept was developed in 1979 [90] and adopted to Java in 1998 [91], called Model 2. Due to this concept, the application is split into three interactive components, called "Model", "View" and "Controller". An advantage of this concept is a clear separation of program logic and user interface.

The Model is the entirety of the objects, e.g. the Java source code. It interacts with the PostgreSQL database and manages the operations. The View provides the user interface. It extracts data from the model and converts these into a graphical display. Different to the rest of the MasterProtocol-Creator, the View source code is not written in Java, but with JavaServer Faces [92]. This technique allows easy generation of websites using predefined components as check boxes and panels. The established webpages are interpreted by the Tomcat web server and converted into code, which can be displayed by the browser of the client (user). The third component, the Controller, is provided by the Spring Framework and takes care of communication with the user and handles access control ([93], pp. 518 – 522).

### **3.4.2 Hibernate Framework**

The Hibernate Framework manages the linkage of the MasterProtocol-Creator to the PostgreSQL data base by usage of the Object-Relation Mapping technique. This technique enables direct storage of Java objects in the database. A user-managed conversion of these objects into SQL code is not necessary. Once again this technique significantly reduces programming effort and supports program maintenance [94]. In addition the Hibernate Framework provides backup and version control capabilities.

## **3.5 Paragraphs**

The data of the study protocol are stored in the database in several independent packages called paragraphs. Each of the paragraphs contains the data required by one chapter or subchapter of the SIOPE template. The paragraphs are merged into the final study protocol not before the PDF printout.

The standard protocol consists of 34 paragraphs. These are named in accordance to the chapters and subchapters of the SIOPE template and contain the data required by the corresponding chapter. The paragraphs are stored in the order, which is required by the template (see Figure 14). Each paragraph can be one of

five types. Each type has an individual input mask and can process different data types (see Figure 13).

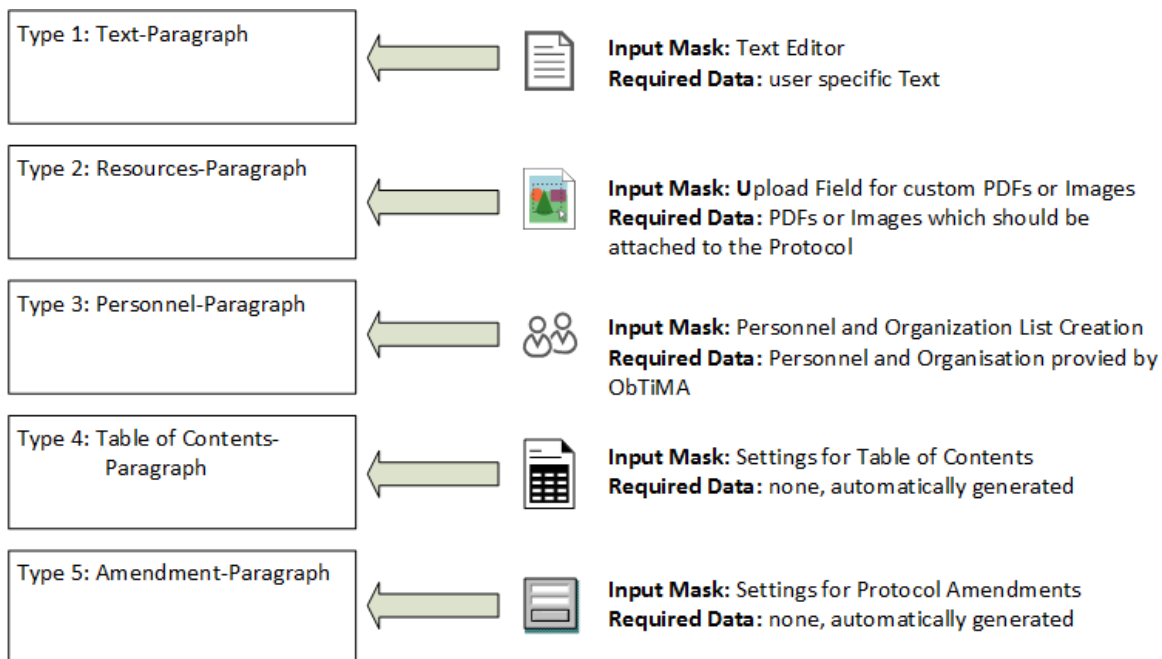


Figure 13: Five different Types of Paragraphs

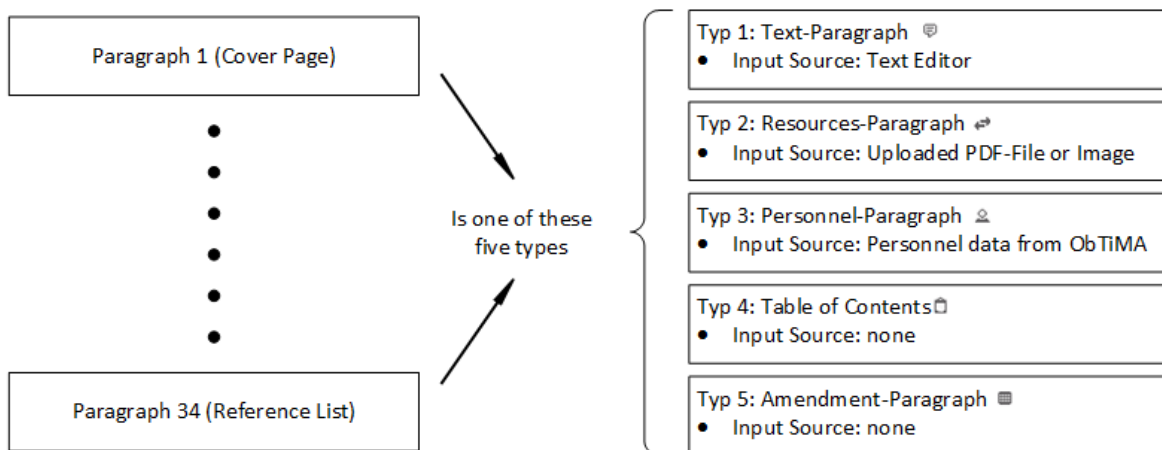


Figure 14: Paragraph Order

In addition to the paragraphs there are 4 folders in the basic protocol. Every folder comprises several paragraphs with related content. This simplifies keeping an overview (4.2.2.2 Folders).

However the user is not bound to a static protocol structure. The MasterProtocol-Creator provides any freedom to generate customer specific protocols (4.2.2.3 Customizing the Protocol).

The separation into paragraphs has several advantages. First of all there is a highly transparent link to the SIOPE template. Second, integration into ObTiMA is significantly simplified by this data structure.

The most frequently used paragraph is the Text-Paragraph. It provides a standard word processor and a protocol author can fill in any free text. Another paragraph, the Personal-Paragraph gets its data from the ObTiMA database and prepares lists of individuals associated with the trial.

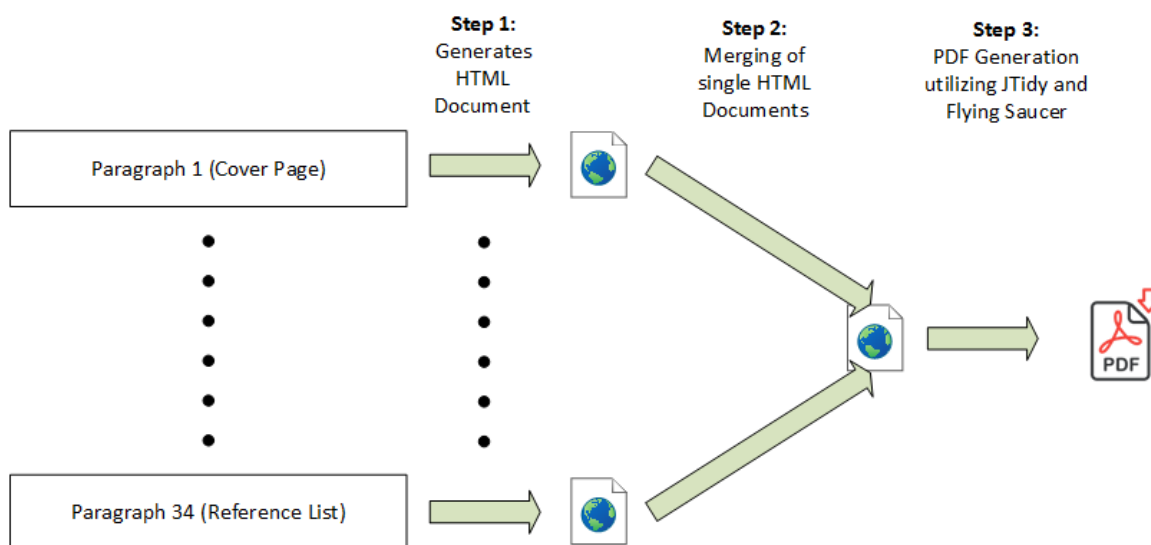
Segregation enables parallel processing. Several users can populate different paragraphs completely independent. Because of the web access they even do not need to be at the same location. This option might be utilized by a statistician who will probably not be located in the hospital together with a study sponsor or a physician supervising the study.

Data transfer is significant faster, as just the paragraph, which will be edited, needs to be transferred via Internet. Despite the enormous progress of the web throughout the recent years a complete document including pictures would take a while until loaded.

Due to the different data structure of the paragraphs, utilization of ObTiMA data is significantly simplified and new paragraphs can be added without affecting the existing ones.

### 3.6 Generation and Printout of the Study Protocol

If all paragraphs are populated with the data required by the study, the protocol can be exported to a PDF file. During creation of the PDF file, the paragraphs are merged into one single document in accordance to the previously stored order. The PDF file can be printed out and serves as the study protocol.



**Figure 15: Protocol PDF Generation Process**

Each paragraph represents a separate HTML<sup>6</sup> page. Before PDF generation, the single pages are merged into one HTML document. It cannot be completely excluded that syntax failures occur in the final HTML file. In addition some country specific characters as mutated vowels will be wrongly displayed in the PDF. Therefore the MasterProtocol-Editor was designed to apply the JTidy (Version: Snapshot 938) library before any conversion. This library removes all syntax errors and converts mutated vowels in a way that these can be displayed correctly. Afterwards the table of contents is generated and headers and footers are added.

The subsequent transformation of the HTML document into the PDF format utilizes the Flying-Saucer library, an extension of iText 2.17 [95]. Flying-Saucer supports headlines, table of contents, footer and header, but is not capable to render pictures and diagrams embedded in the HTML source code. To manage this conversion an

<sup>6</sup> HTML (**H**ypertext **M**arkup **L**anguage): Language to create webpages

extension was written. After finalizing the conversion, the generated PDF is stored in the PostgreSQL database. Thereafter the study protocol can be printed in PDF format. This format was chosen as it is independent of the operating system and independent of word processors. Content and formatting are not easily impacted during transfer, handling and printout and PDF format is widely used and accepted.

### **3.7 Additional Libraries used by the Program**

**PrimeFaces** [96]: This open source component library offers plenty of useful items to extend JavaServer Faces. Many of those have been utilized to establish the user interface of the MasterProtocol-Creator. PrimeFaces was used in Version 5.1.

**Jsoup** [97]: This library offers routines to create and modify HTML pages. It is frequently used by the different paragraphs to convert complete HTML pages into Java objects and back again. An example for a program utilizing Jsoup is the Personnel-Paragraph which generates user lists with data from the ObTiMA database. Another example is the Table of Contents-Paragraph which scans all other paragraphs using the headlines to create the table of contents.

**Gson** [98]: Analogue to the Hibernate Framework (3.4.2 Hibernate Framework) Gson enables easy data transfer from Java objects to text files. These text files, in the widely used JSON format, are stored in the ObTiMA database. In opposite to Hibernate, which generates one table per object, Gson just generates one single text file to store all attributes of an object. The JSON transformation was applied to rarely used objects. This saves storage area and minimizes the size of the ObTiMA database.

### **3.8 Software Licenses**

One objective for software development was minimization of cost. This was fully achieved by utilization of royalty free software and libraries, many of these open source code. The following software has been used:



Programm / Library	Version	License
Apache Tomcat	8.0.26	Apache License 2.0
PostgreSQL	9.4.4	PostgreSQL License
Java Runtime Environment	8 Update 60	Oracle Binary Code License (BCL)
Apache Subversion	1.9.0	Apache License 2.0
TortoiseSVN	1.9.1	GNU General Public License
Eclipse	4.5	Eclipse Public License
Spring	4.1.6	Apache License 2.0
PrimeFaces	5.2	Apache License 2.0
Programs within the Java Community Process, e.g.: <ul style="list-style-type: none"> <li>• JavaServer Faces and Java Servlet</li> <li>• Enterprise Edition 6 Specification</li> </ul>		different, but royalty-free licenses [99]
Jsoup	1.8.2	MIT License
Gson	2.3.1	Apache License 2.0
JTidy	r938	JTidy License
Flying Saucer	9.0.9 SNAPSHOT	LGPL
iText	2.1.7	LGPL

**Table 1: License Listing**

## 4 Results

The MasterProtocol-Creator was developed as an extension of the medical study administration program ObTiMA (**O**ntology-**b**ased **T**rial **M**anagement **A**pplication) to easily set up trial protocols. The MasterProtocol-Creator consists of three modules. These are the MasterProtocol-Wizard, the MasterProtocol-Editor and the MasterProtocol-Helpcenter.

The **MasterProtocol-Wizard** provides all essential knowledge needed to setup a protocol for a clinical study. As the program is aimed towards inexperienced users, it includes an elaborated support system. This is based on a step-by-step guide for protocol preparation. Among others, it explains classification of studies, the registration process, gives definition of sponsors and provides access to the guidelines. Once a user has completed all steps, he should have an understanding of the applicable regulations and based on the data entered the wizard automatically generates a basic study protocol in accordance to the SIOPE guidelines.

The **MasterProtocol-Editor** is used to customize the previously generated protocol. It offers various modules to utilize data already available in ObTiMA and enables input of other study specific data. In addition, the editor handles version management and offers printing and exporting features.

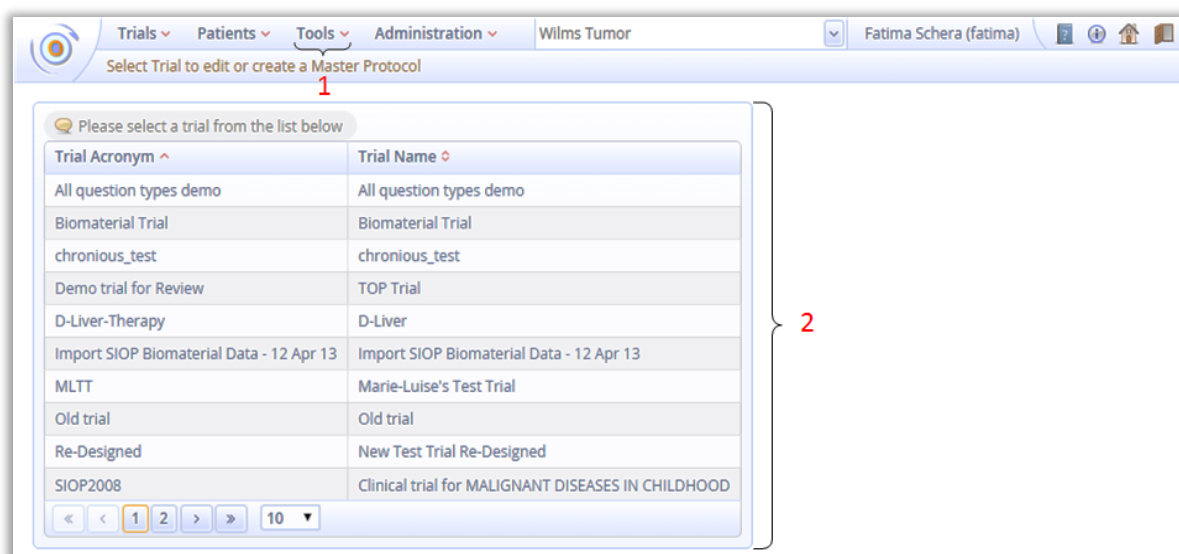
The **MasterProtocol-Helpcenter** is accessible at any time from the MasterProtocol-Wizard and the MasterProtocol-Editor modules. It displays help screens supporting usage of the other two modules and it provides many links to external websites. At these websites the user will find rules, regulations and further guidelines applicable to study protocols.

All three modules are accessible by the user-interfaces of ObTiMA (Figure 16). The MasterProtocol-Creator can be started by the option “Tools” in the menu bar (Figure 16 (1)). If the MasterProtocol-Creator is opened for the first time within an ObTiMA session<sup>7</sup>, a selection of all studies already available is shown (Figure 16 (2)). Now

---

<sup>7</sup> ObTiMA session: At any time a user signs in to ObTiMA a session is started.

one of the studies can be selected and a protocol for the study can be designed or a protocol, which has been generated previously, can be edited.



**Figure 16: ObTiMA User Interface, Study select Screen (2)**

If a study is chosen and the associated protocol is already available, the MasterProtocol-Editor will start immediately. If there is no protocol available, the MasterProtocol-Wizard will appear on the screen instead.

## 4.1 MasterProtocol-Wizard

The MasterProtocol-Wizard provides user support to generate a novel study protocol. A user just needs to process every single step of the menu (Figure 17 (1)) and at the end he has got a lecture on the study protocols and a basic protocol will be generated.

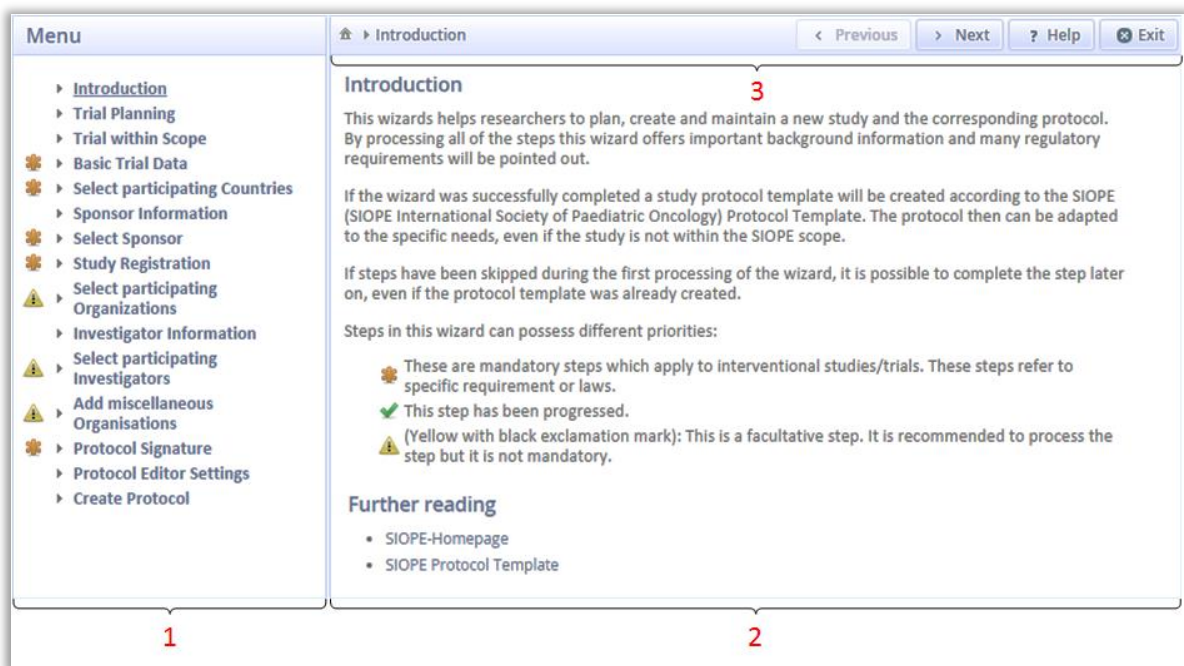


Figure 17: User Interface of the MasterProtocol-Wizard

### 4.1.1 Wizard Structure

On the left hand side of the screen (Figure 17 (1)) is a menu. It lists all potential steps. Some of these are mandatory statutory provisions, others are based on recommendations only and there are some which just provide information. The icon in front of each option indicates the classification and the check at the end of the line indicates the status:

- Step without icon, information only and links to web resources.
- Orange star (★), mandatory steps
- Yellow exclamation mark (⚠), recommended but not mandatory
- Green check (✓), step is completed

All steps can be processed in the given or in a free order. Single steps can be skipped and processed later.

On the right hand side of the screen (Figure 17 (2)) there is the Wizard space. It displays introductory text concerning the step selected from the menu. In addition there are input fields. A user is required to enter some data required to generate a basic, non-customized protocol. Close to the upper frame of the screen, there is the navigation panel (Figure 17 (3)). It displays the current step and right of it there are the navigation buttons. These are “Next” (step), “Previous” (step), “? Help” and “Exit”. By use of the “Exit” button the actual status will be saved, the Wizard will close and the study selection list will appear again.

#### 4.1.2 Wizard Steps

If one step from the menu is selected the corresponding screen opens. The step “Basic Trial Data” is displayed in Figure 18.

The screenshot shows a software interface for the 'Basic Trial Data' step. On the left is a 'Menu' with a tree view of steps: Introduction, Trial Planning, Trial within Scope, Basic Trial Data (highlighted with a green checkmark), Select participating Countries, Sponsor Information, Select Sponsor, Study Registration, Select participating Organizations, Investigator Information, Select participating Investigators, Add miscellaneous Organisations, Protocol Signature, Protocol Editor Settings, and Create Protocol. The main area is titled 'Basic Trial Data' and contains instructions: 'In order to create a protocol, some general information is needed.' It has two sections: 'Trial Naming' with input fields for 'Trial Name' (Clinical trial for MALIGNANT DISEASES IN CHILDHOOD) and 'Trial Acronym' (SIOP2008); and 'Trial Extent' with a 'Multicenter Trial' checkbox set to 'Yes'. Below is 'Protocol Default Language' with a dropdown menu set to 'English'. Navigation buttons at the top right are '< Previous', '> Next', '? Help', and 'Exit'.

**Figure 18: MasterProtocol-Wizard Step "Basic Trial Data"**

Most of the screens include input fields. Adherent to each data field explanations are given concerning the data and the data format. Most pages include a section “further reading”. This section provides web links to homepages containing detailed information about the topic addressed by the data fields. On these webpages, the user will find rules, regulations, guidelines, tool kits and more.

The menu offers the following steps:

- **Introduction:** Information on the wizard. In addition there is a button “Skip wizard” on this page. A more advanced user can click this button and will immediately be at the last step “Create protocol”.
- **Trial Planning:** A lesson regarding trial planning principles and applicable guidelines of the European Union.
- **Trial within Scope:** Selection of study type, interventional or non-interventional study. An interventional study requires a SIOPE template; a non-interventional study can utilize an empty form (see below).
- **Basic Trial Data:** Name and acronym of the study, protocol language, study characteristics (single or multicenter study).
- **Select participating Countries:** Countries can be selected from a predefined list.
- **Sponsor Information:** Definition and tasks of the sponsors.
- **Select Sponsors:** Sponsors can be selected from a list provided by the ObTiMA database. Functionality equivalent to the “Personnel Paragraph” (4.2.2.1.3 Type Personnel-Paragraph)
- **Study Registration:** Explains the process of study registration with various organizations, main focus on EudraCT.
- **Select participating Organizations, Select participating Investigators, Add miscellaneous Organizations:** Generate lists. These need not to be completed; they can be extended at any time.
- **Protocol Signature:** Identification of individuals, who have to approve (sign) the study (sponsors, principal investigator, statisticians and others).

- **Create protocol** (Figure 19): Two options are offered.
  - **Create empty Protocol:** An empty protocol template is issued. This option supports non interventional studies.
  - **Use SIOPE Template:** All previously entered data will be used to generate a protocol in accordance to the SIOPE template.

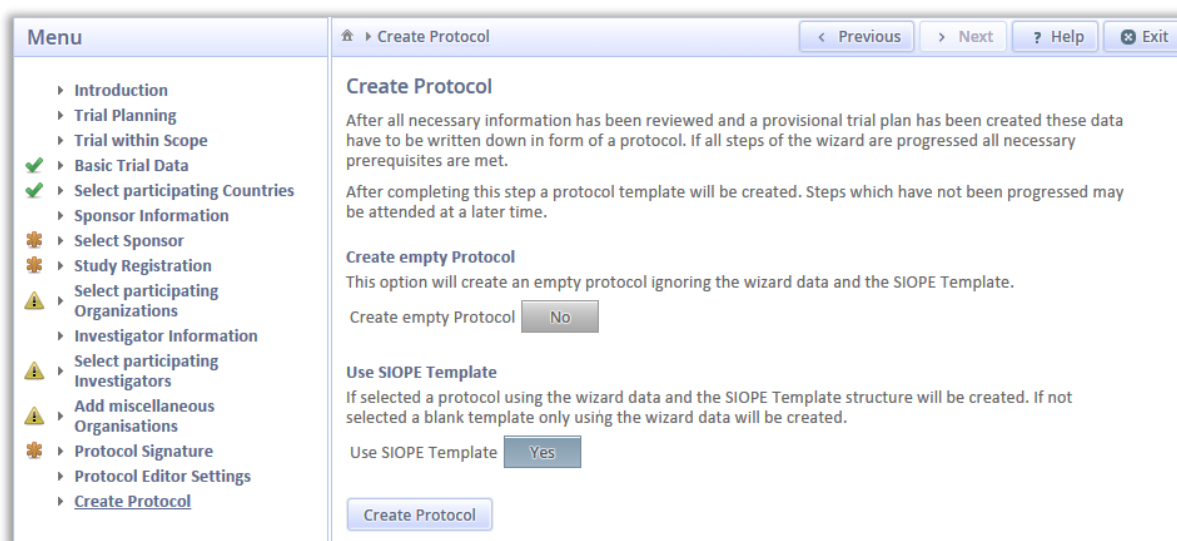


Figure 19: Select Generic or SIOPE Protocol Template

## 4.2 MasterProtocol-Editor

Once all requested data have been entered into the MasterProtocol-Wizard, a generic study protocol is available in the MasterProtocol-Editor. This protocol includes 34 independent parts called paragraphs.

### 4.2.1 Editor Structure

A screen shot of the user interface is given in Figure 20. In the menu on the left hand side of the screen the paragraphs are listed (Figure 20 (1)). On the right hand side is the help screen (Figure 20 (2)) and in the center is the editor space (Figure 20 (3)).

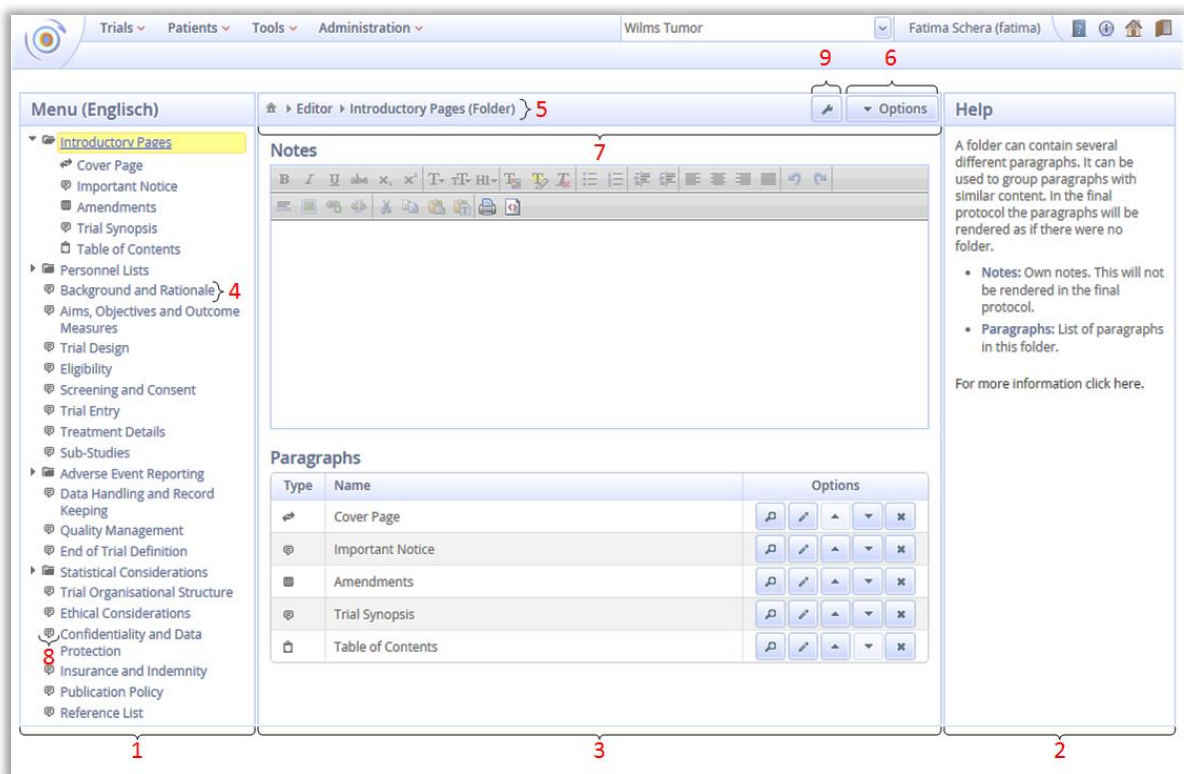


Figure 20: User Interface of the MasterProtocol-Editor



### 4.2.1.1 Paragraph Section

In the basic protocol version every paragraph listed in the paragraph section (Figure 20 (1)) has a title, e.g. “Background and Rationale” (Figure 20 (4)), in accordance to one of the SIOPE chapters. The user is free to change the titles and he can add or delete paragraphs. The icon in front of the title (Figure 20 (8)) indicates the type of the paragraph (🗨️, 📄, 👤, 🗑️, ↕️) or folder (📁). If the user clicks on one of the items with the left mouse button, the input mask will appear in the editor space. Now the user can adopt the content to the specific study.

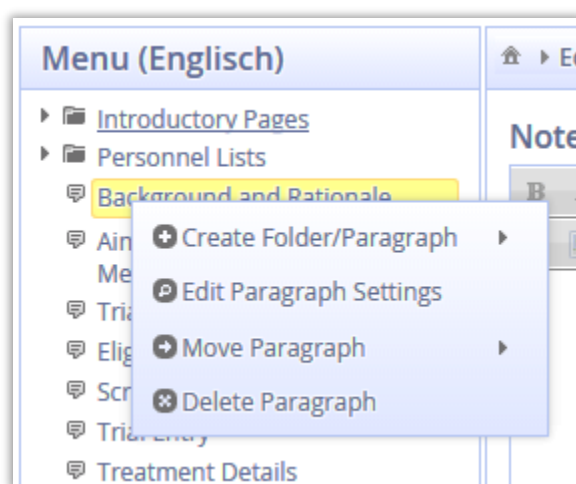


Figure 21: Paragraph Edit Menu

If a user selects a paragraph with a click on the right mouse button a different menu opens (Figure 21). This menu can be used to delete, rename or move a paragraph up- or downwards. In addition it enables integration of additional paragraphs. The various options of the menu are described in 4.2.2.3 Customizing the Protocol.

### 4.2.1.2 Editor Space

The editor space is located in the center of the screen (Figure 20 (3)). If a paragraph is selected, all information becomes visible and can be altered. The corresponding editing functions are explained in the following chapters.

The navigation bar is located above to the editor space (Figure 20 (7)). On the left hand side of this bar the name of the selected paragraph (Figure 20 (5)) is displayed and on the right hand side the extendible option menu (Figure 20 (6)) can be accessed. This menu is given in Figure 22.

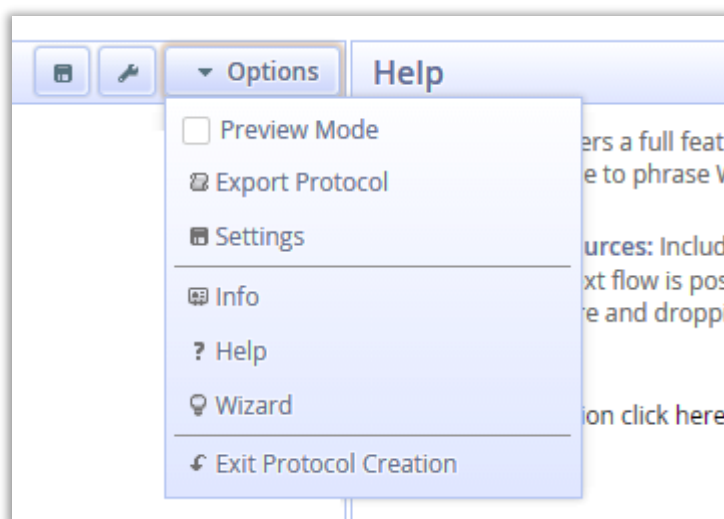



Figure 22: Extendible Options Menu, located in the Navigation Bar


The single items of the Options menu are:

- **Preview Mode:** Displays the PDF preview.
- **Export Protocol:** Lists all available protocol versions and download links.
- **Settings:** The MasterProtocol-Editor can be customized to individual users requirements (See chapter 4.2.6 Editor Settings).
- **Info:** Displays key parameters of the current study protocol.
- **Help:** Access to the MasterProtocol-Helpcenter.
- **Wizard:** If the MasterProtocol-Wizard has not orderly closed before, it can be restarted again.
- **Exit Protocol Creation:** Current protocol is saved and the editor will close.

Other elements of the MasterProtocol-Editor navigation bar are:

**Quick Setting Menu** : Several functions accessible. First the current language can be changed. Second, depending on the selected paragraph type, type specific

options become available. These are described below in 4.2.2.1 Types of Paragraphs.

**Save button** : Wherever this button appears, the current protocol can be stored into the ObTiMA database.

### 4.2.1.3 Help Section

The help section (Figure 20 (2)) visible on the right hand side of the screen, briefly describes the options available in the editor space. In addition, there are links leading to the corresponding section of the MasterProtocol-Helpcenter. There the user will find an extended description of all options. A more advanced user can close the help section in the “Editor Settings”. This will enlarge the editor space.


## 4.2.2 Paragraphs

The paragraphs are the backbone of the editor. As described above, every single paragraph contains one part of the protocol and each paragraph can be populated with data in a type specific input mask.

### 4.2.2.1 Types of Paragraphs

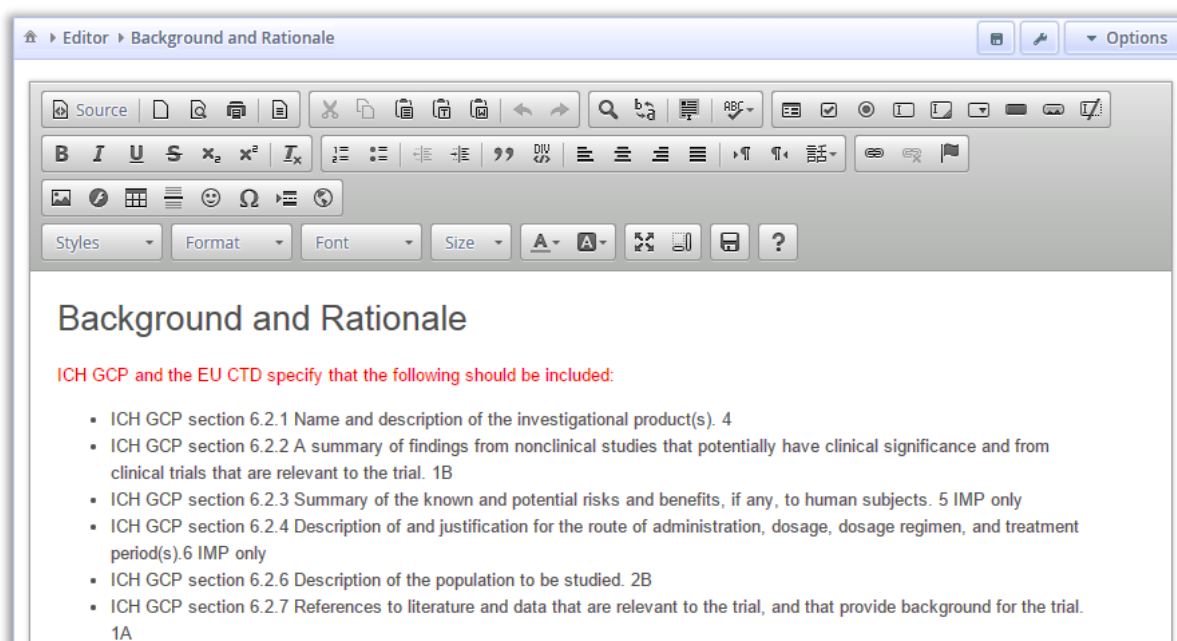
All over all there are five different types of paragraphs available (Figure 13). Every type offers different functionality. The very flexible program design enables a user to create additional fully customized types. However this is not guided by menus and therefore it is only feasible for a more advanced user. Although this extension is not needed to meet current legal requirements, it enables adaption of the MasterProtocol-Creator future needs.

#### 4.2.2.1.1 Type Text-Paragraph

The Text-Paragraph provides highest flexibility and therefore it is the most frequently used type. In the paragraph section these paragraphs are indicated by the speech bubble icon  in front of the paragraphs titles (Figure 20 (8)).




Basically, this paragraph is a text editor. It is comparable with Microsoft Word or LibreOffice Writer. A screen shot is given in Figure 23. By use of the Text-Paragraph

free text and tables can be edited. By drag and drop pictures in the JPEG, PNG and GIF format can be embedded into the text. Furthermore, the editor can handle Microsoft Word documents. It is even possible to set URL links to pictures available in the internet. In this case there is a limitation as the URL must not use SSL encryption (HTTPS). In addition a spellchecker with multi language support is available.



**Figure 23: Input Mask of the Text-Paragraph**


Most of the editor icons offer the same functionality as the equivalent icons of the standard word processors. Therefore a detailed description of the functionality is not given in this document. In addition there are three unique icons which need explanation:

-  **Word Icon:** Transfer of Word files into the editor.
-  **Full screen mode:** Extends the editor space to full screen. Another click on the icon restores the previous view again.
-  **Help Screen:** Explanation for all editor icons is given.

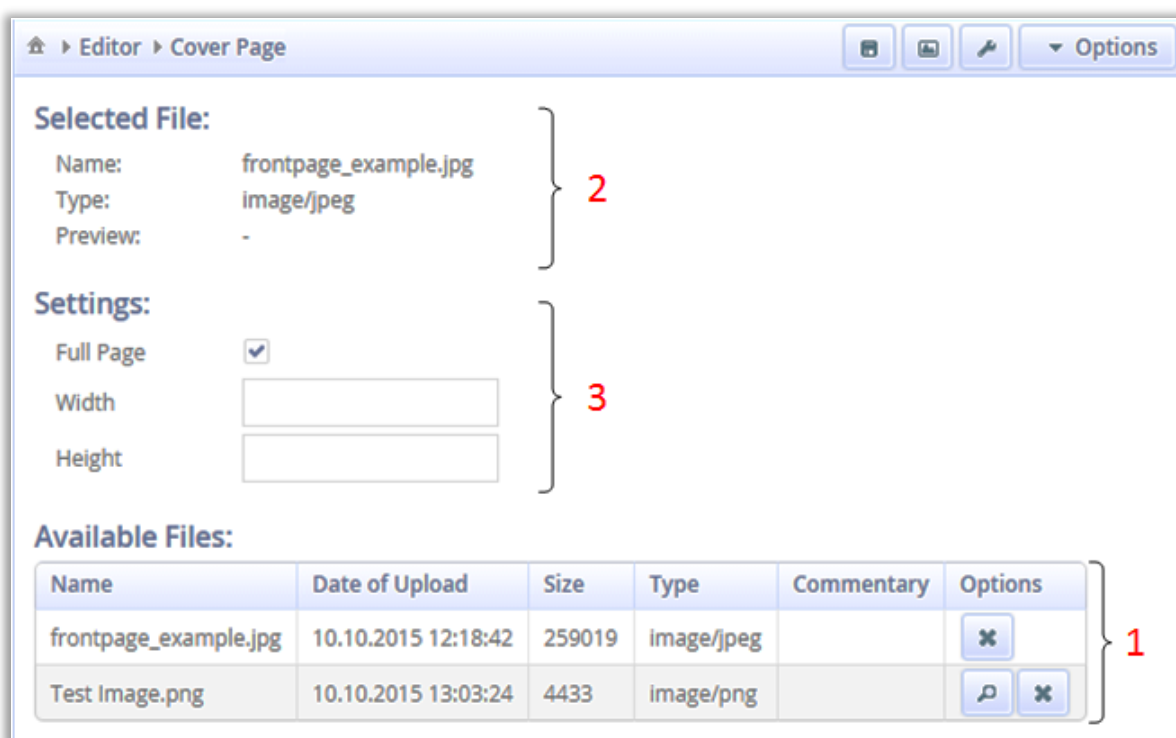
Like a standard word processor, e.g. Microsoft Word, the text editor is capable to structure voluminous documents into chapters and add headlines to each of the chapters. There is no limitation on the number of chapters and the headlines will

automatically be inserted into the table of contents. This feature is unique to the Text-Paragraph. Other paragraphs as the Personnel-, the Amendment-Paragraph and the table of contents offer limited headline capabilities only. Just one headline per paragraph can be set by a specific option (4.2.2.1.3 Type Personnel-Paragraph).


#### 4.2.2.1.2 Type Resources-Paragraph

This paragraph indicated by the icon  supports importation of pictures (JPEG, GIF, PNG) and PDF documents. The imported documents and pictures are treated as separate pages. The size of the pictures can be adopted. Maximum size is one full DIN A4 page, minimum size is not limited. If PDF is imported size and format of the original file remains completely unchanged. This can be used to generate attachments to the study protocol, frequently utilized for the “Informed Consent”.

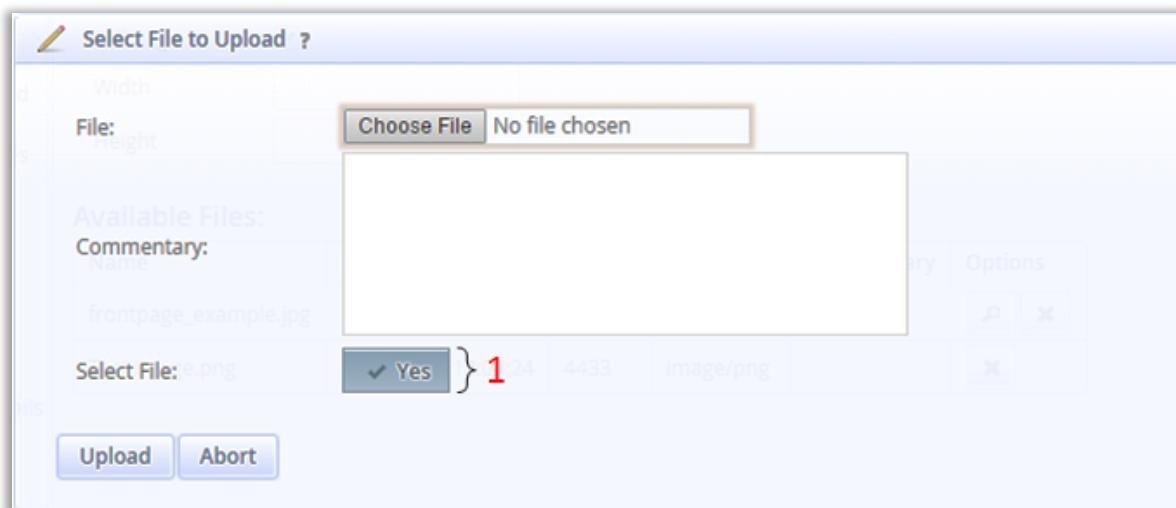
The input mask of the Resources-Paragraph is shown in Figure 24.



**Figure 24: Input Mask of the Resources-Paragraph**

The option menu bar on top of the screen provides the same basic functionality as explained in Figure 22. In addition there is the “Upload” button . It can be used


to import PDF documents and pictures. Upon pressing the button, another dialog shown in Figure 25 appears.



**Figure 25: Dialog for Uploading new Files**

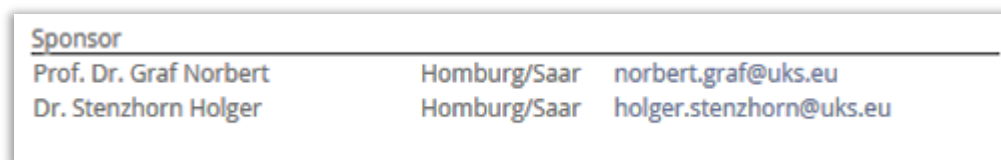
By this dialog a user can upload any file from the local drive and attach descriptive comments. The uploaded file appears in the “Available Files” list (Figure 24 (1)) of the Resource-Paragraph. If any further files are uploaded they will be attached to the “Available Files” list as well, but only one of these will be displayed in the “Selected File” area (Figure 24 (2)) and will be used by the Paragraph. This file can be selected in two different ways. First before uploading by setting the option “Select File” (Figure 25 (1)) to “yes”, second at any time by clicking on one of the files which are displayed in the “Available Files” list. If a file is not needed any longer it can be deleted from the “Available Files” list by clicking the cross button. The “Settings” panel (Figure 24 (3)) is only applicable to pictures. It can be determined if the picture should cover the complete page or just a specified area.

### 4.2.2.1.3 Type Personnel-Paragraph

It is mandatory to list all personnel and institutions in the study protocol, which are associated with the trial. The Personnel-Paragraph automatically generates these lists utilizing data provided by ObTiMA. If these data are modified in the ObTiMA database, the Personnel-Paragraph updates the previously generated lists without user intervention. This paragraph is indicated by the icon  in the paragraph section (Figure 20 (1)).

#### 4.2.2.1.3.1 Different List Types

All over all, the Personnel-Paragraph offers five different types of lists. Every type can either list individuals, organizations or both of them. The user can determine appearance and content of a specific list by choosing one of several templates available. If no template meets the expectation, a user can create additional completely customized templates. Figure 26 illustrates appearance of a sponsor list. In this example only two researchers are included in the list, but there are no limitations by the program to extend a list to any lengths. The completed list can be printed in the Portable Document Format (PDF).



Sponsor		
Prof. Dr. Graf Norbert	Homburg/Saar	norbert.graf@uks.eu
Dr. Stenzhorn Holger	Homburg/Saar	holger.stenzhorn@uks.eu

**Figure 26: Example of List Type 1: Sponsor List**

The five list types of the Personnel-Paragraph are:

- **Type 1:** The “Sponsor-List” can include individuals, organizations or both of these. This is necessary as a sponsor can be an individual or an organization as well. If there are several sponsors with concurrent characteristics, they can be combined to groups. Group specific names can be attached to pinpoint roles and responsibilities. For example, all sponsors from UK can be combined in one group named “UK Sponsors”.

This type enables identification of all sponsors involved into a clinical trial.

- **Type 2:** The “Simple Personnel-List” comprehends individuals only. It is just a listing of researchers and other personnel associated with the trial. Each person can be linked to a specific responsibility. In Figure 27 Prof. Dr. Norbert Graf is indicated as “Lead Investigator” and Yvonne Braun and Dr. Holger Stenzhorn as “Investigators”. The user can freely enter any responsibility and it is feasible to allocate one responsibility to several individuals.

Investiagtors	
Lead Investiagtor	Prof. Dr. Norbert Graf Klinik für Pädiatrische Onkologie und Hämatologie Email: norbert.graf@uks.eu
Investiagtor	Yvonne Braun Email: Yvonne.Braun@uniklinikum-saarland.de
Investiagtor	Dr. Holger Stenzhorn Klinik für Pädiatrische Onkologie und Hämatologie Email: holger.stenzhorn@uks.eu

Figure 27: List Type 2: Simple Personnel-List

- **Type 3:** The “Personnel-List” is similar to the “Simple Personnel-List”. Contrary to the “Simple Personnel List”, this list summarizes several individuals into one group and allocates one single responsibility. In Figure 28 two researchers act as investigators. In the “Simple Personnel-List” the title investigator would appear as often a new name is added. Thus “Simple Personnel-List” is an 1 : 1 allocation, the “Personnel-List” is an 1 : n allocation.

Investigators	
Lead Investigator	Prof. Dr. Norbert Graf Klinik für Pädiatrische Onkologie und Hämatologie Email: norbert.graf@uks.eu
Investigators	Yvonne Braun Email: Yvonne.Braun@uniklinikum-saarland.de
	Dr. Holger Stenzhorn Klinik für Pädiatrische Onkologie und Hämatologie Email: holger.stenzhorn@uks.eu

Figure 28: List Type 3: Personnel-List



- **Type 4:** The “Simple Organization-List” comprehends organizations only. Analogue to the “Simple Personnel-List”, it enables allocation of one specific responsibility to one specific organization (1 : 1 allocation). This type can be utilized to generate a listing of all institutions associated with a trial.
- **Type 5:** The “Complex Organization-List” comprises organizations and the associated employees. Each of the organizations can be linked to a specific responsibility and every employee of each organization can be linked to a specific function within this organization. Figure 29 illustrates a “Complex Organization-List” with two organizations and three employees.

Trial sites	
<b>Frauenheilkunde, Geburtshilfe und Reproduktionsmedizin</b> Kirrberger Straße 66421 Homburg/Saar Main trial site	
Prof. Dr. Graf Norbert	<a href="mailto:norbert.graf@uks.eu">norbert.graf@uks.eu</a>
Braun Yvonne	<a href="mailto:Yvonne.Braun@uniklinikum-saarland.de">Yvonne.Braun@uniklinikum-saarland.de</a>
<b>Zentrum für Frauen, Kinder und Adoleszente</b> Kirrberger Straße 66421 Homburg/Saar Trial site	
Dr. Stenzhorn Holger	<a href="mailto:holger.stenzhorn@uks.eu">holger.stenzhorn@uks.eu</a>

**Figure 29: List Type 5: Complex Organization-List**

#### 4.2.2.1.3.2 User Interface of the Personnel-Paragraph

All five list types can be generated by one common user interface. A screen shot is given in Figure 30. The input mask must be processed line by line and a user is guided through all steps necessary to generate a Personnel-List. In the first step the type can be selected from a pull down menu (Figure 30 (1)).

The screenshot shows a web-based editor interface for creating a personnel list. At the top, there is a breadcrumb trail: 'Editor > Miscellaneous institutions'. Below this, a 'Preview' section shows a red '5' next to a plus icon and a closing curly brace. The main configuration area is titled 'Type and Settings'. It features a 'Type' dropdown menu currently set to 'Personnel List', with a red '1' next to it. Below this is a 'Template' dropdown menu set to 'User List 3 (Select)', with a red '3' next to it. A red '2' is placed under the '(Select)' part of the template name. Under the 'Personnel List' heading, there are several options: a checked checkbox for 'Use Headline' with a red '7' next to it, a text input field containing 'Investigators', a checked checkbox for 'Hide empty Fields' with a red '6' next to it, and two 'Space between Groups' input fields, both set to '5'. A red '4' is next to an 'Add new Group' button. At the bottom, there are two list items. The first item has a 'Title/Function' of 'Lead Investigator' and a 'Name' of 'Graf Norbert'. The second item has a 'Title/Function' of 'Investigators' and two names: 'Braun Yvonne' and 'Stenzhorn Holger'. Each list item has a set of control buttons (person icon, up/down arrows, and a close 'x' button) and an 'Options' column.

Figure 30: Input Mask of the Personnel-Paragraph

In the second step the layout can be selected by clicking on the “Select” link (Figure 30 (2)). This will open a dialog as given in Figure 31. Now all available templates for the specific list type are accessible.



**Figure 31: Dialog, Select Template Type**

Each row within this dialog gives name (Figure 31 (1) e.g. “User List 2”) and preview (Figure 31 (2)) of one of the predefined templates. The preview provides a dummy view how the list will look like, if chosen. The row highlighted in yellow indicates the active (selected) template, which will be utilized by the Personnel-Paragraph to generate the list. The selection can be changed easily by clicking the “Select template” button (Figure 31 (3)) or by clicking on the preview image of the desired template on the right hand side of the dialog. This will determine the template, close the dialogue and the name of the selected template appears in the input mask ((Figure 30 (3)). This setting can be revised at any time by clicking on the “Select” link (Figure 30 (2)) again.

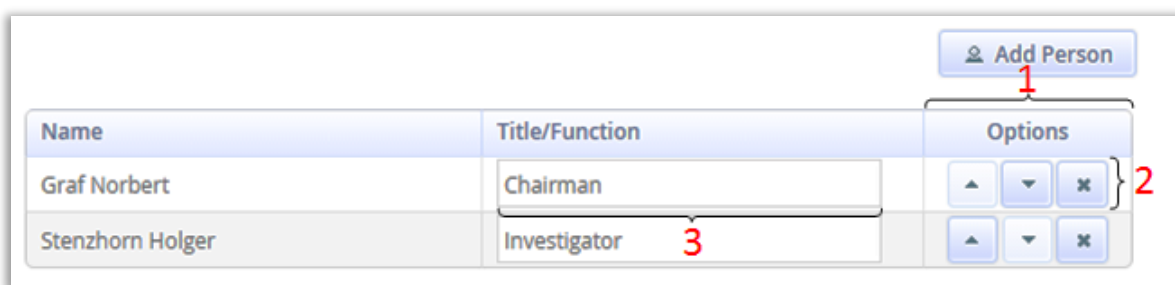
After these two steps have been completed, the list type is selected and the template is defined. Now a new button (Figure 30 (4)) becomes available. Depending on the list type, this button enables different actions. In case of the “Simple Personnel-List” or the “Organization-List” either persons or organizations can be added to the list. In case the “Personnel-List” or the “Sponsor-List” has been selected, a group will be

created in a first step and thereafter people or organizations can be attached to the group.

The following examples illustrate the two options described above.

**Example 1**, “Simple Personnel-List” or “Organization-List”:

In case of these options a screen as given in Figure 32 will open and a button “Add Person” or “Add Organization” will appear.



**Figure 32: Input Mask of the Simple Personnel-List**

If these buttons are clicked, another dialog opens displaying all individuals or organizations, which are stored in the ObTiMA database. Any person or organization can be selected by a mouse click and will be added to the list. Figure 32 illustrates such a list already populated with two scientists. The order of the entries can be changed by using the up and down arrow buttons in the option column (Figure 32 (1)) and entries can easily be removed from the list by clicking the delete button (Figure 32 (2)). If additional scientists or organizations become involved into the study, they must be added via the ObTiMA administration panel<sup>8</sup>. Roles and responsibilities can be defined in the input field “Title/Function” (Figure 32 (3)) by typing in any responsibility, in this example “Chairman” and “Investigator”.

<sup>8</sup> ObTiMA administration panel is a tool of the main program ObTiMA. It was given and is not part of this paper.

## Example 2, “Personnel-List” or “Sponsor-List”

The screenshot displays the 'Personnel-List' input mask with three distinct groups. At the top right, a blue button labeled 'Add new Group' is marked with a red '1'. Below this, the first group is titled 'Lead Investigator' and lists 'Graf Norbert'. The second group is titled 'Investigators' and lists 'Braun Yvonne' and 'Stenzhorn Holger'. The third group is titled 'Personnel Function' and displays 'No records found.' This group is marked with a red '2'. Each group includes a 'Title/Function' input field, a list of names, and an 'Options' column with navigation buttons (up, down, and delete).

**Figure 33: Input Mask of the Personnel-List**

Utilizing the “Personnel-List“ or “Sponsor-List” several individuals can be assigned to one single responsibility. By using the “Add new Group” (Figure 33 (1)) an empty frame is generated (Figure 33 (2)). Now any responsibility can be typed into the field “Title/Function” and allocated individuals can be selected in the ObTiMA administration panel. There is no limitation by the software in terms to the number of functions as well as number of individuals assigned to one function. It is feasible as well to assign one individual to several functions.


If the input mask of the Personnel-Paragraph is completed, a preview of the printout will be displayed by use of the associated button (Figure 30 (5)).

If ObTiMA does not offer a complete set of personal information, the corresponding fields in the generated lists will remain blank. To get visibility of missing data the “Hide empty Fields” checkbox (Figure 30 (6)) must not be marked. As result wildcards are displayed replacing missing data. If the missing piece of information is entered at a later stage into the ObTiMA database, the data will automatically be

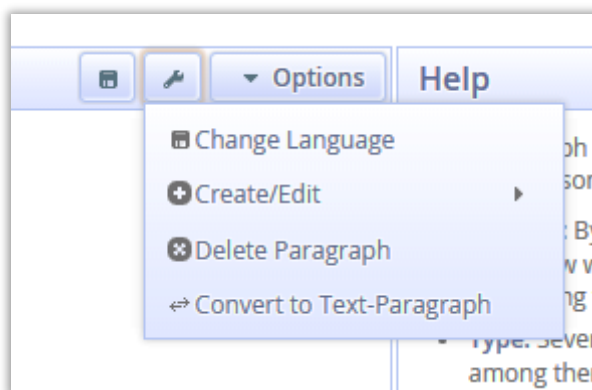
transferred into the “Personnel Paragraph” and appear in the printout. There is no user action needed to initiate this activity.

Another feature which needs explanation is the “Use Headline” option (Figure 30 (7)). If a check is set in this field a headline will be generated to structure the protocol. This feature is not unique for the Personal-Paragraph, it is available in the Amendment-Paragraph and the Table of Contents-Paragraph as well.

#### 4.2.2.1.3.3 Personnel-Text-Paragraph Conversion

The MasterProtocol-Editor supports conversion from the Personnel- to the Text-Paragraph and vice versa. This is most helpful to customize a Personnel-List generated by the Personal-Paragraph. The conversions can be initiated in the “Quick Settings Menu”  located in the editor space (Figure 20 (9)) by use of the “Convert to Text-Paragraph” option.

It is important to know that there are some limitations with regard to the converted




**Figure 34: Convert to Text-Paragraph Function**

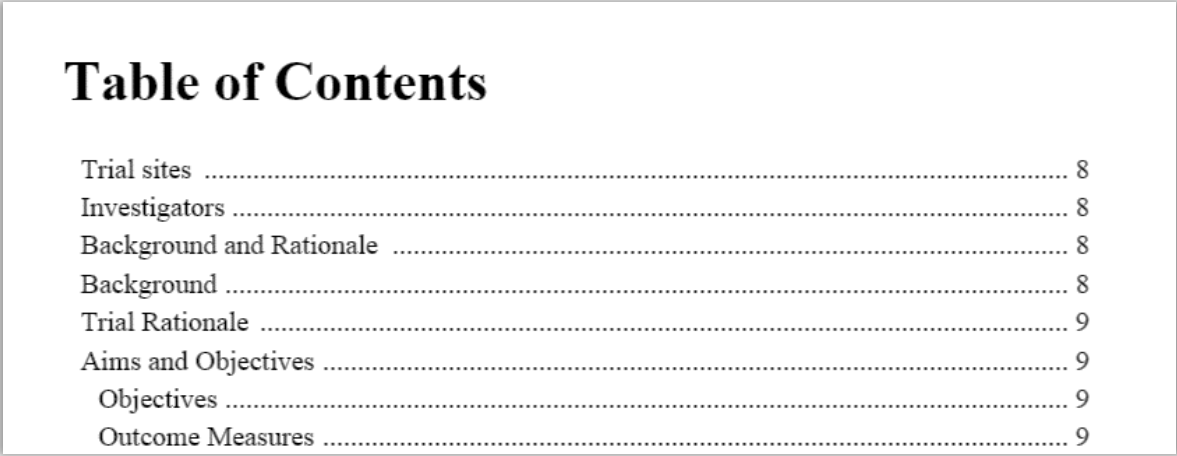
paragraph. The content of the Text-Paragraph will remain unchanged, even if data in the ObTiMA database are altered, whereas the original Personnel-Paragraph updates the content automatically. In case the Text-Paragraph is converted back again into a Personnel-Paragraph, all changes made in the Text-Paragraph will get lost and the original Personnel-Paragraph will be reestablished again.

Contrary to the process described above there is no way to convert a file which originally was set up as a Text-Paragraph into a Personnel-Paragraph. This is

caused by the fact, that a Text-Paragraph is designed for highest flexibility and does not have a default structure.

#### 4.2.2.1.4 Type Table of Contents-Paragraph

The paragraph is indicated by the  icon in the paragraph section (Figure 20 (1)). It automatically generates a table of contents as shown in Figure 35. In the standard settings, all headlines used in other paragraphs are automatically transferred into the table of contents and a hyperlink is established to the corresponding paragraph. This option can be disabled for any individual paragraph (4.2.2.3 Customizing the Protocol). This is done by default for the introductory chapter.

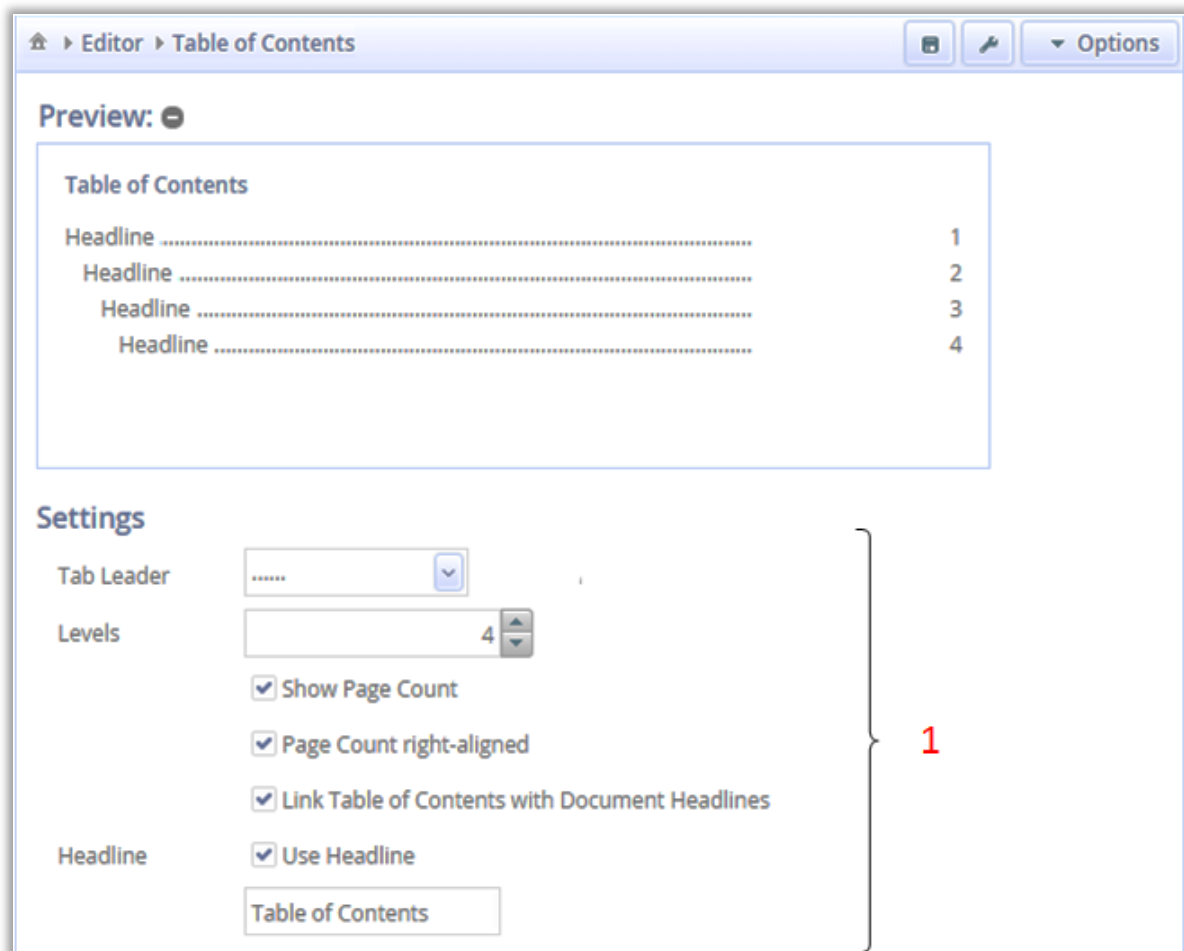


The image shows a screenshot of a 'Table of Contents' page. The title 'Table of Contents' is centered at the top in a large, bold, black serif font. Below the title is a list of sections with dotted lines leading to page numbers. The sections and their page numbers are: 'Trial sites' (8), 'Investigators' (8), 'Background and Rationale' (8), 'Background' (8), 'Trial Rationale' (9), 'Aims and Objectives' (9), 'Objectives' (9), and 'Outcome Measures' (9).

<b>Table of Contents</b>	
Trial sites .....	8
Investigators .....	8
Background and Rationale .....	8
Background .....	8
Trial Rationale .....	9
Aims and Objectives .....	9
Objectives .....	9
Outcome Measures .....	9

Figure 35: Table of Contents, PDF view, automatically generated

The user interface of the Table of Contents-Paragraph is shown in Figure 36.



**Figure 36: User Interface of the Table of Contents**

The appearance of the table of contents is determined by the setting options (Figure 36 (1)):


- **Tab Leader:** Several options as continuous lines, dotted lines and others.
- **Levels:** Number of sub-headlines included in the table of contents.
- **Show Page Count:** If disabled, page count will be skipped.
- **Page Count right-aligned:** See Figure 37
- **Link Table of Contents with Document Headlines:** If this option is selected headlines in the table of contents will be highlighted in blue and provide a hyperlink to the corresponding chapter in the document.
- **Use Headline:** See 4.2.2.1.3.2 User Interface of the Personnel-Paragraph
- **Preview:** Preview view of the PDF printout.



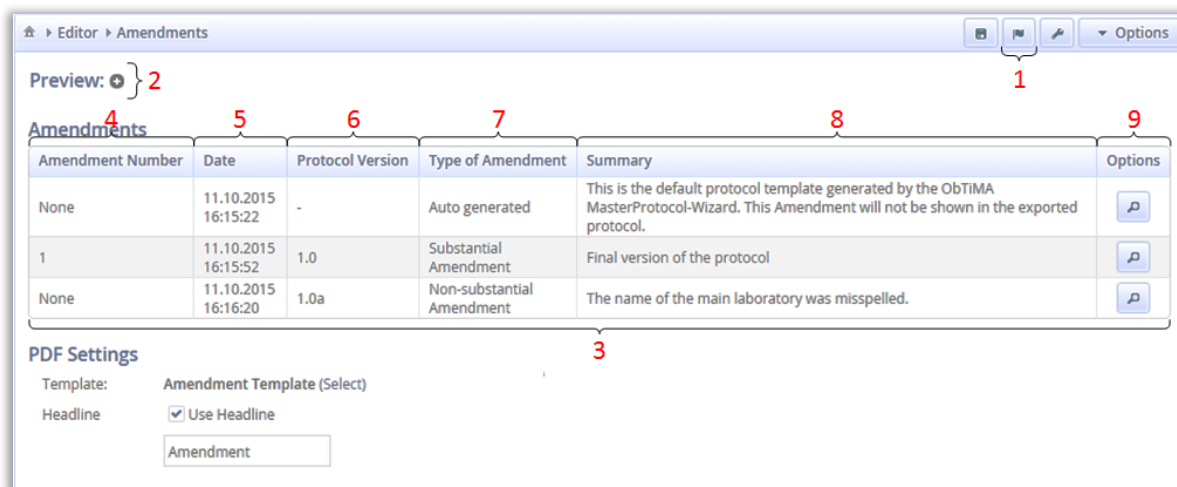
Table of Contents		Table of Contents	
Headline 1		Headline .....	1
Headline 2		Headline .....	2
Headline 3	a	Headline .....	3 b

**Figure 37: Page Count right-aligned, Option inactive (a), active (b)**

#### 4.2.2.1.5 Type Amendment-Paragraph

Once all study specific data are entered and the protocol is completed for the first time, the actual status is frozen as version one. This and all other consecutive versions are saved as secured read only files in the ObTiMA database. There is a unique consecutive number allocated to each of the files. This cannot be altered by the user. If a new version is generated all changes with regard to the previous version are documented. Changes are classified into “substantial” and “non-substantial”. A “substantial” change affects execution and evaluation of the study results so significant that protocols must be reapproved by the authority. “Non-substantial” changes, for example correction of typos and formatting are less critical. Both type of changes impact the version number. In case of non-substantial the version number will be extended by a character, in case of substantial the version number will increase by one. The Amendment-Paragraph keeps track of every change. The user has the option to choose any of the versions and make printouts of the protocol. The printouts will include a table listing all the changes since version one. The position of the table in the printouts is in the same order as the Amendment-Paragraph, indicated by the  icon and has been arranged within the paragraph section of the MasterProtocol-Editor (Figure 20 (1)). In each protocol there is just one Amendment-Paragraph included.

#### 4.2.2.1.5.1 User Interface of the Amendment-Paragraph



**Figure 38: User Interface of the Amendment-Paragraph**

The user interface of the Amendment-Paragraph is shown in Figure 38.

The icons in the navigation bar in the upper frame of the user interface are not unique and they have already been explained above. Just the “Create Amendment” button (Figure 38 (1)) is specific to this paragraph. The corresponding functionality will be explained in the next chapter.


The preview (Figure 38 (2)) displays the PDF view of the amendment table. Core of the screen is the amendment listing (Figure 38 (3)). This table displays all amendments and each row represents one of these. The Amendment number is given in the first column (Figure 38 (4)). Only amendments resulting from major protocol changes are indicated as “substantial amendment” and carry a number. “Non-substantial” amendments have no amendment number. The second column (Figure 38 (5)) provides date and time of amendment creation. As explained above, every new amendment triggers a new protocol version. This is characterized by the protocol version number (Figure 38 (6)). It is generated in accordance to the SIOPE guidelines. The next column (Figure 38 (7)) marks the type of change. Beside substantial and non-substantial there is one unique type indicated as “auto generated” in the first row of the table. It has been set up by the MasterProtocol-Wizard on completion and it does not carry any number. This document represents the SIOPE guideline structure and it just includes basic trial data. It can serve as a

backup for clinical study protocol generation in case some errors have occurred during the later steps of protocol generation. This document is only listed on the screen but it will not be included in the PDF printout of the amendment history.

The text, given in the next column (Figure 38 (8)) characterizes the amendment. Every protocol indicated in the amendment list is frozen. By clicking on the options button (Figure 38 (9)) a frozen document can be accessed and printed out, but it cannot be altered.

The PDF settings section has been already described in chapter 4.2.2.1.3.2 User Interface of the Personnel-Paragraph.

#### 4.2.2.1.5.2 Amendment Generation

A new amendment can be generated at any time by use of the “Create Amendment” button  (Figure 38 (1)). The dialog as shown in Figure 39 will appear.

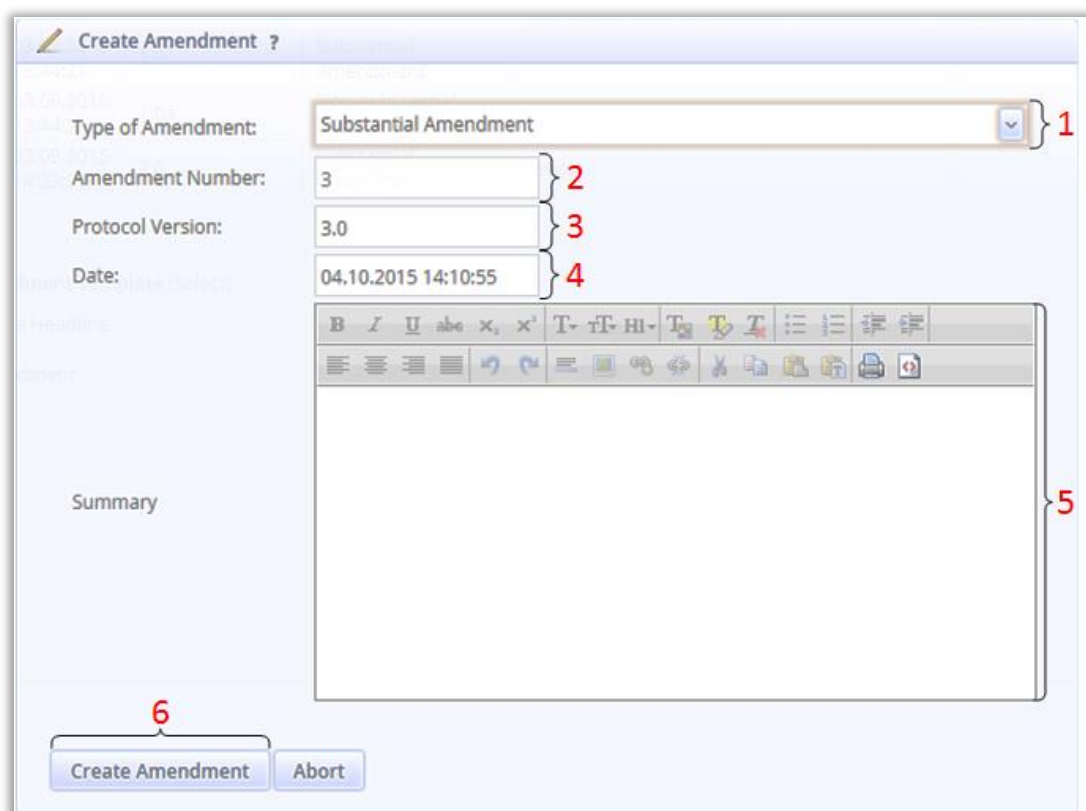



Figure 39: Dialog for creating new Amendments

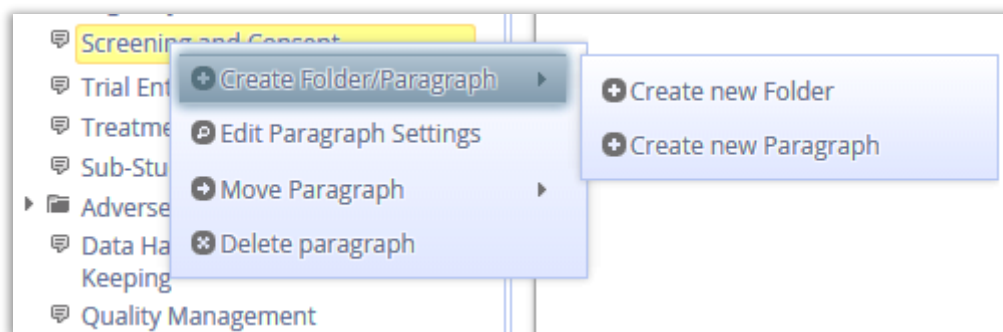
Under “Type of Amendment” (Figure 39 (1)) the user can select “Substantial Amendment” or “Non-substantial Amendment” to characterize the changes with regard to the previous version. The amendment number (Figure 39 (2)), the protocol version (Figure 39 (3)) and date (Figure 39 (4)) are automatically generated by the program. Different to the “Amendment Number” the auto generated settings (Figure 39 (3), (4)) can be overwritten by the user. However it is recommended to keep the default. The summary box (Figure 39 (5)) should be used for a brief characterization of the changes with regard to the previous version. By use of the “Create Amendment” button (Figure 39 (6)) all paragraphs are merged into a PDF file and the version of the new amendment is frozen. As there are plenty of operations carried out in the background, this step might take a while.

#### **4.2.2.2 Folders**

The Folders displayed in the menu section of the MasterProtocol-Editor (Figure 20 (1)) are a measure to increase clarity of the paragraph section. A folder may include one or several paragraphs. They can be identified by a specific icon . Folders are a measure to increase clarity of the paragraph section. During creation of the PDF printout, the paragraphs will be extracted from the folders and included into the protocol at the position of the folder. It is not indicated in the final printout if a paragraph has been stored in a folder before.

### 4.2.2.3 Customizing the Protocol

Number and structure of paragraphs and folders in the standard protocol generated by the MasterProtocol-Wizard are arranged in accordance to the SIOPE guidelines.



**Figure 40: Paragraph/Folder Context Menu of the MasterProtocol-Editor**

To obtain standardization this should not be modified. In rare cases however it might be advantageous to make some adoptions to meet requirements of a specific study. That is why the editor offers the option to edit, move or delete paragraphs and folders. In addition new paragraphs and folders can be created. This can be done by selecting any paragraph or folder with the right mouse button from the paragraph section (Figure 20 (1)) of the MasterProtocol-Editor. Following the selection a context menu (Figure 40) will open.

#### 4.2.2.3.1 Move and delete Paragraph

By use of the “Move Paragraph” option of the “Paragraph/Folder” context menu, a paragraph/folder can be shifted up- or downwards. Delete paragraph/folder erases the selected item.

#### 4.2.2.3.2 Create new Paragraph

By clicking “Create new Paragraph” another window will open. Now the characteristics of the new paragraph can be specified (Figure 41).

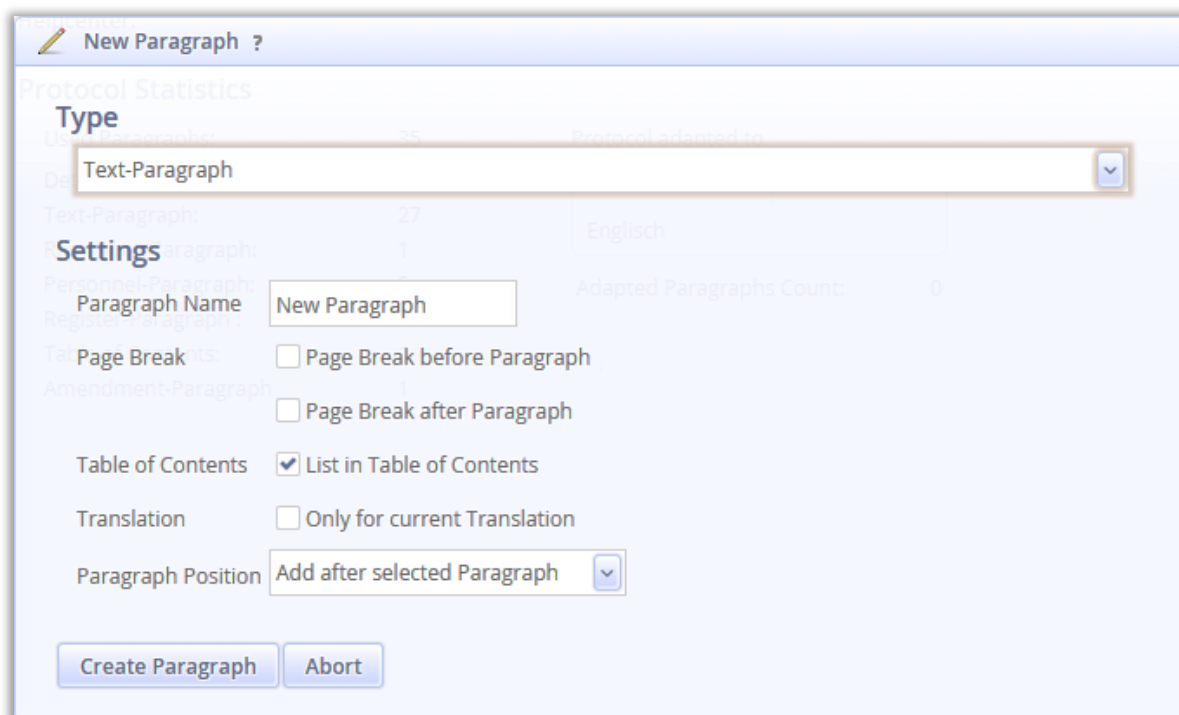


Figure 41: Dialog for Creating new Paragraphs

- **Type:** A drop down menu offers the selection of the 5 paragraph types (4.2.2.1 Types of paragraphs).
- **Paragraph Name:** The name can freely be chosen, but it should be characteristic.
- **Page Break:** A forced page break can be inserted either before or after the paragraph.
- **Table of Contents:** If selected, the headline of the paragraph will be included into the table of content.
- **Translation:** If the paragraph should only appear in one language and should not be included into protocols of different languages this checkbox must be activated (4.2.3 Internationalization).
- **Paragraph Position:** The new paragraph can be inserted either before or after the paragraph by which the context menu was opened. If a folder was selected instead, a further option is offered. Here it can be determined if the new paragraph will be inserted before, after or in the selected folder.

### 4.2.2.3.3 Edit Paragraph Settings

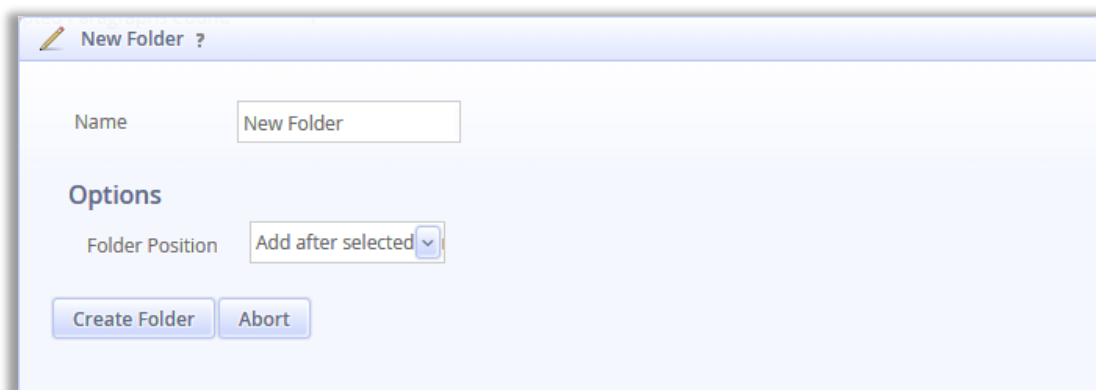
Paragraphs already existing can be edited using the dialog given in Figure 42. This dialog can be accessed through the Paragraph/Folder Context Menu (Figure 40) of the MasterProtocol-Editor by clicking the option “Edit Paragraph Settings”. Within this dialog, all parameters of the paragraph can be determined. However, there is one exception. Once the type of the paragraph has been chosen in the MasterProtocol-Editor, it cannot be altered at a later stage. The information panel of this dialog will be explained later (4.2.3 Internationalization).

Language	Independent	Translatable	Translated	Converted to Text	Options
Englisch	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not Supported	<input type="button" value="↺"/> <input type="button" value="✕"/>
Deutsch	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not Supported	<input type="button" value="↺"/> <input type="button" value="✕"/>

Figure 42: Dialog for Editing the Paragraph Settings

#### 4.2.2.3.4 Create new Folders

A new folder can be created by use of the dialog given in Figure 43. This dialog can be opened with the option “Create Folder” in Paragraph/Folder Context Menu (Figure 40) of the MasterProtocol-Editor.



**Figure 43: Dialog for Creating new Folders**

- **Name:** Name of the new folder.
- **Folder Position:** The new folder can be inserted either before or behind the paragraph/folder which was selected to open the dialog.

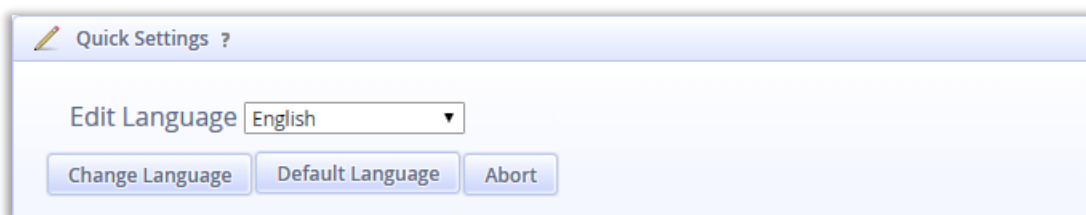
#### 4.2.3 Internationalization

If a multicenter study is performed in several countries, there is a need to provide some parts or even the complete protocol in two or several languages. This is particularly mandatory for the Informed Consent as each study participant must precisely understand and agree to the medical trial and the associated risks. To avoid any misunderstanding this document must be provided in the mother tongue of the individuals affected.

With the MasterProtocol-Editor some paragraphs or the complete protocol can be translated into several languages. The language which was selected while the MasterProtocol-Wizard was executed the first time is the default language. The corresponding document is stored as master document. It will remain as default and will not be altered if some paragraphs or the complete document is translated into another language. Paragraphs in other language are stored in addition and during



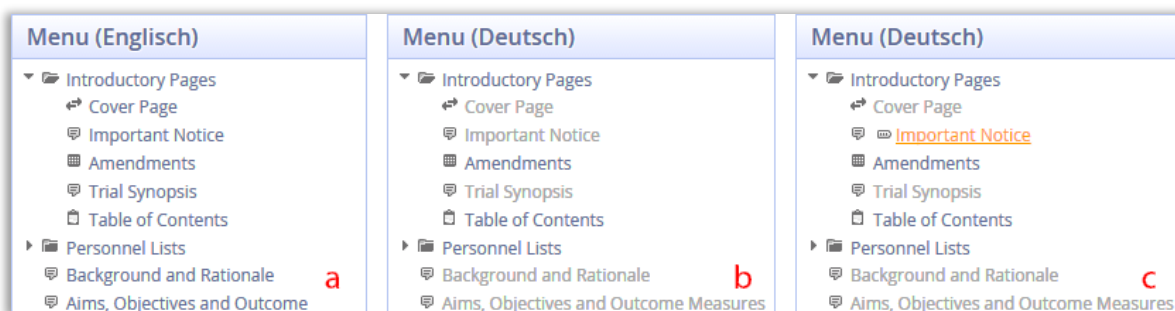
printout multi or single language protocols can be chosen. To translate a document, the MasterProtocol-Editor needs to be set to the desired language. This can be done in the quick settings menu of the MasterProtocol-Editor (Figure 20 (9)) by selecting the option “Change Language”.



**Figure 44: Quick setting Menu, Change Language**

The “Change Language” dialog (Figure 44) offers a drop down menu, displaying all available languages. The editor can be set back to the default language by clicking the “Default Language” button.

If a novel language is selected from the menu, the paragraph section as given in Figure 45 will change its appearance.



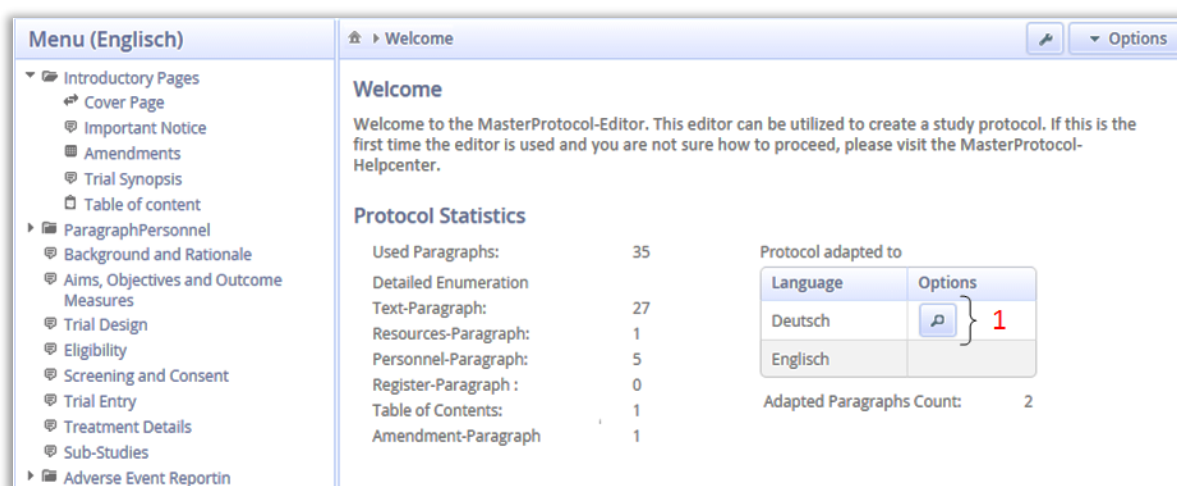
**Figure 45: Paragraph Section: Default language English (a), Editor set to German (b), Editor set to German, paragraph “Important Notice” translated into German orange highlighted (c)**

Paragraphs which cannot be translated are still displayed in blue letters. Among the non-translatable paragraphs there are the Amendment-Paragraph and the Table of Contents-Paragraph. All paragraphs which can be translated are displayed in grey letters. The translation is done in the “Paragraph Settings Dialog” (Figure 42) using the „Translate” button. As a result a copy of the already existing paragraph will be generated serving as basis for the translation. Once a document has been

translated by a user it can be stored and is immediately available for protocol generation. It is important to know, that the original paragraph will remain completely unchanged. The translated paragraph can be identified by the orange letters in the paragraph section of the MasterProtocol-Editor (Figure 45 (c)). If a PDF-protocol is printed out in a different than the default language, all paragraphs that have not been translated will be included into the printout in the default language. As a result there might be a German Protocol with some English chapters included. As an example this might be required for the Informed Consent of a German trial including some native English-speaking individuals.

#### 4.2.4 Overview over Paragraphs in various Languages

An overview over all paragraphs and the corresponding languages is displayed on the Welcome screen of the MasterProtocol-Editor. It appears once the editor is opened but it can be accessed during an editor session at any time by usage of the navigation bar.



**Figure 46: MasterProtocol-Editor Information Page**

The information page is illustrated in Figure 46. Under “Protocol Statistics”, all paragraphs in use are listed. On the right side of the screen there are the utilized languages are given. In the picture (Figure 46) the editor is set to English. By clicking the “Change Language” button  (Figure 46 (1)) it will switch to German. Thereafter the language is set to German and the “Change Language” button  will appear behind English.

More information concerning a specific paragraph is available by selecting the paragraph with the right mouse button and clicking “Edit Paragraph Settings” (4.2.2.3.3 Edit Paragraph Settings). As a result the “Paragraph Settings” dialog given in Figure 42 will appear. Figure 47 displays an enlarged section of this dialog featuring the “Paragraph Translations” table.

As indicated by the yellow highlighted row, the current language of the editor is German.

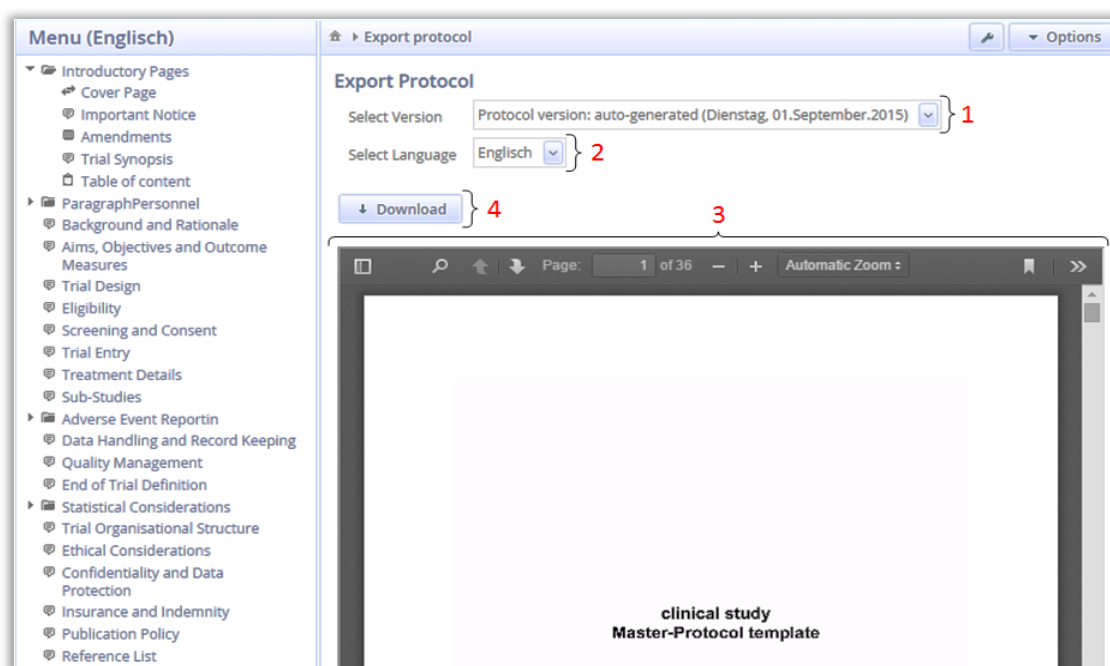
Language	Independent	Translatable	Translated	Converted to Text	Options
Englisch	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Not Supported	<input type="button" value="↻"/> <input type="button" value="✕"/>
Deutsch	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Not Supported	<input type="button" value="✕"/>

**Figure 47: Enlarged section of the Paragraph Settings Dialog (Figure 42), indicating the utilized languages.**

- **Independent:** If a paragraph was set up in the “Dialog for creating a new Paragraph” (Figure 41) using the option “Only for current Translation” this paragraph will only be available in the language it was created. In this case, a checkmark will become visible in the column “Independent” and there will be no option to translate this paragraph into any other language.
- **Translatable:** Paragraph in the default language, it can be translated.
- **Translated:** Paragraphs already translated.
- **Converted to Text:** If the paragraph has been converted into a Text-Paragraph a checkmark appears in this box. If the paragraph can not be converted “Not Supported” is displayed instead.
- **Options**
  - **Change Language** : If used, the editor is switched to the language of the selected paragraph. The dialog will close thereafter and the paragraph is displayed in the editor space of the MasterProtocol-Editor (Figure 20 (3)).
  - **Delete (Cross)** : Deletes the paragraph. If a paragraph in the default language is selected all translations will be deleted as well. In contrast, deletion of a translated paragraph will not affect the other language files.

## 4.2.5 PDF Export

Each finished protocol version can be downloaded to a local computer by authorized users. The download function is accessible via the options menu of the MasterProtocol-Editor (Figure 20 (6)). Once the options menu has opened, the “Export Protocol” button (Figure 22) becomes available. When using this button the “Export Protocol” page will open (Figure 48).



**Figure 48: Export Protocol Page**

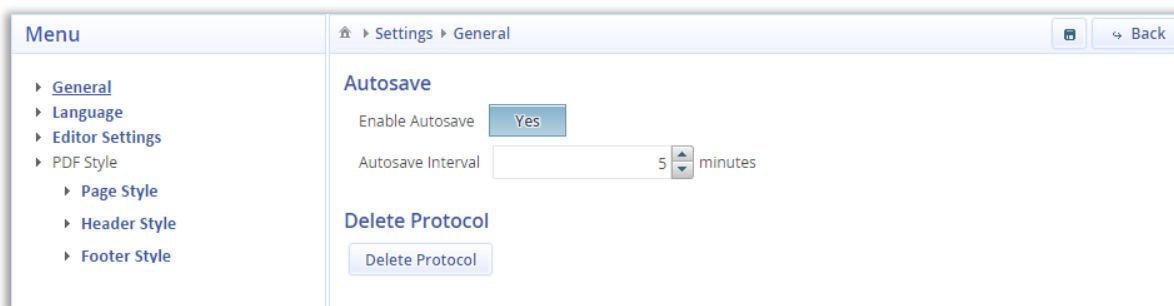
In the drop down menu “Select Version” (Figure 48 (1)) all available protocol versions are listed. Among these all previous finalized versions and the currently processed protocol are archived.

If several languages are available, these are given in the “Select Language” (Figure 48 (2)) panel and the desired one can be selected. Details concerning multi language protocols see 4.2.3 Internationalization.


Before starting the download a preview of the selected PDF protocol will appear in the “Preview” section of the screen (Figure 48 (3)). If the protocol meets all expectations, the download can be initiated by the “Download” button (Figure 48 (4)). As a final step any location on the local drive can be selected to store the protocol.

## 4.2.6 Editor Settings

Appearance of the MasterProtocol-Editor and the PDF printout are defined in a menu, which is accessible via the “Editor Options Menu” (Figure 20 (6)) by clicking the option “Settings” in the option menu (Figure 22).



**Figure 49: MasterProtocol-Editor Settings, General Tab opened**

The user interface (Figure 49) is similar in structure to the input mask of the MasterProtocol-Editor. On the left hand side there is a menu listing all potential options. The first three entries (“General”, “Language”, “Editor Settings”) affect the editor, all other impact layout of the PDF. If one of the keywords is selected, all potential settings will appear on the right hand side of the screen. By using the “Back” button in the very right hand upper corner of the screen, the window will close and the user is back again in the MasterProtocol-Editor. It is important to know, that any entries in this input mask will get lost unless they have been confirmed (saved) by the “Store File”  icon .

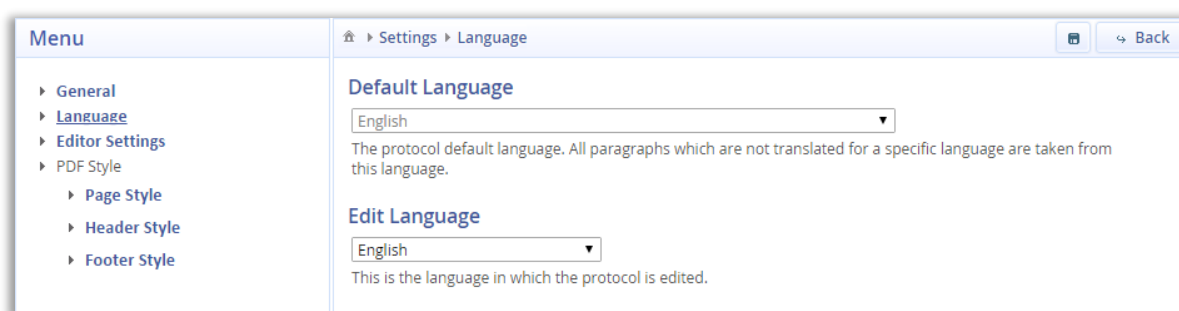
### 4.2.6.1 General

The input mask “General” (Figure 49) has two purposes. One enables saving of the current work status, the other is designed to delete a protocol. Via “Autosave”, frequency of background saving can be configured. To avoid data loss that might occur by issues with the internet connection, it is recommended to select rather narrow intervals. The default is 5 min.

The “Delete Protocol” only works with administrator rights. It completely deletes all protocol versions, including the default one. This command will be very rarely needed, it is predominately intended for developmental purposes.

#### 4.2.6.2 Language

The “Language” input mask (Figure 50) displays the default protocol language and enables a switch between the different languages available.



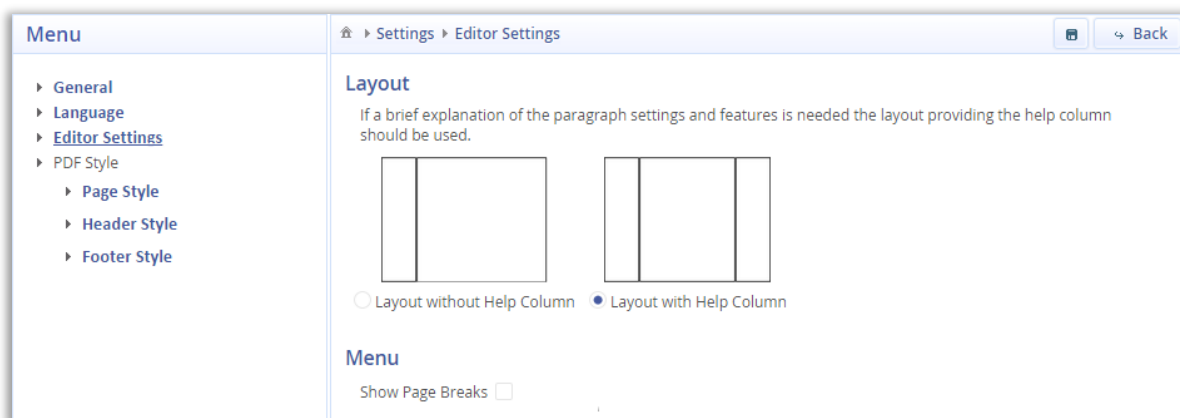
**Figure 50: MasterProtocol-Editor Settings, Language Tab opened**

The default language of the study protocol has been set in the MasterProtocol-Wizard at the very beginning of protocol creation. This setting is indicated as “Default Language” in the screen given above. If a different language is selected with “Edit Language”, any paragraph, which is generated by the Editor thereafter, will be saved in the selected language. The new file might be a translation of one of the paragraphs already existing, or a newly generated paragraph. In case of translation the new file will be saved as additional document, but the original file will be kept and not overwritten. Utilizing the “Export Protocol” page (4.2.5 PDF Export), the user can make a selection before download of the study protocol, to have it just in the default language or with all the translated paragraphs being included.

#### 4.2.6.3 Editor

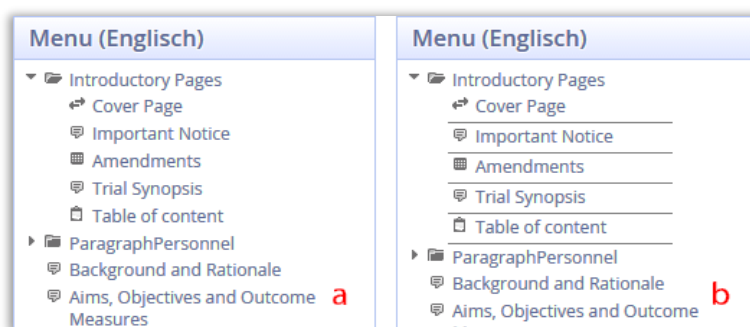
The input mask “Editor” of the editor settings is used to customize appearance of the display screen.

Under “Layout” (Figure 51) it can be selected if two or three columns will be displayed. If the option two columns is set, only the paragraph section and the editor space of the MasterProtocol-Editor is displayed. If three columns are selected, the third column will appear at the right side of the editor screen, showing the help menu (Figure 20 (2)).



**Figure 51: MasterProtocol-Editor Settings, Editor Tab opened**

The “Show Page Breaks” option defines if the printout will utilize a new page or continue on the same one for any single paragraph (4.2.2.3 Customizing the Protocol). The page breaks are indicated on the computer screen by underlining the corresponding paragraphs. Figure 52 shows an example for the activated “Show Page Breaks” option on the right side and the disabled option on the left side (default value).



**Figure 52: Show Page Breaks, deactivated (a), activated (b)**

#### 4.2.6.4 PDF Style

Appearance of the PDF can be determined by three input screens, “Page”, “Header” and “Footer”.

##### 4.2.6.4.1 Page Style

This impacts the protocol layout with regards to margins, orientation of the pages and bookmarks.

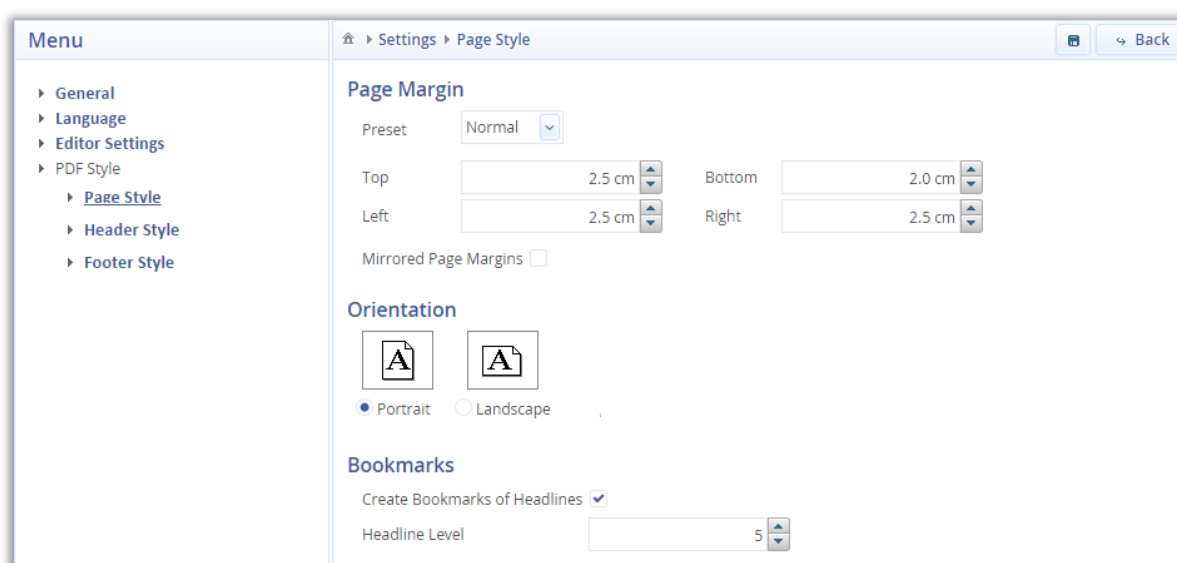


Figure 53: MasterProtocol-Editor Settings, Page Tab opened

- **Page Margin:** This drop down menu offers several predefined page margins. If none of these meets expectations, page margins can be individualized by overwriting the figures in the dropdown boxes.
- **Mirrored Page Margins:** Intended purpose of this option is the generation of protocol pages suitable for booklets. If activated by the check mark, “Inner Margin” and “Outer Margin” appear and recommendations for the optimal values are displayed.
- **Orientation:** Portrait or Landscape format.
- **Bookmarks:** If “Create Bookmarks of Headlines” is selected, the editor will utilize the headlines present in the paragraphs to generate bookmarks within the exported PDF. With the option “Headline Level”, number of sub headlines can be determined.



#### 4.2.6.4.2 Header/Footer

The Header and the Footer input masks are set up similar and most of the options are self-explanatory.

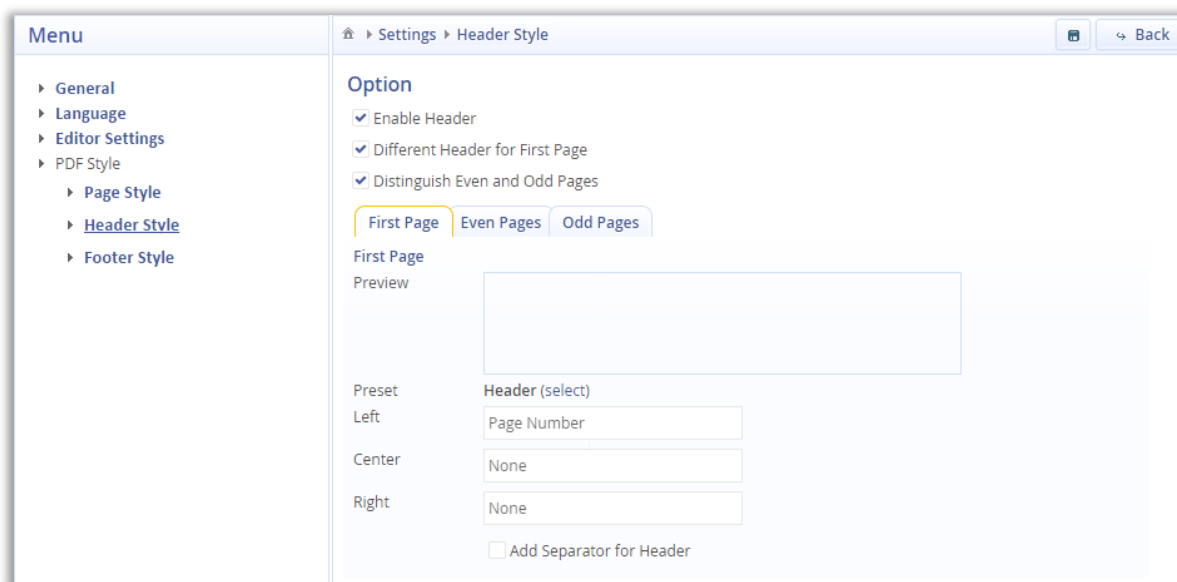


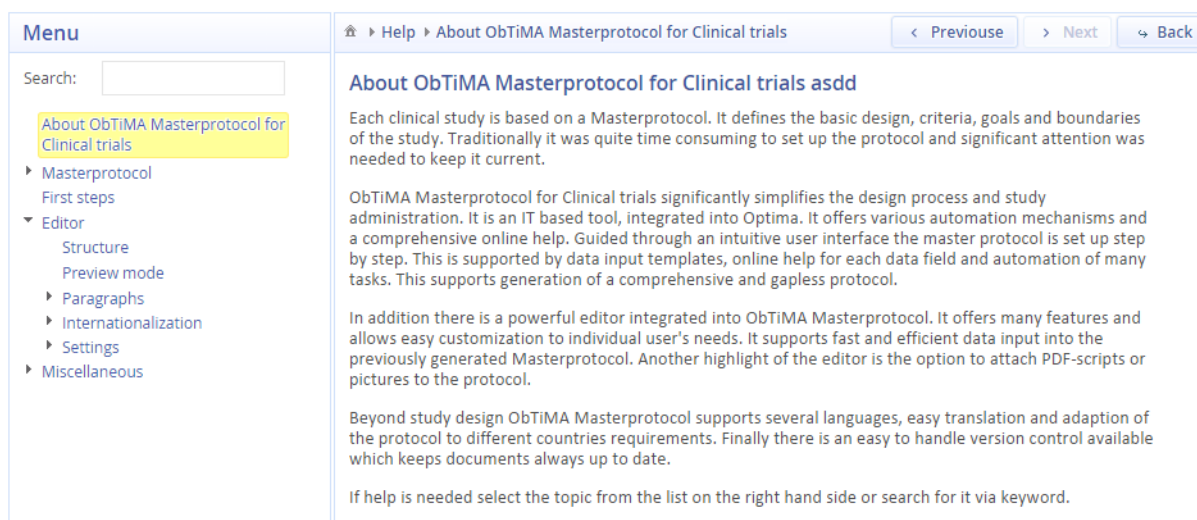
Figure 54: MasterProtocol-Editor Settings, Header Tab opened

Just the following needs explanation (Figure 54):

- **Different Header for First Page:** If the first page of the document should not carry any or a different header, this option needs to be activated. If this is done, a further dialog opens to enable individual settings for the first page.
- **Distinguish Even and Odd Pages:** If the single pages will be combined into a booklet, location of the header can be separately set for even and odd pages.

## 4.3 MasterProtocol-Helpcenter

The MasterProtocol-Helpcenter can be called up in the MasterProtocol-Wizard as well as in the MasterProtocol-Editor at any time. It provides extended help for program handling, it offers further readings concerning regulatory background and there are hyperlinks given for internet access to the applicable guidelines and regulations. The start screen of the Helpcenter is displayed in Figure 55.



**Figure 55 Start Screen of the MasterProtocol-Helpcenter**

All available help topics are listed in the left column of the screen. The online help for any of these topics can be called up by a mouse click. The help text will appear on the right hand side of the screen. In addition there is a search box. Free text can be entered and the program will perform an associative search displaying the best matches. Navigation through the pages is enabled by the “Previous” and “Next” buttons. Utilizing the “Back” button the program will jump back to the screen from which the Helpcenter has been approached.

## 5 Discussion

As discussed in this dissertation many study protocols are not properly elaborated and not all publications meet the required standards. This is why there have been many attempts and initiatives to improve accuracy and completeness of protocols and study reports. It has been shown that significant improvement has been achieved throughout the recent decades. However it cannot be ignored that even today there are still major deficiencies evident. It has been proven that these issues result in misinterpretation of scientific results, increased cost and additional workload (2.2 Necessity of Study Protocols). Therefore it is important to take further actions to eliminate the remaining deficiencies. Hence it seems all the more surprising that only very little use has been made to utilize modern IT software.

### 5.1 Solution

To evaluate the basic question of this work „ Are there any means to utilize IT to generate a perfect study protocol”, determining factors of significance and potential impact parameters have been reviewed. The most important of these are:

- Supporting materials and tools already available (guidelines, protocol templates, toolkits)
- Identification of communalities and differences among international guidelines and regulations
- Review of scientific literature to understand major protocol gaps and study impact
- Framework for programming:
  - Identification of a suitable protocol template
  - Usability for IT implementation of supporting materials already available
  - Potential boundaries to utilize a standard protocol template for international use in various jurisdictions

- Multi language for the complete protocol or single paragraphs
- Single and multicenter studies
- Parallel work of several scientists in various locations
- Failure tolerance through transparent user guidance
- Extendible and service friendly program architecture
- Audit trail and version control of the protocols
- Data protection
- Minimization of IT cost

As a starting point for program design, many protocols of clinical studies were checked and the conclusions drawn were elaborated by discussions with IT specialists and experienced investigators. Good advice was received and once the first program modules were set up they were put up as a basis for discussion on a medical congress. During this event there was a lively debate and many expert provided optimization ideas. Among those there was the proposal for drag and drop import of pictures, the functionality to hide help screens by more advanced users and many hints to optimize the intuitive usability of the MasterProtocol-Wizard.

As research became more and more international and conclusions drawn from clinical trials had to support multinational drug registrations, international guidelines were developed post Second World War. This was reflected by the Declaration of Helsinki of 1964 and the ICH GCP Guidelines dated from 1996. Specifically the latter was a milestone as the first time the USA, Europe, Australia and Japan agreed on rather comprehensive guidelines in a mutual recognition process [9], [10]. It took a while until these guidelines were transferred into national law, which was done for the first time by the US in 1974 [11]. Although transcriptions differ among the various nations, a valid basis for international protocol acceptance has been set. Nevertheless there are discrepancies among the diverse transcriptions. The whole area is still in a constant move and many of the regulations and guidelines still lack of clarity or are difficult to access [26]. Therefore selection of a suitable protocol template was one of the crucial points of this work. The high level of harmonization reached within the European Union has simplified this task and the SIOPE template was selected as basis for program development. This template is in full accordance

to the ICH GMP Guideline. It is in full compliance with all rules and regulations of the EU and it completely meets German provisions. In addition the SIOPE template is highly elaborated with regards wording and format of the protocol pages. It also provides standard text blocks and only study specific key words need to be inserted (For example see Appendix 6.4 SIOPE-TEMPLATE, Chapter 11.1 Site Set-up and Initiation). To ensure that all local (German) legal provisions are met it was verified that transcription of the EU guidelines into national laws had been progressed to a point that no additions needed to be made to the SIOPE templates.

Initial analyses revealed issues regarding a completely standalone program. It would have been very costly and extremely time consuming to set it up from the scratch and code a complete program environment. Therefore the MasterProtocol-Creator was designed as extension of the study administration program ObTiMA [76]. ObTiMA already contains a data base with a large amount of study data, provides access control and personal data protection. Due to the modular design of ObTiMA and the strong support of its developer's team, the MasterProtocol-Creator could seamlessly be integrated. Existing infrastructure could be utilized and development efforts could be kept within the bounds of what is reasonably possible within the boundaries of doctoral theses without jeopardizing functionality and usability of the program.

The MasterProtocol-Creator consists of three parts. These are the MasterProtocol-Wizard, the MasterProtocol-Editor and the MasterProtocol-Helpcenter. The complete software architecture is structured modularly through to the lowest level of program code. This provides a transparent and easy to maintain program structure and bug fixing could be reduced to a minimum. As important future program extensions can easily be attached and the program can be adapted to changes in the underlying legislative or to new user requirements.

The modular approach was not only applied to the program code, but to the structure of the study protocol as well. These consist of independent modules, called paragraphs. Each of the paragraphs contains one section of the SIOPE template. The paragraphs are merged to a protocol just before printing. This enables study

protocols which are easy to customize. With very little efforts and without coding a user can add new and modify or delete existing paragraphs.

It cannot be expected that physicians and other personnel involved into a clinical study are trained computer experts or highly educated with regard to the relatively complex legal requirements. That is why the program provides a graphical user interface. The required data are clearly defined in the input masks. A user just needs to enter the data into input fields and he is guided step by step through to the complete dataset needed for protocol generation. Each input mask includes explanatory text about the data and data format and at any time a user has access to a highly elaborated help system. This includes further information and hyperlinks to helpful websites. Among these there are the SIOPE-Template [41], the ICH Guideline [12], the EudraCT documents [30] and many more.

At the end of the process, the MasterProtocol-Creator automatically merges the single paragraphs into a complete protocol. This is done without any user involvement. The final PDF protocol can be downloaded and printed out by authorized users. Before downloading, a user can utilize the preview function to ensure that expectations are met.

Clinical studies might be performed across several countries or might include patients of different nationalities. Sponsors, scientists and other personal must completely understand the study protocol and precisely act in accordance therewith and therefore it is helpful to have the document in the mother tongue. For the „Informed Consent“ it could be useful that this document is accessible in native language of the individuals. To meet these requirements the MasterProtocol-Creator can manage single items or even complete protocols in several languages.

The MasterProtocol-Creator is web based. To create a study protocol a user just needs a standard computer, a common web browser and permanent internet access. He does not need to purchase a specific software package, he has not to take care for software updates and he does not need any hardware extensions.

Since the MasterProtocol-Creator is linked to ObTiMA it gets many study data transferred from the database. This avoids redundant data entry and once ObTiMA data are updated or amended by a user they are immediately available for protocol generation by all other users as well. The independent paragraphs and the web based architecture of the MasterProtocol-Creator enables multicenter, parallel work. Several scientists in different locations can access the MasterProtocol-Creator simultaneously. Independent of the number of individuals working with a document, there is just one valid version of the protocol. Once a protocol is finalized a version number is attached and the protocol is stored. By a numbering system in accordance to SIOPE and an auto-generated amendment table, seamless audit trail and version control is ensured.

All data remain on the server and are only accessible by the MasterProtocol-Creator. Data transfer is secured by encryption of the data and ObTiMA provides a highly elaborated access control. Only users with appropriate credentials can access data to a predefined extent. These measures meet all requirements of personal data protection.

The objective of cost minimization has been completely met by utilization of royalty free open source software. These have been the UNIX operating system, the Tomcat webserver, the PostgreSQL database and some others. Another contributing factor was the selection of Java for program coding. This highly flexible computer language is very widely used. There is a worldwide community willingly provided support and many Java royal free toolkits simplified programming.

## **5.2 Programm Advantages**

The MasterProtocol-Creator provides unique capabilities that have not been achieved before and is unknown for any other software dealing with clinical trials.

The most important are:

- High data security by centralized data storage, access control and transfer of encrypted patients data
- Parallel access by several users at different locations

- Multilingual study protocols
- One single set of data at any time
- Central version control and audit trail
- Global access to electronic protocol in PDF format and electronic keyword screening capability
- Cost minimization
- Simple adaptation to new requirements
- Failure tolerant graphical user interface and elaborated help system
- No need to become acquainted in detail with complex guidelines
- Avoidance of vague protocols and gaps in study documentation

### 5.3 Comparison to other Programs available

As shown in this work, until now several attempts were made to improve quality and accuracy of clinical study protocols by means of IT tools. As result of our reviews there are three different groups of IT tools available. Each of these focuses on specific aspects but none of these completely supports protocol generation. Presently available there are either customized text editors, knowledge databases or tools, which translate a protocol into a machine readable format. Most advanced and comprehensive are the CT Toolkit, the CDISC Protocol Wizard Demonstration Tool and the SOWG Protocol Reviewing System.

The CT Toolkit (2.4.5.1 CT Toolkit) [63] is one example for a knowledge database. It provides plenty of information and improves transparency of study flow. However, there is no direct support for drawing up the protocol. Although the applicable guidelines are referenced, the user is left alone with the adequate transcription in a protocol.

In contrast the PRM (**P**rotocol **R**epresentation **M**odel) issued by CDISC [66] supports completeness and machine readability of trial documentation. However a user can only access an online demonstration tool, which just provides 30 protocol core items out of the original approximately 300 item model. A PDF list with these



30 items can be printed out. This can serve as a checklist, but a valid study protocol is not generated.

Finally the SWOG Protocol Reviewing System [68] makes an online Editor available and enables parallel access by several users. In addition there is a highly complex review system integrated through which authors can communicate to each other and improve a drafted protocol. There have been field trials made by the SWOG group with this program but it did not prevail, as there were some deficiencies. The review system has been regarded as too technical and time consuming for some users and the word processor just provides very basic functionality. This fact and the lack of a predefined protocol template make it difficult to prepare a clear and transparent protocol. Major deficiencies however are a missing step by step user guidance and the unavailability of templates which exclude unexperienced scientists from protocol generation and bears the risk of incomplete protocols. Unlike the MasterProtocol-Creator it does not offer user training and there are no help screens or comprehensive online help links available as given by the MasterProtocol-Helpcenter.

In a study conducted by Caroline Barnes et al [24], it was shown that even limited electronic support has the potential to significantly improve quality of study protocols. The MasterProtocol-Creator is building on these findings and in extension to the previous attempts the MasterProtocol-Creator consequently utilizes web based IT to seamlessly guide a user step by step through the complete process of protocol generation. The failure tolerant graphical user interface and comprehensive online help enable even less experienced users to generate a state of the art study protocol. It can be expected that the MasterProtocol-Creator closes the current gap and has the potential to significantly improve quality of study protocol and validity of clinical trials.

## 5.4 Limitations

One limitation of the program results from the basic design. The MasterProtocol-Creator is not a standalone program. It is seamlessly integrated into ObTiMA. It exchanges data and utilizes data protection mechanisms of the database. Thus it cannot be used as a single-station system. It requires permanent internet access and user registration for ObTiMA.

The current version of the MasterProtocol-Creator is based on the SIOPE template. By design it is customized for pediatric oncology research. Even though the program enables easy adaptation to various medical trial areas, this requires an engagement of the study authors with the guidelines and templates applicable to the specific research area. To simplify protocol generation it might be helpful for very inexperienced users to add additional or alternative templates for other research areas to the MasterProtocol-Creator.

To further develop the MasterProtocol-Creator one might think about cooperation with one of the well-known institutions as the SPIRIT Statement Group [50]. By cooperation with organizations being at the forefront of study evolution the MasterProtocol-Creator would not only be advertised to a broader user group but it could always be kept up to date by getting input from a highly experienced scientist community.

Another idea is the integration of the SPIRIT statement or the RPM of CDISC [66] into the MasterProtocol-Creator. It is commendable to extend the MasterProtocol-Creator in a way that a user can perform a check of the finalized protocol with help of these checklists. By marking key phrases in the study protocol a core document as proposed by the PRM could be generated automatically. This might simplify customization of the MasterProtocol-Creator to research areas with unique requirements. A checklist would not only ensure that no important detail is missed, but it would support standardization and simplify electronic screening of the clinical protocols.

Finally the MasterProtocol-Creator enables parallel work of several scientists but it does not have a reviewing system integrated unlike the SWOG Protocol Reviewing System. Authors need to share their ideas and comments by mail or phone. Although this does not affect version control, a clearly arranged, simple to handle and fully integrated reviewing system could foster discussions and knowledge sharing among the authors.

## **5.5 Perspectives**

As the software development, testing and bug fixing of the MasterProtocol-Creator is completed, the program can be applied to a clinical study. This is now done with the next SIOP nephroblastoma trial, called UMBRELLA. This is a multicenter, multinational prospective trial that will include all European countries, in addition Brazil, Argentina, Uruguay, Russia, Egypt, Hong Kong, and centers in Japan, Australia and New Zealand.

## 6 Appendix

### 6.1 References

- [1] P. Ambroise, *Journeys in Diverse Places*, In public domain. Hoboken, N.J., 1537.
- [2] R. M. Merrill and T. C. Timmreck, *Introduction to Epidemiology* 4<sup>th</sup> Edition, Jones & Bartlett Pub, 2006, p. 26.
- [3] M. Dean, "'An innocent deception': placebo controls in the St Petersburg homeopathy trial, 1829-1830", *Journal of the Royal Society of Medicine*, vol. 99(7), pp. 375-376, Jul 2006.
- [4] J. Vollmann and R. Winau, "Informed consent in human experimentation before the Nuremberg code", *BMJ*, vol. 313(7070), p. 1445–1449, Dec 7 1996.
- [5] R. B. Ghooi, "The Nuremberg Code-A critique", *Perspectives in Clinical Research*, vol. 2(2), pp. 72-76, Apr-Jun 2011.
- [6] A. Speer, *Spandauer Tagebücher: Mit einem Vorwort von Joachim Fest*, Propyläen Verlag, 2002.
- [7] V. Mallardi , "The origin of informed consent", *Acta Otorhinolaryngologica Italica*, vol. 25(5), pp. 312-27, Oct 2005.
- [8] A. Mitscherlich and F. Mielke, *Medizin ohne Menschlichkeit. Dokumente des Nürnberger Ärzteprozesses*, Frankfurt a.M: Fischer, 1960, p. 272 f.
- [9] World Medical Association, "WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects", [Online]. Available: <http://www.wma.net/en/30publications/10policies/b3/index.html>. [Accessed Sep 9 2015].
- [10] C. Richter and R. Bussar-Maatz, "Standard ärztlicher Ethik", *Deutsches Ärzteblatt*, vol. 102(11), pp. A730-A734, Mar 18 2005.
- [11] M. Imran, S. Samad, M. Maaz, A. Qadeer, A. Najmi and M. Aqil, "Hippocratic oath and conversion of ethico-regulatory aspects onto doctors as a

- physician, private individual and a clinical investigator", *Journal of Mid-Life Health*, vol. 4(4), pp. 203-209, Oct 2013.
- [12] ICH Expert Working Group, "ICH harmonized tripartite guideline: Guideline for Good Clinical Practice E6", 10 Jun 1996. [Online]. Available: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf). [Accessed Sep 9 2015].
- [13] ICH International Council for Harmonisation, "ICH History", [Online]. Available: <http://www.ich.org/about/history.html>. [Accessed Sep 14 2015].
- [14] The European Parliament and the Council of the European Union, "Directive 2001/20/EC", Apr 4 2001. [Online]. Available: [http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_2001\\_20/dir\\_2001\\_20\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf). [Accessed Sep 10 2015].
- [15] Commission of the European Communities, "Commission Directive 2005/28/EC", Apr 8 2005. [Online]. Available: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF>. [Accessed Sep 10 2015].
- [16] BGBl, "Gesetz über den Verkehr mit Arzneimitteln", [Online]. Available: [http://www.gesetze-im-internet.de/bundesrecht/amg\\_1976/gesamt.pdf](http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf). [Accessed Sep 11 2015].
- [17] BGBl, "Verordnung über die Anwendung der Guten Klinischen Praxis bei der Durchführung von klinischen Prüfungen mit Arzneimitteln zur Anwendung am Menschen", [Online]. Available: <http://www.gesetze-im-internet.de/bundesrecht/gcp-v/gesamt.pdf>. [Accessed Sep 11 2015].
- [18] E. Deutsch, G. Duttge, H. Schreiber, A. Spickhoff and J. Taupitz, Die Implementierung der GCP-Richtlinie und ihre Ausstrahlungswirkungen, Heidelberg: Springer, 2011, pp. 3-16.
- [19] M. Herschel, Das Klifo-Buch, Praxisbuch Klinische Forschung, Stuttgart: Schattauer GmbH, 2009, pp. 13-17.
- [20] A. Chan, A. Hróbjartsson, K. J. Jørgensen, P. C. Gøtzsche and D. G. Altman, "Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols", *BMJ*, vol. 337, p. a2299, 2008.
- [21] K. Dwan, D. Altman, L. Cresswell, M. Blundell, C. Gamble and P. Williamson, "Comparison of protocols and registry entries to published reports for

- randomised controlled trials", *Cochrane Database of Systematic Reviews*, vol. 1, p. MR000031, Jan 19 2011.
- [22] S. Al-Marzouki, I. Roberts, Evans S and Marshall T, "Selective reporting in clinical trials: analysis of trial protocols", *The Lancet*, vol. 372(9634), p. 201, Jul 19 2008.
- [23] O. Scharf and A. Colevas, "Adverse event reporting in publications compared with sponsor database for cancer clinical trials", *Journal of Clinical Oncology*, vol. 24(24), pp. 3933-8, Aug 20 2006.
- [24] J. Pildal, A. Chan, A. Hróbjartsson, E. Forfang, D. G. Altman and P. C. Gøtzsche, "Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study", *BMJ*, vol. 330, p. 1049, 2005.
- [25] T. C. Hoffmann, C. Eructi and P. P. Glasziou, "Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials", *BMJ*, vol. 347, p. f3755, 2013.
- [26] M. Calvert, D. Kyte, H. Duffy, R. Mercieca-Bebber, J. Ives, H. Draper, M. Brundage, J. Blazeby and M. King, "Patient-reported outcome (PRO) assessment in clinical trials: a systematic review of guidance for trial protocol writers", *PLoS One*, vol. 9(10), p. e110216, Oct 15 2014.
- [27] P. C. Gøtzsche, A. Hróbjartsson, H. K. Johansen, M. T. Haahr, D. G. Altman and A. Chan, "Ghost Authorship in Industry-Initiated Randomised Trials", *PLoS Med.*, vol. 4(1), p. e19, Jan 16 2007.
- [28] K. Rising, P. Bacchetti and L. Bero, "Reporting Bias in Drug Trials Submitted to the Food and Drug Administration: Review of Publication and Presentation", *PLoS Med*, vol. 6(1), p. e217, Nov 25 2008.
- [29] I. Simera, D. Moher, A. Hirst, J. Hoey, K. F. Schulz and D. G. Altman, "Transparent and accurate reporting increases reliability, utility, and impact of your research: reporting guidelines and the EQUATOR Network", *BMC Med.*, vol. 8, p. 24, Apr 26 2010.
- [30] European Medicines Agency, "EudratCT", [Online]. Available: <https://eudract.ema.europa.eu/>. [Accessed Sep 15 2015].
- [31] K. Dickersin and D. Rennie, "Registering clinical trials", *JAMA*, vol. 290(4), pp. 516-523, Jul 23 2003.

- [32] European Commission, "Detailed guidance on the European clinical trials database (EUDRACT Database) April 2003", [Online]. Available: [http://ec.europa.eu/health/files/eudralex/vol-10/13\\_cp\\_and\\_guidance\\_eudract\\_april\\_04\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-10/13_cp_and_guidance_eudract_april_04_en.pdf). [Accessed Sep 14 2015].
- [33] European Commission, "Horizon 2020", [Online]. Available: <http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020>. [Accessed Nov 08 2015].
- [34] European Commission, "Horizon 2020 : Template for essential information to be provided for proposals including clinical trials / studies / investigations", Sep 2015.
- [35] I. Simerá, D. Moher, J. Hoey, K. F. Schulz and D. G. Altman, "A catalogue of reporting guidelines for healthresearch", *European Journal of Clinical Investigation*, vol. 40 (1), p. 35–53, 2010.
- [36] H. Bridge, M. Smolskis, P. Bianchine, D. O. Dixon, G. Kelly, B. Herpin and J. Tavela, "Development and Implementation of Clinical Trial Protocol Templates at the National Institute of Allergy and Infectious Diseases", *Clin Trials*, vol. 6(4), pp. 386-391, Aug 2009.
- [37] H. Mann, "ASSERT Statement", [Online]. Available: <http://www.assert-statement.org/explandoc.pdf>. [Accessed 23 Nov 2015].
- [38] Pfizer, "Investigator-Initiated Research & Requests for Pure Substance (Pfizer Guideline)", [Online]. Available: [http://www.pfizer.com/sites/default/files/research/iir\\_information.pdf](http://www.pfizer.com/sites/default/files/research/iir_information.pdf). [Accessed Nov 3 2015].
- [39] WHO, "Recommended format for a Research Protocol", [Online]. Available: [http://www.who.int/rpc/research\\_ethics/format\\_rp/en/](http://www.who.int/rpc/research_ethics/format_rp/en/). [Accessed Sep 14 2015].
- [40] National Institute of Health, "National Institute of Health: Clinical Research Study Start-up Documents", [Online]. Available: <http://www.nidcr.nih.gov/research/toolkit/#startup2>. [Accessed Sep 14 2015].
- [41] Siope, "Siope: Protocol template for clinical trials", [Online]. Available: <http://www.siope.eu/european-research-and-standards/clinical-trials-in->

- paediatric-oncology/protocol-template-clinical-trials/. [Accessed Sep 14 2015].
- [42] J. M. Tetzlaff, A. Chan, J. Kitchen, M. Sampson, A. C. Tricco and D. Moher, "Guidelines for randomized clinical trial protocol content: a systematic review", *Syst Rev.*, vol. 1, p. 43, Sep 24 2012.
- [43] The EQUATOR Network, "Equator network Enhancing the QUALity and Transparency Of health Research", [Online]. Available: <http://www.equator-network.org/>. [Accessed Sep 15 2015].
- [44] CONSORT Statement, "CONSORT Transparent Reporting of Trials", [Online]. Available: <http://www.consort-statement.org/>. [Accessed Sep 3 2015].
- [45] D. Moher, S. Hopewell, K. F. Schulz, V. Montori, P. C. Gøtzsche, P. J. Devereaux, D. Elbourne, M. Egger and D. G. Altman, "CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials", *BMJ*, vol. 340, p. c869, 2010.
- [46] C. Begg, M. Cho, S. Eastwood, R. Horton, D. Moher, I. Olkin, R. Pitkin, D. Rennie, K. Schulz, D. Simel and D. Stroup, "Improving the quality of reporting of randomized controlled trials. The CONSORT statement", *JAMA*, vol. 276(8), pp. 637-639, Aug 28 1996.
- [47] D. Moher, K. F. Schulz and D. G. Altman, "The CONSORT Statement: Revised Recommendations for Improving the Quality of Reports of Parallel-Group Randomized Trials", *The Lancet*, vol. 357(9263), pp. 1191-1194, Apr 14 2001.
- [48] D. Moher, A. Jones, L. Lepage and CONSORT Group, "Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation", *JAMA*, vol. 285(15), pp. 1992-1995, Apr 18 2001.
- [49] J. Wang, T. Sun, Y. Lin, R. Lu and J. Fang, "Methodological reporting of randomized controlled trials in major hepato-gastroenterology journals in 2008 and 1998: a comparative study", *BMC Med Res Methodol.*, vol. 11, p. 110, Jul 30 2011.
- [50] SPIRIT Statement, "SPIRIT Statement", [Online]. Available: <http://www.spirit-statement.org/>. [Accessed Sep 4 2015].



- [51] SPIRIT Statement, "SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents", [Online]. Available: <http://www.spirit-statement.org/wp-content/uploads/2013/01/SPIRIT-Checklist-download-8Jan13.pdf>. [Accessed Sep 20 2015].
- [52] J. Tetzlaff, D. Moher and A. Chan, "Developing a guideline for clinical trial protocol content: Delphi consensus survey", *Trials*, vol. 13, p. 176, Sep 24 2012.
- [53] A. Chan, J. M. Tetzlaff, D. G. Altman, A. Laupacis, P. C. Gøtzsche, K. Krleža-Jerić, A. Hróbjartsson, H. Mann, K. Dickersin, J. A. Berlin, C. J. Doré, W. R. Parulekar, W. Summerskill, T. Groves, K. F. Schulz, H. C. Sox, F. W. Rockhold, D. Rennie and D. Moher, "SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials", *Ann Intern Med.*, vol. 158(3), pp. 200-207, 2013.
- [54] A. Chan, J. M. Tetzlaff, P. C. Gøtzsche, D. G. Altman, H. Mann, J. A. Berlin, K. Dickersin, A. Hróbjartsson, K. F. Schulz, W. R. Parulekar, K. Krleža-Jerić, A. Laupacis and D. Moher, "SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials", *BMJ*, vol. 346, p. e7586, 2013.
- [55] The EQUATOR Network, "Equator network Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide", [Online]. Available: <http://www.equator-network.org/reporting-guidelines/tidier/>. [Accessed Oct 1 2015].
- [56] T. C. Hoffmann, P. P. Glasziou, I. Boutron, R. Milne, R. Perera, D. Moher, D. G. Altman, V. Barbour, H. Macdonald, M. Johnston, S. E. Lamb, M. Dixon-Woods, P. McCulloch and J. C. Wyatt, "Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide", *BMJ*, vol. 348, p. g1687, 2014.
- [57] Clinical Data Interchange Standards Consortium, "CDISC Vision and Mission", [Online]. Available: <http://www.cdisc.org/CDISC-Vision-and-Mission>. [Accessed Sep 24 2015].
- [58] FDA , "FDA Study Data Standards Resources", [Online]. Available: <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>. [Accessed Sep 24 2015].
- [59] V. Huser, C. Sastry, M. Breymaier, A. Idriss and J. J. Cimino, "Standardizing data exchange for clinical research protocols and case report forms: An

- assessment of the suitability of the Clinical Data Interchange Standards Consortium (CDISC) Operational Data Model (ODM)", *Journal of Biomedical Informatics*, pp. S1532-0464(15)00133-1, Jul 15 2015.
- [60] A. Vadakin, B. Hinkson, B. Hinkson and Genzyme Corporation, "Organizing and Accelerating the Clinical Research Process from the Beginning: The CDISC Protocol Representation Model and Toolkit", *CDISC Journal*, Oct 2012.
- [61] G. Booch, J. Rumbaugh and I. Jacobson, *The Unified Modeling Language User Guide*, Addison Wesley Pub Co Inc, Mai 19 2005.
- [62] L. Koumakis, H. Kondylakis, E. Maniadi, M. Psaraki, M. Tsiknakis, N. Graf, M. Hendriks, M. Hendriks, C. Krykwinski, S. Yu, S. M. Marshall, J. Keijser and K. De Schepper, "Enabling information re-Use by linking clinical REsearch and CAre", Aug 31 2015.
- [63] NETSCC 2015, "Clinical Trials Toolkit", [Online]. Available: [www.ct-toolkit.ac.uk](http://www.ct-toolkit.ac.uk). [Accessed Sep 20 2015].
- [64] S. Treweek, K. McCormack, E. Abalos, M. Campbell, C. Ramsay, M. Zwarenstein and PRACTIHC Collaboration, "The Trial Protocol Tool: the PRACTIHC software tool that supported the", *Journal of Clinical Epidemiology*, vol. 59(11), pp. 1127-1133, Nov 2006.
- [65] Practihc , "Pragmatic Randomized Controlled Trials in Healthcare", [Online]. Available: <http://www.practihc.net/index.htm>. [Accessed Nov 08 2015].
- [66] Clinical Data Interchange Standards Consortium, "CDISC Protocol", [Online]. Available: <http://www.cdisc.org/protocol>. [Accessed Oct 5 2015].
- [67] C. Barnes, I. Bourtron, B. Giraudeau, R. Porcher, D. Altman and P. Ravaud, "Impact of an online writing aid tool for writing a randomized trial report: the COBWEB (Consort-based WEB tool) randomized controlled trial", *BMC Med.*, vol. 13(1), p. 221, Sep 15 2015.
- [68] SWOG, "Southwest Oncology Group", [Online]. Available: <http://www.swog.org/>. [Accessed Nov 15 2015].
- [69] C. Weng, J. Gennari and D. McDonald, "A Collaborative Clinical Trial Protocol Writing System", *MEDINFO*, vol. 107(Pt 2), pp. 1481-1485, 2004.

- [70] C. Weng, D. McDonald, D. Sparks, J. McCoy and J. Gennari, "Participatory design of a collaborative clinical trial protocol writing system", *medicalinformatics*, vol. 76 Suppl 1, pp. 245-251, Jun 2007.
- [71] C. Weng, "Why It Is Hard to Support Group Work in Distributed Healthcare Organizations: Empirical Knowledge of the Social-Technical", *AMIA Annu Symp Proc.*, pp. 804-808, 2005.
- [72] InferMed Limited, "Design-a-Trial", [Online]. Available: [http://www.openclinical.org/prj\\_dat.html](http://www.openclinical.org/prj_dat.html). [Accessed Nov 5 2015].
- [73] Stanford Medical Informatics, "EON", [Online]. Available: [http://www.openclinical.org/gmm\\_eon.html](http://www.openclinical.org/gmm_eon.html). [Accessed Oct 5 2015].
- [74] Ben-Gurion University of the Negev, Israel, "DeGel", [Online]. Available: [http://www.openclinical.org/gmm\\_degel.html](http://www.openclinical.org/gmm_degel.html). [Accessed Oct 4 2015].
- [75] R. Shankar, S. Arkalgud, M. O'Connor, K. Boyce, D. Parrish and A. Das, "TrialWiz: an ontology-driven tool for authoring clinical trial protocols", *AMIA Annu Symp Proc.*, p. 1226, Nov 6 2008.
- [76] ObTiMA, "Ontology-based Trial Management Application", [Online]. Available: <https://obtima.org/>. [Accessed Oct 4 2015].
- [77] M. R. Wolf, "Client-Sever Anwendung BWL/ Wirtschaftsinformatik", [Online]. Available: [http://winfor.uni-wuppertal.de/fileadmin/wolff/Downloads/Hauptstudium/WIModul1/DBMS/WS05\\_06/09Client-Server-Anwendungen.pdf](http://winfor.uni-wuppertal.de/fileadmin/wolff/Downloads/Hauptstudium/WIModul1/DBMS/WS05_06/09Client-Server-Anwendungen.pdf). [Accessed Sep 12 2015].
- [78] Canonical Ltd, "<http://www.ubuntu.com/>", [Online]. Available: <http://www.ubuntu.com/>. [Accessed Dec 12 2015].
- [79] The Apache Software Foundation, "Apache Tomcat", [Online]. Available: <https://tomcat.apache.org/index.html>. [Accessed Oct 4 2015].
- [80] J. Farley and W. Crawford, *Java Enterprise in a Nutshell Auflage: 3*, O'Reilly and Associates, 2005.
- [81] B. Kurniawan and P. Deck, *Servlet, JSP and Spring MVC: A Tutorial*, Brainy Software, 2014.
- [82] R. Fielding, J. Gettys, J. Mogul, H. Frystyk, L. Masinter, P. Leach and T. Berners-Lee, "Internet Engineering Task Force, RFC 2616 Hypertext

- Transfer Protocol -- HTTP/1.1", 1999. [Online]. Available: <https://www.ietf.org/rfc/rfc2616.txt>.
- [83] T. Dierk and C. Allen, "Internet Engineering Task Force, RFC 2246, The TLS Protocol Version 1.0" Oct 03 2015. [Online]. Available: <https://www.ietf.org/rfc/rfc2246.txt>.
- [84] K. Douglas and S. Douglas, PostgreSQL: A Comprehensive Guide to Building, Programming, and Administering PostgreSQL Databases, 2. edition ed., Sams Publishing, 2003.
- [85] C. Ullenboom, Java ist auch eine Insel, Galileo Computing, Auflage: 11 (Mai 26. 2014).
- [86] Oracle, "Java - JRE", Sep 03 2015. [Online]. Available: <https://www.java.com/de/download/>.
- [87] The Eclipse Foundation, "Eclipse", [Online]. Available: <https://eclipse.org/>. [Accessed Oct 5 2015].
- [88] THE TORTOISESVN TEAM, "TortoiseSVNthe coolest interface to (Sub)version control", [Online]. Available: <http://tortoisetsvn.net/>. [Accessed Oct 5 2015].
- [89] A. Zeitner, L. Brigit, M. Maier and T. Göckeler, Spring 2.5 Eine pragmatische Einführung, Addison-Wesley Verlag, 2008.
- [90] T. Reenskaug, "MODELS - VIEWS - CONTROLLERS", 1979. [Online]. Available: <http://heim.ifi.uio.no/~trygver/1979/mvc-2/1979-12-MVC.pdf>. [Accessed Sep 06 2015].
- [91] Sun, "JavaServer™ Pages™ - Specification 0.92", Nov 12 1998. [Online]. Available: <http://www.kirkdorffer.com/jspspecs/jsp092.html#model>. [Accessed Aug 06 2015].
- [92] Oracle, "JavaServer Faces Technology," [Online]. Available: <http://www.oracle.com/technetwork/java/javaee/javaserverfaces-139869.html>. [Accessed Sep 14 2015].
- [93] B. Lahres and G. Rayman, Praxisbuch Objektorientierung, Rheinwerk Computing, 2006.
- [94] Red Hat, "What is Object/Relational Mapping?", [Online]. Available: <http://hibernate.org/orm/what-is-an-orm/>. [Accessed Sep 21 2015].

- [95] iText Group NV, iText Software Corp., iText Software BVBA, "iText", [Online]. Available: <http://itextpdf.com/>. [Accessed Sep 12 2015].
- [96] PrimeTek, "Prime Faces", [Online]. Available: <http://www.primefaces.org/>. [Accessed Oct 6 2015].
- [97] J. Hedley, "jsoup: Java HTML Parser", [Online]. Available: <http://jsoup.org/>. [Accessed Oct 1 2015].
- [98] Google Inc., "GitHub gson," [Online]. Available: <https://github.com/google/gson>. [Accessed Sep 23 2015].
- [99] Oracle Corporation, "JAVA SPECIFICATION PARTICIPATION AGREEMENT", Jan 2005. [Online]. Available: <https://jcp.org/aboutJava/communityprocess/JSPA2.pdf>. [Accessed Sep 20 2015].
- [100] N. I. f. H. Research, "CT Toolkit Routemap," [Online]. Available: <http://www.ct-toolkit.ac.uk/routemap>. [Accessed Oct 10 2015].
- [101] Clinical Data Interchange Standards Consortium, "CDISC Protocol Wizard Demonstration Tool", [Online]. Available: <https://cdiscprm-sandbox.imedidata.net/>. [Accessed Oct 10 2015].
- [102] Clinical Data Interchange Standards Consortium, "CDISC Protocol Model Version 1.0," [Online]. Available: <http://www.cdisc.org/cdisc-protocol-model-version-1.0>. [Accessed Oct 10 2015].

## 6.2 List of Tables

Table 1: License Listing.....	48
-------------------------------	----

### 6.3 List of Figures

Figure 1: Best in Class Guidelines, recommended by EQUATOR [43] .....	19
Figure 2: Difference between a traditional Study Protocol and the CDISC Protocol Representation Model [60] .....	22
Figure 3: UML Diagram of the Protocol Representation Model [103] .....	23
Figure 4: Clinical Trials Toolkit Interface [100].....	25
Figure 5: User Interface of the Trial Protocol Tool.....	27
Figure 6: Web Tool of CDISC for the PRM [101].....	28
Figure 7: PDF Printout of the CDISC Toolkit [101] .....	29
Figure 8: Online Tool for “Blinding” Domain [67] .....	30
Figure 9: SWOG Protocol Reviewing System User Interface .....	31
Figure 10: SWOG Protocol Reviewing System .....	32
Figure 11: Software Environment of the MasterProtocol-Creator .....	41
Figure 12: Model View Controller Concept.....	42
Figure 13: Five different Types of Paragraphs .....	44
Figure 14: Paragraph Order .....	44
Figure 15: Protocol PDF Generation Process .....	46
Figure 16: ObTiMA User Interface, Study select Screen (2) .....	50
Figure 17: User Interface of the MasterProtocol-Wizard .....	51
Figure 18: MasterProtocol-Wizard Step "Basic Trial Data" .....	52
Figure 19: Select Generic or SIOPE Protocol Template.....	54
Figure 20: User Interface of the MasterProtocol-Editor .....	55
Figure 21: Paragraph Edit Menu .....	56
Figure 22: Extendible Options Menu, located in the Navigation Bar.....	57
Figure 23: Input Mask of the Text-Paragraph.....	59
Figure 24: Input Mask of the Resources-Paragraph.....	60
Figure 25: Dialog for Uploading new Files.....	61
Figure 26: Example of List Type 1: Sponsor List.....	62
Figure 27: List Type 2: Simple Personnel-List.....	63
Figure 28: List Type 3: Personnel-List.....	63
Figure 29: List Type 5: Complex Organization-List.....	64

Figure 30: Input Mask of the Personnel-Paragraph.....	65
Figure 31: Dialog, Select Template Type .....	66
Figure 32: Input Mask of the Simple Personnel-List .....	67
Figure 33: Input Mask of the Personnel-List.....	68
Figure 34: Convert to Text-Paragraph Function .....	69
Figure 35: Table of Contents, PDF view, automatically generated.....	70
Figure 36: User Interface of the Table of Contents.....	71
Figure 37: Page Count right-aligned, Option inactive (a), active (b) .....	72
Figure 38: User Interface of the Amendment-Paragraph.....	73
Figure 39: Dialog for creating new Amendments.....	74
Figure 40: Paragraph/Folder Context Menu of the MasterProtocol-Editor.....	76
Figure 41: Dialog for Creating new Paragraphs .....	77
Figure 42: Dialog for Editing the Paragraph Settings .....	78
Figure 43: Dialog for Creating new Folders .....	79
Figure 44: Quick setting Menu, Change Language .....	80
Figure 45: Paragraph Section.....	80
Figure 46: MasterProtocol-Editor Information Page .....	81
Figure 47: Enlarged section of the Paragraph Settings Dialog .....	82
Figure 48: Export Protocol Page .....	83
Figure 49: MasterProtocol-Editor Settings, General Tab opened.....	84
Figure 50: MasterProtocol-Editor Settings, Language Tab opened.....	85
Figure 51: MasterProtocol-Editor Settings, Editor Tab opened .....	86
Figure 52: Show Page Breaks, deactivated (a), activated (b).....	86
Figure 53: MasterProtocol-Editor Settings, Page Tab opened .....	87
Figure 54: MasterProtocol-Editor Settings, Header Tab opened.....	88
Figure 55 Start Screen of the MasterProtocol-Helpcenter .....	89





- o Where the protocol is not being developed for a clinical trial the word 'trial' may be substituted with 'study' or 'research project'
- o Adapt to the treatment being studied e.g. chemotherapy maybe substituted with radiotherapy
- Ensure any instructions in *red italic text* and/or grey highlighted text are removed prior to finalising the protocol
- Ensure the use of abbreviations and terminology is consistent throughout the protocol
- If logos are used (e.g. funders) ensure prior permission is sought

The lay-out used in this template may be adjusted to bring the document in line with other trial specific documents. Changes should be kept to a minimum as this will help users of the SIOPE /ENCCA protocols to become used to a standard template protocol, regardless of the trial that the protocol is used in.

DRAFT

*<insert protocol cover sheet here; do not include header and footer>*

DRAFT

**INTRODUCTORY PAGES**

*The following should be included in the introductory pages of the protocol (where applicable):*

- Protocol title
- Protocol short name or acronym
- Protocol version and date
- Protocol identifying number
  - o *The protocol should include:*
    - *EudraCT number (for IMP trials)*
    - *Sponsor number (a unique identifier assigned by the Sponsor to the trial)*
    - *ISRCTN reference number (The ISRCTN is a simple numeric system for the unique identification of randomised controlled trials worldwide and is available via <http://www.isrctn.org/>)*
    - *Other identifiers in accordance with the regulatory requirements of the nation state(s)*
- Any amendment(s) should also bear the amendment number(s) and date(s) and need to be provided also with tracked changes
- Name and address of the Sponsor and monitor (if other than the Sponsor)
- Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the Sponsor
- Name, title, address, and telephone number(s) of the Sponsor's medical expert for the trial
  - o *This would typically be the Chief Investigator in the lead nation state*
- Name and title of the Lead Principal Investigators who are responsible for conducting the trial in the respective nation states, and the address and telephone numbers of any relevant advisory groups, committees or panels related to the running of the trial study committee, name etc. → experts involved in protocol design and writing
- Name, title, address, and telephone number(s) of the qualified physician who is responsible for all trial-site related medical decisions (if other than investigator)
  - o *This would typically be the Chief Investigator and any Clinical Coordinators*
- Name and address of the clinical laboratory (ies) and other medical and/or technical department(s) and/or institutions involved in the trial
  - o *E.g. Pathology, laboratories conducting translational sub-study analysis, regional coordinating centres, Quality of Life centres*
- The protocol should be signed by the Sponsor and Chief Investigator

*All contacts should only be listed according to their role in the trial; ie Trial Management Group, DMC, etc. even where listed in multiple indications above.*

*Telephone numbers of medical personnel would normally be listed as that of a switchboard or a secretary, not personal or mobile numbers.*

*Ensure the protocol cover sheet does not include the header and footer. Note: As per EC guidance (ENR/CT 2) the protocol should be signed by the CI of the nation state and by the Sponsor.*

---

**SIGNATURE PAGE**

<insert trial name> Trial Protocol <insert version number and date>

This protocol has been approved by:

**Name:** <insert name of Chief Investigator> **Trial Role:** Chief Investigator

**Signature:** \_\_\_\_\_ **Date:** DD / MON / YYYY

**Name:** <insert name of Sponsor's representative> **Trial Role:** <insert role of Sponsor's representative >

**Signature:** \_\_\_\_\_ **Date:** DD / MON / YYYY

*Consider having the signature page immediately inside the front cover of the protocol.*

This protocol describes the <insert trial name> trial and provides information about procedures for patients taking part in the <insert trial name> trial. **The protocol should not be used as a guide for treatment of patients not taking part in the <insert trial name> trial.**

*Where appropriate include a summary of protocol amendments; this section should be omitted in the first version of the protocol*

**AMENDMENTS**

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

e.g. Sponsor & CI need to keep tracked changes versions of each amendment even if cleared for distribution

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	28th Oct 2005	2.0	Substantial amendment	Change in eligibility criteria
N/A	15th Sep 2006	2.0a	Non-substantial amendment	Change in trial contact details
2	16th Oct 2007	3.0	Substantial amendment	Change in max. number of chemotherapy cycles a patient may receive from 6 to 10

**TRIAL SYNOPSIS**

*As a guide this should be no longer than 2 sides of A4*

Example sub-headers include:

**Title**

**Name of Chief Investigator**

**Name Sponsor**

**Trial Design**

*E.g. prospective, phase III, international, 2 arm, multicentre, randomised, double-blinded clinical trial*

**Objectives (primary, secondary)**

**Outcome Measures**

**Treatment details**

**Patient Population**

**Sample Size**

**Main Inclusion and Exclusion Criteria**

**Trial Duration**

**Trials Office Contact Details**

**Trial Schema**

*E.g. Diagrammatic representation e.g. from screening through to follow up, treatment allocation*

**Schedule of Events**

*In complex multi-arm trials a schema should direct the reader to the relevant schedule of events. This can be best presented in a table. Each schedule should include all trial investigations and assessments.*

**Abbreviations**

*Include a list of all abbreviations used in the main text*

---

Table of contents

<b>1. Background and Rationale</b> .....	3
1.1 Background.....	3
1.2 Trial Rationale.....	3
1.2.1 Justification for patient population .....	Fehler! Textmarke nicht definiert.
1.2.2 Justification for design .....	Fehler! Textmarke nicht definiert.
1.2.3 Choice of treatment .....	Fehler! Textmarke nicht definiert.
<b>2. Aims, Objectives and Outcome Measures</b> .....	3
2.1 Aims and Objectives .....	3
2.2 Outcome Measures .....	3
<b>3. Trial Design</b> .....	3
<b>4. Eligibility</b> .....	4
4.1 Inclusion Criteria .....	4
4.2 Exclusion Criteria .....	4
<b>5. Screening and Consent</b> .....	4
5.1 Screening.....	4
5.2 Informed Consent .....	4
<b>6. Trial Entry</b> .....	5
<b>7. Treatment Details</b> .....	5
7.1 Trial Treatment .....	6
7.2 Treatment Schedule .....	6
7.3 Assessments <i>Use of tables is encouraged</i> .....	6
7.3.1 Blood chemistry .....	Fehler! Textmarke nicht definiert.
7.3.2 Haematology.....	Fehler! Textmarke nicht definiert.
7.3.3 Physical examination/symptom assessment.....	Fehler! Textmarke nicht definiert.
7.4 Sample Collection.....	Fehler! Textmarke nicht definiert.
7.4.1 Archival Tumour samples <i>Including address/site of collecting centre &amp; make sure informed consent is given for sample collection!</i> .....	Fehler! Textmarke nicht definiert.
7.4.2 New blood or tissue samples.....	Fehler! Textmarke nicht definiert.
7.5 Dose Modifications .....	6
7.6 Treatment Compliance <i>Consideration should be given as to how this will be monitored, particularly if oral formulations are used. Patient diaries and drug reconciliation by pharmacy</i> .....	6
7.7 Supportive Treatment .....	6
7.8 Concomitant Medication .....	6
7.9 Patient Follow Up.....	6
7.10 Patient Withdrawal.....	6
<b>8. Adverse Event Reporting</b> .....	6
8.1 Reporting Requirements.....	7
8.1.1 Adverse Events.....	7
8.1.2 Serious Adverse Adverts .....	7
8.1.3 Reporting period .....	10
8.2 Reporting Procedure.....	10
8.2.1 Site.....	10
8.2.2 Trials Office <i>e.g. either the national co-ordinating centre or Sponsor</i> .....	11
8.2.3 Reporting to the CA(s) and EC(s).....	11
8.2.4 Investigators.....	12
8.2.5 Data Monitoring Committee .....	12
8.2.6 Manufacturer of Investigational Medicinal Product.....	12

8.2.7	Reporting to the Ethics Committee(s) according to national requirements	12
8.2.8	Investigators	12
8.2.9	Data Monitoring Committee	12
<b>9.</b>	<b>Data Handling and Record Keeping</b>	<b>12</b>
9.1	Data Collection	13
9.2	Archiving	14
<b>10.</b>	<b>Quality Management</b>	<b>14</b>
10.1	Site Set-up and Initiation	14
10.2	On-site Monitoring	14
10.3	Central Monitoring	15
10.4	Audit and Inspection	15
10.5	Notification of Serious Breaches	15
<b>11.</b>	<b>End of Trial Definition</b>	<b>15</b>
<b>12.</b>	<b>Statistical Considerations</b>	<b>16</b>
12.1	Power Calculations	17
12.2	Definition of Outcome Measures	Fehler! Textmarke nicht definiert.
12.2.1	Primary outcome measures	Fehler! Textmarke nicht definiert.
12.2.2	Secondary outcome measures	Fehler! Textmarke nicht definiert.
12.3	Analysis of Outcome Measures	17
12.4	Planned Sub Group Analyses	17
12.5	Planned Interim Analysis	17
12.6	Planned Final Analyses	17
<b>13.</b>	<b>Trial Organisational Structure</b>	<b>17</b>
13.1	Sponsor	17
13.2	Coordinating Centre	17
13.3	Trial Management Group	18
13.4	Trial Steering Committee	18
13.5	Data Monitoring Committee	18
13.6	Finance	18
<b>14.</b>	<b>Ethical Considerations</b>	<b>18</b>
<b>15.</b>	<b>Confidentiality and Data Protection</b>	<b>19</b>
<b>16.</b>	<b>Insurance and Indemnity</b>	<b>19</b>
<b>17.</b>	<b>Publication Policy</b>	<b>20</b>
<b>18.</b>	<b>Reference List</b>	<b>20</b>
<b>Appendix 1 - Tumour Staging -</b>		<b>20</b>
<b>Appendix 2 - WMA Declaration of Helsinki</b>		<b>20</b>
<b>Appendix 3 - Definition of Adverse Events</b>		<b>20</b>
<b>Appendix 4 - Common Toxicity Criteria Gradings</b>		<b>22</b>
<b>appendix 5 – definitions</b>		<b>22</b>



## 1. BACKGROUND AND RATIONALE

*ICH GCP and the EU CTD specify that the following should be included:*

- ICH GCP section 6.2.1 Name and description of the investigational product(s). 4
- ICH GCP section 6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial. 1B
- ICH GCP section 6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects. 5 IMP only
- ICH GCP section 6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s). 6 IMP only
- ICH GCP section 6.2.6 Description of the population to be studied. 2B
- ICH GCP section 6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial. 1A
- EU CTD requirement: A discussion of the relevance of the clinical trial and its design 2A
- EU CTD requirement: An evaluation of the anticipated benefits and risks 3
- EU CTD requirement: A justification for including subjects who are incapable of giving informed consent or other special populations 2C

### 1.1 Background

### 1.2 Trial Rationale

## 2. OBJECTIVES AND OUTCOME MEASURES

*ICH GCP specifies that the following should be included:*

- ICH GCP Section 6.3 A detailed description of the objectives and the purpose of the trial.
- ICH GCP section 6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

*Provide a succinct overview of the aims/goals of the trial and then define the primary and secondary objectives to be answered by the trial*

*Example sub-headers include:*

### 2.1 Objectives

### 2.2 Outcome Measures

*Include trial endpoints*

## 3. TRIAL DESIGN

ICH GCP section 6.4 states that the scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include (if not covered in other sections):

- ICH GCP section 6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.
- ICH GCP section 6.4.3 A description of the measures taken to minimize/avoid bias, including:
  - o Randomization.
  - o Blinding.

- ICH GCP section 6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- ICH GCP section 6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

#### 4. ELIGIBILITY

*ICH GCP specifies that the following should be included:*

- ICH GCP section 6.5.1 Subject inclusion criteria.
- ICH GCP section 6.5.2 Subject exclusion criteria.

*In complex multi-arm trials consistency should be maintained for all arms wherever possible and these should form the core criteria. Specific criteria for individual arms should be clearly identified as additional to the core criteria.*

*Example sub-headers include:*

##### 4.1 Inclusion Criteria

##### 4.2 Exclusion Criteria

#### 5. SCREENING AND CONSENT

*EU CTD indicates that the following should be included:*

- EU CTD requirement: a description of the recruitment and informed consent procedures, especially when subjects who are (temporarily or permanently) incapable of giving informed consent are included or when a procedure with witnessed consent is to be used

*Example sub-headers include:*

##### 5.1 Screening

*If relevant*

##### 5.2 Informed Consent

*If there are multiple Patient Information Sheets (PIS) and Informed Consent Forms (ICF) the text should be amended to reflect this fact. In addition a paragraph explaining the purpose of the different Patient Information Sheets and Informed Consent Forms may be required.*

It is the responsibility of the Investigator *<specify in parenthesis any others allowed to take consent (e.g. Research Nurse if local practice allows and this responsibility has been delegated by the Principal Investigator as captured on the Site Signature and Delegation Log)>* to obtain written informed consent from the patient or an approved guardian prior to performing any trial related procedure. A Parent/guardian and age-specific patient Information Sheets are provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The parent/approved guardian and /or patient should be given ample time (e.g. 24 hours *<or specify trial specific alternative>*) to read the Information Sheet and to discuss their participation with others outside of the site research team. They must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the parent/approved guardian and/or patient to refuse to participate in the trial without giving a reason must be respected.

If the parent/approved guardian and/or patient expresses an interest in the patient participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form. The Investigator *<and if applicable specify "or designate">* must then sign and date the form. A copy of the Informed Consent Form should be given to the parent/approved guardian and/or patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once

the patient is entered into the trial the patient's trial <or specify registration> number should be entered on the Informed Consent Form maintained in the ISF.

*<If review of Informed Consent Forms is being performed by a centralised body such as a national co-ordinating centre, the following text should also be included "In addition, if explicit consent has been obtained, a copy of the signed Informed Consent Form must be sent in the post to the <insert relevant body> for review"*

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include who was present, date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Parent/patient Information Sheet and Informed Consent Form. Throughout the trial the parent/approved guardian and/or patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the Parent/approved guardian and/or patient Information Sheets and Informed Consent Form are available from the <insert relevant body> and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log and with the patient's prior consent their General/Medical Practitioner should also be informed that they are taking part in the trial. A Letter to their General/Medical Practitioner should be provided for this purpose.

## 6. TRIAL ENTRY

## 7. TREATMENT DETAILS

This section should include a description of the treatment details including IMPs and NIMPS. The IMPs should be clearly identified in the trial protocol

Below are details of the information required by ICH GCP and the EU CTD for the IMPs defined in the trial protocol

*ICH GCP and the EU CTD specify that the following should be included:*

- ICH GCP section 6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- ICH GCP section 6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- ICH GCP section 6.6.3 Procedures for monitoring subject compliance.
- ICH GCP section 6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
- ICH GCP section 6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- EU CTD requirement: a description of the plan for the provision of any additional care of the subjects once their participation in the trial has ended, where it differs from what is normally expected according to the subject's medical condition.
- ICH GCP section 6.7.1 Specification of the efficacy parameters.
- ICH GCP section 6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.
- ICH GCP section 6.8.1 Specification of safety parameters.

- 
- ICH GCP section 6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.
  - ICH GCP section 6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
    - o When and how to withdraw subjects from the trial/ investigational product treatment.
    - o The type and timing of the data to be collected for withdrawn subjects.
    - o Whether and how subjects are to be replaced.
    - o The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

*Examples of sub-headers include:*

#### **7.1 Trial Treatment**

*Ensure details of IMPs and NIMPs are included;  
Consider method for calculating Body Surface Area (BSA) and/or consider asking sites to confirm method used.*

#### **7.2 Treatment Schedule**

#### **7.3 Assessments**

*Use of tables is encouraged*

#### **7.4 Dose Modifications and delays**

#### **7.5 Supportive Treatment**

#### **7.6 Concomitant Medication**

#### **7.7 Patient Follow Up**

#### **7.8 Treatment Compliance**

*Consideration should be given as to how this will be monitored, particularly if oral formulations are used. Patient diaries and drug reconciliation by pharmacy*

#### **7.9 Patient Withdrawal**

### **8. SUB-STUDIES**

*Description of any sub-studies and biological studies could be included here*

### **9. ADVERSE EVENT REPORTING**

*ICH GCP specifies that the following should be included:*

- ICH GCP section 6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and inter-current illnesses.
- ICH GCP section 6.8.4 The type and duration of the follow-up of subjects after adverse events

*Reference appropriate product information against which SAEs will be categorised e.g. (compendium of) Summary of Product Characteristics, Investigator Brochure, protocol (non-IMP)*

*Refer to Appendix 3 for standard definitions of all types of Adverse Events. This should be specifically included either within the body of the protocol or as an appendix referred to within the body of the protocol.*

**IMP trials**

The collection and reporting of Adverse Events (AEs) will be in accordance with the requirements of the Competent Authority. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the *<insert appropriate Summary of Product Characteristics or Investigator Brochure>*..

**Non-IMP trials**

The collection and reporting of Adverse Events (AEs) will be in accordance with the appropriate competent authorities. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

**9.1 Reporting Requirements**

*This section should include information about the types of AEs for which data will be collected and any exclusions to the reporting process.*

*The type and extent of AE data collected for an individual trial should be risk based. For example it is anticipated that all early phase trials will collect all AEs however phase III trials utilising well characterised IMPs may choose to collect data on selected Adverse Reactions or SAEs only.*

*Standard sub-headers are shown below with examples of text which can be utilised in different scenarios.*

**9.1.1 Adverse Events**

*Example of text for trials collecting all AEs*

All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported. Please note this includes abnormal laboratory findings.

*Example of text for trials collecting selected ARs*

AEs (see Appendix 3 for definition) are commonly encountered in patients receiving chemotherapy. As the safety profiles of the Investigational Medicinal Products used in this trial are well characterised, only Adverse Reactions (ARs) experienced during treatment will be reported (*see section 9.2.1.1 for definitions*).

**9.1.2 Serious Adverse Adverts**

**SAEs must be collected for all trials, for example:**

Investigators should report AEs that meet the definition of an SAE (see Appendix 3 for definition) *<and are not excluded from the reporting process as described below>*.

**9.1.2.1 Events that do not require expedited reporting**

*It is possible to excluded SAEs from expedited (immediate) reporting by sites. SAEs which are to be excluded from expedited reporting process must be clearly defined in the protocol and the type of event that is excluded should be restricted to those events which generate large volumes of SAEs.*

*An example is given below:*

Patients receiving chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment. For this reason the following SAEs do not require expedited (immediate) reporting by site and are not regarded as unexpected for the purpose of this trial:

- Admissions to control symptoms of nausea and vomiting unless the condition is life threatening or proves fatal
- Admissions for supportive treatment during an episode of myelosuppression, for example an episode of febrile neutropaenia, unless this proves fatal or requires admission to a high dependency or intensive care facility

An SAE should be reported according to the specific reporting requirements of the trial and in compliance with national/international regulations.

#### 9.1.2.2 Events that do not require reporting on a Serious Adverse Event Form

*This section should be used to list SAEs which will not be captured using an SAE form.*

*Events that do not require reporting on an SAE Form include*

- A) Those events that do not require reporting because they fall outside of the definition of an SAE (see Appendix 3).
- B) SAE related to IMPs (Serious Adverse Expected Reactions SAR) that has been defined in the protocol as expected. Expected Serious Adverse Reactions (SARs) can be captured on an Expected SAR Form or on a toxicity form rather than an SAE Form/reporting procedure. These events do not require expedited (immediate) reporting by sites.

*The data collected for this type of event is significantly less than that collected for an SAE. Such events do not require expedited reporting by site and do not require evaluation by the clinical co-ordinators (as they are by definition expected). Again the number of Expected SARs should be restricted to common events*

*For example:*

The following events should not be reported on an SAE Form:

- Hospitalisations for:
  - o Protocol defined treatment
  - o Pre-planned elective procedures unless the condition worsens
  - o Treatment for progression of the patient's cancer
- Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the Case Report Form

The following events should be reported on an Expected SAR Form rather than an SAE Form:

- Admissions to control symptoms of nausea and vomiting unless the condition is life threatening or proves fatal
- Admissions for supportive treatment during an episode of myelosuppression unless this proves fatal or requires admission to a high dependency or intensive care facility; for example; an uncomplicated febrile neutropenic episode

Expected SAR Forms should be completed and returned in the post as soon as possible.

#### 9.1.2.3 Expected Serious Adverse Events

*This section is compulsory for non-IMP trials.*

*This section can be used to list expected and related SAEs that will not be reported for the purposes of the trial. It would replace the section "Events that do not require reporting on a Serious Adverse Event Form" listed above.*

*For example:*

We are not expecting any SAEs to occur as a result of participation in this non-interventional study.

The following are regarded as expected SAEs for the purpose of study and should not be reported on an SAE form:

- SAEs that are thought to have occurred as a result of the patient's cancer treatment
- SAEs that are related to a pre-existing condition
- SAEs that are related to symptoms or progression of the patient's cancer
- Death from cancer, as a result of the patient's cancer treatment or from a pre-existing medical condition

This is not an exclusive list and Investigators should only report SAEs that are attributable to the study protocol.

#### 9.1.2.4 Monitoring pregnancies for potential Serious Adverse Events

*This section should be included for all trials where there is a risk of congenital anomalies or birth defects in the offspring of patients as a result of their participation in the trial. If relevant, for female patients consent to collect this information may be addressed in the main trial Patient Information Sheet or a separate pregnancy release of information form for pregnant trial patients and/or partners of trial patients may be used.*

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

*Examples of possible text:*

*For trials involving females only (and where pregnancy is addressed in the main trial PIS) include:*

In the event that a patient becomes pregnant during the SAE reporting period it should be reported to the <insert relevant body, eg. National co-ordinating centre, Sponsor> as soon as possible. Provide details of the subsequent outcome of the pregnancy and if necessary also complete an SAE Form.

*For trials involving females only (and where pregnancy is not addressed in the main PIS) include:*

In the event that a patient becomes pregnant during the SAE reporting period please notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> as soon as possible. The patient should be given a <insert pregnancy release of information form or appropriate form name>. If the patient is happy to provide information on the outcome of their pregnancy they should sign the <insert pregnancy release of information form or appropriate form name>. Once consent has been obtained provide details of the outcome of the pregnancy and if necessary also complete an SAE Form.

*For trials involving males only include:*

In the event that a patient's partner becomes pregnant during the SAE reporting period please notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> as soon as possible. The patient should be given a <insert pregnancy release of information form or appropriate form name> to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the <insert pregnancy release of information form or appropriate form name>. Once consent has been obtained provide details of the outcome of the pregnancy and if necessary also complete an SAE Form.

*For trials involving both genders (and where pregnancy is addressed in the main trial PIS) include:*

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the <insert relevant body, eg. National co-ordinating centre, Sponsor> as soon as possible. If it is the patient who is pregnant provide outcome data on <insert pregnancy release of information form or appropriate form name>. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a <insert pregnancy release of information form or appropriate form name> to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the <insert pregnancy release of information form or appropriate form name>. Once consent has been obtained provide details of the outcome of the pregnancy and if appropriate also complete an SAE Form as detailed below.

*For trials involving both genders (and where pregnancy is not addressed in the main trial PIS) include:*

In the event that a patient or their partner becomes pregnant during the SAE reporting period please notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> as soon as possible. The patient should be given a <insert pregnancy release of information form or appropriate form name> or the patient should be asked to give this to their partner. If the patient/partner is happy to provide information on the outcome of their pregnancy they should sign the <insert pregnancy release of information form or appropriate form name>. Once consent has been obtained provide details of the outcome of the pregnancy and if necessary also complete an SAE Form.

### 9.1.3 Reporting period

*This section is mandatory and should include information on the length of the AE reporting period. This should be defined on a trial specific basis.*

*Careful consideration should be given as to when the reporting period will commence. It can be when the patient begins trial treatment or on entry into the trial. However for trials where the screening period includes trial specific tests which may impact on the safety of patients the start date can be the date of informed consent. If the protocol is mandating specific standard chemotherapy prior to trial treatment it may be necessary to include the standard chemotherapy drugs as NIMPs. It is preferable therefore to mandate such standard chemotherapies as inclusion criteria and place the trial entry point as close as possible to the start of the actual trial-mandated treatment.*

*Typically the reporting period will cease 30 days after the patient's last protocol defined treatment, unless there are trial specific assessments that may impact on patient safety scheduled to take place after this 30 day window. If the latter is the case, consider setting the end date in such a way that it allows for reporting of any AEs that may be related to this trial specific assessment.*

*For example:*

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

## 9.2 Reporting Procedure

### 9.2.1 Site

#### 9.2.1.1 Adverse Events

*The version of the CTCAE quoted should be agreed by the Trial Steering Committee.*

*If the CTCAE document is also provided in the Investigator Site File reference can be made to this also.*

*Example of text for trials collecting all AEs:*

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the <insert relevant body, eg. National co-ordinating centre, Sponsor>.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version <insert appropriate version number>. Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

*Example of text for trials collecting selected ARs:*

AEs experienced during treatment should be recorded in the toxicity section of the Treatment Form.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version <insert appropriate version number>. Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

#### 9.2.1.2 Serious Adverse Events

*This section is used to describe the SAE reporting process.*

*For example:*

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in section <insert section name or number> of the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE <insert appropriate version number>.



On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be transmitted as defined within the protocol, < insert trial specific details fax, e-mail, RDE database> to <insert relevant body, eg. National co-ordinating centre, Sponsor> as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE < insert details of fax number or email or RDE process >

On receipt the <insert relevant body, eg. National co-ordinating centre, Sponsor> will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the <insert relevant body, eg. National co-ordinating centre, Sponsor>. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the <insert relevant body, eg. National co-ordinating centre, Sponsor> should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the <insert relevant body, eg. National co-ordinating centre, Sponsor> in the post and a copy kept in the ISF.

Investigators should also report SAEs to the relevant bodies in accordance with local practice.

#### 9.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

#### 9.2.2 Trials Office e.g. either the national co-ordinating centre or Sponsor

##### *For IMP Trials*

Unexpected Serious Adverse Reaction (SUSAR).

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Co-ordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the <insert (compendium of) Summary of Product Characteristics, or Investigator Brochure as applicable>) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

##### *For non-IMP trials*

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

*The following headings can be used for IMP trials*

#### 9.2.3 Reporting to the CA(s) and EC(s)

##### 9.2.3.1 Suspected Unexpected Serious Adverse Reactions

The <insert relevant body, eg. National co-ordinating centre, Sponsor> will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the CA(s) and EC(s) in accordance with current regulations i.e. 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

#### 9.2.3.2 Serious Adverse Reactions

The <insert relevant body, eg. National co-ordinating centre, Sponsor> will report details of all SARs (including SUSARs) to the relevant CAs and ECs annually from the date of the initial Clinical Trial Authorisation, in the form of an Annual Safety Report.

#### 9.2.3.3 Adverse Events

Details of all AEs will be reported to the CA(s) on request.

#### 9.2.3.4 Other safety issues identified during the course of the trial

The CA(s) and EC(s) will be notified immediately if a significant safety issue is identified during the course of the trial.

#### 9.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

#### 9.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs

#### 9.2.6 Manufacturer of Investigational Medicinal Product

*If a pharmaceutical companies supplying an Investigational Medicinal Product will usually wish to be notified of either: all SAEs, SARs or SUSARs. This may not be relevant for many paediatric oncology trials however, if there is any such requirement, it should be defined contractually with the pharmaceutical company. Such contracts will not be contained within the body of the protocol but may be referred to in order clarify delegated task roles to national co-ordinating centres.*

##### *Example text:*

All SAEs will be reported to the manufacturer of the Investigational Medicinal Product within 24 hours by fax.

*The following headings should be used for non-IMP trials:*

#### 9.2.7 Reporting to the Ethics Committee(s) according to national requirements

##### 9.2.7.1 Unexpected and Related Serious Adverse Events

The <insert relevant body, eg. National co-ordinating centre, Sponsor> will report all events in accordance with national requirements

##### 9.2.7.2 Other safety issues identified during the course of the trial

The EC(s) and CA(s) will be notified in accordance with national requirements if a significant safety issue is identified during the course of the trial.

*Needs clarity of the different national roles of Ethics Committee and Competent Authorities*

#### 9.2.8 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File

#### 9.2.9 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

## 10. DATA HANDLING AND RECORD KEEPING

Required as per ICH GCP section 6.13

*ICH GCP also specifies that the following should be included*

- ICH GCP section 6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

### 10.1 Data Collection

*It is good practice to include a list or table of forms and indicate the timeframe in which each form should be completed. A reference to the relevant protocol section may be required. For example:*

The Case Report Form (CRF) will comprise the following forms:

Form	Summary of data recorded	Schedule for submission
Eligibility Checklist	Confirmation of eligibility and satisfactory staging investigations where necessary	Transmitted at point of randomisation
Randomisation	Patient details; details of stratification variables; optional consent issues	As soon as possible after randomisation
Baseline	Details of biopsy histology; (with copy of diagnostic biopsy report); details of planned surgery	Within 1 month of randomisation
Relapse Form	Date and site of relapse	Immediately upon patient relapse
Death Form	Date and cause of death	Immediately upon notification of patient's death
Deviation Form	Completed in the event of a deviation from the protocol	Immediately upon discovering deviation
Withdrawal Form	Used to notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> of patient withdrawal from the trial	Immediately upon patient withdrawal
Serious Adverse Event Form		Immediately on becoming aware of the event
Pregnancy Notification Form		
Others?		

*Many international trials will have remote electronic data capture (REDC). Such electronic systems should have mechanisms built in to record and track changes to the data set.*

*For paper CRFs, the following text must be entered and/or a paragraph referring to additional CRF completion guidelines should be used:*

The CRF must be completed, signed/dated and returned to the <insert relevant body, eg. National co-ordinating centre, Sponsor> by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above <indicate any exceptions to this, for example "The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator">

Entries on the CRF should be made in ballpoint pen, in black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

*<If applicable, provide information on data, which may not be captured in the source data, e.g. Quality of Life or health economic data which will be recorded directly onto the CRF>.*

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

*<Select one of the following as appropriate (a) The completed originals should be sent to the <insert relevant body, eg. National co-ordinating centre, Sponsor> and a copy filed in the Investigator Site File OR (b) On completion, the top copy of each form must be submitted to the <insert relevant body, eg. National co-ordinating centre, Sponsor> and the bottom copy filed in the Investigator Site File.>*

Trial forms may be amended by the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

## 10.2 Archiving

It is the responsibility of the Principal Investigator at each site to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc) at their site are securely retained for at least 5 years *<if trial results are to be used for licensing, then the number of years should be increased to at least 15; consult the Chief Investigator to discuss this possibility. Also refer to relevant regulatory guidelines>* after the end of the trial *<or following the processing of all biological material collected for research, whichever is the later>*. Do not destroy any documents without prior approval from the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*.

## 11. QUALITY MANAGEMENT

Required as per ICH GCP section 6.11

*ICH GCP also specifies that the following should be included*

- ICH GCP section 6.10 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

### 11.1 Site Set-up and Initiation

All sites will be required to sign a *<insert "Clinical Study Site Agreement" or other appropriate Sponsor's term>* prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements *<specify other documents as appropriate for the trial e.g. registration forms>* and supply a current CV to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*.

All members of the site research team will also be required to sign the *<insert "Site Signature and Delegation Log" or appropriate external Sponsor term>*, which should be returned to the *<insert relevant body, eg. National co-ordinating centre, Sponsor>*.

Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference *<if required amend to specify only "meeting" or only "teleconference">* covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping.

Sites will be provided with an Investigator Site File *<where applicable insert "and a Pharmacy File">* containing essential documentation, instructions, and other documentation required for the conduct of the trial. The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* must be informed immediately of any change in the site research team.

### 11.2 On-site Monitoring

*Monitoring will be carried out as required by the regulations of the nation state and as defined in the trial protocol. The Sponsor will define the monitoring requirement based on a risk analysis of the trial. The minimum requirements for on-site monitoring should be described,*

If a monitoring visit is required the <insert relevant body, eg. National co-ordinating centre, Sponsor> will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the <insert trial name> trial staff access to source documents as requested.

### 11.3 Central Monitoring

*Where applicable include the following paragraph:*

*<Where a patient has given explicit consent sites are requested to send in copies of signed Informed Consent Forms for in-house review.>*

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check data received for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests missing data or clarification of inconsistencies or discrepancies. For REDC trials these requests may be generated by automated data validation checks.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to <specify trial specific committees and/or stakeholders e.g. Trial Management Group, Trial Steering Committee> and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the EC(s) and CA(s).

### 11.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> of any CA inspections.

### 11.5 Notification of Serious Breaches

*The following should be included either in the body of the protocol or as an appendix referred to within the body of the protocol:*

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a "serious breach" is a breach, which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the <insert relevant body, eg. National co-ordinating centre, Sponsor> of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the <insert relevant body, eg. National co-ordinating centre, Sponsor> is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the <insert relevant body, eg. National co-ordinating centre, Sponsor> in providing sufficient information to report the breach to the CA where required and in undertaking any corrective and/or preventive action.

## 12. END OF TRIAL DEFINITION

Required as per EU CTD

*The definition of end of a trial must be clearly defined in the protocol. Definitions of end of trial will differ according to whether the trial is an Investigational Medicinal Product (IMP) or non-IMP trial and whether the trial involves long-term follow-up.*

*For all types of trial, where ethical approval for a sub-study (e.g. sample collection) has been (or will be) granted as part of the main protocol, the date of last data capture must also include the final*

*processing / testing of all samples, as specified in the protocol. Note: where analysis is not expected to be completed in an acceptable timeframe (e.g. sub-study does not form part of primary or secondary endpoints) it is preferable to have a separate protocol and ethics approval for the sub-study.*

*The following text should be used according to the type of trial and modified as appropriate:*

*Non-IMP trial*

The end of trial will be *<the date of or x months after>* the last data capture. The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* will notify the EC(s) that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

*IMP trial without long-term follow-up*

*When calculating the end of trial date for IMP trials without long-term follow-up the end of trial date should be defined as the same date for both the CA(s) and EC(s). Allow sufficient time following the last patient visit for all relevant trial data to be received and entered onto the trial database. Consider the size of the trial and anticipated rate of data return.*

The end of trial will be *<the date of or x months after >* the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* will notify the CA(s) and EC(s) that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

*IMP trial with long-term follow-up*

*When calculating the end of trial date allow sufficient time following the last patient visit for all relevant trial data to be received and entered onto the trial database. Consider the size of the trial and anticipated rate of data return.*

For the purposes of the CA(s) the end of trial will be *<x>* months after the last patient has completed *<insert last protocol defined interventional treatment e.g. chemotherapy, radiotherapy, surgery>*. This will allow sufficient time for the completion of protocol procedures, data collection and data input. For the purposes of EC(s) approval, the trial end date is deemed to be *<the date of or x months after>* last data capture following *<x>* years of long-term follow-up.

After closure of the trial with the CA(s) the Sponsor is no longer required to notify the CA(s) and EC(s) of changes of Principal Investigator. However, sites should continue to notify the *<insert relevant body, eg. National co-ordinating centre, Sponsor>* of changes in Principal Investigator by completing and returning (where required) an Investigator Registration Form together with a current signed and dated CV.

The *<insert relevant body, eg. National co-ordinating centre, Sponsor>* will notify the CA(s) and EC(s) that the trial has ended at the appropriate time and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

### 13. STATISTICAL CONSIDERATIONS

*ICH GCP specifies that the following should be included:*

- ICH GCP section 6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- ICH GCP section 6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(es).
- ICH GCP section 6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- ICH GCP section 6.9.3 The level of significance to be used.

- 
- ICH GCP section 6.9.4 Criteria for the termination of the trial.
  - ICH GCP section 6.9.5 Procedure for accounting for missing, unused, and spurious data.
  - ICH GCP section 6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
  - ICH GCP section 6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

*Example sub-headers include:*

### **13.1 Power Calculations**

*Provide a rationale for the sample size, i.e. a statement of the size of difference and significance level and power that contributed to the sample size calculations for the primary outcome measure(s) and any other measures (secondary or subgroups).*

*Specify any adjustments that have been made for drop-outs (e.g. inflation by X%) or interim analyses (e.g. adjustment of p-values)*

### **13.2 Analysis of Outcome Measures**

*Full details will be specified in a Statistical Analysis Plan but an outline of the plan will be given here.*

*Give details on the following:*

- *The statistical analysis by describing the comparisons that are planned between treatment arms and any adjustments being made for multiple comparisons and by describing the methods that may be used to compare each outcome measure, i.e. summary measures and hypothesis tests*
- *Selection of patients to be used in the analyses (if not intention to treat) e.g. definition of evaluable*
- *Rationale for the analysis of stratification factors*
- *If applicable, give the criteria for the termination ("stopping rules") of the trial and cross reference the DMC and TSC*

### **13.3 Planned Sub Group Analyses**

*Give details of any subgroup analysis by describing in which subgroups the treatment effects will be investigated and the statistical methods that will be used*

### **13.4 Planned Interim Analysis**

*Give trial milestones with the number of participating sites (approximate) and the timing of interim analyses*

*Specify the type of analyses that will be presented at the interim analyses*

### **13.5 Planned Final Analyses**

*Give the timing of final analysis (there may be several final analyses that relate to different outcome measures or to different lengths of follow-up)*

*If applicable, give the criteria for the termination ("stopping rules") of the trial and cross reference the DMC and TSC*

## **14. TRIAL ORGANISATIONAL STRUCTURE**

### **14.1 Sponsor**

### **14.2 Coordinating Centre**

*Can also include a list of National coordinating centres*

**14.3 Trial Management Group**

*Do not need to list the names of the members as they may change over the period of the trial but describe the oversight role of the Trial Management Group*

**14.4 Trial Steering Committee**

*Do not need to list the names of the members as they may change over the period of the trial but describe the oversight role of the Trial Steering Committee*

**14.5 Data Monitoring Committee**

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with appropriate regulatory guidelines. *<In consultation with the Trial Statistician insert details of when the DMC will meet. Unless there is a specific reason (e.g. safety phase) avoid stating that the DMC will meet following the recruitment of XX patients, because if the recruitment rate is not as predicted the DMC may meet too early or too late which may affect their ability to effectively monitor the trial. Instead consider a time-based schedule. For example consider the following text for trials involving Investigational Medicinal Products (IMPs) "During the recruitment phase of the trial the DMC is scheduled to meet one month prior to the due date of the Annual Safety Report and annually thereafter". For a non-IMP trial consider "The DMC will be scheduled to meet one year after the trial opens to recruitment and then annually thereafter until the trial closes to recruitment." >*

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the *<insert Trial Management Group (TMG) or Trial Steering Committee as applicable>* who will convey the findings of the DMC to *<specify to whom the report will be sent e.g. Trial Steering Committee, CA, funders, and/or sponsors as applicable>*.

The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial may stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community. *<If the trial includes stopping rules indicate here and reference the relevant section of the protocol>*.

**14.6 Finance**

*Where payments are made e.g. pathology payments, amend accordingly.*

This is a clinician-initiated and clinician-led trial funded by *<list all relevant funders, and acknowledge companies that provide free drug>*.

No individual per patient payment will be made to healthcare providers, Investigators or patients.

**15. ETHICAL CONSIDERATIONS**

*ICH GCP specifies that the following should be included*

- ICH GCP section 6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- ICH GCP section 6.12 Description of ethical considerations relating to the trial.

**IMP trials**

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18<sup>th</sup> World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48<sup>th</sup> World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: <http://www.wma.net/en/30publications/10policies/b3/index.html>).

The trial will be conducted in accordance with the relevant legislation in the nation state and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP).



Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain all applicable regulatory approval(s). Sites will not be permitted to enrol patients until written confirmation of such approval(s) have been received by the <National Co-ordinating Centre/Sponsor>.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

#### *Non-IMP trials*

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18<sup>th</sup> World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48<sup>th</sup> WMA General Assembly, Somerset West, Republic of South Africa, 1996 (website: <http://www.wma.net/en/30publications/10policies/b3/index.html>).

The trial will be conducted in accordance national regulations for conducting non-IMP trials and the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP).

The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

## 16. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the National Data Protection Laws. With the patient's consent, their <specify patient identifiers e.g. full name, date of birth, hospital identifying number>, address, post code, hospital number, general/medical practitioner details> will be collected at trial entry <indicate why e.g. to assist with long-term follow-up via other health care professionals>.

Patients will be identified using only their unique <insert registration/trial> number, <insert other identifiers e.g. initials, hospital number and date of birth> on the Case Report Form and correspondence between the Trials Office and the participating site.

<For trials collecting consent forms specify "However patients are asked to give permission for the Trials Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process". Trials with long term follow-up may also wish to add "and may also be forwarded to other health care professionals involved in the treatment of the patient.">

The Investigator must maintain documents not for submission to the <insert relevant body, eg. National co-ordinating centre, Sponsor> (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The <insert relevant body, eg. National co-ordinating centre, Sponsor> will maintain the confidentiality of all patient's data and will not disclose information by which patients may be identified to any third party <include exceptions to this e.g. "other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (e.g. Cancer Registries, laboratory staff)">. Representatives of the <insert trial name> trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

## 17. INSURANCE AND INDEMNITY

*This is the standard text for a University of Birmingham sponsored UK clinical trial, and will need to be amended as appropriate for other sponsors.*

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The Sponsor cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

## 18. PUBLICATION POLICY

Required as per ICH GCP section 6.15

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of <specify name of Sponsor>. Intellectual property rights will be addressed in the <insert "Clinical Study Site Agreement" or appropriate external Sponsor term> between Sponsor and site.

<For international trials taking place in more than one country and coordinated at a national level the following text may also be inserted, "Individual countries will be allowed to publish their efficacy results, however the publication of efficacy results from the pooled analysis will take precedence over efficacy result publications of individual countries, unless the TMG decides otherwise.">

## 19. REFERENCE LIST

Examples for tables/appendices include:

### APPENDIX 1 - TUMOUR STAGING

Include here the tumour staging scheme relevant to the disease

### APPENDIX 2 - WMA DECLARATION OF HELSINKI

At the time of writing the 1996 version is the legally required version in the EU; see link to shared drive: <S:\General\Reference documents\WMA Declaration of Helsinki version 1996.docx>

### APPENDIX 3 - DEFINITION OF ADVERSE EVENTS

For IMP trials

#### Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

#### Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

#### Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- Results in death *<for phase III trials with long term follow-up where survival is an endpoint consider adding text "(unrelated to original cancer)">*
- Is life-threatening\*
- Requires hospitalisation\*\* or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator\*\*\*

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

\* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

\*\*Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

\*\*\* Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

#### Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

#### Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information, such as drug monograph, SmPC or Investigator Brochure.

A SUSAR should meet the definition of an AR, UAR and SAR.

#### Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

#### *For non-IMP trials*

#### Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

#### Related Event

An event which resulted from the administration of any of the research procedures.

#### Serious Adverse Event

An untoward occurrence that:

- Results in death *<for phase III trials with long term follow-up where survival is an endpoint consider adding text "(unrelated to original cancer)">*
- Is life-threatening\*
- Requires hospitalisation\*\* or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator\*\*\*

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

\* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

\*\*Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

\*\*\* Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

#### Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

#### Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

### APPENDIX 4 - COMMON TOXICITY CRITERIA GRADINGS

*The version of the CTCAE quoted should be the one currently being used at a unit level. At the time of finalisation of this document this was <insert appropriate version number>.*

*If the CTCAE document is also provided in the Investigator Site File reference can be made to this also.*

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), <insert appropriate version number>. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

### APPENDIX 5 – DEFINITIONS

**IMP** - An investigational medicinal product is any medicinal product which is being tested within a trial or any product, including placebo, used as a reference in a clinical trial. This includes products with a marketing authorisation where the product is:

- used in a different form from the marketing authorisation
- used for an indication not included in the summary of product characteristics for that product or
- used to gain further information about the product as authorised in the clinical trial authorisation.

<Identifier, e.g. Trial Name>

Protocol

---

*Consider adding Trials Office and national co-ordinating centre contact details to the back page of the protocol.*

DRAFT