universität wien

MASTERARBEIT / MASTER'S THESIS

Titel der Masterarbeit / Title of the Master's Thesis

Submission of Clinical Trials for Medicinal Products in the course of time and comparison of EU and non-EU countries

verfasst von / submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Master of Science (MSc)

Wien, 2021 / Vienna 2021

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	UA 066 606
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Masterstudium Drug Discovery and Development
Betreut von / Supervisor:	Mag. Dr. Majid-Reza Kamyar, MSc

Acknowledgements

I hereby want to thank by supervisor Mag. Dr. Majid-Reza Kamyar, MSc for supporting me throughout the process of writing this Master's Thesis and for helping me with all organisational and scientific aspects. In addition, I would like to thank the whole staff of ZAK-Pharma for cooperating with me and giving me an insight on their work. Especially, I am grateful for the support from Mag. Barbara Markhardt, who invested her time and answered all my specific questions regarding the field of clinical trials from a professional point of view.

Importantly, I also want to thank Ao.Univ.-Prof.i.R. Dipl.-Ing. Dr.techn. Josef Haas, chairperson of the Ethics Commission of the Medical University of Graz, for gifting me his time and sharing his experience and opinion with me.

Aside from that, I want to thank my friends for their emotional support. Most importantly, I want to honour my parents, who always were my biggest supporters and without whom, none of my accomplishments would have been possible.

Abstract

Clinical Trials are one of the most important steps in the development of a new investigational medicinal product (IMP) and therefore, are highly regulated by different legislatives and guidelines to ensure patient safety and data reliability. In accordance with that, the application of a clinical trial to competent authorities and Ethics Committees (ECs) is quite complex, as detailed documents on the trial and a thorough validation and scientific assessment by the authorities are required. Naturally, because of the complexity, the requirements and authorisation procedures differ quite a lot between different countries, which makes the submission of a clinical trial, especially multinational trials, very difficult for sponsors. Further, with the beginning of the COVID-19 pandemic the regulatory authorities and ECs of countries worldwide had to very quickly adapt their procedures to ensure ongoing subject safety. Due to its topicality, the changes in the application procedures of clinical trials in EU-countries (through the example Austria) and non-EU countries (through the example Switzerland) due to the pandemic will as well be addressed in this thesis. Lastly, a more general topic, which has been topical for many years already, is the harmonisation of the complex procedures for clinical trial applications in different countries, mentioned above. The European Union (EU) has already aimed for more harmonisation between Member States with the currently applicable EU Directive 2001/20/EC. However, the submission of multinational trials is still very complex. Therefore, the new EU Regulation 536/2014 will come into force in the near future to enhance harmonisation.

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1. Introduction

Clinical trials are an essential tool for the development of new investigational medicinal products (IMPs), as they allow testing new substances on safety and efficacy directly in human beings. As they generate important data on an IMP and depict the usefulness and safety of an IMP for patients, clinical trials are also essential to get a marketing authorisation for a specific product by competent authorities (1). The importance of clinical trials can also be seen in the number of conducted trials in Austria. In 2019 alone, 268 clinical trials were submitted to the competent authority in Austria, as can be seen in Table 1. Out of these, 221 applications, which are 82,5% of all submitted trials, were applications for multinational trials. This high percentage shows the ever-growing importance of multinational trials in times of globalisation in modern society (2). Further, it pictures that harmonised procedures for clinical trial submissions in different countries will become more and more important in the future to increase the feasibility of multinational trials (3).

Table 1: Numbers for commercial, academic and multinational clinical trials (2)

year	total applications	commercial applications (%)	academic applications (%)	multinational applications (%)
2010	336	250 (74,4)	86 (25,6)	243 (72,3)
2011	329	232 (70,5)	97 (29,5)	195 (59,3)
2012	295	186 (63,1)	109 (36,9)	191 (64,7)
2013	318	219 (68,9)	99 (31,1)	221 (69,5)
2014	249	179 (71,9)	70 (28,1)	188 (75,5)
2015	303	216 (71,3)	87 (28,7)	224 (73,9)
2016	257	187 (72,8)	70 (27,2)	193 (75,1)
2017	236	167 (70,8)	69 (29,2)	186 (78,8)
2018	278	205 (73,7)	73 (26,3)	220 (79,1)
2019	**268**	**205 (76,5)**	**63 (23,5)**	**221 (82,5)**

However, clinical trials are not only a modern matter, as the very basic concept goes back until ancient times. Naturally, these ancient experiments on humans were lacking basic concepts of study design, which make the results reliable, as well as ethical considerations. The area of modern trials began in the 1920s when Sir Ronald A. Fisher developed his “Principles of experimental design”, introducing the concept of randomisation among others. The methods and concepts for clinical trials were further extended by Sir Austin Bradford Hill at the same time, leading to the official recognition of the importance of clinical trials from the 1930s. Since then, the concepts, methods and regulations of clinical trials are under constant refinement (4).

1.1 Types and Phases of Clinical Trials

A clinical trial is defined by the WHO as *"a type of research that studies new tests and treatments and evaluates their effects on human health outcomes* (5)." The two most important types of clinical trials, which also the Austrian Medicines Act (AMG) distinguishes between, are non-interventional studies (prior observational studies) and interventional clinical trials (6). (cf. AMG §2a Abs. 2,3) In a non-interventional clinical trial (NIS), the medicinal product has to already have an approval and has to be used strictly according to the requirements of the approval. In addition to that, there are no additional burdens or examinations for patients involved in the study allowed. In contrast to that, in interventional clinical trials, unauthorised medicinal products can be used and additional investigations are possible (6,7). In these trials, the subjects are receiving interventions during the conductance of the trial, according to the trial protocol (8,9). These interventions can be diagnostic, therapeutic or of some other type. Examples for invasive interventions are IMPs, medical devices, procedures or vaccines. However, there are also non-invasive interventions e.g., behavioural changes (e.g., changes in the subject's diet) or education. The aim of such trials is that the investigators evaluate the safety and efficacy of the applied intervention, by measuring certain biomedical or health-related outcomes (9,10) Other common types of clinical trials are prevention trials and diagnostic and screening trials. In prevention trials, it is aimed to test prevention methods for particular medical conditions or reoccurrence of such. Diagnostic and screening trials are conducted to test new ways of detection and diagnosis of medical conditions (11).
However, in this thesis the focus will be on investigational trials with IMPs. There are four phases of these trials (12):

Phase I: In a phase I clinical trial, the IMP is administered for the first time into humans. In this phase, there are usually no therapeutic objectives and the subjects are usually healthy volunteers. However, if the IMP has significant potential toxicity, as for example cytotoxic drugs, phase I is usually conducted in patients. The main objective of a phase I study is to generate data on safety and tolerability, pharmacokinetics and pharmacodynamics of the IMP (12). In this phase, typically 20 to 80 healthy volunteers are included (13).

Phase II: In contrast to phase I, the main objective of phase II studies is to collect data on the efficacy of the IMP in patients. This incorporates the determination of dosage and regimen for the following phase III trials. Further objectives might be to evaluate study endpoints and target populations for following studies (12). In phase II studies, usually around 100 to 800 patients are participating (13).

Notably, phase II studies can be divided into phase IIa and phase IIb studies. A phase II a study focuses mostly on dosing requirements and includes the administration of the IMP in different quantities to a small number of patients, to evaluate a possible dose-response relationship and the optimal dose frequency. In contrast, in phase IIb clinical trials, the focus lies specifically on testing the efficacy of an IMP and therefore in evaluating how successful an IMP can prevent, treat or diagnose as disease (14).

Phase III: Clinical trials in phase III are usually conducted to confirm and demonstrate the therapeutic benefit of the IMP and its safety and efficacy for the intended indication and are therefore called proof of concept trials. Such studies might be conducted to also investigate the use of the IMP in wider populations and different stages of disease, or in combinations with other drugs (12). For this reason, phase III studies involve hundreds or up to thousands of patients (13). Further, these studies are aimed to provide the basis for a marketing approval (12).

Phase IV: The fourth phase starts after a drug has already been approved and includes all studies conducted after drug approval with relation to the approved indication. Therefore, all phase IV studies are NIS by definition. Further, Phase IV studies are quite important for optimising the use of the drug by e.g. investigating drug-drug interactions or dose-response (12). These trials usually involve thousands of patients all over the world (13).

1.2 Study Design

The clinical study design describes how a trial is formulated and there are numerous design types for clinical studies used nowadays. However, the main distinction is made between interventional studies (treatment studies) and non-interventional studies (NIS) (15). NIS can be again divided into descriptive studies (case report, case series and population study) and analytical studies (cohort study, case-control study, cross-sectional study and ecological study) (16,17). However, as the focus of this thesis is on the development of IMPs and therefore on interventional studies, the study types of NISs will not be described here further. In case of interventional studies, particularly in phase II and phase III, the most commonly used study design is the randomized controlled trial (18). The aim of such a study design is to reduce sources of bias in the testing of the effectiveness of an IMP. Therefore, study subjects are randomly allocated to two or more groups, which receive different treatments and the responses to the treatments are

compared. One of these groups is the experimental group, meaning that the subjects in this group receive the IMP, which is being assessed in the trial. In parallel, the subjects allocated to the other group, called control group, receive an alternative treatment (19). This alternative treatment is often a placebo or no intervention, but there are also active control studies, in cases where it would be unethical to give a placebo to a diseased person (e.g. in trials on cancer drugs) or if a superiority or non-inferiority of the IMP is intended to be shown (19,20). The “active control” or “active comparator” in these trials is an approved treatment of which the effectiveness is already known (20). Further, a randomised controlled trial can be either blinded or non-blinded (21–23). In the course of a blinded trial, any information that might influence a participant of a trial in some way is withheld until the completion of the trial. The aim of such a study design is to reduce any bias, which might result from the expectations of a participant. A participant in this case is any person involved in the trial, e.g., researchers, trial subjects, data analysts or technicians. Therefore, blinding of all of these participants is possible (24). In general, most commonly a single-blind, double-blind or triple-blind study design is used, meaning that either one party (mostly the trial subjects), two parties (mostly the trial subjects and the researchers) or even three parties (mostly the trial subjects and the researchers and some third party) are blinded to treatment allocation (25). In contrast to that, in a non-blinded trial (or open trial) no information is withheld form participants of the trial and therefore researchers and trial subjects know which treatment is administered. This study design may be for example applicable for trials in which two similar treatments are compared, e.g., active control studies. However, the risk of bias is quite high in such trials. (26,27). Further study designs possible for a treatment study are adaptive clinical trials and nonrandomised trials (28,29). In an adaptive clinical trial, patient outcomes are observed according to a prescribed schedule and parameters of the trial protocol are modified according to the observations (30). However, the adaptation process is always prescribed in the protocol of a clinical trial and mostly continues throughout the conduction of the trial (31). Modifications taken based on observations could be for example on dosage, patient selection criteria or sample size (30). In addition to that, the aim of an adaptive study design is to make the identification of IMPs that have a therapeutic effect more quickly (32). In the case of nonrandomised trials, there are many similarities with randomised controlled trials. However, the main difference is that in nonrandomised trials the allocation of a study subject to a treatment is not randomised but decided by the researcher based on some criterion (e.g. an eligibility cut-off) (33). Because of this lack of randomisation, these trials are often subject to discussion and

concerns about internal validity, as it may be difficult to show that the treatment is casually linked to the observed outcomes (34).

1.3 Regulation of Clinical Trials

As the participation in clinical trials always carries a risk for subjects, they are highly regulated. A clinical trial has currently to be approved by a competent authority and an Ethics Committee (EC) in every country it is intended to be conducted in the European Union (EU). The approval process will be based on a number of documents, specifying the characteristics of the trial and the IMP, as well as preclinical data. The person that submits the clinical trial is usually the sponsor, who also finances the trial and/or the investigator, who is the responsible person at the site of conductance of a trial. After the initial approval of a clinical trial by competent authorities and ECs, the trial will be thoroughly monitored during its conductance and upon termination (35). There are several harmonised guidelines by organisations, which are applicable worldwide or throughout the EU (36,37). In addition to that, the EU also has its currently applicable Clinical Trial Directive 2001/20/EC and there are numerous national laws in the Member States (35). However, the EU Directive is going to be replaced in the near future by the EU Regulation 536/2014, causing also many changes in national law. The EU Regulation's main goal is to meet the mentioned need for harmonisation of the application procedure of clinical trials, to make multinational trials more feasible throughout Europe (3,38).

2. Aim

As the field of clinical trials is extensive, the focus of this thesis lies on the submission of clinical trials for IMPs. To cover this topic comprehensively, the following four main aims were established for this thesis.

Firstly, it is aimed to explain and analyse the importance of preclinical drug development for the application of a clinical trial to competent authorities and according Ethics Committees (ECs) and which non-clinical data is required and how it has to be implemented in the documents of the application dossier.

Secondly, the aim is to analyse and summarise the current requirements for application documents and the according application procedure in EU countries (through the example of the country Austria) and non-EU countries (through the example of the country Switzerland). Further, these requirements and procedures are aimed to be compared and the similarities and differences will be analysed.

Thirdly, the changes in the application requirements and procedures in relation to the COVID-19 pandemic, starting in 2020, are aimed to be analysed and summarised for EU countries (through the example of the country Austria) and non-EU countries (through the example of the country Switzerland).

Lastly, the impact of digitalisation on the application procedures for clinical trials and efforts regarding the harmonisation of these procedures throughout the EU are aimed to be discussed. In addition to that, also according to ongoing pilot projects will be analysed.

To also include a more practical point of view and experience, the thesis will be concluded with an interview with the chairman of the Ethics Committee of the Medical University of Graz.

3. Connection of preclinical drug development and application for clinical trials

Preclinical data about an investigational medicinal product (IMP) is crucial for the application of a clinical trial with the according IMP, as it has to be contained in different application documents such as the Investigator's Brochure (IB), study protocol or elsewhere, depending on the country where the trial is intended to be conducted. Therefore, valuable preclinical data is essential for achieving an approval of a clinical trial (36,39–41).

According to the BSAG in Austria for example, relevant preclinical data should be provided in clear, recapitulatory tables by the applicant. The following issues should be addressed in these (39):

- type of study e.g., carcinogenicity or acute or chronic toxicity studies
- GLP-status
- animal species/strain
- study ID
- route of administration
- duration of animal dosing
- substance
- number and gender of animals per group
- no observed adverse effect level (NOAEL)
- dose selection
- major findings

The applicant should also discuss safety limits as compared to the intentional dose in humans as well as severity and clinical relevance and time to recovery (39).

In the Community Guideline on Good Clinical Practice (GCP) (CMP/ICH/135/95) a detailed description of which nonclinical data should be included in the application of a clinical trial is given. The summary of all nonclinical studies conducted in relation to the IMP in question should be included into the investigator's brochure (IB), a document required for the application of a clinical trial. This summary should contain information about all toxicology, pharmacology and pharmacokinetic nonclinical studies and the methodologies used in the studies as well as their findings. Further, a discussion about the relevance of the results regarding the IMP and about possible unwanted effects in

humans is needed in the IB. In more detail, the information given on previous nonclinical studies should contain the following aspects, where available (36):

- tested species
- unit dose
- sex and number of animals in each group
- dose interval
- duration of dosing
- information about systemic distribution
- route of administration
- Duration of follow-up after exposure

Regarding the results of a study there are as well certain important aspects that are strongly recommended to be included (36):

- intensity/severity of toxic or pharmacological effects
- frequency and nature of toxic or pharmacological effects
- onset time of effects
- duration of effects
- reversibility of effects
- dose response

The necessary information mentioned above should, if possible, be presented as listings or tables to enhance clarity. In the following discussion in subsequent sections, the most important results of the studies should be addressed. This includes relevance to humans, dose response of occurring effects as well as statements about which aspects need to be investigated in humans. Importantly, if possible, nontoxic and effective dose findings should be compared in the same animal species (rather as blood/tissue levels than as mg/kg) and it should be addressed how this comparison is relevant for the proposed dosing in humans. In one of the subsequent sections, the findings of the nonclinical studies regarding bioavailability (local and systemic) and absorption of the IMP have to be discussed as well as a possible relation of the findings to pharmacology and toxicity seen in animals. In addition to that, a section on IMP metabolism in animals and pharmacokinetics is needed, which should contain a summary of biological transformation as well as disposition and pharmacokinetics in general of the IMP. One of the further subsequent sections should be on nonclinical pharmacology and contain a

summary of all pharmacological aspects of the IMP and its metabolites in animals. Included in this summary should be studies about potential therapeutic activity and safety. These could for example be studies on receptor binding, specificity and efficacy models in case of therapeutic activity and special studies to discover pharmacological actions that are not intended as therapeutic effect(s) in case of safety. Another important topic that needs to be covered is toxicity. Herein, the toxicological effects seen in nonclinical studies in different animal species ought to be described. Therefore, the headings single dose, repeated dose, special studies, carcinogenicity, genotoxicity and reproductive toxicity should be used were appropriate (36).

4. Current situation of submission process and required tools in the EU through the example of Austria

4.1 Regulatory Authorities

The regulatory authorities for the application of clinical trials conducted in Austria are the Austrian Federal Office for Safety in Health Care (Bundesamt für Sicherheit im Gesundheitswesen (BASG)) / the Austrian Agency for Health and Food Safety (Österreichische Agentur für Gesundheit und Ernährungssicherheit (AGES)). (39)

Further, clinical trials need to achieve a favourable opinion of an Ethics Committee (EC) prior to their conductance. In Austria, the competent body is one of the 7 possible Lead Ethics Committes, namely the Ethics Committee of Lower Austria, the Ethics Committee of Upper Austria, the Ethics Committee of the Federal State Salzburg, the Ethics Committee of the Medical University of Graz, the Ethics Committee of the Medical University of Innsbruck, the Ethics Committee of the Medical University of Vienna and the Ethics Committee of the City Vienna. The commissions evaluate clinical trials on medicines and medicinal devices, the application of new medical methods and applied research in humans on their ethical innocuousness. Hereby adherence is given to the principles of the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use's (ICH's) Guidelines for good clinical practice (GCP) (ICH-GCP) and the regulations of the Austrian Medicinal Products Act (AMG), the Austrian Medical Devices Act (MPG) as well as all applicable legal provisions. (42,43) Every EC in Austria has to consist of a balanced amount of men and woman and has at least to contain the following persons (6): (cf. AMG §41 Abs. 2)

- a medical doctor, who is authorised for self-employed professionalism and who is not the investigator
- a medical specialist in the field of the clinical trial, who is not the investigator
- a representant of the higher service in health and patient care
- a jurist
- a pharmacist
- a representant of patients
- a representant of a representative disability organisation and a representant of senior citizens
- a person with biometric expertise

- another person, who is not falling in one of the categories above and who is assigned to the perception of pastoral matters or has any other applicable ethical qualification

For any of the persons mentioned above, a representative with the same qualification has to be available (6). (cf. AMG §41 Abs. 2) Further, the members of an EC and their representant have to lay open any relationship with the pharmaceutical industry to the governor and have to step back from their function, if this relationship might influence their impartiality (6). (cf. AMG §41 Abs. 3)

4.2 Required Documents for Regulatory Authorities

Which documents are required for the submission of a clinical trial to the regulatory agencies in Austria is regulated in § 40 AMG. The AMG hereby invokes the documents listed in the EudraLex Volume 10 CT-1, described in the following. In addition, the EudraCT Application Form needs to be filled out and submitted (39,44).

4.2.1 Cover letter

The purpose of the cover letter is to give the applicant the possibility to draw attention to the individuality of the trial (41). There are several guidelines in the EudraLex Volume 10 CT-1 about the prospects for the cover letter. Firstly, it has to be signed by the applicant either manually and scanned or electronically (39). The subject of the letter has to comprise the EudraCT number, the title of the trial and if available, the invariable sponsor protocol number (41).

Notably there is no need to replicate information already given in the application form in the cover letter. However, there are a few exceptions to this rule. First of all, if the trial population has specific features (e.g., participants are not able to give informed consent or participants are minors) this has to be stated again in the cover letter, even if it is already mentioned in the application form. The same accounts for the statement whether it is intended in the course of the trial to administer a new active substance to humans for the first time. Further, what has to be reproduced in the letter is whether there is related scientific advice on the IMP or the trial by the competent authority of a Member State or third country or by the European Medicines Agency (EMA). Lastly, what is necessary to be repeated in the cover letter is whether there is an intention for the trial to be or the trial actually is part of a Paediatric Investigational Plan (PIP). If a Decision of

the Agency on the PIP is already available, the applicant has to include the link to it in the cover letter (41).

Furthermore, what is important is that the applicant states in the cover letter whether the IMP or the non-investigational product (NIMP) is narcotic and psychotropic. Also, the letter has to contain a description on where relevant information can be found in the application dossier, especially on where the reference safety information is included. The latter is important for seeking out suspected unexpected serious adverse reactions (SUSARs) from adverse reactions (41).

If an applicant wishes to withdraw the initial application due to unexpected events or additional information and resubmit it, he has to highlight the resubmission in the cover letter and depict the changes compared to the initial submission (41).

4.2.2 Clinical trial application form / EudraCT application form

Regarding the application form for clinical trials, regulated by the current Directive 2001/20/EC, there is one unique form, which is utilised EU-wide. The form is published in the 10th volume of the EudraLex and is called EudraCT application form (41).

The EudraCT application form has to be signed by the applicant either manually and scanned or electronically (39). This signature confirms that the given information on the form is comprehensive and that the amount of available information given in the residual documents is accurate. Further, with signing the form it is corroborated that the trial will be conducted according to the protocol and results and SUSARs will be reported (41).

With regard to the EudraCT form in Austria, it is important that the form has to be completed in English with a few exceptions (39):

- contact information on Austrian sponsors
- legal representatives
- request for the competent authority
- study sites
- clinical investigators

The responsibility for the completeness and accuracy of the information on this application form lies with the sponsor (39).

4.2.3 Protocol

In Article 2(h) of the EU Directive 2001/20/EC the protocol is described as *"a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial* (35)*."* To enable the definite identification of a protocol it should contain the title, a date, the sponsor's protocol code, the number of version and a name or short title allocated to it (41). The general content which should be included in a clinical trial protocol is precisely described in Section 6 of the ICH-GCP E6(R2) (36).

Firstly, there is a lot of general information required in the first part of the protocol, such as names, addresses and telephone numbers of sponsor, monitor, medical experts, investigators, laboratories, trial sites and generally all persons and institutions involved in the trial. Equally as important is the background information to be given, this includes a description of the IMP including findings from nonclinical and clinical studies, a summary of known risks and benefits, a description of administration route and dosage and a statement about the study population intended to be included. Also, a declaration that compliance with GCP, the protocol and regulatory requirements will be given during the conduction of the trial has to be contained in this section. In the subsequent chapter, a detailed description of the purpose and the objectives of the trial is required (36,41).

Following to that and because the credibility of a trial's data and its scientific integrity strongly depend on it, the trial design has to be depicted. Main points of the trial design which need to be represented are: trial endpoints, the type/design of a trial (e.g., double-blind or placebo-controlled), measures taken to avoid bias, trial treatments, sequence and duration of trial periods, discontinuation criteria for subjects, accountability procedures of IMPs, maintenance of possible randomization codes and code break procedures, identification of any data on the Case Report Form (CRF) and source data (36,41).
In the next two sections the selection and withdrawal of subjects (inclusion, exclusion and withdrawal criteria) and the detailed treatment that subjects are intended to receive have to be illustrated (36,41).

Further, it has to be explained how exactly the efficacy and safety (e.g., identification of serious adverse events and adverse events) of the IMP(s) tested will be assessed in the trial and which statistical methods are intended to be used (36,41).

In the latter sections of the protocol topics as direct access to source data and documents, quality control and assurance, ethics, data handling and record keeping, financing and insurance and publication policy should be discussed (36,41). The protocol or the protocol signature page has to be signed by the sponsor and the coordinating investigator in case of a multicentre and/or multinational trial or the principal investigator in case of a trial only conducted at one site, either manually and scanned or electronically (39,41).

4.2.4 Investigator's Brochure (IB) or document replacing the IB

The investigator's brochure is defined in Article 2(g) of the current EU Directive from 2001 as *"a compilation of the clinical and non-clinical data on the investigational medicinal product or products which are relevant to the study of the product or products in human subjects* (35)*."* The IB in a clinical trial has the function to educate the investigator and other persons involved on key features of the protocol, to ensure their understanding and compliance. These key features most importantly include dose and dose frequency/intervals as well as possible methods of administration and the procedures needed for safety monitoring (41). Further, it is stated in Article 8 of the EU directive from 2005 that the sponsor has to validate and update the IMP at least once a year (45).

Importantly format and content of the IB are regulated in a separate Directive, namely by Article 8(1) of Commission Directive 2005/28/EC as well as in the Community Guideline on GCP (CMP/ICH/135/95). The content of the IB has to be simple, objective, concise, balanced and non-promotional so that a potential investigator or clinician can unbiasedly assess the risk-benefit rate of a certain trial (45). It should be in the form of summaries of all available evidence (e.g., nonclinical and clinical data) and information supporting the rationale for the clinical trial and the safety of the use of the IMP (41).

According to the ICH guideline on GCP the title page of an IB should contain the sponsor's name as well as the identity of each IMP used and the according release date. Further, an edition number of the IMP and the number and date of the edition it replaces should be provided. An example of an IB title page is given in Figure 1 (36).

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:
Research Number:
Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:
Release Date:

Replaces Previous Edition Number: Date:

Figure 1: Example of the title page of an IB (36)

Following the title page, confidentiality statement and table of contents a summary of relevant chemical, physical, pharmacological, pharmaceutical, pharmacokinetic, toxicological, clinical and metabolic information should be included. In the subsequent introduction, the following issues should be addressed: the chemical name of the IMP(s), the IMP(s) pharmacological class and its position in it, all active ingredients, the rationale for the trial with the IMP(s) and the expected prophylactic, therapeutic and diagnostic indications. Herein, also the general approach for the evaluation of the IMP should be provided. The introduction is followed by a description of physical, chemical and pharmaceutical properties and the formulation of the IMP(s). In this section, also information on storage, dosage form(s) and structural similarities to known compounds ought to be included (36).

Subsequently a section with a summary of all applicable nonclinical studies (pharmacology, pharmacokinetic, toxicology and investigational product metabolism) should follow. Similarly, information on the already known effects of the IMP on humans (pharmacokinetics, pharmacodynamics, metabolism, dose response, efficacy, safety and other pharmacological activities) has to be contained in the IB. To the extent possible, there should be a summary of every completed clinical trial in relation to the

IMP given. Further, information collected outside of clinical trials about the use of the IMP(s) (e.g., experience during marketing) also ought to be included here (36).
The last section of an IB is a summary of the data and a guidance for the investigator, where a discussion of all included data should be provided. This last part of the IB is crucial as it provides the investigator with clear information on possible adverse reactions and risks and possibly necessary observations, specific tests and precautions for the trial. It should guide the investigator to recognize and treat possible adverse drug reactions and overdose and is therefore very important for the safety of a clinical trial (36).

If there is a marketing authorisation for the IMP in any Member State of the EU or in an ICH country an approved summary of product characteristics (SmPC) may be used instead of the IB (36,41,45).

4.2.5 Investigational Medicinal Product (IMP) dossier (IMPD)

The purpose of an IMPD is to give information on quality, control and manufacture of the IMP (41). An IMP is defined as *"a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial including products already with a marketing authorization but used or assembled (formulated or packed) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form"* in Article 2(d) of the Directive 2001/20/EC (35).

Further, results and data from relevant non-clinical studies and possible clinical use of the IMP should be included as well as an according risk and benefit assessment. In the latter case, there is also the possibility for the applicant to refer to the IB for this data, if it is depicted there preferably in tables and in enough detail to allow assessment of potential toxicity and a decision on how safe the use of the IMP is in the proposed clinical trial. Moreover, also quality data regarding the IMP needs to be presented in the IMPD, which includes information on nomenclature, structure, general properties, manufacture, characterisation, control of the drug substance and reference standards or materials (41,46).

If there is a marketing authorisation for the IMP in the EU an IMPD is most likely not required (41). One important topic regarding IMPs is compliance to good manufacturing practice (GMP), which has not to be documented in the submission of a clinical trial if

there is a marketing authorization for the IMP in the EU or an ICH country and it is manufactured in the EU. In other cases, an importation authorisation is required, as well as a certification given by the qualified person in the EU that states that the manufacturing of the IMP is compliant to GMP (41,47).

In the cases that the IMP is a placebo, only quality data needs to be presented in the IMPD. Further, if the manufacturer and the composition are the same for the placebo and the IMP and the placebo is non sterile or if the placebo has been submitted in a previous clinical trial application neither quality, nonclinical nor clinical data has to be presented (41).

4.2.6 Non-Investigational Medicinal Product (NIMP) dossier (NIMPD)

NIMPs are medicinal products which are used in a clinical trial but do not fit the definition of IMP(s) in Directive 2001/20/EC (35,41). Examples for such NIMPs are Rescue medication or medicinal products, which are used to assess end-points in the course of the clinical trial (48).

There is a strong recommendation from the European Commission to use NIMPs which have marketing authorisation in the Member State where the trial is intended to be conducted or at least in another Member State or an ICH country or a third country with a mutual recognition agreement. Only if none of the above is possible NIMPs which have a marketing authorization in a different third country or no marketing authorization at all should be considered (41).

Regarding the documentation requirements for NIMPs in the application dossier the same rules apply as for IMPs (see Chapter 4.2.5). In this sense quality and manufacturing data as well as documentation of GMP compliance and a justification for effective and safe use are required. However, depending on the situation of marketing authorizations of an NIMP there is the possibility for simplified dossiers (48).

4.2.7 Informed consent

A copy of the informed consent form (ICF) should also be submitted to the authority although it will not be reviewed by the BASG but rather only be the EC. Therefore, the ICF is only needed as supportive documentation by the authority (44).

4.2.8 Additional documentation

Some additional documents that might be necessary for the application are described in the CT-1 document of the European commission in Section 2.9. These include the opinion of the EC, if it is already available, as the application to the EC can take place before or simultaneously with the application to the BASG. Further and again only if it is available and relevant for the clinical trial, the summary of scientific advice from the EMA or any Member State has to be submitted. If the case occurs that a clinical trial is part of an agreed PIP the opinion of the Paediatric Committee as well as the EMA's decision on the agreement on the PIP have to be submitted. When the mentioned documents are accessible online, the applicant does not have to submit them but only include the link to these papers in the cover letter. In addition to that, a proof of payment has to be submitted if there are any fees, as well as the labelling of the IMP (41).

4.3 Required Documents for the Ethics Committees (ECs)

Which documents are required for application of a clinical trial to an EC might differ between different Member States of the EU. However, in the EudraLex Volume 10 CT-2 an overview is given accompanied by a detailed guideline on content and format of the documents. Notably, all submitted documents should contain the trial identification consisting of the protocol code number of the sponsor, the EudraCT number and the date and/or version as well as the date and/or version of the specific document (49). Further, requirements specific to Austria can be found on the homepage of the responsible EC (e.g., the Ethics Committee of the Medical University of Graz) (50).

4.3.1 Covering letter

Similar to the application to competent authorities the application to the EC has to comprise a signed covering letter which's heading should contain the trial identification and the title of the trial. Regarding the content of the letter any special issues related to the trial should be discussed. These could be the first administration of an IMP to humans, a special trial population or an unusual trial design or IMP etc. Further, it should be indicated where the relevant information can be found in the application. Also, the sponsor's chosen reference documents for the identification of unexpected serious adverse reactions should be specified and any available scientific advice in relation to the IMP or the specific trial by any EC or competent authority of another country should

be summarised. There should also be an indication on where a copy of the related advice is included in the application (49,51).

According to the Austrian EC, the following points have to be contained in the covering letter in addition, if the trial is multicentric (52):

- the denomination of the leading EC which is applied to
- the date of the meeting to which is submitted
- a list of all local ECs responsible for the trial in Austria
- a confirmation that copies of the application were sent to all ECs listed above
- a list of the submitted documents

4.3.2 Application form

The application form for submission to the EC might consist of two different modules. The first module is obligatory and common in all Member States. It is the application form described in 4.2.2 Clinical trial application form / EudraCT application form, so the same form which is also used for application to competent authorities. Therefore, it should also contain information on the IMP(s), the trial design, trial site(s) and principal investigator(s) as well as administration of the trial. The second module is not obligatory and mostly consists of a national or local application form specific for a certain Member State (49). For an application to an Austrian EC such an Austrian application form is mandatory. It consists of 2 parts, whereas part A is about general information on the trial and the sponsor and part B is more specific and requires information on the specific trial sites involved (50).

However, in all cases the application form has to be signed either by the sponsor or by his/her legal representative. In trials where research is only done at one single site the principal investigator can also sign the form alternatively or additionally. The same accounts for the coordinating investigator, responsible for coordinating principal investigators at different trial sites in one Member State. In Austria, if the sponsor is not the applicant, there is the need for an authorisation, which enables the applicant to apply on behalf of the sponsor, called Letter of Authorisation (49).

4.3.3 Clinical Trial Protocol

Requirements for the protocol according to ICH/135/95 have already been described in 4.2.3 Protocol and apply likewise for the application to the EC. The most substantial points that should be included are (36):

- risks- benefits evaluation of the trial
- justification for the assortment of subjects, especially if they are not able to give informed consent or belong to special populations
- description of the procedures of recruitment and informed consent
- description of the plan for additional care provision for subjects after their participation in the trial

Importantly the submitted version should further contain all amendments and the end of the trial should be defined (49).

In addition to that, for the application to the Austrian EC a peer review of the trial is required, if available, as well as a summary of the trial protocol in German, so the national language. This summary is already included in the national EC application form in Section 7, which is why there is no need to submit an additional document for that (49,51).

4.3.4 Information on the IMP

To provide the EC with enough information on the IMP to make an informed decision on a clinical trial the IB (described in 4.2.4 Investigator's Brochure (IB) or document replacing the IB) or an expertise of the Pharmaceutical Advisory Board (in Austria) has to be part of an application. However, if there is a marketing authorisation for the IMP in any Member State and the IMP is intended to be used according to this authorisation the IB can be replaced by an authorised SmPC. In Austria, it is not required to submit an IMPD to the EC, but this might differ in other Member States. Regarding manufacturing, the EC Guideline CT-2 form 2006 indicates that the Austrian ECs require quite a few documents like manufacturer authorisation, declaration of GMP status and information and data on viral safety (49). However, this responsibility seems to have shifted to the BASG as the current version of the Checklist of documents of the Austrian ECs marks all of these documents as not required (51).

4.3.5 Recruitment arrangements / Advertising for trial subjects

The description of the practices for enrolment of trial subjects should in general be contained in the trial protocol, however if the procedures vary between different trial sites they have to be described in a separate document. This is specifically important if subjects who are not able to give informed consent are included in a trial (49).

If it is intended that the recruitment of subjects is carried out by advertisement, all material including the text and layout of prints like insertions, posters or notices as well as recordings or videotapes have to be appended to the application (49,50). In addition to that, it is important to include information on how and by whom answers to the advertisement will be handled and which resources and procedures are intended to be put in place for patients that are not suitable to participate in the trial. This could be for example advice or help to get a patient into contact with a suitable institution or clinic which is not related to the trial (49).

4.3.6 Case Report Form (CRF)

The EC also requests the submission of the CRF intended to be used in the clinical trial (50). The CRF is used in clinical trials to collect the data of the subjects during their participation in the trial (53). In the ICH-GCP E6(R2) guidelines it is stated that the CRF can be either a printed, electronic or optical document and that it is intended to capture all information on each subject, which regarding to the protocol has to be conveyed to the sponsor (36). In case of web-based CRFs screenshots of these can be submitted to the EC (50).

4.3.7 Subject information and the informed consent procedure

The informed consent is defined in the ICH-GCP E6(R2) guideline as the decision freely made by a subject to take part in a clinical trial after being thoroughly informed about the trial's nature, implications and risks and its significance. The decision must be written, signed and dated and appropriately documented. If the subject is not able to give consent, a legal representative can do so for them and if the subject cannot read or write oral consent may be given in the presence of a witness (36).

All the information provided to potential subjects and/or where necessary their legal representatives in the process described above has to be submitted to the EC, together

with the from for written informed consent. In general, all information given to potential subjects or their legal representatives should be understandable for lay persons, short, relevant, clear and in a language known by the subject (49).

Guidance on the elaboration of these required documents is given in the ICH-GCP E6(R2) guidelines. According to these, the following points have to be covered in the written information given to the subject or their legal representative and in the according oral discussion (36).

- The fact that research is involved in the trial.
- The aim of the trial.
- The treatments intended in the trial and the probability for being randomly assigned to each treatment.
- The procedures that have to be followed in the trial. This includes all invasive procedures.
- The responsibilities of the subject.
- Experimental aspects of the trial.
- Possible risks and inconveniences.
- Expected benefits for the subject. If there are none this also has to be stated.
- Alternative treatment procedures or courses that may be available and the according potential risks and benefits.
- Compensation and/or treatment for the subject in case of trial-related injury.
- Payment to the subject, if any, for the participation in the trial.
- Expenses to the subject, if any, for the participation in the trial.
- That the participation is voluntary and the subject can withdraw at any time without any given reason and does not have to face negative consequences or loss of benefits. The withdrawal of informed consent has the consequence that no new information on the subject will be collected and added to an existing database or data.
- The fact that with signing the informed consent form/the data privacy statement the subject or their legal representative authorizes that the regulatory authorities, the ECs, the monitors and the auditors have direct access to the original medical records of the subject to verify clinical trial data and/or procedures.
- That any records which identify the subject will not be made public but will be kept confidential, also if the results of the trial are published.

- That if information becomes available which might influence the subject's willingness to continue participating in the trial, the subject or their legal representative will be informed directly.
- Contact persons for further information on the trial and the rights of subjects as well as contact persons in case of trial-related injury.
- Circumstances and/or reasons that might lead to the termination of the subject's participation.
- Expected duration of participation of the subject in the trial.
- Approximate quantity of subjects participating in the trial.

In addition to all the points mentioned above the arrangements for additional care after the participation in the trial, if needed, have to be described. Further points that should be included are names and addresses of investigator, study nurse etc, (financial) ties to the sponsor and sources of funding as well as name and address of the sponsor and the EC's positive opinion (49).

As the issue of data protection and privacy is very important and has been arising even more since the EU Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation), it becomes clear that data protection is also essential in the case of clinical trial subjects. Notably the General Data Protection Regulation from 2016 replaces the Directive 95/45/EC on which the document "Guidance on the application for an Ethics Committee of the European Commission" is still based. Therefore, close attention has to be paid to the data protection part of the written information provided to trial subjects (49,50,54,55). The information should include the ways of coding, storing and protecting biological material from the subject, the subject's identity and any recorded data (49).

Regarding the code list, it has to be stated which persons have access, where and for how long it is stored and who is the responsible person for keeping it. Subjects have further to be informed about their right to request and receive updated information on the recorded data and to require the correction of any occurring errors. In addition, in the case of retention of data or subject samples it has to be stated that subjects have the right to know who will have access to their data and samples, how long and where the retention will be, who is responsible for keeping data and samples, how retained

identifiable samples will be handled and how samples will be anonymised or destroyed after analysis (49).

As a consequence of the EU Regulation 2016/679 there have been a few substantial changes, which have an impact on the data protection procedures in the course of clinical trials. Since then, it is required to obtain additional explicit consent on the data protection procedures. Further, already compiled data can still be used after the withdrawal of consent, if this is stated in the data protection declaration/informed consent form or if it is for scientific or statistical purposes. In addition to that, for the time of the retention period of data the right of the subject to have their data deleted is omitted (54).

In the case of trials with subjects which are not able to give consent themselves (minors or incapacitated persons) is has to be described why these subjects have to be included and how consent from their legal representative but also from the subject, where appropriate and to the extent possible, is intended to be obtained. This can lead to the need of two separate information sheets. In Austria, if minors are intended to be included in a clinical trial, their consent has to be obtained from the age of 8 and from the age of 14 also written consent is necessary in addition to the consent of their legal representative. Also, the procedure for the case that the legal representative would be willing to give consent but the subject does not want to participate in the trial or wants to withdraw has to be described in the protocol. According to the Austrian ECs, the participation of the subject is not allowed if one of the two consents is withdrawn. Further, in the event of temporarily incapacitated subjects, consent has still to be obtained from a legal representative and as soon as possible from the subject itself. The procedure for that and the information given to the subject have to be described as well in the application. For the occasion that the legal representative is not available, the measures for the enrolment of the subject have to be described and rated positively by the EC (36,49,50).

The informed consent form is used to verify that the subject has been given and consented all the required information. It should contain at least three important points: the consent of the subject to participate in the given trial, the consent of the subject to give direct access to their personal information to relevant personnel for quality control and assurance and the consent to collect coded information and, where applicable, transmit it outside the community (49).

4.3.8 Suitability of the investigator and quality of the facilities

To demonstrate the qualification of a coordinating investigator in case of multicentre trials and a principal investigator at a specific trial site, current curricula vitae (CVs) should be provided in which any experiences with clinical trials and patient care as well as GCP training should be described (49–51). Further, a declaration of conflicting interests, such as economic interests, for each investigator should be presented. This declaration however can also be included into the according CV (49,50). In addition to that, the Austrian ECs also demand appropriate information about supporting staff involved in a clinical trial (51).

For multicentre clinical trials a list of all locations where the trial is intended to be conducted and the responsible local ECs that received a copy of the application documents, should be submitted (50). In the decision process, the EC has to consider the suitability of the proposed investigator as well as the quality of the facilities (including availability of resources, laboratory facilities and personnel) of the proposed trial sites in the Member State (49).

4.3.9 Insurance and indemnity

The arrangements for compensation and indemnity in case of death or injury of a participating trial subject as well as for indemnity or insurance to cover the obligation of the investigator or sponsor ought to be stated (49). In Austria, the submission of the related insurance certificates is required (50).

4.3.10 Financial arrangements

It is required to include information on financial dealings and compensation to subjects as well as the investigator or the trial site in the application. The Austrian ECs demand a list of amounts of these compensations (50). In addition to that, the agreement between the trial site and the sponsor has to be reviewed by the EC and a certificate of agreement between investigator and sponsor has to be submitted if not already contained in the trial protocol (49,51).

4.3.11 Additional Documents

There are a few additional documents which should be submitted to the Austrian ECs, if available. These are: a list of the competent authorities from different countries to which

the application has also been submitted and details of their decisions, votes of different ECs and patients' cards, patient diaries, questionnaires etc. However, it is obligate to submit a verification of the payment of the handling fee or a proposal for enacting of the fee. This proposal can be informal but should state an appropriate reason for the requested enacting (50,51).

4.4 Application Procedure

The required documents and the EudraCT application form have to be submitted to the regulatory authorities solely electronically e.g., via CD, whereat the application form has to be in PDF and XML format (39). Notably, during the current situation of the COIVD-19 pandemic, only submissions via email are accepted (56). The BASG suggests a certain structure of the folders on the data medium submitted. At first there should be a folder called "1_General Information" which should contain for example the covering letter and the EudraCT application form followed by a folder called "2_Protocol" which should contain e.g., the current version of the protocol, signature pages and synopsis. The investigator's brochure should be in an own folder called "IB" accordingly just as the investigational medicinal product dossier (or simplified IMDP or SmPC) with all further relevant manufacturing information should be in the folder "4_IMPD". Lastly, the folder "5_Additional information" should contain all additional information that has to be given such as patient information, the summary of scientific advice or the Paediatric Investigation Plan (39).

The submission to the BASG can be made either via mail, which should contain a separate signed cover letter and the data medium or by e-mail via an attached zip-file. However, if it is not possible to submit via a single email the submission has to be done by mail. Notably, as mentioned, during the COVID-19 pandemic a submission is only possible via email. After the submission reaches the BASG, the applicant will receive a confirmation of receipt via e-mail, containing the BASG reference number. Also, a fee has to be paid to the BASG for the initial application of a clinical trial. The fees are linked to index price adjustment and the current fees, which have to be paid, are published and updated on the website of the BASG (6,39).

After application, the competent authority first assesses the formal completeness, and if this is not given, requests the missing information from the applicant via phone or e-mail. As soon as the application is formally complete (no matter if initially or after handing in

missing information), the validation date is set as the date of receipt of either the complete submission or the requested missing information. This date is also confirmed to the applicant in the confirmation of formal completeness via e-mail. From the validation date on, the scientific assessment period starts and lasts 35 days. If after these 35 days no objection has been communicated from the BASG or if the decision has been published on the BASG website even earlier, the clinical trial can be considered as approved (6,39). (cf. AMG §40 Abs. 2) However, if there are major deficiencies, such as the non-fulfilment of scientist or legal requirements, the applicant will receive a deficiency letter with the lacking information and further objections via e-mail. The applicant then has the opportunity to adjust the application within a certain timeframe, which has to be agreed on by both parties (6,39). (cf. AMG §40 Abs. 3) The request of an extension of the timeframe is possible once. If the applicant is not able to meet the requirements in this time period an official notification of rejection will be sent. However, if the deficiencies have been addressed appropriately the applicant will get a confirmation about that via e-mail and the procedure of approval can continue (39). In addition to that, if the IMP in the clinical trial is connected to gene therapy or somatic stem cell therapy the BASG has to reach a decision no later than 90 days after submission (6). (cf. AMG §40 Abs. 7)

Nevertheless, to get a clinical trial approved not only the approval by the competent authority is necessary, but also a positive vote by the responsible Lead EC (43). In choosing the Lead EC in case of a multicentre trial, it should be considered that the Committee should be responsible for at least one of the trial sites. Notably, there are 17 other ECs in Austria, which cannot be chosen as Lead ECs, but can still function as responsible local ECs, just as the remaining 7 possible Lead ECs (57). However, the responsibility of local ECs in a multicentre clinical trial is limited to the assessment of the suitability of the responsible investigators and according staff as well as the specific trial site itself. Any general documents regarding the trial also have to be submitted to the local ECs simultaneously to the submission to the Lead EC (6). (cf. AMG §41b Abs. 5) Despite all that, the terminal decision will be made solely by the Lead EC, representative for the country Austria (6,57).
(cf. AMG §41b Abs. 1) The application to the EC can be submitted either simultaneously or prior to the application to the BASG. Notably, the date of the submission to the EC has also to be stated in the cover letter to the BASG (39).

According to the EU Directive 2001/20/EC the responsible EC, after receiving a complete and valid application, should have 60 days from the date of receipt to come to an opinion and communicate it to the applicant as well as the concerned competent authority. During this time period the EC should have the possibility to ask once for supplementary information, which suspends the time frame until receipt of the information (35). In Austria all documents need to be submitted electronically in PDF format via the electronical submission system called ECS to the Ethics Committee of Upper Austria, the Ethics Committee of the Federal State Salzburg, the Ethics Committee of the Medical University of Graz, the Ethics Committee of the Medical University of Innsbruck and the Ethics Committee of the Medical University of Vienna (42). To the other ECs a submission is required or possible via e-mail or mail. However, part A of the application form, so the national part, has still to be signed and submitted as original in paper form as well. Further, a fee has to be paid to the EC. Notably, the submission has to be made before the due day of a monthly meeting indicated on the websites of the according Lead EC and simultaneously to the submission to local ECs, if applicable. If the documents are formally complete, the EC will send a confirmation within 5 workdays (50,57,58). After that, the application will be examined in one of the monthly meetings of the EC (50,58). Notably, the local ECs have the possibility to plead obligations to the Lead committee until 5 day before the meeting the latest. If this is not the case, the Lead EC can act on the assumption of a positive vote (6). (cf. AMG §41b Abs. 5)

The monthly meetings are not public; however, there is the possibility that the applicant is invited to give statements about the trial. In this case, the decision will be communicated to the applicant immediately and the written resolution will be issued not later than two days after. In general, the decision of the EC has to be communicated to the applicant, the competent authority as well as if applicable the sponsor in written form with an explanatory statement (50,58). Notably, the sponsor has the possibility to make changes to the trial protocol after the start of clinical trial, if necessary. If these changes are substantial (e.g., influencing the safety of the trial participants), the sponsor has to inform the BASG and the responsible Lead EC about reasons and content of the changes. In the case that the substantial change is the addition of a further trial site, an assessment of a local EC is necessary, as in the assessment of the initial submission mentioned above (6). (cf. AMG §37a Abs. 1, AMG §41b Abs. 5)

In general, the Lead EC has, in accordance with the procedure regarding an initial submission, to draw a conclusion no later than 35 days after the receipt of the substantial

change (6). (cf. AMG §37a Abs. 2, AMG §41a Abs. 1, AMG §41b) Further, the same accounts for the BASG and a substantial change can be considered approved if there has been no rejection after 35 days (6). (cf. AMG §37a Abs. 3) Nevertheless, if the safety of the trial participants may be impaired, the sponsor and the investigator have to take the urgent measures necessary to protect the trial participants from immediate danger. After that, the sponsor has to inform the BASG and the responsible EC immediately (6). (cf. AMG §37a Abs.4)

5. Current situation of submission process and required tools in non-EU countries through the example of Switzerland

5.1 Regulatory Authorities

In Switzerland, the competent authority for the submission of a clinical trial, which is intended to be conducted in the country, is the Swiss Agency for Therapeutic Products, called “Swissmedic”. The institute is responsible in addition for the authorisation of therapeutic products and their supervision (59). All activities undertaken by Swissmedic are based mainly on the Law on Therapeutic Products but also on many other national laws like The Federal Act on Research Involving Human Beings from 2011 or the Ordinance on Clinical Trials in Human Research. Further, also applicable international guidelines are considered by the institute, namely the ICH-GCP E6(R2) Guidelines and the WMA Declaration of Helsinki from 2013 (60).
In addition to the application to the Agency for Therapeutic Products, a submission has to be made to one of the 7 cantonal ECs, which are the cantonal Ethics Committee Bern, the Ethics Committee for north western and central Switzerland EKNZ, the Ethics Committee for eastern Switzerland EKOS, the “Commission Cantonale d’Ethique de la Recherche sur l’être humain CCER, which is responsible for the canton Geneva, the Ethics Commitee Tessin/Ticino, the “Commission cantonale d’éthique de la recherche sur l’être humain CER-VD and the Ethics Commitee Zürich/Zurich (61). As there are many local ECs, the umbrella organisation “Swissethics” has been founded to harmonise and coordinate the working procedures and promote high ethical research standards (62). Just as Swissmedic, Swissethics also works according to the federal law of Switzerland as well as even more international standards and guidelines (63).

Superior of both institutions (Swissmedic and Swissethics) is the Federal Office of Public Health (FOPH), which has the responsibility to ensure uniform and efficient application of the law by the subsequent bodies. This is done by coordinating the activities undertaken by the different approval bodies (64).

In the subsequent chapters it will be described which documents are needed for an application to Swissmedic as well as Swissethics. However, it has to be noted that in Switzerland clinical trials are classified into categories A, B and C. Therefore, there are different requirements for trials in the different categories. A clinical trial is of category A if the IMP is authorised in Switzerland and one of the following points applies (65):

- The IMP is used according to the prescribing information.

- The IMP is used in different indication or dosage than in the prescribing information, but the indication lies within the same disease group according to the International Classification of Diseases (ICD) or the disease for which it is intended to be used is self-limiting and the dosage is lower than the one in the prescribing information.
- The usage of the IMP is accepted as standard in guidelines that were prepared according to international quality criteria.

If the IMP of a clinical trial is authorised in Switzerland but not used according to the points mentioned above, the clinical trial is grouped into category B. Category C applies for clinical trials with IMPs, which are not authorised in Switzerland at all. Therefore, the main difference between category B and C trials, is that the IMPs in category C trials do not yet have a marketing authorisation for any indication in Switzerland (65).

5.2 Required Documents for Swissmedic

The documents which are needed for an application of a clinical trial to Swissmedic, and should therefore be contained in the according clinical trial application dossier, are listed in Annex 4 of the Ordinance on Clinical Trials (ClinO, SR 810.305) (65,66). As Swissmedic, like the BASG in Austria, works among others according to the ICH-GCP E6(R2) guidelines, all of the requirements from these guidelines described in chapter 4.2 regarding structure and content of specific documents apply equally to the required documents in Switzerland (36,66). Therefore, these requirements and guidelines will not be mentioned again in the present chapter.

5.2.1 Cover letter to the Clinical Trial Application and related correspondence

Similar to the application in EU-countries a cover letter has to be submitted to Swissmedic. Notably, in the case of auxiliary medicinal products, information on these products, their import and possible marketing approvals, have to be included. If it is necessary for confidentiality reasons that some of the documents are provided by a different person or company, this has to be stated in the cover letter and reference to the presenter has to be made. In addition to that, if there were any answers which were requested before the approval of the study e.g., answers to further information requests or formal deficiencies, these have to be submitted alongside the cover letter. In general, of any correspondence of the applicant with Swissmedic (also via e-mail) a copy has to be provided (66).

5.2.2 Clinical Trial Application Form (CTA)

The required CTA is available on the homepage of Swissmedic and has to be filled out completely and accurately (66). In this form only one sponsor ought to be named, who must have his headquarter or a representative in Switzerland (65). In the case that the sponsor is not headquartered in Switzerland, the according representative has to be named in the CTA. Further, the sponsor or his Swiss representative or the clinical research organisation (CRO) as per contractual authorisation has to sign the form and it has to be dated. In the IMP section of the form the complete information has to be given for each individual IMP intended to be used, including the placebo(s) and the comparator(s). Further, if the IMP consists of diverse active substances, the information has to be provided on each of them (66).

5.2.3 Authorisation of Research Ethics Committee (REC) and/or correspondence with the REC

As part of the application to Swissmedic any decision of a REC in Switzerland regarding the trial has to be included, as well as information on currently reviewed applications by a REC (65). Therefore, the “Research Project Application Form” of the REC has to be submitted in copy as well as the cover letter, which was submitted to the REC. Further, details on raised issues or conditions regarding the trial should be provided by submitting any relevant correspondence (without attachments) between the responsible REC and the applicant (66).

5.2.4 Approvals of foreign drug Regulatory Authorities (RAs) and/or correspondence with other RAs

Decisions of foreign RAs and/or according correspondence with such have naturally only to be submitted if the intended trial is multinational. In this case, a list of RAs to which the application was sent, including information on the status of the approval has to be included in the submission. Further, if there are any conditions imposed in the decision of a foreign RA, this has to be stated and according reasoning has to be provided (65). In general, all relevant documents about a finished or ongoing approval process by a foreign RA that are available at the time-point of submission to Swissmedic have to be included in the application. These could be e.g., the entire correspondence (without attachments), grounds for non-acceptance, issues and conditions, approvals or refusals or a list of the versions of required documents approved or submitted. However, it is

sufficient to submit this information only regarding the first 3 European countries which the trial was applied to and the USA, if applicable (66).

5.2.5 Clinical Trial Protocol

As it is a very important part of every clinical trial, the protocol has as well to be submitted to Swissmedic. Notably, the application has to contain the version of the protocol that has already been approved by or was submitted to the REC. Regarding the format, the pages have to be numbered and the protocol has to be dated and signed by sponsor and investigator, whereas the sponsor-signed protocol only has to be submitted to Swissmedic (36,66). If the signature on the protocol is only electronically the responsibility for the validity of it lies with the person who signed the CTA. Further, if there is reference made in the protocol to any additional documents (e.g., working instructions), these documents have to be submitted as well (66).

5.2.6 Investigator's Brochure, Product Information or Summary of Product Characteristics

The application dossier to Swissmedic also has to contain the current version of the IB for all IMPs which do not already have a marketing authorisation in Switzerland or any country with a recognised equivalent GMP control system, so category C studies (65,66). This IB has to conform to the ICH-GCP Guideline E6(R2) chapter 7, described in 4.2.4 (40). However, if there is a current marketing authorisation for the IMP, only the Product Information has to be included in the application as long as the usage is according to the terms of the authorisation (Category A). Otherwise, if for example the route of administration or the dosage changes, an IB specifically regarding the new use has to be submitted or a specific section should be included in the general IB. This IB then has to be submitted together with the Product Information or the SmPC. Similarly, if the IMP which is intended to be used in the trial has a marketing authorisation in a so called GMP-equivalent country, it is sufficient to submit a SmPC or Product Information in German, French, Italian or English as long as the IMP will be used according to the terms of the authorisation (65,66). A current list of these GMP-equivalent countries can be found on the Swissmedic homepage (66). In contrast to that, if the trial is a first-in-human study, so the IMP is intended to be used in humans for the first time, the application has to contain an IB with complete pre-clinical study reports, joined as electronic copy (e.g., CD) (65,66).

Notably, any version of an IB for submission should be up-to-date, so no older than 18 months, and should contain a reference-safety information (RSI) section, clearly identified as such. The detailed requirements regarding RSIs are given by the Clinical Trial Facilitation Group (CTFG) in the “Q&A document – Reference Safety Information” from 2017 and the according RSI cover note from 2018. The RSI generally is a list of expected serious adverse reactions to the IMP(s) and is used in a clinical trial to assess the expectedness of all occurring “suspected” serious adverse reactions (SARs). However, the listed “expected SARs” should only be “suspected” SARs of which reasonable evidence exists that there is a causal relationship between the IMP and the reported event. Moreover, nature, severity and frequency of the expected SARs listed in the RSI should also be included in the list. An expectedness assessment by the sponsor on every single “suspected” SAR during the course of the trial is necessary to ensure efficient reporting of suspected unexpected serious adverse reactions (SUSARs) (67).

In cases, where there are different Product Information documents or SmPCs for an IMP available, the sponsor has to select one of them as RSI and justify the choice. One such case could be that an IMP has a marketing authorisation in more than one GMP-equivalent country. Also, if an IMP is only characterised by its active substance and this substance is used in different products, which all have a marketing authorisation, one RSI has to be selected for submission. However, in the latter case a list of the products intended to be used in the trial, including their name and authorisation number has to be submitted. If auxiliary medicinal products (AxMPs) with marketing authorisations in one or more GMP-equivalent countries are intended to be part of a given trial the applicant has to submit the according Product Information or SmPC. However, if there is no marketing authorisation for the AxMP(s) an according IB has to be included in the application (66).

5.2.7 Pharmaceutical quality documentation of IMP

Every clinical trial submitted to Swissmedic has to adhere to Good Manufacturing Practice (GMP), defined by the Pharmaceutical Inspection Conventions/Cooperation Scheme (PIC/S) and the Eudralex Volume 4, to be approved. This compliance has to be proven among others in the document Pharmaceutical Quality Dossier (PQD) of an IMP. In this case IMPs are defined as any test products, placebos or comparators. However, instead of the submission of a PQD also a European IMPD is accepted if only the section Drug Substance and Drug Product, so the quality part, of this document is provided (66).

Regarding the PQD there is detailed guidance on the formal aspects provided by Swissmedic in the “Guidance on Pharmaceutical Quality Dossier” document. According to this guideline, the first section concerning the drug substance itself has to be named “2.1.S DRUG ” with the following chapters numbered accordingly. The fist subchapter should be named “2.1.S.1 General Information” and include a subsequent section on “Nomenclature”, providing the international non-proprietary name (INN), the chemical or other names or codes defining the drug substance. Further a subsection on “Structure” has to be included which defines the structural formular and the molecular weight of the substance, or for substances which have biological or biotechnological origin the primary structure as well as higher order structures and if appropriate any post-translational modifications. Lastly, the subchapter should contain a section on “General Properties”, including the most important physio-chemical properties (e.g., solubility or pH and pK) of the defined substance (40).

In the following subchapter on the drug substance, namely “2.1.S.2 Manufacture”, according subsections have to be included on “Manufacturer(s)”, pointing out the name(s) and address(es) of the manufacturer(s) as well as on “Description of Manufacturing Process and Process Controls”. In the section mentioned lastly, for chemical substances a flow chart of the manufacturing process as well as the starting materials, intermediates, used solvents and reagents, at least for the last synthesis steps should be included. If biological or biotechnological substances are intended to be used the cell culture system ought to be described here as well as according purification steps and the storage of intermediates. Subsequently the section “Control of Material” has to be included, providing a list of all material used in the course of the manufacture with the according purity grade. For trials which include biotechnological substances this section has to include information on the according genetic development and the cell bank system in addition to their control regarding identity, purity and stability. Lastly, if there is information available on “Controls of Critical Steps and Intermediates” this has to be provided as well as “Process Validation and/or Evaluation” in sections 2.1.S.2.4 and 2.1.S.2.5 (40).

Further, in chapter “2.1.S.3 Characterization” subsections on “Elucidation of structure and other characteristics” and “Impurities” ought to be included. For chemical substances, the first subsection should contain a summary of available results and for phase II studies additional information on data and methods may be requested. In the

case of biological or biotechnological substances any information has to be provided that could contribute to the establishment of the primary structure or higher order structures as well as according biological activity, possible post translational modification or other transformations. In the “Impurities” section potential impurities, of chemical substances should be discussed, no matter where they arise from, and for biological and biotechnological substances process related and product related impurities have to be distinguished. In general, typical observed levels of impurities have to be listed in this section (40).

The following chapter, numbered 2.1.S.4, is dedicated to the topic “Control of Drug Substance” and should contain the subsections “Specification”, “Analytical procedures”, “Validation of Analytical Procedures”, “Batch Analyses”, “Justification of specification”, “Reference standards or materials” (this section is not required), “Container and closure system” (brief description of those) and “Stability”. The first subsection should contain the specification of the according drug substance as well as the methods which were used and related acceptance criteria which were applied. Further, upper limits for impurities should be set in this paragraph and justified regarding the safety of use. In the subsequent two sections covering analytical procedures concerning to the drug substance, reference can be made to Pharmacopoeias or, if the applied methods cannot be found in such, a summary of these should be provided. Again, for phase II studies data and methods may be requested. Additionally, it has to be demonstrated that the analytical methods used are suitable for the purpose. Subsequently, in section 2.1.S.4.4 the results of batch analyses have to be presented, if possible, in tabular format. Alternatively, certificates of analysis can be included for the batches of the substance used in non-clinical trials as well as for the batches or representatives of those of the drug substance which is intended to be used in the according clinical trial. Additionally, number and size of the batch as well as site and date of manufacturing, methods of testing, acceptance criteria and the results of testing have to be mentioned. In the following subsection, the choice of specification has to be justified with the description of according methods and acceptance criteria. Further, the limits of total as well as individual impurities should be mentioned again and be explained in reference to preclinical results. Lastly, in the terminal section of this subchapter, a summary of stability data and results in tabular form has to be included and storage conditions as well as a re-test period for the chemical substances of the trial have to be outlined (40).

In the second important chapter 2.1.P “DRUG PRODUCT” all information regarding the final drug product, which is used in the trial, has to be provided to Swissmedic. This firstly includes the subchapter “Description and Composition of the Drug Product”, wherein the formular of the drug product should be declared as well as the according composition (qualitative and quantitative). Subsequently it should also be described how the selected dosage form suits its intended use in the subchapter “Pharmaceutical Development” (40).

Further the subchapter “2.1.P.3 Manufacture” should include several subsections, which are “Manufacturer(s)” (should include name(s) and address(es) of manufacturer(s) and according control site(s), “Batch formula” (not required), “Description of Manufacturing Process and Process Controls” (should preferably contain a flow chart), “Control of critical steps and intermediates” and “Process Validation and/or Evaluation” (only for non-standard dosage forms). If sterile products are intended to be used in a trial, it has to be described in subsection “2.1.P.3.4 Control of critical steps and intermediates” what the strategy is to ensure product sterility (40).

Similarly, the subsequent subchapter “2.1.P.4 Control of Excipients” also consist of many subsections, namely “Specifications” (reference to Pharmacopoeias or certificate of analysis), “Analytical procedure” (reference to Pharmacopoeias or summary of non-compendial methods), “Validation of analytical procedure” (not applicable), “Justification of specifications” (not applicable), “Excipients of Human or Animal Origin” (standard formular available) and “Novel Excipients” (only if applicable, as outlined for Drug Substance) (40).
For the subchapter “2.1.P.5 Control of Drug Product” and its subsections “Specification(s)”, “Analytical procedures”, “Validation of Analytical Procedures”, “Batch Analyses” and “Justification of Specification(s)” the same requirements apply as for Drug Substance mentioned above. However, the subsection “2.1.P.5.5 Characterisation of the Impurities” is required in addition if there are any impurities which have not already been described in the “Impurities” subsection of the chapter “DRUG SUBSTANCE” (40).
Following, a short description of labelling and packaging of the drug product under investigation has to be added in the subchapter “2.1.P.7 Container Closure System” (40).

The last subchapter “2.1.P.8 Stability” should contain a tabular summary of stability studies as well as conclusions drawn from these. Furthermore, available data should be

evaluated and the proposed shelf-life of the drug product has to be justified, and it has to be defined under which criteria this shelf-life will be extended during the trial (40).

Lastly, the appendix “2.1.A.2 Adventitious Agents Safety Evaluation” should contain detailed information on Transmissible spongiform encephalopathy (TSE) safety and viral safety (40).
If any of the sections mentioned above are not applicable for a specific trial this has to be clearly marked by “NA” (66).

In general, no matter if a PQD or an IMPD is submitted, the document has to have a title, the version date has to be noted and sequential pagination is required. If the points mentioned are not the case for such a document, an Overview-PQD has to be included, which provides a listing of all sections with titles, numbers and version dates of each. Further, the Overview-PQD itself also has to have a version date as well as a title (66).

If the investigated IMP already has an CTA approved in Switzerland and if there is no new data available the same PQD or IMPD can be submitted. However, if there is new data there is the need for the submission of a summary of changes and/or a track change version, stating also why each change has been applied (66).

Generally, depending on previous assessments of an IMP regarding marketing authorisation in Switzerland or a GMP-equivalent country (for category B studies only in Switzerland), there are different requirements for the submission of quality data (66):

- If there is a marketing authorisation in Switzerland and the market batch is unchanged, there is no requirement for the submission of any documents. However, if the marketing authorisation is only in a GMP-equivalent country, the according SmPC or Product Information has to be submitted.
- If there is a marketing authorisation and the market batch is unchanged but the IMP will be blinded or modified in any way, the SmPC and Product Information are required, as well as the Drug Product part of the PQD or IMPD.
- If there is a marketing authorisation but the IMP is of another pharmaceutical strength or form the Drug Product part with appendices has to be included, as well as a simplified PQD or IMPD in which differences to the PQD or IMPD of the approved product form have to be explained. In addition to that, a summary table of every change in each sub-section of the Drug Product part and according

appendices has to be submitted and it has to become clear from that summary, that there were no changes in the Drug Substance chapter.

- If there is no marketing authorisation for the specific IMP, but the drug substance is already part of an authorised product and the IMP in question is provided by the same manufacturer, the requirements mentioned in the point above apply. Additionally, the country of reference of the IMP with the marketing authorisation has to be provided. However, if there are only differences to the authorised IMP which concern secondary labelling and packaging, a confirmation that the production of the IMP in question and the primary packaging are according to the marketing authorisation can be submitted in place of a simplified PQD or IMPD. This confirmation has to be from the marketing authorisation holder and has to include a list of all manufacturers responsible for secondary labelling and packaging. Further, the confirmation has also to be signed by the "Responsible technique" situated in Switzerland or by another qualified person.
  However, if the IMP is provided by a different manufacturer than the authorised one, both sections of the PQD (Drug Substance and Drug Product part) have to be submitted with according appendices.
- If there is no marketing authorisation, also both sections (Drug Substance and Drug Product part) have to be submitted.

Regarding placebos, the Drug Product part of the PQD with appendices has to be included in the application either as a separate document or as part of the PQD of the according active IMP. Furthermore, if AxMPs are intended to be included in a trial, data about the pharmaceutical quality of these has to be submitted conferring to the requirements of IMPs (66).

5.2.8 Proof of compliance to GMP

Similar to the pharmaceutical quality data of an IMP there are also different submission requirements for proof of GMP compliance depending on the assessment status regarding marketing authorisation of the IMP in Switzerland or another GMP-equivalent country. In the case of IMPs, so the actual drug products, these are the following (66,68):

- If there is a marketing authorisation and the market batch is unchanged, only with the addition of a reduced study label (consisting of number or name of the trial, patient number or randomisation number and name of sponsor, principal

investigator or CRO) there are no documents which have to be submitted regarding to GMP compliance.

- If there is a marketing authorisation and the market batch is unchanged, but the IMP will be blinded or modified in any way, either the manufacturing license of all steps of the production, which is currently valid and not older than 3 years has to be submitted. Alternatively, a GMP certification which is also not older than 3 years, a declaration by the qualified person or a document of the authority confirming the compliance of the manufacturer with PIC/S GMP which is also not older than 3 years can be included.
- If there is a marketing authorisation but the IMP is of another pharmaceutical strength or form the requirements mentioned in the point above apply, if the provider of the IMP is the marketing authorisation holder.
- If there is no marketing authorisation but the IMP is produced in Switzerland or in a GMP-equivalent country, again one of the four documents mentioned above has to be submitted. However, if the IMP is produced in any other country that is not recognised as GMP-equivalent a current (not older than 3 years) GMP-Certificate from the authority of this country has to be included in the application. In addition, one of the following documents, derived form a recognised country, has to be included in the submission: a GMP certification which is not older than 3 years, a document of the authority confirming the compliance of the manufacturer with PIC/S GMP which is also not older than 3 years or a current (again not older than 3 years) declaration by the qualified person on GMP compliance supported by an audit or the audit report itself.

Additionally, and if applicable, the import authorisation for the IMP has to be submitted in copy if the import of the drug product is not executed directly to the site of the trial (66). The requirements depending on the assessment status of a marketing authorisation in Switzerland or a GMP-equivalent country for active pharmaceutical ingredients, so drug substances, which are used for the manufacture of IMPs, are relatively similar to the ones for drug products (66).

However, there are also cases where the there is no marketing authorisation for the specific IMP, but the drug substance of the IMP is already part of another authorised product. If the drug substance in the IMP is provided by the same manufacture that already holds the marketing authorisation for another product with the same drug substance, only one document has to be submitted. This document is a confirmation of

the marketing authorisation holder, that the manufacture of the drug substance used in the IMP was in accordance with the marketing authorisation (66).

For AxMPs, there is no need for the submission of any documentation, if they have a marketing authorisation. However, if there is no authorisation, all the same documents have to be submitted as for drug products (66).

5.2.9 Trial product labels

If the intended clinical trial is of category B or C, exemplary IMP labels have to be submitted. The requirements for identification labels specifically for trial products are listed in the EudraLex Volume 4 Annex 13. According to this document, the subsequent information has to be included (68):

- contact information of the sponsor, the CRO or the principal investigator
- the batch number
- the name of the clinical trial or the according identification number
- the identification number of the trial subject and the according randomisation number
- the indication “For clinical trial use only”
- the required storage conditions for the IMP
- the period of use in the form of re-test date or expiry date
- the indication “keep out of reach of children” (only if trial subjects take the IMP home)
- instructions for the use of the IMP (reference can also be made to another explanatory document like a leaflet)
- the route of administration, dosage form, number of dosage units, and if the trial is an open trial, the name or identifier of the IMP as well as its strength or potency

However, in case of an application to Swissmedic the instructions for use have not essentially to be included on the label. The same accounts for the route of administration, dosage form and number of dosage units (66).

For clinical trials which fit the characteristics in Article 14 of Directive 2001/20/EC, so non-commercial clinical trials with no participation of pharma industry, in which the IMP is being bought directly from the market, there are specific requirements for the label used in the trial (35,68). Essentially, the name or number of the trial, the number of the trial subject and the according randomisation number and the name of the sponsor, the CRO or the principal investigator has to be included, preferably added to the box (66,68).

According to Swissmedic, the application dossier has to contain copies of the labels for primary (outer) and secondary (inner) packaging in Swiss national language. However, if the IMP is intended to be administered to the subject directly at the trial site by the investigator, the labels might also be written in English (66).

If AxMPs are used in the trial which have a marketing authorisation in a recognised GMP-equivalent country or Switzerland itself and the packaging is in Swiss national language, there is no need for the submission of study-specific labels. However, if this is not the case, labels have to be submitted as for IMPs (66).

5.2.10 Other or additional documents

If there are any other relevant documents available related to the trial which might influence the approval process by Swissmedic (e.g., any scientific advice of a foreign competent authority), these also may be included in the application (66).

5.3 Required Documents for Swissethics

The documents required for Swissethics depend on the type of clinical trial and uploaded by the applicant and automatically displayed by the online portal Business Administration System for Ethics Committees (BASEC) after entering information about the intended study (69). In general, the documents shall comply to a number of international guidelines such as ICH-GCP, similar to the requirements of European ECs (63). For simplicity, these intersecting requirements will not be mentioned again in this chapter. However, there are also specific templates provided by Swissethics in BASEC for some of the required documents (70).

5.3.1 Research application form

The application form, which has to be submitted to Swissethics, is implemented in the electronical submission system BASEC. In that, sections have to be filled out about basics and origin of the project, funding and further detailed information, like the phase, type, requested category of the study and reasons for the requested category. In addition, information for the Swiss National Clinical Trials Portal (SNCTP) has to be provided, including a summary of the protocol (65,71).

5.3.2 Cover letter and information on reviews by other ECs or competent authorities

Likewise, as in all previously mentioned applications, also the submission to Swissethics has to contain a cover letter. In general, this letter can be quite freely configured and is obligatory for all three categories of clinical trials (72,73). However, there are a few things which should be contained regardless. Firstly, the type and the reason for the submission has to be stated. Further, if there are any previous studies related to the current submission, reference to those has to be made in the cover letter. In the case of multicentric clinical trials, the lead EC has to be depicted as well as a list of all additional ECs involved (74). In addition to that, Swissethics requires any information on reviews, already completed or not, from competent authorities or other ECs, if available. These can be submitted in a separate document or can also be mentioned in the cover letter (73).

5.3.3 Study Plan (Protocol) + Synopsis of the Study Plan

A separate synopsis of the study plan is not required for clinical studies, if it is already included in the protocol. In this case, references should be made in this section of the BASEC (71). In general, the submitted protocol has to be dated and signed by the investigator. It is strongly recommended by Swissethics to develop the protocol according to the template provided on BASEC and the Swissethics website. This template is in compliance with the Swiss Federal Act on Research involving human beings (HRA) and applicable ordinance, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement from 2013, the section 6 of the ICH-GCP Guidelines E6(R2), the Annex A of the ISO standard 14155:2011 for Clinical investigation of medical devices for human subjects – Good clinical practice and the MEDDEV 2.7/3 revision 3, May 2015 (75–79).

According to this template, the study synopsis should be contained in the protocol in tabular format, summarising the most important information about the trial, followed by the study schedule intended to be used. The first chapter of the protocol should include information on the administrative structure of the study, so on the staff, monitoring institutions and any other relevant organisations, persons, committees or institutions. Further, the protocol should include any ethical and regulatory aspects, such as study registration, categorisation of the study, competent ECs and competent authorities, a statement about the ethical conduct of the study, the declaration of interest and the

procedure of patient information and informed consent as well as the procedure with protocol amendments (75). Notably, regarding the study registration it is stated in the HRA that any authorised trial has to be chronicled in a public registry (76). The according Ordinance on Clinical Trials in Human Research also regulates the declaration of interest by prohibiting the missing disclose of any conflicts in any state of the trial. Following the chapter about ethical and regulatory aspects, information about the background and the rationale of the trial should be given, namely research question, summary of relevant previous studies, disease background and purposes of the study (65).

Further, the section of the protocol should include subsections on the IMP itself, according preclinical and clinical evidence which is relevant, the dose rational, an explanation for the choice of the comparator or placebo, risk/benefits of the treatment and a justification of the choice of the study population, especially when there are vulnerable subjects intended to be included in the trial. Subsequently, study objectives and study outcomes should be addressed (65).

A very important part of the protocol is the study design. In this section, every detail on how the trial is intended to be conducted has to be provided. This includes a general summary of the design and a justification for the chosen design, methods of minimising bias (e.g., randomisation and blinding procedures) as well as the according unblinding procedures (code break) (65). Notably, Swissethics requests patient codes to not include the initials or the full date of birth of the subject (80).

Furthermore, details on the study population have to be included by providing information on eligibility criteria (inclusion and exclusion criteria), the recruitment and screening procedure, the assignment of subjects to study groups and criteria and procedures for withdrawal or discontinuation of participants. In addition to that, all the information regarding the study intervention has to be given which comprises the identity of all IMPs, so the experimental intervention as well as the control intervention and according packaging and storage conditions, the administration of those IMPs, the dose and when and why they might be changed, procedures for monitoring patient compliance, procedures of data collection and follow-up on withdrawn participants, any specific preventive measures (e.g., rescue medication), permitted and not permitted concomitant interventions and treatments, drug accountability and return or destruction of the IMPs (40,65,77,78).

In the subsequent chapter the procedures of the study, the procedures at each visit, the measurements of outcomes, as well as the collection and storage of samples and any other relevant information regarding these topics has to be provided (40,65,77,78).

Furthermore, according to the template, the subsequent 10th chapter should be on the safety of the IMP(s), addressing the definition, assessment, reporting and follow up of any safety related events (40,65,77,78).

Subsequently, statistical methods including the hypothesis, procedures for the determination of the sample size, statistical criteria for the termination of the trial, planned analyses as well as the handling of missing data and drop-outs have to be described (40,65,77,78).

In the following chapter, measurements taken on quality assurance and control have to be included in the protocol, which comprises general information on data handling and record keeping, a description of case report forms, the identification of source documents and details on data management and monitoring procedures including audits and inspections, data protection and the storage of samples and health data. Also, the publication and dissemination policy of the trial has to be described if it is not addressed in a separate document. Lastly, any funding or other support has to be stated in the protocol as well as insurance agreements, if not submitted as a separate document (40,65,77,78).

5.3.4 Participation information, informed consent and recruitment documents

Regardless of the category of the submitted clinical trial the participant information sheet as well as the informed consent form (ICF) has to be included in the application to Swissethics (73). As for many other documents, there is also a template available for informed consent on the Swissethics homepage, which is strongly recommended to be used (81). The template is based on the Federal Act on Research involving Human Beings (HRA) and according ordinances and should contain an abbreviated form of the detailed information as outline for the oral consultation with the subject. This abbreviated form should only contain the essential information for subjects, be geared to the subject's point of view and be in an easy language (82). For the latter purpose, there is a glossary for medical terms and according abbreviations available on the website of Swissethics for German and French to make the informed consent form more comprehensive (81).

The abbreviated form as guideline for oral consent should address who the sponsor is, that the participation is completely voluntary, why the clinical trial is conducted, what the duties of the subject are and what will happen to the subject in case of participation and the benefits and risks for the subject. In general, the following detailed information including the consent should not be longer than 16 pages (82).

According to the HRA oral and written information has to be given to a potential subject on the nature, duration and purpose of the trial as well as according procedures, possible risks and burdens, expected benefits for themselves or others, measures taken for the protection of personal data and their rights in general. It is further stated that potential subjects have to be given an appropriate period of time for reflection before their decision (76). The Ordinance on Clinical Trials in Human Research (ClinO) extends the points potential participants have to be informed of, mentioned above, by the following (65):

- if there are any alternatives to the intervention used in the trial
- duties and effort of the participant
- the right of the subjects to not give consent or revoke their consent without reasoning and without any disadvantages
- consequences of the revocation of their consent regarding subsequent medical treatment and further use of biological material and personal data already collected
- the right of subjects to receive further information on the clinical trial at any point (time)
- the right of the subjects to be informed about any results with regard to their health if they want to, or to designate someone to decide for them
- measures taken to cover damage which might arise from the trial including the case of a claim
- the sponsor and sources of financing
- any other points which might me relevant for their decision

In accordance with national laws, the template for informed consent includes sections with detailed information on the purpose of the trial and the selection of appropriate participants, general information on the trial (type of study, duration, treatment, situation of authorisation etc.), procedures of the trial, benefits of participation, voluntariness of the participation and obligations of subjects in case of participation, risks and burdens, alternative treatments, results of the trial, confidentiality of personal data and samples

(including data handling and coding, protection of samples, data protection in the case of potential further use, data protection in the case of genetic analysis and the right of access in case of inspections by Ethics Commissions, Swissmedic or the sponsor), withdrawal, compensation for subjects, accountability, financing, contact persons and a glossary. Subsequent the detailed information, the declaration of consent has to be added, which has to have positions for the signatures of the subject and the investigator. In the case of further use of samples or personal data, a second declaration of consent has to be included as well (82).

Special attention has to be paid to clinical trials involving persons who are not able to give consent themselves. In any case, effort has to be made to get consent from the concerned person to the extent possible. In trials with minors, a legal representative has to give their written consent, but also the consent from the child has to be obtained, in the case of adolescents even in written form. If persons who lack capacity are intended to be included in a clinical trial their consent also has to be obtained as far as possible, while in a state of capacity. In addition, the legal representative, the next of kin or a trusted person has to give written consent and the concerned person should not show any opposition e.g., verbally or in their behaviour to the research intervention (76).

For clinical research in emergency situations the sponsor and investigator have to take according measures to make sure that post hoc consent is obtained from the concerned person or a legal representative as soon as possible (65). Further, the patient in an emergency situation can only be included in the trial if there is no expression of opposition, verbally or in his or her behaviour and if an independent physician is present, safeguarding the interests of the patient. However, there are rare exceptions where the physician can be called later on (76).

Additionally, apart from the informed consent procedure, any other documents which are intended to be handed over to potential or already included subjects have to be submitted to Swissethics, if available. This includes for example advertisements for the recruitment process, questionnaires, patient journals, recruitment letters, scores, translations of study documents etc. Further, also details on the intended compensation for trial subjects, including nature and value/scope, have to be provided either in the patient information form or in a separate document. This is obligatory for clinical trials of any risk category (71,73).

5.3.5 Case Report Form (CRF)

The Case Report Form intended to be used in the trial to collect data of the patients has also to be reviewed by the lead EC, regardless of the clinical trial's category. There is no according guideline or template available on Swissethics. However, it is accepted to only submit a draft of the CRF in the initial application and provide the final document within 30 day for monocentric trials and withing 45 days for multicentric trials (73).

5.3.6 Investigator CV, proof of GCP training and suitability of the site

Another document required regardless of the category of the clinical trial is the investigators or project leaders' CV. Notably, this document has to be dated and contain evidence of the investigator's knowledge and experience (65,73). However, the according GCP training of the investigator has to be proven in a separate document (73). A list of all GCP courses, of which the course certificates are recognized by Swissethics can be found on their homepage (83). However, if a researcher has a not-recognized or a foreign GCP certificate, the person has to attend one of the recognized courses. In general, an investigator of a clinical trial should have a certificate of a course on Investigator Level, whereas if the investigator is also the sponsor a certificate of an Investigator Level+ or Sponsor-Investigator Level course is required (84).

Additionally, a list of all people that are involved in the trial but are not mentioned in any other document, called staff list, might be submitted optionally. However, the lead EC might request a staff list nevertheless, if a trial is a high-risk project (e.g., phase I clinical trials) (71). The staff list should contain the full name, education, actual function in the trial, study task/responsibility as well as information on possible GCP training for each person with an important role in the trial (65,71).

Regarding the suitability and availability of the site where the trial is intended to be conducted, it is optional to submit an according document for trials of all categories. According to the template available on the Swissethics homepage, information should be given on the study team and organisation regarding the experience with clinical trials of the staff involved and any participating departments, clinics or if applicable external institutions like laboratories, pharmacies etc. Further, the suitability of the infrastructure in terms of resources and facilities, e.g., rooms and equipment, and emergency care has to be addressed. Another important point for the suitability of a site is the number of patients that are treated per year at the site in the indication under research and the

intended number of patients to be included in the clinical trial. Lastly, also the research activity of the site has to be addressed, namely the number of studies already ongoing in general and more importantly in the same indication and how overlapping studies will be handled (85).

5.3.7 Agreements

Any agreement, if available, between the investigator and the sponsor, a commissioned institution, the grant provider or any other third party has to be submitted to the lead EC, regardless of the category of the trial. These agreements should concern the financing of the trial, the allocation of the different tasks in the trial, the compensation to the investigator and the publication (71,73). A template for such an agreement is again available on the Swissethics homepage (86). According to this template, the investigator has to declare that the study will be conducted according to the site policy, laws and regulations which are applicable as well as the study protocol. Further, the total amount of compensation to the investigator and the timepoints of receipt should be regulated in the document. Other points which should be included in the agreement contract are the time of applicability and the procedures for termination of the agreement as well as procedures for indemnification, publication and confidentiality, especially in multi-centre studies. In addition to that, the topic of intellectual property has to be included and agreed on. The agreement has to be signed and dated by the site/principal investigator and the sponsor (86,87). However, the submission of a draft is accepted as long as the final document is made available prior to the inclusion of the first subject, so within the next 30 days for monocentric trials or the next 45 day for multicentric trials (71,73).

5.3.8 Insurance

For clinical trials of category B and C, it is mandatory to submit information on insurance and liability coverage to Swissethics, while for category A trials this is only necessary if the methods used for the collection of personal health data or biological samples can cause more than merely minimal stresses and risks (73,88,89). According to the Ordinance on Clinical Trials in Human Research it is required for liability coverage that the sponsor either takes out insurance or provides another security that has equivalent value. In any case, the coverage has to apply to any damage, which might occur within 10 years after the clinical trial was completed (65).

For Category A trials, the minimum policy values should be 250 000 Swiss francs per person, 20 000 Swiss francs for potential damage to property and 3 million Swiss francs for the entire trial. Further, for any other clinical trial the minimum policy values should be 1 million Swiss francs per person, 50 000 Swiss francs for potential damage to property and 10 million Swiss francs for the entire trial (65). Namely, the documents which have to be submitted to the lead EC to prove proper liability coverage are the General Insurance Conditions (GIC) for clinical trials in Human Research and the Insurance for clinical trials certificate (73).

The GIC document is generally a contract between the insurant/sponsor and the insurance company. It contains general contract data like the policy number, the policyholder, the sponsor, the insured clinical trial, the number of participants, insured amounts, policy period etc. Further, the insured interest should be defined, meaning the liability of the sponsor for bodily injury of a participant, including losses caused by a violation of data privacy and property damage, occurring in connection with the insured trial. In a similar manner, the procedure of the insurer's indemnification, the insured person (the sponsor), territorial limits and triggers as well as limitations of coverage have to be defined. Additionally, the procedure of the calculation and the payment of the premiums has to be agreed on in the contract. What also has to be covered are procedures in the case of claims, including the duty to notify of the insured, the handling of claims and litigation, the assignment of right to injured or third parties, remedies for breach of duties and the possibility of recourse (89,90).

Importantly, also the duties of the policyholder/sponsor, to obtain confirmation from the study subjects to immediately inform the investigator of any illnesses, symptoms, other treatments or bodily injury and to undergo all measures for determination of the cause of these, and according procedures in case of a breach of these duties have to be defined (89,90).

Further topics that have to be agreed on in the GIC contract are the policy period, the abdication of the termination in the event of claim, notifications to the insurer, data protection and the place of jurisdiction and applicable law. The GIC contract has to be signed and dated by the insurer and the policy holder (89,90).

The certificate of insurance for the attention of the Swiss Association of Ethics Committees has to be issued by the insurer, who has to confirm herein that insurance coverage is provided to the sponsor/policyholder in accordance with the present document, the provisions in the policy and the HRA and Ordinance on Clinical Trials. In general, the certificate should contain information on the insurer, the policyholder and/or sponsor (if the sponsor is not the policyholder), the insured risk (type and category of the clinical trial trial), the name of the trial, the number of participants, the policy number, study reference, insured amount, duration and claims handling by the insurer. Importantly, the certificate of insurance is only valid with signature and stamp of the insurer (88,89).

5.3.9 Information on secure handling of biological material and personal data

According to the Ordinance on Clinical Trials, the responsibility for taking appropriate measures for health-related data protection lies with every person who stores this data in the course of a clinical trial. Particularly, it is obligatory to restrict the right of handling personal data to persons who require the health-related data for their work in the trial. Further, measures have to be taken to prevent any accidental or unauthorised alteration, copying, disclosure or deletion of stored personal data and any processing operation has to be thoroughly documented to ensure traceability. Notably, the same principles apply for storage of any biological material in connection with a clinical trial. Additionally, the responsible person also has to ensure the suitable storage of biological samples and make according resources available (65). All these measures taken have to be described in a document and be submitted to the EC. However, there is also the possibility to make reference to any other document which might already contain the according information (e.g., the study protocol) (71,73).

5.3.10 Proof of proper labelling, GMP compliance and deviation from prescribing information

To prove that the labelling of an IMP used in a clinical trial is appropriate, a description of the according study specific label and/or a sample thereof has to be included in the submission for category A clinical trials. In the case of a category A clinical trial where non-proprietary products (e.g., repacked IPMs) are used, some proof of GMP compliance has also to be included additionally. The according documents of proof are mentioned in 5.2.8 Proof of compliance to GMP. Additionally, a document describing the deviation of the usage of the IMP according to the study protocol from the prescription information in a clinical trial of category B has to be submitted (73). However, in the latter

case reference can also be made to the study protocol itself if the information is included there (71).

5.3.11 Investigator's Brochure (IB)

Similar to the submission to Swissmedic, the application to Swissethics has to contain the current version of the IB for studies with IMPs that have no marketing authorisation in Switzerland, so category C studies. Notably, the IB explicitly has to comprise information on current clinical as well as non-clinical data on the IMP and all of its compounds (73).

5.3.12 Additional documents

In addition to all the documents mentioned above, there are still a few more requested by Swissethics. Firstly, a monitoring plan is required, if applicable, for clinical trials of all categories. However, if the final version is not available at the time of the submission, a draft version as well as a general outline of the monitoring strategy is also accepted (73). In any case, it is also possible to refer to another document that includes this information e.g., the study protocol. Further, for clinical trials of the categories A and B any relevant professional product information, which was already approved by Swissmedic has to be submitted. In the case that a CRO or the representative of the sponsor acts as applicant, the submission has to include a delegation letter of the sponsor. However, if this is already regulated in a contract, reference can be made to that document as well (71).

If it is applicable, a Pharmaceutical Quality Dossier for the non-IMPs used in the clinical trial will be requested in addition. This document should fulfil the requirements of Swissmedic mentioned in 5.2.7 Pharmaceutical quality documentation of IMP. Any additional documents, which the applicant wants to submit, should be uploaded under the section Miscellaneous/Varia. However, attention should be paid that solely documents that strictly do not belong to any other category mentioned above, can be submitted here (73).

5.4 Application Procedure

The application of a clinical trial to Swissmedic can be submitted in parallel to the application to Swissethics for studies of the categories B and C. Both agencies have to give their approval before the clinical trial can start. In the case of category A trials, there is no need for an authorisation from Swissmedic (65,66,91). For the application to

Swissmedic an A4 hard copy of each document, including cover letter and application form, has to be submitted in a folder. The required colour for this folder changes every year and the current requirement can be found on the Swissmedic homepage. Further, the folder has to be a ring blinder with 2 perforations and a spine width of 7 cm. The documents in paper form have to be punched and placed into the folder according to the sequence of the headings in chapter 5.2, divided by a 20-tab file divider, which has to be numbered. The application documents have to be filed in sections 1-10 and sections 11-20 have to be left empty so they can be used by Swissmedic (66,91). Notably, also the submission of the documents in electronic form e.g., on a CD is required. Similar to the organisation in the hard copy folder, the electronic files of the documents also have to be filed into folders numbered from 1-10, according to the sections in chapter 5.2, and named reasonably (66).

After submission, Swissmedic should confirm the receipt of the clinical trial application dossier and contact the sponsor about any detected formal deficiencies in the submitted documents. From the day that the agency confirms the receipt of the complete and formally correct application dossier, a decision should be reached within 30 days. However, if the IMP intended to be used in the trial is being used for the first time in humans or if the manufacturing process is new, Swissmedic might extend the review period to a maximum of 60 days and has to notify the sponsor about the extension. The agency also has the possibility to request further information to come to a decision. If this is the case, the clock is stopped until the requested information is provided by the applicant. After a decision has been reached, it is the responsibility of the agency to inform the according EC as well as further competent cantonal authorities about that decision (65,66). Notably, a fee has to be paid to Swissmedic by the applicator, according to the current version of the Ordinance on Fees levied by the Swiss Agency for Therapeutic Products (92,93).

The application to Swissethics has to be submitted via the online portal BASEC, no matter in which canton(s) the trial will be conducted (94). Since the Human research act of 2014, all ECs in Switzerland use BASEC for receiving and managing their research projects. The applicant has to sign into the portal and fill in several screens regarding the clinical trial before getting to the upload section, where they should provide all necessary documents (95). Notably, during the submission process BASEC will automatically ask for the required documents depending on the applicant’s entries on the first 3 screens

and therefore the selected project-type (73,94). Similarly, the responsible EC is determined depending on the canton where the research is intended to be conducted (76). After the submission of the application, the EC should confirm the receipt within 7 days and, if there are any formal deficiencies of the submitted documents, notify the applicant about these. Once the EC has received a formally correct application and confirmed this receipt, it should reach a decision no later than 30/45 days after. However, the EC might request additional information, if required for their decision. In this case, the clock is stopped until the receipt of the additional information. After reaching a decision, the EC should inform the corresponding agency, if the clinical trial reviewed is of category B or C (65).

In the case of multicentre clinical trials (carried out in different cantons), the coordinating investigator is responsible for submitting the application to the lead committee. A coordinating investigator in Switzerland is the person who is responsible for coordinating all investigators at the specific sites where the trial is conducted (65). For such multicentre trials, authorisation is required from the lead committee, which is the EC responsible for the canton where the project coordinator is active. Similar to monocentric trials the lead committee should confirm the receipt of the application documents no later than 7 days after submission and notify the investigator about any formal deficiencies. During the review period the lead committee should contact further ECs concerned, so the ECs responsible for the cantons where the different trial sites are situated, to seek their opinion on the fulfilment of operational and professional requirements (76). To do so, the lead committee can request the coordinating investigator to submit copies of the application documents to the concerned ECs as well. These then should communicate their assessment of the local conditions to the lead committee within 15 days. Because of this time period, the final decision of the lead committee should be reached within 45 days after confirmation of receipt of the application documents, which were formally correct (65). If the decision of the EC contains conditions, the applicant has to upload the reviewed or additional documents again in BASEC, where they will be assessed again as soon as possible, but within 45 day the latest (96). Further, the lead committee shall communicate its decision to the applicant via mail, to other ECs concerned and to the agency ,if the reviewed clinical trial is of category B or C (65,96). Notably, there is also the need to pay a fee to Swissethics, which is based on a harmonised tariff system. Therefore, the EC(s) will send an invoice to the indicated billing address, which has to be paid within 30 days upon receipt (97).

5. 5 Comparison to the procedure in EU countries (Austria)

In summary, the procedures regarding the submission of clinical trials to competent authorities and ECs in non-EU countries (example Switzerland) and EU countries (example Austria) are superficially quite similar. However, there are still quite a few major differences. One of these is that while Austria has 7 possible lead ECs and 17 additional local ECs, Switzerland has 7 different cantonal ECs and all of them can possibly be lead ECs (43,57,61). Further, an umbrella organisation like the FOPH in Switzerland, responsible for coordinating the competent authorities and the several cantonal ECs, does not exist in Austria (64). Notably, the international guidelines that the agencies and ECs in both countries follow are the same, namely the Declaration of Helsinki and the ICH-GCP guidelines. However, of course there are quite a few national laws which have to be considered in both countries (43,60,63,98). One of the main differences in the application procedures between the two countries is the classification of clinical trials into different risk categories and specific requirements regarding the submission of documents. In Switzerland clinical trials are categorised into risk categories A, B and C, all of which are connected to specific submission requirements (65). In Austria, only non-interventional studies (NIS), which are studies with approved IMPs that do not involve additional diagnostic or therapeutic procedures or additional burdens for patients, are distinguished form studies with unapproved IMPs (c.f. AMG§2a Abs. 2) (6,99). Further, the countries require different application forms. While in Austria the EudraLex CT-1 application form is accepted by both, the competent authority and the EC, in Switzerland there is a separate trial application form for Swissmedic and the application form for the EC is interactively integrated into the online submission system BASEC (39,49,50,65,66,71). In addition, the Austrian EC also requests a national application form, specific for the country (49,50).

Interestingly, for a submission to Swissmedic it is necessary to submit any correspondence related to the clinical trial between the sponsor and Swissmedic itself, any foreign competent authority and the responsible ECs, while there is no such necessity for the submission to the BASG (65,66). In case of information about the according IMP intended to be used in a clinical trial, there are also different documents required for the two competent authorities. In Austria, the BASG requests the European IMP or non-IMP dossier, while Swissmedic demands a document called Pharmaceutical Quality Dossier. However, a European IMPD will also be accepted in Switzerland. Additionally, while information on GMP is contained in the IMPD, Swissmedic requests

a separate document that proofs GMP compliance (41,66). However, also in Austria documents about GMP and the manufacturer have to be submitted, if the IMP has no marketing authorisation in the EU and is also not manufactured in the EU (41,47). An additional document which is needed for an application to the competent authority in Switzerland but not in Austria are the trial product labels for the IMPs used in the trial (66). Conversely, an application to the BSAG can optionally contain a copy of the informed consent form and has to contain a proof of payment of the according fee for the submission, while in Switzerland, there is no need for a proof of payment document. However, the informed consent form is reviewed by ECs in both countries (41,44,73).

Additionally, regarding the submission of a trial to the national ECs, there are some differences between the two countries. Firstly, a document which is obligatory for a submission to an EC in Austria but not in Switzerland is a confirmation of the payment of the according fee for a submission (50,51). Conversely, Swiss, but not Austrian ECs, request proof of proper labelling, detailed separate information on handling of biological material and personal data and a monitoring plan (if not included in the study protocol), as well as a PQD for non-IMPs. However, information on handling of biological material and personal data should be contained in the ICF of a submission to Austrian ECs (71,73). Additionally, in Austria it is sufficient to submit a draft of the contract with the investigator to the EC, whereas Swiss ECs request the signed contract to be submitted before the according meeting. In conclusion, the documents required for an application of a clinical trial to Austrian versus Swiss competent authorities and ECs are similar and the differences present are not fundamental (39,66,91).

In addition to that, also the procedures and timeframes for the submission of clinical trials to competent authorities and ECs differ in some points. For example, the submission of documents to the BASG has solely to be electronically while Swissmedic requests an electronic form as well as a hard copy folder (39,66,91). Furthermore, the time of assessment for the competent authority in Austria is 35 days, while in Switzerland it is 30 day and can be extended to 60 days under certain circumstances. In case of objections or request of further information during the scientific assessment, in Austria the sponsor and the competent authority have to agree on a timeframe to adjust the application, while in Switzerland the clock is simply stopped until receipt of the requested information (39,65,66). Notably, in Switzerland it is also only necessary to get approval from Swissmedic if the intended clinical trial falls within category B or C. (60,61,86).

Furthermore, in Austria there are NISs, which are similar to category A trials in Switzerland. For these NIS, a registration of the trial is usually sufficient and if an approval is necessary, the procedures for NISs also differ from the procedures for interventional studies (99). However, the procedures of assessment of formal completeness are the same (39,65,66).

With regard to the procedure of a submission to responsible ECs in Switzerland and Austria, there are also a few differences. However, one similarity is that both countries try to harmonise the procedure between the different ECs by umbrella organisations, namely the Forum of Austrian Ethics Committees and Swissethics (43,71). Further, both require an online submission via a portal (ECS and BASEC), whereas in Austria two of the Lead ECs (EC of Lower Austria and EC of the City Vienna) do not participate and still require a submission via e-mail, CD or paper. Additionally, in Austria part B of the Austrian EC application form has also to be submitted in paper in any case, because of the requested original signature of the investigator. (43,50,58,69).

Regarding the timeframe for the conformation of receipt of the formally correct application Austrian ECs have 5 days while Swiss ECs have 7 days (57,65). In addition, one major difference is the importance of the monthly meetings in Austria, after which the due date of the submission is directed and to which the applicant or investigator may be invited to answer questions and give statements about the trial (50,58). For that reason, the assessment period for Austrian ECs is 35 days in any case, while for Swiss ECs it is 30 days for monocentric and 45 days for multicentric trials (35,65). In multicentric trials in Switzerland, the time period is extended compared to monocentric trials, because the local ECs have 15 days to communicate their vote to the lead EC and if they are not capable of doing so, the assessment is made without the opinion of that local EC (65,96). In contrast, in Austria, the local ECs can communicate their vote until 5 days before the monthly meeting and if they do not do so, the Lead ECs just takes that as a positive vote (6,57). Further, in Austria, Lead ECs can request additional information only once, while in Switzerland there is no such regulation (35).

Another important difference is the determination of the responsible Lead EC. In Austria, the only requirement for the applicants chosen Lead EC is that at least one trial site is in the geographical purview of the EC. Conversely, in Switzerland the Lead EC has to be the EC responsible for the canton in which the coordinating investigator of the trial is

active (57,76). Further, the documents have to submitted to the Lead EC and local ECs simultaneously in Austria, while in Switzerland one submission to BASEC is sufficient as local ECs can also be reached via the portal, which makes the submission less labour-intensive (57,65).

It can be concluded that the procedure of the submission to ECs is more different in the two countries than the submission to the component authority and the required documents for both institutions.

6. Changes in submission process in relation to the COVID-19 pandemic in EU and non-EU countries

The COVID-19 pandemic with the SARS-CoV-2 virus, which had reached Europe in early 2020, had an impact on basically all aspects of social and professional life, especially the scientific and health care sector. Naturally, also the impact on the conduct and initiation of clinical trials was immense, due to for example quarantine of participants, limited access to hospitals, risk of spreading and health care workers being committed to other critical tasks (100).

To ensure continuing high standards of clinical research and especially trial subject safety during the health crisis, the EMA quickly published an according document, the "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic". The guidelines were established in cooperation with the Good Clinical Practice (GCP) Inspectors Working Group (GCP IWG), the Clinical Trials Expert Group (CTEG), the Clinical Trials Facilitation and Coordination Group (CTFG) and the European Commission and are updated regularly. Notably, the CTFG is a working group of the Heads of Medicines Agency (HMA) and the CTEG is a working group of the European Commission, in which ECs and national competent authorities are represented (100). Interestingly, Austria (as an example for an EU country) and Switzerland (as an example for a non-EU country) both based their national guidelines for the conduct of clinical trials during the pandemic on the according EMA guidance document (101–103). However, the EMA indicates that also national legislation has to be followed, even though the guidance document was intended to include most current guidelines of the Member States of the EU, to serve as a harmonised recommendation. Further, the guidance is only valid until its revocation, when there is consensus that the COVID-19 outbreak in Europe has passed (100).

Regarding the initiation of new clinical trials, the EMA states in the guidance document that sponsors, investigators and possible other relevant parties should critically assess whether the start of a new trial is immediately necessary and feasible. Further, any additional risk arising to subjects from the participation in the trial and appropriate risk mitigation measures have to be addressed in the protocol, more specifically in the according benefit-risk section. Especially the safety of trial participants, which are part of a risk-group for COVID-19 or participants in trials with treatments increasing these risks, should be strongly considered before deciding to start such a clinical trial. In general, any

submission for a clinical trial regarding treatment or prevention of COVID-19 will be prioritised before any other submission by the competent authorities (100).
The Austrian Forum of Ethics Committees even recommends to not start any clinical trial during the pandemic, except for trials with regard to treatment, diagnostics or prevention of COVID-19. In accordance with that, submission of clinical trials regarding treatment or diagnostics of COVID-19 and submissions of trials regarding the development of vaccines, have the highest priority for the examination by Austrian ECs. The second highest priority are submissions of clinical trials regarding data collection for a gain in knowledge concerning COVID-19, followed by any other submissions of clinical trials. Notably, there is the need for extended risk management by the sponsor and investigator for any clinical trial during the health crisis, according to the Austrian ECs. Generally, in Austria questions regarding formal execution of trials should be directed to the competent authority, while questions regarding informed consent should be discussed with the responsible EC (101).

Further, the Forum of Ethics Committees in Austria relegates to the AMG, where it is regulated that sponsor and investigator have to implement certain measures immediately, if the safety of trial participants might be impaired, and inform the BASG and responsible EC about it (6,101). (c.f. AMG §37a Abs. 4).

Similar to the procedure in Austria, also the Swiss authorities Swissmedic and Swissethics prioritise applications for clinical trials with IMPs for the treatment of COVID-19 and suggest to not include any trial subjects in other trials during the pandemic. Hereby, an exception is made for patients with life threatening diseases, without any other treatment option. Further, the authorities request the sponsors of such trials to submit a complete dossier, which is also high in quality, to ensure a most efficient review of the application. Due to the fact that many applicants might work from home throughout the health crisis, Swissmedic abstains form the submission in paper form and accepts a fully electronical submission via email. This email should contain the note “COVID-19”, if the trial is connected to the disease, as well as the note “Submission_CTA_xxxxxxx” in the subject line. Nevertheless, the applicant still has to provide the documents in paper format as soon as possible, together with a cover letter, in which it is stated that the dossier has already been submitted electronically (102).

In general, as any trials regarding prevention or treatment of COVID-19 and related diseases should be given priority in recruiting new subjects, there is also the need to revisit the informed consent procedure, as some subjects might be in isolation. The sponsor therefore should seek advice on alternative procedures to obtain informed consent, if physical consent is not possible e.g., because it cannot leave the isolation room of the patient. In such cases, as written consent is not possible, oral consent has to be obtained from the participant, while an impartial witness is present. The witness further has to sign and date the according informed consent form and the investigator has to record reasons for the selection of the specific witness. In addition to that, it would also be possible that the subject and the person who is obtaining the consent, sign and date a separate information sheet each. However, in both cases a correctly dated and signed consent form should be obtained from the participant as soon as possible (100).

Similar to the considerations regarding informed consent, also topics as the distribution of the IMP and the possible delivery to subjects' homes and any changes to usual monitoring or auditing procedures have to be assessed (100).

In the case of monitoring procedures, especially in trials involving COVID-19 prevention or treatment, there is for example the possibility of remote source data verification (SDV), which should focus on the control of the quality of critical data e.g., primary efficacy data and safety data. Secondary efficacy data should only be monitored if it does not result in an increased burden for involved site staff. However, every sponsor should carefully assess the extent and nature of remote SDV needed for each trial and consider the extra burden, which would be put on the site staff with the introduction of alternative measures. Further, if remote SDV is foreseen in a submitted clinical trial, this has to be stated in the initial protocol and the informed consent form of the application (100,102).

However, according to the BASG, Austria is still very critical of remote SDV, despite the recommendations at EU level, because there is a lack of experience and deficits in the establishment of the according technical requirements. Further, the access to trial centres is possible for monitors in Austria. Therefore, the regulations for remote SDV have been adapted as follows. In Austria, remote SDV is only possible if the IMPs investigated in a trial are for the treatment or the prevention of COVID-19 or according sequelae, or for phase III trials on IMPs for the prevention or treatment of life-threatening or serious conditions, and in specific situations in which a lack of SDV may lead to

unacceptable risks to the safety of the subjects or the integrity and reliability of trial data. In addition to that, if remote SDV is intended to be introduced, it has to be approved as a substantial amendment by the BASG and the intended introduction has to be mentioned already in the cover letter (103).

Notably, the submission and conduction of large, multinational clinical trials involving new treatments for COVID-19 is highly supported by Member States of the EU and the EMA. Therefore, the EMA encourages sponsors of such trials to submit their applications via an accelerated Voluntary Harmonisation Procedure (VHP) (100).

The VHP and according guidance has been developed by the Clinical Trial Facilitation Group (CTFG) to organise the coordinated assessment of multinational clinical trials in different Member States and will be discussed in more detail in the subsequent chapter 7 (104). However, to minimise harmonised review times, sponsors ought to contact the reference national competent authority in advance, to discuss the feasibility of such an accelerated VHP process. Similarly, the EMA invites developers of vaccines or medicines for COVID-19 to contact the organisation as soon as possible via a provided e-mail address and offers a fast-track and a full fee waiver procedure for scientific advice to them (100).

Scientific advice from the EMA, on appropriate measures to generate robust data and evidence of the benefits and risks of an IMP, can be obtained by medicine developers at any state of the development of a new drug, to avoid major objections regarding test design during the marketing authorisation procedure (105).

7. Digitalisation and future of the submission of clinical trials

As any aspect of professional and personal life, also clinical trials and their submission are subject to fundamental changes with regard to the ongoing digitalisation. In some aspects, these changes have already taken place, as can be seen for example in the possibility to submit the required documents for an application via an online portal (ECS) to the ECs and via CD to the competent authority (BASG) in Austria (39,50,57,58). However, through the example of Swissmedic it is indicated that there is still a long way to go, as many authorities still request all or some documents in paper format (66,91).

Besides the difficulties coming along with non-digital submission of clinical trials, also the fact that there are so many different submission procedures in place, complicates the process for sponsors. This becomes even more important in the case of multinational trials, which, because of the globalisation, are getting more and more important in the development of medicinal products. Therefore, the future of the submission of clinical trials has to be a harmonised, simplified and digitalised approach to increase the feasibility of such valuable trials. A first step in this direction is the EU Regulation 536/2014 on clinical trials on medicinal products for human use from April 16th 2014. With this regulation, it is intended to create a harmonised online submission portal for all Member States of the EU, to obviate complex and time-consuming submissions to each Member State with different regulations, requirements and processes (38).

7.1 Harmonisation of application procedures

Ever since globalisation and digitalisation became dominant in modern society, different institutions and agencies tried to harmonise the application procedure for clinical trials to make the process simpler and less time-consuming for sponsors (43,71,104). Even on national levels, harmonisation has been an important topic for years, which can be seen through the examples of the ECs of Switzerland and Austria. In both countries there are several ECs, responsible for different areas. In order to harmonise the ECs and also to simplify the procedure for application of clinical trials, both countries established according umbrella organisations (Swissethics and the Forum of Austrian Ethics Committees). Furthermore, both countries also require only one submission via the according online portals BASEC and ECS (43,71). However, in Austria for example, there are still two lead ECs which do not accept applications via the online portal and thereby minimise harmonisation (43,69). Even so in Switzerland full harmonisation is not

reached yet, as it is still necessary to look on the different websites of the ECs for guidance on the application documents (61).
However, harmonisation is not only desired on national levels but most importantly internationally, especially throughout the EU. Already the current directive in force, Directive 2001/20/EC, aimed for more harmonisation regarding the conduct of clinical trials within Member States of the EU. In the context of implementing this direction, the EU-Commission gave detailed information and guidance on major topics of the conduct of clinical trials, such as the format of clinical trial applications to competent authorities and ECs, documentation on IMP quality and on the EudraCT database (35,68,104). Further, for even more implementation of the Directive 2001/20/EC across the Member States, the HMA has set up the CTFG as another major step towards harmonisation in Europe in 2004 (104).

The CTFG is a working group consisting of representatives of the clinical trial departments of the competent authorities of the Member States. Among others, it promotes harmonisation in the assessment decisions on clinical trials and according national procedures and operates the voluntary harmonisation procedure (VHP) for clinical trial applications of multinational trials (106). To fulfil these functions the CTFG has set up a document called “Guidance document for sponsors for a Voluntary Harmonisation Procedure (VHP) for the assessment of multinational Clinical Trial Applications”. In this document a harmonised procedure for the assessment of clinical trials intended to be carried out in different Member States of the EU is proposed. However, the countries Croatia, Lichtenstein, Cyprus, Luxembourg, Slovenia and Slovakia do not participate in the VHP and therefore a parallel submission to the national competent authorities of these countries is necessary, if a clinical trial is intended to be conducted there (104).

However, it should be noted that the participation of a multinational trial in the VHP of the CTFG is voluntary and each national competent authority remains responsible for the assessment and approval of a clinical trial application in its country. Further, the submission to the CTFG and the harmonised assessment procedure takes place before the national application process (104).

In general, the VHP consists of three phases in total, whereas the first two phases are composing the actual submission to the CTFG and the third phase is the formal

submission to national competent authorities in accordance with national laws and regulations. In phase one, the sponsor has to request a VHP via e-mail to the CTFG and highlight important aspects of the according trial and include the required documents. These are a covering letter, a list of the competent authorities the application is intended to be submitted to in the national phase, the study protocol including the synopsis, the IB, the IMPD, additional information on the IMP, if not included in the IMPD (GMP compliance, manufacturing authorisation, importation authorisation etc.), the NIMPDs and any scientific advice and a PIP summary, if applicable. In addition to that, for first in human trials, also applicable non-clinical and clinical data should be submitted and the according possible influence on the conduct of the trial and the study design should be discussed (104).

Moreover, the sponsor should propose one reference competent authority of the participating ones. After receipt of the documents, the VHP-Administrator (VHP-A) forwards the documents to the participating competent authorities electronically and informs the applicant within 5 working days about which will be the reference national competent authority and whether or not all requested competent authorities are willing to participate in the VHP (104).

In the next step, the application dossier will be validated and the sponsor will be informed about the VHP starting date or deficiencies of the application. In the assessment period of the VHP, the application dossier will be assessed a maximum of 32 days, after which the applicant will receive information of the reference national competent authority, regarding the decision of all participating competent authorities. If there were no grounds for non-acceptance (GNAs) of the trial raised, the applicant can proceed to phase three, the submission of the application to each participating national competent authority. However, comments on how to facilitate the submission on the national level of a Member State might be added. If any GNAs were raised during the assessment, a list of those will be sent to the applicant, who then has 10 days to respond and revise the documents. If all participating national competent authorities agree on the approval of the clinical trial, the applicant will be informed on day 56 since the starting date or day 60 the latest and can proceed to phase three. However, the participating national competent authorities can again raise conditions, which have to be fulfilled by the applicant again within 10 days or it can be decided that the revised documents are not acceptable at all and a VHP-resubmission is encouraged (104).

In the case that the participating national competent authorities do not come to an agreement regarding the approval, a list of the competent authorities with GNAs will be sent to the applicant, who has to resolve them before or during the national procedure. In any case, the shortened timeframe for national assessment in phase three does not apply for these countries. In general, in phase three a full application dossier of the trial has to be submitted to all responsible competent authorities in accordance with Directive 2001/20/EC and CT-1, no later than 20 days after the approval by VHP. In this submission, the applicant should state in the covering letter that the trial is part of the VHP and the competent authorities will review the application within 10 days, without restarting a scientific discussion on the already approved documents. However, it is still necessary to make a submission to the national ECs in parallel to VHP, if applicable in the according countries. Notably, some Member States offer a VHP Plus procedure, meaning that the EC is already involved in the application procedure and assesses the submitted IB, study protocol and documents on benefits and risks of the trial (104).

However, despite the efforts for harmonisation in the Directive 2001/20/EC, there are still many divergent practices throughout different Member States, especially in areas as the distribution of responsibilities between the competent authorities and the ECs, the timelines for application review, the application dates by the sponsor, the workload and human resources against number of applications and requirements regarding content, format or language of the documents (3,104,107). Further, the Directive was under a lot of criticism by stakeholders, because of the disharmonised application and interpretation of it, throughout the Member States, which led to administrative burdens, increased costs and delays, especially in the case of multinational trials (3,108).

With VHP another step was taken by the EU, towards more harmonised procedures in the Member States, but as VHP is still voluntary, further improvement became necessary. Therefore, a new Regulation for Clinical trials, namely Regulation 536/2014, was published in 2014, which addresses coordinated procedures for multinational trials. Accordingly, the need for VHP will be limited when all clinical trials will be regulated by Regulation 536/2014 and therefore be terminated (3,104).

Consequently, the main goal of the new Regulation is harmonising the evaluation and the conduct of clinical trial across the EU, and therefore reducing bureaucratic barriers and making Europe more competitive in IMP development (38,107–109).

Furthermore, multicentre, multistate trials shall be made more feasible, which supports research in global epidemics, rare diseases, personalized treatment strategies and innovative therapies, as enough patients can be recruited (3). In addition to that and in contrast to the Directive from 2001, any EU Regulation, and therefore also Regulation 536/2014, is directly binding for all Member States and has to be included in national law (107,108). To ensure less bureaucratic barriers, the EMA, in collaboration with the EU Commission and the Member States, is setting up a Clinical Trials Information System (CTIS), consisting of an EU portal and an EU database, in which every trial has to be registered before its start, and through which an application for a clinical trial has to be submitted. In accordance with this, the EU portal will be the single entry point for any data or information regarding clinical trials and only one submission is necessary also for multinational trials (38,108,110). Subsequently, all the submitted information and data will be stored in the according EU database, which also identifies each clinical trial by assigning a unique EU trial number, and be publicly available (38,108).

In general, the CTIS will contain a workspace for sponsors as well as one for the authorities. The sponsors will be able to cross-reference to documents regarding the IMP in other clinical trials, compile clinical trial application dossiers, upload application documents, respond to requests of information, view according deadlines, receive notifications and alerts for trials, etc., via the CTIS system. Similarly, also the authority workspace allows the authorities to view clinical trial application dossiers, collaborate between Member States, manage tasks in relation to the assessment, download submitted documents, receive alerts and notifications, record inspections of clinical trials and trial sites, etc (110).

Regarding the content of the application documents that have to be submitted, not much will change. However, the required documents are listed in a detailed manner in the Annex of the Regulation and are therefore regulated bindingly throughout the EU (38,107).

As will be explained in the assessment procedure, the application dossier is separated in part I and part II. Part I contains general information on the clinical trial, so the cover letter, EU application form, trial protocol, IB, documentation regarding GMP compliance, IMP dossier, auxiliary medicinal product dossier, paediatric investigation plan and scientific advice, content of labelling and proof of payment. Further, part II contains

information for the specific Member State concerned, namely recruitment arrangements, informed consent and subject information, suitability of the investigator, proof of insurance or indemnification, financial and other arrangements, proof of payment of fee and proof that data collected in the trial will be only possessed in compliance with Directive 95/46/EEC on data protection (38).

To simplify the assessment of a clinical trial application, described in the following, each Member State of the EU has to assign one competent authority as contact point and communicate it to the EU Commission. In the primary submission of a clinical trial to the EU portal, the sponsor has to propose one of the Member States, in which the trial is intended to be conducted, as the reporting Member State, which then has to assess the dossier and further inform the sponsor of its completeness via the EU portal. The other concerned Member States have the possibility to communicate any considerations on their site to the reporting Member State, until seven days after the initial submission. If the application dossier is not considered complete, the sponsor is informed via the EU portal and can adjust it within 10 days. However, if the dossier is complete the first assessment period can start, in which the reporting Member State has to compile an assessment report part I, based on the submitted documents for part I, draw a conclusion and submit the report to the EU portal within 45 days after the completeness of the dossier was verified. However, for trials with more Member States concerned, so multinational trials, a different procedure applies. In that case, the reporting Member State has 26 days for an initial assessment and the development of the assessment report part I, and has then to circulate the report to other Member States concerned. These then have 12 days of a coordinated review phase for reviewing part I of the application and communicate their considerations to the reporting Member State. After that, the reporting Member State has a consolidation phase of 7 days for taking possible considerations into account, finalising part I of the assessment report and finally submit it to the sponsor and the other concerned Member States. During this first assessment only the reporting Member State can request additional information via the EU portal from the sponsor, which extends the assessment period by a maximum of 31 days (38). In the second assessment period, each Member State concerned has to assess the documents of part II on its own and for its own territory and has to submit an assessment report of part II via the EU portal within 45 days, including a conclusion about the trial and an according decision. The decision can be either that the trial is authorised, authorised with conditions or not authorised. During this second assessment period,

each Member State concerned can ask for additional information via the EU portal, which again extends the period for a maximum of 31 days. In the case that part I of the application dossier is authorised or refused by the reporting Member State, it is considered as authorised or refused by all other concerned Member States. However, a concerned Member State can still disagree, if one of three points apply: the participants would get inferior treatment than if treated according to normal clinical practice in that Member State, there is an infringement of national law or the Member State has considerations regarding data reliability and robustness and safety (38).

However, if a Member State concerned disagrees with part I of the application, this has to be communicated and justified through the EU portal to the sponsor, the EU Commission and all Member States. In addition to that, if a concerned Member State refuses the authorisation of a clinical trial due to part II of the application, it shall arrange an appeal procedure. Despite the harmonised procedure in the EU Regulation 2014, the review by ECs still remains the responsibility of the Member States and shall therefore be performed in accordance with the applicable national law. However, the Member States should still ensure the compatibility of the timelines and procedures of ethical review with the timelines and procedures in the Regulation. Further, also the informed consent procedure as well as damage compensation is still quite delegated to the Member States and national requirements, and also the decision on language requirements for the application dossier is left to the concerned Member States (38). As pointed out above, the oversight and authorisation of clinical trials in the EU will still remain a responsibility of the Member States, while the EMA is only managing the CTIS and supervises the publication of content on the public website (110).

Notably, the application of the EU Regulation 2014 depends on the full functionality of the developed EU portal and database, which has to be verified by an independent audit by the Management Board of the Agency. After the verification, the EU Commission will publish a note in the Official Journal of the European Union and 20 days after the Regulation will enter into force (38). Further, after another six months the Regulation will apply and a transition period, lasting for three years, will start. Hence, the Directive 2001/20/EG will be fully replaced then (3,38,107). However, even though the putting into service of the EU portal and database was endorsed at the end of 2015, the go-live date of the CTIS system has been postponed. As reason for that, technical difficulties during the development of the system have been given. Therefore, in the year 2021 the EMA

will focus on improving the usability, quality and stability of the system, findings of a system audit and knowledge transfer for the preparation of users and according organisations for CTIS. Following that, the CITS is currently planned to go live on 31 January 2022 the latest (110).

7.2 Pilot projects

As harmonisation of the submission process of a clinical trial, and generally any submission throughout the conduction, has been an important topic in the EU for several years now, and the Clinical Trial Regulation 2014 is thought to be implemented in 2022, there are already quite a few pilot projects on that subject ongoing (110,111). Probably the most expansive of these projects is the Common EU Submission Platform (CESP) of the HMA. The CESP is an online platform through which submissions regarding clinical trials and marketing authorisation can be submitted to all competent authorities of European countries that participate in the project (112). However, not all participating countries (e.g., Austria) already accept an initial application for a clinical trial through the portal, but rather only the submission of applications for marketing authorisation are currently possible (39).

The currently participating countries in the overall project, accepting some kind of submission through the portal, are Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom. In general, the CESP has the goal to provide a secure and simple system for the exchange of data and information between applicants and according regulatory agencies, through one single platform. Therefore, its purpose is to enable the single submission of an application to reach all applicable competent authorities and to reduce the burden of submitting and handling CD-ROMs or DVDs. Because of these goals, the CESP system can be seen as a pilot project for the initial submission via the EU portal, which will be put into place in the near future (112,113). Further, also regarding the procedure and time limits, there are pilot projects on national level in several European countries, to prepare for the Regulation 536/2014 (111,114–116).

In Austria for example, the declared aim of the pilot project is to test and develop scenarios, which will enable the BASG and ECs to reach a single decision and adhere

to the timelines, as required by the EU Regulation. The BASG highly recommends that also the applicant in such a pilot procedure adheres to the according timelines, to prepare for responding to considerations and other requests within the timelines of the Regulation. However, in any case the current legal timelines are the fallback positions. In general, if an applicant wants to participate in the pilot project, a letter of intention has to be sent to the BASG via email at least one week before the submission is planned. After confirmation of the participation, the submission to the BASG and the Lead EC has to be made in parallel and a coordinated validation will be performed by the BASG and the EC within 10 days. Following, the applicant may receive a validation request, which needs to be resolved, and after the submission is valid, a confirmation by the BASG will be sent. If applicable, the applicant will receive a combined list of the considerations from the BASG and the Lead EC, which will lead to a clock-stop. Following, the applicant has to respond to possible questions within 12 days and the BASG and the Lead EC will review any responses and questions within 19 days. Finally, the BASG and the EC will issue a written decision and an EC opinion within 5 days. Notably, there are still some limitations connected to the pilot project. Firstly, a participation in the project is only possible if either the EC of the Medical University of Graz or of the Medical University of Vienna acts as Lead EC. Secondly, it is still required to make separate submissions in parallel to the BASG and the lead EC and therefore the submission has to be timed according to the meeting dates of the EC. However, the BASG plans to remove the mentioned limitations in the following steps of the pilot project (116). As already mentioned, similar pilot projects are conducted in countries throughout Europe to prepare the competent authorities and the according ECs for the implementation of the requirements of the EU Regulation 2014 into national law (111,114,115).

8. Interview with Ao.Univ.-Prof. Dipl.-Ing. Dr.techn. Josef Haas, chairperson of the Ethics Committee of the Medical University of Graz

Ao.Univ.-Prof.i.R. Dipl.-Ing. Dr.techn. Josef Haas is the chairperson of the Ethics Committee of the Medical University of Graz, a position with many responsibilities according to the standing order of the EC. As his main duties as chairman, Univ.-Prof. Dr. Haas mentions the preview of submissions, the scheduling of the agenda, the appointment of expert reports, the organisation of the monthly meetings, consolidating opinions and to settle votes and records. Additionally, he states that also the interaction with the BASG is one of his responsibilities, as well as external representation, for example in connection to the Clinical Trails Expert Group. As all members of the EC are volunteers, also his career in the EC of the Medical University of Graz started as a voluntary member of the EC as biometry expert. From this on, he states that he just grew into his current position as a chairman:

“Da bin ich dann einfach hineingewachsen und geworden.“

Regarding the workload and number of submissions at the EC of the Medical University of Graz, Univ.-Prof. Dr. Haas estimates that around 120 clinical trials are submitted per year and in 30 of them the EC functions as Lead EC.

According to Univ.-Prof. Dr. Haas, the evaluation of a clinical trial in which the EC is lead EC usually starts with the examination of the formalities, ensuring the completeness of the submitted documents. From this on, the EC has 35 days to evaluate the trial. During this time, the EC only once has the possibility to contact the sponsor regarding questions or requirements. Additionally, a consultant is commissioned and a meeting is convened, in which a discussion takes place. Usually, the sponsor or applicant also attends the meeting to answer questions and provide information. After that, a preliminary vote is reached and the sponsor has the possibility to meet certain requirements and eliminate deficits. Depending on these improvements, a positive vote or a rejection will be declared. If the re-evaluation of the study in a second meeting is necessary, is normally decided in the initial meeting and depends on the situation. If the study has gross deficits a re-evaluation is necessary. Further, there is also the possibility for so called “expedited procedures” in any case. These are also often carried out if a study only has minor deficits, e.g., if only small changes to the informed consent form are necessary.

The monthly meetings of the EC of the Medical University of Graz usually start with reports about what happened since the last meeting and for which studies a vote has been issued, based on what happened in the previous meetings. Univ.-Prof. Dr. Haas further states that sometimes also professional trainings take place. After that the different studies are discussed. This usually starts with a summary of the study by the medical specialist, followed by discussions about different aspects of the study. These aspects are medical, scientific, statistical and also formal. Following the discussion, a general formation of opinion takes place with regard to weak points of the trial, what is good about the trial, if the benefits outweigh the risks and what has to still be done in general. Based on that, a formal voting takes place and most of the members also submit written comments, which are collected.

Regarding the cooperation with the BASG, Univ.-Prof. Dr. Haas states that the interaction depends on the type of clinical trial. In general, the submission to the BASG could or should be in parallel to the submission to the EC. This means that the applicant can submit to both institutions at the same time and when both come to a positive conclusion, an authority notice will be issued, in which the authority states that according to the vote of the EC and their own decision, the study can start. In this state, there are necessarily regular interactions between the EC and the authority, as some parts are rather directed to the EC, some to the authority and some overlap.

As a simple example Univ.-Prof. Dr. mentiones the classification of clinical trials with regard to COVID-19 vaccines or titer determination, in which the authorities have the final say. In accordance with that, if there are any obscurities regarding classification of trials, the EC simply references to the authority. Further, both, the authority and the ECs, made and effort to assess clinical trials in connection to COVID-19 as soon as possible, which also made a lot of communication necessary:

“…da muss Hand in Hand gearbeitet werden.“

In addition to that, the Austrian Medicines Act and the Austrian Medical Device Act are currently changed in accordance with the EU-Regulation 2014, which also necessitates communication between authority and ECs.

During the assessment by ECs, questions or deficits are often raised, which have to be answered or resolved before a positive vote can be issued. According to Univ.-Prof. Dr. Haas, the nature of these deficits is very different. He stated that if there are formal deficits, e.g., if an insurance policy is wrongly issued or a CV is missing the signature, the assessment of a study can become difficult, as even if they are minor, these issues have to be resolved before a positive vote can be given. Even more complicated are deficits with regard to content, e.g., if of one arm of a clinical trial is connected to a high risk for the patients or subjects and it is not obvious why the patients or subjects are exposed to that risk. In such cases, there will be a request of the EC and an according answer of the sponsor once, and if the answer is not satisfying, the clinical trial can only be conducted without the questionable study arm or cannot be conducted at all.

As on many other aspects of society, the COVID-19 pandemic also had an impact on the field of clinical trials and therefore the work of ECs. Univ.-Prof. Dr. Haas explains that the work of the EC has mostly changed in two aspects. Firstly, the pace of assessments has changed as the EC of the Medical University of Graz was naturally affected by the pandemic itself and regular monthly meetings were not possible for some time. Fortunately, the standing order of the EC holds the possibility of a so called “circulation procedure” (“Umlaufverfahren”), which was used during that time.

A circulation procedure means that the documents regarding a clinical trial are sent to the members of the EC and the voting takes place by some other mode (e.g., via FAX or e-mail) within a certain time after the documents have been sent (58).

Further, also additional meetings were convened, if the assessment of a trial was urgent and the EC had the goal to assess it until a certain timepoint. These trials were therefore not assessed during the regular monthly meetings, but were assessed separately.

As the new EU-Regulation 536/2014 is intended to be implemented in 2022, the BASG and the Austrian ECs have started a pilot project to prepare for its implementation. With regard to this pilot project, Univ.Prof. Dr. Haas states that the sponsors are very willing to take part in the project, as all bodies involved (the authority, the ECs and the sponsors) are learning together. Until now, the focus of the pilot project was mostly on the new timelines of the EU-Regulation:

“Wir haben in unserem Pilotprojekt bis jetzt praktisch versucht die Zeitfristen durchzuspielen…“

However, the goal is to also include the technical aspects of the assessment with regard to according software in the pilot project, but there might not be enough time left before the implementation to do that.

With regard to the EU-Regulation, Univ.-Prof. Dr. Haas also agrees that the interaction and cooperation with the BASG will increase, because both bodies are affected by the Regulation:

“…weil wir ja im gleichen Boot sitzen und mit der gleichen Geschwindigkeit rudern.“

Further, in the CTIS (EU-portal and EU-database) there is the role of the “Submitter”, who finally releases everything contained in the portal. This role will be taken by the BASG, which will increase the necessity for tighter cooperation. Nevertheless, the ECs will also be able to access the EU-portal.

However, Univ.-Prof. Dr. Haas also has some considerations regarding the new EU-Regulation:

“Am Beginn wurde ganz klar vergessen zu bedenken wie Ethikkommissionen arbeiten.“

One consequence of the Regulation is that the current monthly meetings of the EC will be held at least every two weeks in the future. The problem with that is that the members of the EC are volunteers, which often pursue another profession:

“…das heißt man muss erstmal einen Arzt, Patientenanwalt, einen Seniorenvertreter etc. finden.“

Secondly, such collective decisions with the BASG, as required by the Regulation, take time, which makes it difficult to adhere to the timeframes of the regulation. In addition to that, as everything runs via the EU-portal, the whole procedure is basically IT-driven, which means that any EC that wants to participate in the assessment has to deal with the according IT requirements. It is necessary for ECs to have an interface, adapt their

own documentation etc., which all costs a lot of money. Further, there is no possibility for a sponsorship and the software is not provided, etc. The consequence in Austria will be, that there will be less active ECs in the future, as many just do not have the resources to participate in the procedure. This is especially unfortunate as ECs are basically the representants of the public. Another possible challenge mentioned is to coordinate the interface between the workflow of the ECs and the workflow within the CTIS. This is mostly because the workflow of the ECs includes the distribution of received documents to different occupational groups at different sites.

In general, Univ.-Prof. Dr. Haas has a positive attitude towards the goal of the EU-Regulation to harmonise the submission of clinical trials throughout the EU. He mentions the example of the ongoing debate about the COVID-19 vaccines and states that he personally would rather trust a body like the EMA with its experts to decide on the safety and applicability of a vaccine than any local politicians.

Lastly, Univ.-Prof. Dr. Haas is convinced that the implementation of the EU-Regulation 2014 will take place in the first quarter of 2022. He states that the second audit of the CTIS is currently finishing and the EMA Management Board will receive the audit report in the next days or weeks and will then draw a conclusion and the European Commission will publish it in the Official Journal. Six months after that, the Regulation will be implemented. Following, a transition period of three years will start, during which sponsors can decide whether they want to submit their trial according to the old or the new procedure. In conclusion, according to the current plan, the CTIS and therefore the EU-Regulation will come into force in the first quarter of 2022.

9. Discussion

Clinical trials have always been an important tool for the development of drugs and are essential to investigate the safety and efficacy of new IMPs in humans. Therefore, they are also required for a marketing authorisation of new drugs (1). In modern times, the protection of trial participants and their health became more and more important and is nowadays the most important aspect of a clinical trial. To ensure the best possible safety of subjects, extensive preclinical data on the safety, pharmacokinetics, pharmacodynamics and dose finding in animals is required by competent authorities for the approval of a clinical trial. This shows that preclinical data and its correctness is absolutely necessary to have a good foundation for the development and the conductance of a clinical trial. For this reason, the collected preclinical data on an IMP also has to be contained in the application documents for a clinical trial, mostly in the IB (36). Furthermore, the new EU Regulation 536/2014 states that non-clinical data should be collected in studies in accordance with Union law on Good Laboratory Practice (GLP) (38).

In general, there are very detailed international and European guidelines on the form and the content of required documents for the submission of clinical trials. Furthermore, the review procedures of these documents are based on these guidelines in many countries. This is very important, as the detailed guidance simplifies the procedure not only for sponsors, but also for competent authorities and ECs, and helps to ensure the quality of the data collected during the conductance of a clinical trial and the safety of trial participants (35–37,68).

However, there are still national laws, which need to be followed and therefore some major differences between different countries regarding required documents and the process of the authorisation of a clinical trial (3). To give an example for such differences, the document requirements and application procedures in the EU country Austria and the non-EU country Switzerland were analysed in this thesis. (Chapter 4 and Chapter 5) In general, the required data and information that has to be contained in the main documents as the study protocol, the IB etc. is quite similar, as it is needed by the competent authorities in both countries to draw a conclusion about a clinical trial. However, there are some differences regarding the required application forms and the required correspondences, which have to be submitted (39,49,50,65,66,71). In addition to that, also regarding the proof of payment of according fees and separate information

on handling of biological material and personal data there are differences in requirements by the competent authorities and ECs of the two countries (71,73). However, it can be concluded that the requirements regarding information and data on the trial contained in the documents do not differ a lot between the countries. The actual differences rather lie in the format of the documents and in the division of the responsibilities between the competent authority and the EC. However, the greatest discrepancy regarding document requirements and assessment procedure between Austria and Switzerland, representative for EU and non-EU countries, is the classification of trials into risk categories in Switzerland and the according differences in document requirements, while in Austria the same documents are required for a clinical trial, regardless of its risk (65). Regarding the processes of assessment of a clinical trial application by competent authorities and ECs in the two countries, the main differences lie within different timeframes and different procedures of choosing a Lead EC (6,35,57,65,76). In general, the procedures after a submission of a clinical trial differ more between the two countries than the document requirements.

Importantly, such differences in requirements and procedures can not only be found between EU and non-EU countries but also in-between EU countries, which makes the conductance of multinational trials in the EU very bureaucratic and difficult for sponsors (3,108,109). This issue was already tried to be addressed by the EU Directive 2001/20/EC, aiming for more harmonisation between Member States. However, this goal has not been fully reached yet, which led to the implementation of the EU Regulation 536/2014, which is currently intended to come into force in 2022 (3,110).

The aim of the coordinated assessment of multinational trials in the EU Regulation is to better enable research in rare diseases, personalized medicine and other areas where multistate trials are essential for the recruitment of enough patients (3). As any EU Regulation and in contrast to the EU Directive 2001/20/EC, the Regulation 536/2014 will be directly legally binding and all Member States are committed to implement the Regulation into their national laws (107,108).

Despite the detailed information in the Regulation on the format and content of submission documents, as well as the harmonised procedure for multinational trials and the paperless submission, there is still room for national interpretation and therefore some criticism (3,107–109). One point is that the informed consent process, which is

critical for subject safety, is still quite delegated to national requirements of the Member States. For example, the Member States can decide who is responsible for the informed consent process and who can be a legal representative etc (38).

Another point of criticism may be that also the language requirements for the application dossier are left to the Member States, which could still be a burden to sponsors. However, it is suggested in the Regulation that the Member States should consider accepting an application dossier, written in a commonly understood language in science and the medical field. In addition to that, also in the case of damage compensation, it is the responsibility of the different Member States to put a system, appropriate for the specific Member State, in place. There is no general EU-wide requirement for that system and therefore it could be either insurance, guarantee or any similar equivalent arrangement (38).

Further, one of the main points of criticism is also the imprecise definition of the investigator and the required qualifications (109). The investigator is defined in Article 49 of the EU Regulation 2014 as *"a medical doctor as defined in national law, or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care"* (38).

This rather vague definition does not allow the assessing party of a clinical trial (the competent authority or the EC) to require higher qualifications for investigators of high-risk clinical trials in national laws. Accordingly, this imprecise, but directly legally binding, definition of the requirements for an investigator's qualifications could raise challenges for the safety of trial participants (109).

Another point which raises concerns regarding subject safety is the absent regulation of duties and responsibilities of ECs (108,109). The Regulation leaves the determination of appropriate bodies that should be involved in the assessment procedure of a clinical trial application and the allocation of responsibilities to the Member States. This also includes the organisation of the involvement of ECs (108). According to critics, this leaves room for the Member States to exclude ECs form the assessment of part I of the application, and therefore the assessment of the risk-benefit balance, and limit the review by ECs only to issues of part II (109). However, some EU countries e.g., Germany, Spain and

Denmark, have already stated that they will include ECs in the whole assessment process of clinical trial applications (107,117,118).

In general, it will be a main challenge for Member States to ensure an effective collaboration between the competent authority and ECs in the assessment of clinical trial applications and therefore an effective implementation of the new Regulation (107,108). Another main challenge for the national competent authorities and according ECs is to adhere to the tight timelines of the Regulation and ensure that the appropriate staffing and scientific expertise is available (3,107). With regard to these points concerning the involvement of ECs, also Ao.Univ.-Prof.i.R. Dipl.-Ing. Dr.techn. Josef Haas, chairperson of the EC of the Medical University of Graz, states that at the beginning of the development of the EU-Regulation, it was definitely forgotten to consider how ECs work. At the EC of the Medical University of Graz of example, the currently monthly held meetings, will be held at least every two weeks in the future to be able to adhere to the timelines of the Regulation. (c.f. Appendix 11.2)

Furthermore, it has to be considered that the member of ECs are volunteers, which will make it difficult to arrange the attendance of the required staff at the meetings. Moreover, Univ.-Prof. Dr. Haas points out that also the IT-requirements for ECs which want to participate in the approval process and the according costs, might become a problem and lead to less active ECs in Austria. (c.f. Appendix 11.2) For that reason, many Member States have already put according pilot projects in place, to prepare for the final implementation of the EU Regulation (111,114–116).

According to Univ.-Prof. Dr. Haas, the sponsors in Austria are very willing to participate in the pilot project. However, he also states that the pilot project was very focused on the timelines of the new EU-Regulation until now and the goal to also include technical aspects might not be reached as the time left before the implementation may be too short. (c.f. Appendix 11.2)

To summarise, there is some criticism regarding the EU Regulation 536/2014, stating that its provisions are too unspecific and leave too much room for national interpretation and therefore are not suitable to harmonise the procedures of clinical trial authorisation throughout the EU (108,109). However, many also see the new Regulation as very detailed and comprehensive, and the paperless single submission and communication

through the EU portal as facilitation for sponsors as well as competent authorities and ECs (3,107).

In general, the implementation of the new EU Regulation is a major step toward enhanced harmonisation and an improved clinical research environment in the EU. However, some challenges still remain and how the Regulation performs finally, after its implementation in 2022, will be seen in the following years (3,110).
Finally, with ever-growing globalisation and the trend of outsourcing clinical trials to emerging markets outside the EU and the United States, an even more effective long-term strategy in dialog with developing countries will become necessary in the future (3).

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11. List of Abbreviations

AGES	Österreichische Agentur für Gesundheit und Ernährungssicherheit
AMG	Austrian Medicines Act
AxMP	auxiliary medicinal product
BASEC	Business Administration System for Ethics Committees
BASG	Bundesamt für Sicherheit im Gesundheitswesen
CESP	Common European Union Submission Platform
ClinO	Ordinance on Clinical Trials
CRF	Case Report Form
CRO	Clinical research organisation
CTA	Clinical trial application form
CTEG	Clinical Trial Expert Group
CTFG	Clinical Trial Facilitation Group
CTIS	Clinical Trial Information System
CV	Curriculum Vitae
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
GCP IWG	Good Clinical Practice Inspectors Working Group
GIC	general insurance conditions
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GNA	ground for non-acceptance
HMA	Heads of Medicines Agency
HRA	Swiss Federal Act on Research involving Human Beings
IB	Investigator's Brochure
ICD	International classification of diseases
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
INN	international non-proprietary name
MPG	Austrian Medical Device Act
NIMP	non-investigational medicinal product

NIMPD	non-investigational medicinal product dossier
NIS	non-interventional study
NOAEL	non-observed adverse effect level
PICIS	pharmaceutical inspection conventions/cooperation scheme
PIP	Paediatric Investigational Plan
PQD	Pharmaceutical Quality Dossier
RA	regulatory authority
REC	Research Ethics Committee
RSI	Reference safety information
SAR	serious adverse reaction
SDV	source data verification
SmPC	Summary of product characteristics
SNCTP	Swiss National Clinical Trials Portal
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR	suspected unexpected serious adverse reaction
TSE	transmissible spongiform encephalopathy
USA	United States of America
VHP	Voluntary Harmonisation Procedure
VHP-A	Voluntary Harmonisation Procedure Administrator

12. Appendix

12.1 Kurzfassung

Klinische Studien sind eine der wichtigsten Stufen in der Entwicklung eines neuen Arzneimittels, weshalb sie durch Gesetzgebung und Richtlinien sehr genau reguliert sind, um die Sicherheit der Studienteilnehmer und die Zuverlässigkeit der gesammelten Daten zu gewährleisten. Daher ist auch die Einreichung einer klinischen Studie bei den zuständigen Behörden und Ethikkommissionen sehr komplex, da detaillierte Dokumente über die Studie, eine genaue Validation dieser und eine wissenschaftliche Prüfung durch die Behörden notwendig sind. Durch die Komplexität der Anforderungen und Zulassungsabläufe gibt es diesbezüglich teilweise große Unterschiede zwischen verschiedenen Ländern, was die Einreichung einer klinischen Studie, insbesondere einer multinationalen Studie, für Sponsoren arbeitsaufwendig macht. Weiters, wurden weltweit zuständige Behörden und Ethikkommissionen durch den Ausbruch der COVID-19 Pandemie gezwungen ihre Zulassungsabläufe schnell anzupassen, um weiterhin die Sicherheit der Studienteilnehmer zu gewährleisten. Aufgrund der Aktualität des Themas werden auch die Änderungen der Zulassungsabläufe durch die Pandemie in EU-Ländern (am Beispiel Österreich) und nicht-EU-Ländern (ab Beispiel Schweiz) in dieser Arbeit erläutert. Ein weiteres Thema, welches bereits seit Jahren aktuell ist, ist die Harmonisierung der komplexen Abläufe im Zusammenhang mit der Zulassung von klinischen Studien in verschiedenen Ländern. Die Europäische Union (EU) hat zu diesem Zweck bereits die Direktive 2001/20/EC erlassen. Allerdings ist die Einreichung von multinationalen Studien immer noch komplex. Daher wird die neue EU-Regulation 536/2014 in naher Zukunft in Kraft treten um die Harmonisierung dieser Prozesse zu erweitern.

12.2 Transkript Interview Ao.Univ.-Prof.i.R. Dipl.-Ing. Dr.techn. Josef Haas

Als Vorsitzender der Ethikkommission der Medizinischen Universität Graz haben Sie laut Geschäftsordnung viele unterschiedliche Aufgaben. Können Sie mir bitte eine Zusammenfassung Ihrer wichtigsten Aufgaben geben und Ihren Berufsalltag beschreiben?

Anträge vorsichten, Tagesordnungen festlegen, Bestellung von Fachgutachten, Organisation der Sitzung, Meinung konsolidieren, Ausfällen von Voten und schriftlichen Unterlagen. Weiters der Kontakt zu Behörden, da einiges hauptsächlich behördlichen Charakter hat. Und auch die Vertretung nach außen, zum Beispiel im Zusammenhang mit der Clinical Trials Expert Group auf europäischer Kommissionsebene, gehört dazu.

Wie sind Sie zu der Stellung des Vorsitzenden der Ethikkommission gekommen?

Die Mitglieder der Ethikkommission sind Freiwillige, die die Arbeit unbezahlt machen und man wächst in die Sache hinein. Bei mir persönlich war es so, ich bin vom Berufsbild Statistiker und zu dem Fachwissen, das in der Ethikkommission vertreten sein muss gehört Jus, Medizin, Patientenvertretung verschiedenster Art, Seelsorge und unter anderen eben auch Biometrie/Statistik. Da bin ich dann einfach hineingewachsen und geworden.

Laut der Statistik des BASG wurden zum Beispiel 2019 268 Arzneimittelstudien eingereicht, wovon 221 multinational waren. Wie viele dieser Einreichungen klinischer Studien gibt es ungefähr pro Jahr an der Ethikkommission der Medizinischen Universität Graz zu bearbeiten?

Geschätzt gibt es bei uns in Graz gefühlte 120 Studien die eingereicht werden und von denen sind ungefähr 30 wo wir leitende Kommission sind. Manchmal hat die Ethikkommission nur den Auftrag als lokale Ethikkommission zu fungieren und manchmal als leitende Ethikkommission, was verfahrenstechnisch einen großen Unterschied macht.

Können Sie bitte übersichtsmäßig einen durchschnittlichen Beurteilungsprozess einer klinischen Studie in der Praxis beschreiben?

Im Normalfall beginnt der Prozess mit dem Beginn der Laufzeit des Teils der Beurteilung einer Ethikkommission. Ich rede jetzt davon, wenn wir nicht nur lokal zuständig sind, sondern wenn es wirklich um eine eigene Beurteilung geht. Der erste Schritt ist hierbei

die Formalprüfung, in Bezug auf Vollständigkeit der Dokumente. Von diesem Tag an hat eine Ethikkommission dann 35 Tage Zeit um eine Studie abschließend zu beurteilen. Die Ethikkommission hat die Möglichkeit genau einmal beim Sponsor anzufragen, wegen möglicher Anfragen, Änderungen oder einer Mängelliste. Das ist also nur ein einmaliger Prozess. Weiters wird ein Gutachter bestellt und es kommt zur Sitzung in der es eine Diskussion gibt. Im Normalfall kommt der Sponsor oder der Antragsteller selbst in die Sitzung, für entsprechende Auskünfte. Es gibt dann ein vorläufiges Votum und der Sponsor antwortet auf dieses Votum und ändert etwas oder ändert nichts und dann gibt es demzufolge eine befürwortende Stellungnahme oder eine Ablehnung.

Gibt es dann erneut eine Sitzung, nachdem der Sponsor Änderungswünschen nachgegangen ist oder Forderungen erfüllt hat?

Das wird in der Sitzung beschlossen. Es gibt Studien mit gröberen Mängeln wo es zu einer Wiedervorstellung kommt. Wenn es um geringere Mängel geht, zum Beispiel kleinere Änderungen in der Patienteninformation, wird das in der Folge in einem sogenannten „expedited Verfahren“ geregelt, wie es auch generell Studien gibt die in einem expedited Verfahren abgewickelt werden. Also es hängt von der Situation ab.

Wie läuft eine Sitzung der Ethikkommission in der Praxis ab?

Die Sitzung beginnt mit Berichten was seit dem letzten Mal passiert ist und wo ein Votum ausgestellt wurde, auf Basis der Dinge die in den letzten Sitzungen vorgekommen sind. Weiters gibt es zwischendurch immer wieder die einen oder anderen größeren Fortbildungen. Dann kommt die Tagesordnung und die einzelnen Studien werden abgearbeitet. Nachdem die Studie schon allen bekannt ist, fasst einer, üblicherweise der Facharzt, die Studie zusammen. Danach kommen die Diskussionspunkte zu verschiedenen Aspekten der Studie, wie medizinische, wissenschaftliche, statistische Themen. Auch formale Dinge zu Patienteninformationen werden diskutiert. Danach kommt es zu einer generellen Meinungsbildung darüber was zu tun ist, welche Schwachpunkte die Studie hat, was gut an der Studie ist und ob die Nutzen die Risiken der Studie überwiegen. Daraufhin kommt es dann zu einer formalen Abstimmung. Weiters geben nicht alle, aber die meisten Mitglieder auch schriftliche Kommentare ab, wie zum Beispiel, dass eine Frage im Protokoll ungeklärt ist oder die Patienteninformation zu viele Fremdwörter enthält. Dies wird dann auch gesammelt verschriftlicht.

Wie läuft die Zusammenarbeit mit dem BASG?

Dies hängt von der Art der Studie ab. Prinzipiell kann oder sollte das Verfahren bei Arzneimittelstudien parallel laufen. Das heißt der Antragsteller kann bei beiden gleichzeitig Einreichen und wenn beide Teilverfahren positiv abgeschlossen sind gibt es am Ende einen Behördenbescheid, wo das zusammenläuft. Da sagt die Behörde dann, dass laut dem Votum einer Ethikkommission und ihrer Stellungnahme, die Studie beginnen kann. In diesem Bereich gibt es zwangsläufig immer wieder Kontakte zwischen der Ethikkommission und der Behörde, weil bestimmte Teile Behörden-lastig und andere Ethikkommissions-lastig sind und es bei manchen Teilen auch Überschneidungen gibt. Als simples Beispiel: In Bezug auf die Einstufung von Studien zu COVID-19 Impfungen und Titer Bestimmungen, haben das letzte Wort die Behörden. Daher wird, wenn es um Unklarheiten bezüglich der Einstufung geht, schlicht und einfach auf die Behörde verwiesen. Weiters haben sowohl die Behörde, als auch die Ethikkommissionen, sich bemüht Studien in Zusammenhang mit COVID-19 möglichst schnell abzuwickeln und da muss Hand-in-Hand gearbeitet werden. Außerdem werden gerade sowohl das Arzneimittelrecht, als auch das Medizinprodukterecht umgestellt, was naturgemäß auch zu Kontakten zwischen der Behörde und den Ethikkommissionen führt.

Bei einer Begutachtung einer Einreichung durch Ethikkommissionen kommt es häufig zu Nachfragen und Änderungsanfragen bevor ein positives Votum abgeben werden kann. Was sind die häufigsten Mängel die solche Nachfragen oder Änderungsanfragen auslösen? Sind diese meist eher inhaltlich oder formell?

Die Mängel sind bunt gemischt. Wenn etwas formal nicht vollständig ist, ist die Beurteilung sehr schwierig. Manchmal muss man sich zum Beispiel um eine Versicherungspolice zwei Monate lang kümmern, bis sie richtig ausgestellt ist, oder ein Lebenslauf ist nicht unterschrieben. Also häufig geht es wirklich um Kleinigkeiten, aber bevor diese nicht erledigt sind, kann kein Votum ausgestellt werden. Das sind sozusagen dann die täglichen Ärgernisse. Schwieriger wird es bei inhaltlichen Fragen, wie zum Beispiel, wenn ein Arm in einer Studie mit einem großen Risiko verbunden ist, bei dem nicht zu verstehen ist wieso die Patienten diesem Risiko ausgesetzt werden. Wenn es um solche inhaltlichen Fragen geht, wird es dann komplizierter. Da gibt es dann eine einmalige Anfrage von der Kommission und eine einmalige Antwort vom Sponsor und wenn die Antwort nicht passt, kann die Studie gar nicht, oder nur zum Beispiel ohne den bedenklichen Studienarm oder die bedenkliche Zusatzuntersuchung durchgeführt werden.

Laut Ausschreibung werden während der COVID-19 Pandemie nur elektronische Einreichungen angenommen und Studien in Zusammenhang mit der COVID-19 Erkrankung bevorzugt. Wie hat sich Ihre Arbeit bzw. die Arbeit der Ethikkommission in der Praxis durch die Pandemie verändert?

Es habe sich vor allem zwei Aspekte verändert, der eine ist Geschwindigkeit. Die Ethikkommission war ja auch selbst von der Pandemie betroffen, insofern dass zum Beispiel reguläre Sitzungen eine Zeit lang überhaupt nicht möglich waren. In Graz gibt es aber Gott sei Dank in der Geschäftsordnung die Möglichkeit eines Umlaufverfahrens. Außerdem wurden auch Akutsitzungen einberufen, wenn eine Studie dringend war und wir sie bis zu einem bestimmen Zeitpunkt behandelt haben wollten. Diese wurden dann eben nicht in den regulären monatlichen Sitzungen behandelt, sondern separat.

Wie läuft das Pilotprojekt mit dem BASG als Vorbereitung auf die EU-Regulation 536/2014? Ist die Anzahl an teilnehmenden Sponsoren zufriedenstellend?

Die Sponsoren sind sehr willig am Pilotprojekt teilzunehmen, da alle zusammen, Behörde, Ethikkommission und Sponsoren, auf der lernenden Seite sind. Wir haben in unserem Pilotprojekt bis jetzt praktisch versucht die Zeitfristen durchzuspielen und möchten eigentlich einen Schritt weiter gehen, also auch die softwaretechnische Abwicklung miteinbeziehen. Das wird sich aber vermutlich nicht mehr ausgehen.

Was denken Sie, wie sich die neue EU-Regulation auf die Arbeit der Ethikkommissionen in Österreich auswirken wird? Und wie wird sie sich auf die Zusammenarbeit mit dem BASG auswirken?

Die Zusammenarbeit mit dem BASG wird stärker werden, weil wir ja im gleichen Boot sitzen und mit der gleichen Geschwindigkeit rudern. Im CTIS gibt es bestimmte Rollenbilder und eines dieser Rollenbilder ist der sogenannte „Submitter“. Der Submitter ist derjenige, der das was im Portal drinnen ist endgültig freigibt und diese Rolle steht dem Bundesamt zu. Da müssen wir dann ganz klar stärker zusammenarbeiten.

Wie sehen Sie die Vor- und Nachteile der EU-Regulation und deren Timelines? Haben Sie Kritikpunkte oder Bedenken?

Am Beginn wurde ganz klar vergessen zu bedenken wie Ethikkommissionen arbeiten. Eine Konsequenz daraus gibt es bereits, nämlich dass die momentan monatlichen Sitzungen der Ethikkommissionen in Zukunft mindestens vierzehntägig stattfinden

werden. Das Problem hierbei ist, dass die Mitglieder der Ethikkommission ja Freiwillige sind, das heißt man muss erstmal einen Arzt, einen Patientenanwalt, einen Seniorenvertreter und so weiter finden. Das zweite Problem ist, dass diese gemeinsamen Entscheidungen natürlich Zeit brauchen, was mit den Timelines der Regulation schwierig wird. Drittens, dadurch das alles über das EU-Portal läuft ist das ganze Verfahren im wesentlichen IT-gesteuert. Das heißt, eine Ethikkommission die mitmachen will, muss sich auch mit diesen IT-Anforderungen auseinandersetzen. Daher sind jetzt dann viele Ethikkommissionen nicht mehr in der Lage mitzumachen. Man braucht eine Schnittstelle, muss seine eigene Dokumentation anpassen etc., was zu immensen Kosten führt. Da fehlt dann auch so etwas wie eine Anschubfinanzierung oder dass bestimmte Software zur Verfügung gestellt wird oder was auch immer. In Österreich wird das vermutlich bedeuten, dass es dann weniger aktive Ethikkommissionen geben wird. Dieser Nachteil betrifft natürlich die Ethikkommissionen auf der einen Seite, aber auf der anderen Seite sind die Ethikkommissionen sowas wie Vertreter der Öffentlichkeit, was dann an weniger Stellen zusammenläuft. Und das ist natürlich Schade.

Werden die Ethikkommissionen auch auf das EU-Portal zugreifen können oder ist die Einreichung an die Ethikkommissionen separat geregelt oder läuft sie über das BASG?

Die Ethikkommissionen können auch auf das EU-Portal zugreifen, das ist nicht das Problem. Das Problem liegt eher im Workflow der Ethikkommission, genauer gesagt im Ankommen von Dokumenten und insbesondere deren Verteilung an verschiedene Berufsgruppen an verschiedenen Standorten. Das wird die Herausforderung sein, die Schnittstelle zwischen dem eigenen Workflow und dem Workflow innerhalb des CTIS (des EU-Portals) zu koordinieren.

Wie stehen Sie zu dem Ziel der EU-Regulation, die Einreichung klinischer Studien EU-weit zu harmonisieren?

Prinzipiell ist das in Ordnung. Wir haben ja jetzt auch die Debatte über die Impfstoffe und darüber, dass einzelnen Länder hergehen und sagen sie verwenden einen bestimmten Impfstoff oder nicht. Da wäre ich persönlich schon dafür, dass die EMA, mit den Möglichkeiten die sie hat, entscheidet und nicht irgendein lokaler Politiker entscheidet welcher Impfstoff gekauft wird. Da verlasse ich mich lieber auf einen, wenn auch etwas langsamen und zähen, Apparat mit Experten.

Die EMA hat auf ihrer Homepage veröffentlicht, dass das EU-Portal und die EU Database 2022 fertiggestellt werden soll und die Regulation somit in Kraft tritt. Gibt es bereits Informationen darüber wann die Umsetzung in Österreich geplant ist?

Momentan ist das zweite Audit im Bereich CTIS gelaufen und der Plan ist dieses auch umzusetzen. Das EMA Management Board wird in den nächsten Tagen oder Wochen den Auditbericht bekommen und wird dann beschließen geht oder geht nicht. Diese Entscheidung geht dann an die EU-Kommission weiter und diese wird das Ergebnis dann veröffentlichen im Amtsblatt und 6 Monate nach der Veröffentlichung tritt das Ganze dann in Kraft. Punkt, aus, Schluss. Danach folgt eine Übergangsfrist von drei Jahren, in der die Sponsoren sich entscheiden können ob sie im alten Verfahren bleiben oder das neue Verfahren wählen. So wie der Plan derzeit aussieht, wird das CTIS und damit die Regulation irgendwann im ersten Quartal 2022 umgesetzt werden.