A Review of the Availability of Information on Ethics Committee Requirements for Clinical Trials in the EU

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LIST OF ABBREVIATIONS

ASR	Annual Safety Report
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Germany)
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects' (Netherlands)
CIOMS	Council for International Organizations of Medical Sciences
CNBC	Cyprus National Bioethics Committee
CPP	Regional Ethics Committee (France)
CRO	Contract Research Organization
CSP	Coordinated System for gaining NHS Permission (UK)
CTA	Clinical Trial Authorisation
CTFG	Clinical Trial Facilitation Group
DOHC	Department Of Health and Children (Ireland)
EC	Ethics Committee
EEA	European Economic Area
EFGCP	European Forum of Good Clinical Practice
ETENE	National Advisory Board of Healthcare Ethics (Finland)
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAQ	Frequently Asked Question
GCP	Good Clinical Practice
HMA	Heads of Medicines Agencies
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System (UK)
LPI	Local Principal Investigator
MEC	Medical Ethics Committee (Czech Republic)
METC	*Dutch*: Medisch-Ethische Toetsingscommissie (synonym for IEC/IRB/EC)
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MoH	Ministry of Health
MS	Member State
NBC	National Bioethics Committee (Iceland)
NHS	National Health Service (UK)
NIHR	National Institute for Health Research (UK)
NIP	National Institute of Pharmacy (Hungary)
NMEC	National Medical Ethics Committee (Slovenia)
NRES	National Research Ethics Service (UK)
OsSC	Osservatorio Nationale sulla Sperimentazione Clinica dei Medicinali (Italy)
PEI	Paul-Ehrlich-Institute (Germany)
REC	Research Ethics Committee
SAE	Serious Adverse Event
SIS	Subject Information Sheet
SUSAR	Suspected Unexpected Serious Adverse Reactions
TUKIJA	Subcommittee on Medical Research Ethics (Finland)
WMA	World Medical Association

1. INTRODUCTION

In accordance with the principles of Good Clinical Practice (GCP) as established by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [1] as well as the Ethical Principles for Medical Research Involving Human Subjects established by The World Medical Association (WMA) it is basic requirement to obtain a favourable opinion from an appropriate Ethics Committee (EC) prior to the conduct of a clinical trial with investigational medicinal products (IMP). In the European Union (EU) this principle has been laid down in the Clinical Trials Directive 2001/20/EC (in the following named "the Directive") that came into force on 04 April 2001 [2]. In addition to the favourable ethical opinion it has become a legal requirement in EU Member States (MSs) to obtain a Clinical Trial Authorisation (CTA) from the responsible National Competent Authority (CA). The deadline for implementation of the Directive by the MSs into their respective national legislations was May 1st, 2004, however it took until 2006 for all MSs to implement the Directive into their national laws [3].

Prior to the coming-into-effect of the Directive and the subsequent transpositions into national laws, there were considerably differing legal requirements and procedures for obtaining approvals for the conduct of clinical trials. Especially the procedures to obtain favourable opinions from ECs varied considerably between the countries, e.g. as a result of cultural differences or certain traditional habits. This resulted in complications, and therefore, could have a negative impact on the effective conduct of particularly multi-national trials within the EU. In this respect, one of the main objectives of the Directive was to establish a procedure for obtaining a single opinion for each concerned Member State to "reduce delay in the commencement of a trial without jeopardising the well-being of the people participating in the trial or excluding the possibility of rejecting it in specific sites". The Directive required MSs to establish ECs on a legal basis and, furthermore, introduced legal obligations and specifications for the scope of the EC's assessment, the formal procedure and respective timelines to be applied, as well as the composition of the members of the EC themselves.

In the context of implementation of the Directive, and with the aim to harmonise the conduct of clinical trials within EU MSs, the European Commission has issued various guidance documents, including the 'D*etailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use (ENTR/CT2)'* [4]. This guideline of which the first revision was published in February 2006 is intended to provide advice to applicants on submissions to ECs in the EU Member States in terms of the initial request for an EC opinion on a planned clinical trial, notifications of substantial amendments and notifications of the end of a clinical trial. Thus, that guideline covers general aspects on how to prepare the application to an EC as well as the interaction and procedures during the conduct and at the termination of a study. It can be considered as counter-part to its 'sister' guideline, the *'Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the European Union, notification of substantial amendments and the declaration of the end of a clinical trial (ENTR/CT1)*' [5]. That document (second revision of October 2005) has a similar structure and is intended to provide the corresponding information on the application format and contents of an application to the competent authorities (CA). In fact, the detailed guidance

ENTR/CT2 partly cross-refers to the detailed guidance ENTR/CT1, and some of the explanations are identical in both documents. Also the ENTR/CT1 guideline contains templates of certain forms which are required for submission to both the EC and the CA (the initial [EudraCT] application form, the form for notification of amendments and for notification of the end of the trial). Further to the general requirements, the ENTR/CT2 guideline contains listings of documentation to be included in the applications to ECs in the different countries.

Considering the commendable objective of the Directive and the associated guidance documents, one might have expected that the overall procedure of obtaining a favourable opinion from an EC has become much more straightforward and foreseeable, especially for multi-national clinical trials across the EU. However, due to its nature as a European Directive MSs had some flexibility for interpretation of the Directive's specifications and as a consequence, some countries have added additional requirements.

It was the European Forum of Good Clinical Practice (EFGCP), an organisation aiming at promoting European values and principles in Ethics across the EU, that had early realised that the Ethical review processes varied greatly among the MSs. As a result of their activities, the EFGCP prepared and published a report to describe country by country in which ways the standards of the Directive were actually transposed into the national laws and how the systems currently work in the different MSs [6]. The report shows a significant level of diversity in the applied systems and procedures.

In this master thesis the current differences and similarities between the EC procedures in Europe have been further investigated in a multi-stage approach. The above-mentioned EFGCP report (last updated April 2009) with its ongoing nature will certainly be of great usefulness to sponsors and investigators planning clinical trials in EU countries, particularly when considering multi-national studies. Consequently, this report has served as a starting point for the examinations. Based on the findings of the EFGCP report, the requirements for EC applications in the different countries have been compared and further analysed. Differences and similarities were highlighted while focussing on characteristics relevant to assess the (expected) level of complexity of the respective ethical review procedures in the countries.

The different systems for EC applications and ethical review are expected to undergo constant evolution in the future, hence it will remain crucial for sponsors and applicants to have access to reliable and up-to-date information in order to adequately fulfil the demands. Therefore, the major intention of this thesis is to explore the availability of such sources of information on respective national websites. Based on the information obtained during the survey the level of detail and the quality of the information have been assessed and, ultimately, it was tried to estimate whether it might be possible to file a formally correct application, especially for foreign applicants. If possible the different country-requirements were compared against those laid down in the Directive and the detailed guidance ENTR/CT2, respectively, in order to further assess the level of harmonisation and to analyse the actual relevance and reliability of that guidance document.

In addition to the requirements for the initial applications for EC opinions, it was intended to obtain relevant information from the MSs on any differences in the procedures for notifications of

amendments and the end of a clinical trial. For these instances, no country-specific listings exist and common requirements should be valid across all MSs.

For the sake of completeness, the requirements for reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR) and Annual Safety Reports (ASR) to ECs have been addressed. Respective provisions are laid down in Article 17 of the Directive, as well as the *'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports (ENTR/CT3) to harmonise the reporting requirements across the EU'* [7], as prepared by the European Commission in accordance with Article 18 of the Directive. However, significant problems have become obvious especially at ECs as they were faced with a tremendous amount of unnecessary reports due to differing interpretations of the reporting procedures by sponsors [8]. Hence, it appeared worthwhile to investigate the current practices applied by the ECs in the MSs as well as the status of consistency with the specifications introduced by the above mentioned guideline ENTR/CT3.

Having collated all the necessary information, the overall status of the EU-wide harmonisation has been analysed. Finally, the current situation and future prospects for further harmonisation are discussed.

2. INVESTIGATIONS

2.1 Review of EC review procedures according to the EFGCP report

The EFGCP report has been reviewed country by country while focussing on those aspects that are relevant for the general application process and for the assessment by the competent EC, hence questions no. 1, 2, 4, 5 – 9, 11, 12, 22, 23, 29 and 30 were taken into account. The index of questions is provided in Annex 1.

From the countries mentioned in the EFGCP report, only those which are actual MSs of the EU have been considered for this survey. From the EEA countries which were not legally obliged to implement the Directive into their national legislation, Norway and Iceland have also been taken into account. The report did, however, not include the EU MSs Luxembourg and the EEA country Liechtenstein. It is noted that Luxembourg wholly relies on corresponding Belgian legislation whereas it is known that Liechtenstein essentially follows the Swiss rules. The survey has been based on the latest published update of the report, as of April 2009.

The EFGCP report reveals that the processes for ethical review of clinical trials in fact vary quite significantly across the MSs. In order to further assess the level of complexity of the different EC procedures, an attempt has been made to categorise the countries by certain parameters which have been addressed in the report and which are considered particularly important for the application procedure. The following criteria have been applied:

- Establishment of a central institution responsible for the application for ethical review
- Adherence to provisions imposed by the Clinical Trials Directive
- Availability of relevant (English) websites providing comprehensive information on the application process.

2.1.1 Establishment of a central institution for ethical review of a clinical trial

First, it is noted that the question about the existence of a single organisation for an application for ethical review (i.e. question # 2 of the EFGCP survey) was apparently interpreted in different ways by some of the countries (or their reporter, respectively). For the purpose of this evaluation, however, that question was answered 'Yes' only in case a real single organisation is solely responsible for the receipt of an application; hence this deviates from respective answers in the EFGCP report for the countries Denmark, Norway, Slovak Republic and Sweden.

Out of the 27 countries eight (≈ 30 %) have in fact established a single institution to which an application has to be submitted, whereas the actual systems differ partly from each other. Only one (central) research EC responsible for any clinical trial has been established in Cyprus and Greece. In contrast, Estonia, Hungary, Malta, Portugal and Slovenia have assigned just one EC that is solely authorised to review clinical trials, even though there are several (local or regional) acting research ECs. Another special system is in place in the UK which is described more detailed in chapter 2.3.2.

In some countries there are both central and local or regional ECs, and depending on the type of study (multi- or single-site) the one or the other may be responsible for the application (e.g. Finland, Lithuania, Iceland). In the majority of the countries, however, there are several (local or regional) research ECs. In general that EC which is responsible for the site of the national coordinating investigator will be appointed for the main ethical review, i.e. for the single opinion (for multi-site studies). Indeed, this is true for Finland, France, Germany, Italy, Norway, Poland, Slovakia, Spain and Sweden. In contrast, in case of Austria, Belgium, Czech Republic, Latvia and the Netherlands it is at the sponsor's discretion to choose one from the authorised research ECs.

Despite the lack of a real central EC the situation is quite specific in the Netherlands. The *'Central Committee on Research Involving Human Subjects'* (CCMO) which usually acts as the CA for clinical trials may take over the function of a central EC in some cases. Furthermore, the CCMO runs the web-based system that has to be used for the completion of the national online application form.

It is obvious that having just one single point of contact for the application process offers certain advantages due to reliable (harmonised) procedures and timelines. On the other hand, it might facilitate the entire process if the sponsor can chose the responsible EC, e.g. if one EC has a specific expertise in the questionable research field or indication, respectively.

2.1.2 Adherence to provisions of the Clinical Trials Directive

With regard to the application for ethical review of clinical trial protocols some of the questions included in the EFGCP report are more or less directly associated with provisions introduced by the Directive.

2.1.2.1 Timelines for review

Article 8 No. 5 of the Directive specifies that "the Ethics Committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion to the applicant and the competent authority in the Member State concerned" whereas it is possible to suspend that period in case of (one) request for supplementary information by the EC. When looking at

the corresponding information obtained from the EFGCP report it can be first determined that this has in fact been implemented as a maximum period in all MSs. Some of the countries have introduced even more strict timelines: Austria (35 days), Belgium (28), Bulgaria (30), France (35), Italy (15 for phase I studies; 28 for other studies) and Latvia (30). In Germany it is differentiated between the review timelines for single site studies (30 days) and multi-site studies (60 days). For some of the countries additional information is provided in the report about the allowed extension of review timelines for studies on somatic cell or gene therapy or xenogenic cell therapy, respectively. It may, therefore, be concluded that in terms of the timelines for EC review all MSs have in fact adhered to the Directive's standards.

2.1.2.2 Single opinion

Article 7 of the Directive requires MSs to establish a procedure for the adoption of a single opinion for that Member State for multi-centre clinical trials. This provision has in fact been one of the key questions of the EFGCP report and it can be stated that a single opinion procedure has been established in all of the countries. Notably, Germany, Poland, Portugal and Spain require that (for multi-site studies) the main EC considers comments from all involved ECs, e.g. concerning assessments of suitability of the sites or investigators. Overall, only one final EC seems to be sufficient in each MS to start the trial.

2.1.2.3 Definition of substantial amendments

Provisions for notifications and assessments of amendments after the commencement of a clinical trial are outlined in Article 10 of the Directive. In case of substantial amendments, the sponsor needs to notify the CAs and the ECs as appropriate. Furthermore, the Directive requires ECs to provide an opinion to the sponsor or applicant within a maximum of 35 days.

In the EFGCP report the amendment procedures have been addressed through question # 30. According to the report, the Directive's definition is applied in that way by the majority of countries. No definitions have been provided for the Czech Republic and Norway. Deviations from the common definition above have become obvious for Cyprus and Iceland. In these countries, apparently no differentiations are made between substantial and non-substantial amendments but any amendment is considered important and needs to be notified to the ECs. For Germany the EFGCP report specifies that discussions about the definitions are ongoing within a consultation group, the criteria for substantial amendments are legally defined in the GCP-ordinance though.

2.1.2.4 Safety reporting requirements

2.1.2.4.1 SUSARs

The requirements for handling of SUSARs (Suspected Serious Unexpected Adverse Reaction) are specified in the Directive as well as the associated European Commission guidelines. SUSARs have to be reported "to the Competent Authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor" (fatal or life-threatening SUARS not later than seven days) [6]. There should be identical requirements in all MSs, especially since the Directive has been transposed into respective national legislation in all countries. The level of harmonisation in terms of processing of safety reports may be derived from question # 29 of the EFGCP report that

enquires how ECs deal with SUSAR reports and Annual Safety Reports (ASR). Looking at the results of the report, however, it can be stated that not much detailed information has been obtained on this aspect in general and that the ECs' procedures of handling such reports vary significantly between the countries. For the majority of countries, the legal requirement for (expedited) SUSAR reporting is reflected by the fact that the reports are simply received, reviewed and filed by the ECs, however without specifying the ways how they are reviewed and assessed. For Denmark, Hungary and Latvia, it is not even specified how and if ECs are dealing with the reports, so it remains unknown whether the reports are reviewed or at least filed. Furthermore, in Belgium and Czech Republic reports are not handled consequently or only with major difficulties. In contrast, particular procedures are in place in the following countries:

- Cyprus: the entire study / programme is re-evaluated in all SUSAR reports.
- Estonia: only quarterly reporting is required.
- Finland and France: only domestic SUSARs are subject to expedited reporting whilst other cases have to be reported in the ASR or quarterly, respectively.
- Netherlands, Portugal and Slovenia: specific (electronic) reporting procedures have been implemented.
- Slovenia: only those cases have to be reported in an expedited manner where the benefit-risk-ratio is affected unfavourably, as per the sponsor's assessment.
- Malta: one member of the EC is appointed as rapporteur to present an overview of the reviewed documentation to the committee during a meeting.
- Norway: there is no routine review of SUSARs by ECs; attempts are undertaken to exempt SUSAR reporting to ECs at all.
- Germany: discussions are ongoing within a consultation group established with representatives from the CAs, associations of the German pharmaceutical industry and of the '*Permanent Working Party of German Research Ethics Committees*' to reach a common approach; the usual SUSAR reporting requirements have actually been implemented by the law though [9].

Although some variance is noted as to the ways ECs are dealing with SUSARs in the different MSs, some progress can be seen in certain countries which have already implemented specific procedures or are planning to do.

2.1.2.4.2 Annual Safety Reports

Another important instrument for safety monitoring in clinical trials is the Annual Safety Report. Article 17 No. 2 of the Directive requires sponsors to provide the EC once a year with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects' safety. Further details on ASR preparation and submission are outlined in the detailed guidance ENTR/CT3 [6]. In addition to the SUSAR procedures, the way ECs are handling ASRs may provide some insight on how the specifications of the Directive are acknowledged and adhered to in routine practice. This aspect has been covered by EFGCP report through questions # 29 and 35, whereas # 35 particularly enquires if and how the receipt of the ASR and the final report will be ensured by ECs.

Again, the level of detail of the provided information is relatively low. In general, such reports are regularly received and reviewed by EC. As with SUSARs, Denmark, Hungary and Latvia did not specify if and how ECs are dealing with ASRs. With regard to the ways to ensure timely submission of the ASR, almost two thirds of all countries do not have any specific method in place yet, apart from the basic legal requirement to submit the reports. Estonia, Hungary, Iceland, Ireland, Malta, The Netherlands and the UK have already implemented procedures to monitor and track the ASR submissions more intensively by sending out reminders or request letters to sponsors in case the reports have not been submitted appropriately. Cyprus represents a particular country because submission of an ASR is not legally required; however, an ASR has to be provided by sponsors in a timely manner upon request by the EC.

Overall, according to the EFGCP report the common requirements for ASRs are applicable in almost all the countries. Nevertheless, it seems that a minority of MSs take this aspect more serious than others by introducing or at least considering progressive and modern procedures for monitoring of this safety instrument.

2.1.3 Availability of internet sources of information on requirements for the application for ethical review

In view of a constantly changing and evolving regulatory environment within Europe and world-wide, it remains crucial for sponsors and applicants to have easy and fast access to publicly available sources of up-to-date information on relevant application procedures. In this regard the internet nowadays plays the most prominent role as it is supposed to provide the most current information, especially from official websites like those run by governments and authorities. Access to current requirements is even more important as apart from binding legal requirements the different institutions have their own internal administrative procedures which should be followed by applicants to ensure a timely and smooth processing of their requests. Also there may be country-specific documents (e.g. certain application forms) to be included in an application dossier.

As regards Clinical Trial Authorisations (CTA), there is usually one single competent authority in each MS to which the application has to be submitted and corresponding information on the application process as well as national particularities may be obtained from the authorities' websites. For example, the CAs concerned with CTAs in Germany, the Paul-Ehrlich-Institute (PEI) and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM) have published a comprehensive guidance document for the CTA process as well as the documentation to be submitted (*'3rd Announcement on Clinical Trials of Medicinal Products in Humans' of 10th August 2006'*) [10]. This as well as similar national guidance published by other CAs enable applicants to learn about the particular issues relevant for the application process and to know what to include in the dossier.

Applications for obtaining EC opinions are somewhat different because the responsible reviewing EC(s), i.e. the recipient(s) of the application(s), is (are) not always the same within a country, unless there is one single national institution responsible for any application for ethical review (see above). Hence, collection of relevant and current information on EC application procedures represents an even bigger challenge compared to the CTA applications. The

EFGCP report addresses this issue through question # 6 of its survey. Moreover, a compilation of the national websites relevant for EC applications is provided in an appendix to that report.

Question # 6 relates to the availability of a national website of the organisation that issues guidelines on the ethical review of a clinical trial for an investigational medicinal product whereas the relevant websites with their hyperlinks are specified in that section. For almost all countries more than one reference has been provided even if a single source of information actually exists in some of them. While checking the web links listed in the EFGCP report it became obvious that some links of institutions are no longer available or have changed, respectively (e.g. Slovakia, Slovenia).

The website links included in the respective sections of the EFGCP report were taken as starting point for an extensive analysis of available information on the different EC application procedures. This will be the subject-matter of the following section of this thesis.

When analysing the corresponding information provided in the EFGCP report it becomes apparent that whilst there is an actual central institution for EC applications in just 30 % of the countries, 21 of the 27 countries (≈ 78%) seem to have a central website with relevant information on the procedures.

Table 2.1.3-1 is intended to summarise the findings described above and to visualise the level of differences in the countries. It may also serve as a basis to estimate how difficult the different application processes may be, based on the parameters considered. It is highlighted that these results are exclusively based on the information obtained from the EFGCP report review.

It is acknowledged that the selected parameters are certainly not equally important in terms of the complexity of the EC application procedures; hence, the overview can not represent a valid assessment. As already mentioned, the procedures applied in the countries will certainly undergo further changes in the future, and it will remain of particular importance to applicants to familiarise themselves with the actual requirements when planning a clinical study in any of the countries. In this respect, the availability of reliable and comprehensive information sources will probably remain to be the crucial aspect.

Consequently, an in-depth examination has been carried out to evaluate which kind of information on requirements for EC applications is publicly available for the different countries. This is the subject of the following section 2.2.

Table 2.1.3-1: Summary of characteristics relevant for EC application procedures in EU/EEA countries (as per information in EFGCP report only)

		Adherence to provisions of Directive 2001/20/EC				
Country	**Central institution for EC application**	**Review timelines**	**Single EC opinion**	**Amendment definition**	**Handling/processing of safety reports**	**Relevant online information sources available?**
Austria	no	ok	ok	ok	ok	no
Belgium	no	ok	ok	ok	unclear	no
Bulgaria	no	ok	ok	ok	ok	yes
Cyprus	yes	ok	ok	ok	unclear	yes
Czech Republic	no	ok	ok	unclear	unclear	yes
Denmark	no	ok	ok	ok	unclear	yes
Estonia	yes	ok	ok	ok	deviation from EU legislation	yes
Finland	no	ok	ok	ok	deviation from EU legislation	yes
France	no	ok	ok	specific definition, similar to EU	deviation from EU legislation	no
Germany	no	ok	ok	ok	ok	no
Greece	yes	ok	ok	ok	ok	no
Hungary	yes	ok	ok	specific definition, similar to EU	unclear	yes
Iceland	no	ok	ok	deviation from EU legislation	ok	yes
Ireland	no	ok	ok	ok	ok	yes
Italy	no	ok	ok	ok	ok	yes
Latvia	no	ok	ok	ok	unclear	yes
Lithuania	no	ok	ok	ok	ok	yes
Malta	yes	ok	ok	ok	ok	yes
Netherlands	no	ok	ok	ok	ok	yes
Norway	no	ok	ok	unclear	ok	yes
Poland	no	ok	ok	ok	ok	yes
Portugal	yes	ok	ok	ok	ok	yes
Slovakia	yes	ok	ok	ok	ok	yes
Slovenia	yes	ok	ok	ok	deviation from EU legislation	yes
Spain	no	ok	ok	ok	ok	no
Sweden	no	ok	ok	ok	ok	yes
UK	yes	ok	ok	ok	ok	yes

(ok = in accordance with EU legislation

2.2 In-depth survey of available information on country-requirements

The EFGCP report is a useful tool to learn how the implications of the Directive for ethical review have been implemented and how the systems work in the different countries. Nevertheless, it will remain important to obtain up-to-date information from relevant national institutions. As already mentioned, the EFGCP report has addressed this aspect by questioning whether a relevant website with guidance to applicants is available. Nevertheless, it was deemed necessary to conduct an in-depth review to find out which kind of information and details on the application procedures have been made publicly available in the different countries. Accordingly, an extensive internet search was conducted in May and June 2009 for a selection of EU and EEA countries.

The compilation of website links specified in the EFGCP report was taken as a starting point whereas a number of additional relevant websites have been identified during the survey. Consequently, all available websites have been taken into account. A comprehensive overview of relevant websites per country is provided in a table in Annex 2.

In order to be able to complete an application it will be useful that as much details as possible are accessible to applicants, i.e. both quantity and quality-related aspects are relevant. Accordingly, the present investigation has particularly focussed on the following criteria:

- *Is the information provided in English language?*

  It was not only checked whether there is a general English website in addition to the site in national language but rather whether the information in English actually contains instructions on the application procedure. Thus, if this criterion was not fulfilled it was categorised as “no English information available”. It might therefore occur that some countries have been categorised in this way although an English version of an EC website is basically available (e.g. because the website is under construction or the actual content is still in local language).

- *Level of detail, accuracy and up-to-datedness*

  Where relevant websites were available in English the information was further assessed in terms of quality, level of detail and usefulness for making the application. Depending on these criteria, this was rated as either “excellent”, “good” or “poor” (or “not assessable” in cases of no English information). Obviously, the degree of available details will serve as the main basis for the assessment of the possibility to complete a valid application.

- *Will the application be accepted in English language?*

  For foreign sponsors it is often challenging to comply with national language requirements. Several study related documents will necessarily have to be prepared in the local language anyway to ensure a proper conduct of the study (e.g. those handed out to patients). However, it will mean a significant burden for applicants if additional documentation or information is required in local language just for the purpose of the application. In this respect, the assessment of whether an application will be accepted in English or not will also depend on whether a national application form or general study

documents (e.g. protocol) are required in the local (non-English) language. This again is important for the estimation of whether an application could be filed successfully by foreign applicants without the need for specific linguistic expertise or local consultants, respectively. For the purpose of this survey any specific requirement to prepare documentation in national language has been taken into consideration, except for those documents which have to be prepared in local language anyway (see above).

- *Possibility of direct contact*

  It will always be helpful for applicants to have the opportunity to contact the institution to which the application will have to be submitted, particularly if available guidance is incomplete, unclear or only available in national language. It could be of great value for applicants to resolve any issues with the actual requirements upfront by direct interaction with the institution. This might save time and efforts on either side. Also it might be extremely valuable for (foreign) applicants to clarify any specific formal expectations (e.g. number of copies, fees etc.) with the EC upfront to ensure a smooth flow of the application and review process. It certainly represents a quality attribute of an EC website if applicants are encouraged to submit inquiries. As a consequence, in instances where sufficient details could not be obtained from the website(s) and associated guidance documents during this survey, an e-mail has been sent to ask for further information on the local application requirements. Where possible, the query has been sent to a central institution in order to obtain a generally valid response. In countries with no such central institution it was tried to obtain some information from alternative sources, like local research ECs. On the other hand, a specific inquiry was not deemed appropriate for countries where sufficient details could be gathered from the website review.

2.2.1 Results

Table 2.2.1-1 summarises the essential results of the survey, taking into account the aforementioned criteria. It also includes hyperlinks of those national websites that have been identified as providing the most relevant information on the application procedures, as applicable. This means that even in cases where there are several websites with relevant information only those links were presented which in fact contain the essential instructions on the application process in the respective countries. In the table some countries have been marked with a green background to highlight that for these ones a complete EC application has been considered possible based on the criteria specified before. A detailed analysis of the results is provided on pages 24 ff.

Furthermore, the table contains a column with comments on the content of the information obtained and where the information has been retrieved from. Also some relevant aspects of the application processes are mentioned. A more detailed description of the documentation requirements for each MS is provided in chapter 2.3.

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Table 2.2.1-1: Overview of information on EC application requirements obtained from a survey of websites

Country	English information on EC procedure available?	URL(s), if applicable (only provided if relevant English information available)	Quality/quantity of information provided	Contact details provided?	Responsiveness to inquiry	Application in English accepted?	Application possible based on available information	Remarks
Austria	yes	http://ethikkommissionen.at/	poor	yes	good	no	no	Info obtained from Austrian Forum of ECs with extensive information in German; application checklist and clinical trial guideline available in English; website content in German only; specific national application form required (in German)
Belgium	yes	http://www.fagg-afmps.be/en/human_use/medicines/Medicines/research_development/clinical_trials/index.jsp	poor	yes	good	unknown	no	Info obtained from CA website. Some general information on clinical trials and functions of the Belgian Advisory committee on Bioethics available; list of recognised ECs provided; several links without any content or inactive
Bulgaria	no	n/a	not assessable	yes	poor	unknown	no	Website without any information in English
Cyprus*	yes	http://www.bioethics.gov.cy/Law/cnbc/cnbc.nsf/DMLindex_en/DMLindex_en?OpenDocument	good	yes	good	yes	yes	Info obtained from Cyprian National Bioethics Committee. Specific national application form required (template provided in English); operational guidelines for establishment of ECs available
Czech Republic	yes	http://www.sukl.cz/external-cooperatin/ethic-committies	poor	yes	poor	unknown	no	Info obtained from CA website. Some general information and guidance documents, also in terms of EC procedures, available in English; links and contact details of MECs responsible for multi-site clinical trials available; check of MEC websites revealed no relevant information.

Country	English information on EC procedure available?	URL(s), if applicable (only provided if relevant English information available)	Quality/quantity of information provided	Contact details provided?	Responsiveness to inquiry	Application in English accepted?	Application possible based on available information	Remarks
Denmark	Yes	http://www.cvk.sum.dk/da-DK/English.aspx	excellent	yes	n/a	no	no	Info from National Committee on Biomedical Research Ethics; extensive information on Danish EC system and application procedures available in English; electronic application form to be used in Danish language
Estonia*	yes	http://www.ravimiamet.ee/222	good	yes	n/a	yes	yes	Info from CA website; national application form to be used (provided in appendix to the Regulation of procedure of medical ethics committee for clinical trials which is available in English)
Finland	yes	http://www.etene.org/e/tukija/index.shtml	good	yes	good	no	no	Info from National Advisory Board of Healthcare Ethics (ETENE); several guidance documents available in English, incl. Checklist for researchers and EC members, general ethics related information on clinical trials, operating procedures for Subcommittee on Medical Research Ethics (TUKIJA); national application form to be used (in Finnish or Swedish)
France	no	n/a	not assessable	yes	n/a	unknown	no	No relevant information available in English language; contact details of regional ECs (CPPs) could be found, some of them contacted by e-mail without responses.
Germany	no	http://www.ak-med-ethik-komm.de/	good (in German language only)	yes	n/a	no	no	Extensive information in German available at website of Permanent Working Party of German Research Ethics Committees. Application seems possible for German speakers

Country	English information on EC procedure available?	URL(s), if applicable (only provided if relevant English information available)	Quality/quantity of information provided	Contact details provided?	Responsiveness to inquiry	Application in English accepted?	Application possible based on available information	Remarks
Greece	yes	http://www.bioethics.gr/index.php?category_id=3	poor	yes	poor	unknown	no	Info obtained from The National Bioethics Commission; information on ethical aspects for clinical trials provided but no guidance on application procedure and requirements
Hungary*	yes	http://www.ogyi.hu/laws_and_regulations/	excellent	yes	poor	yes	yes	Info obtained from the National Institute of Pharmacy; English version of the relevant law provided, incl. detailed information on EC application requirements
Iceland	yes	http://eng.heilbrigdisraduneyti.is/laws-and-regulations/Regulations/ http://www.visindasidanefnd.is/Default.aspx?id=64&cmd=menu	excellent	yes	good	no	no	Main info obtained from website of the National Bioethics Committee as well as from response to personal inquiry; application requirements also specified in the national Regulation which is available English; Icelandic application form required (available on website)
Ireland*	Yes	http://www.dohc.ie/omoi/clinical_trials/	good	yes	n/a	yes	yes	Info obtained from Dept. of Health & Children; relevant guidance on EC application process available; detailed information on post-authorisation activities; specific national application/notification forms provided; list of recognised ECs available
Italy	yes	https://oss-sper-clin.agenziafarmaco.it/faq/FAQ_ING.htm#accesso#accesso	excellent	yes	good	no	No	Info obtained from website of National Monitoring Centre for Clinical Trials; extensive guidance on EC application process available, incl. English FAQ section; various national legislations provided in English; national application form required (available as annex to Italian decree and via online clinical trials registration system)

Country	English information on EC procedure available?	URL(s), if applicable (only provided if relevant English information available)	Quality/quantity of information provided	Contact details provided?	Responsiveness to inquiry	Application in English accepted?	Application possible based on available information	Remarks
Latvia*	yes	http://www.vza.gov.lv/index.php?id=381&sa=381&top=333	good	yes	poor	yes	yes	Info obtained from CA; English version of national Clinical Trial Regulation available (documents to be submitted with EC application are specified here); EU application form accepted; details on independent ECs available; inquiry sent to 4 independent ECs without responses
Lithuania	yes	http://bioetika.sam.lt/index.php?-2054655905	good	yes	n/a	no	no	Info obtained from Lithuanian Bioethics Committee. National application form required (template available); English version of the law on biomedical research available
Malta*	yes	http://www.sahha.gov.mt/pages.aspx?page=134	excellent	yes	n/a	yes	yes	Info obtained from the Health Ethics Committee; comprehensive English guidance document incl. checklist of required documentation available; EU application form and notification forms accepted
Netherlands	yes	http://ccmo-online.nl	excellent	yes	n/a	no	no	Info obtained from CA which may also act as EC for certain kinds of products or trials; comprehensive guidance in English available; specific application form required through an online system (in Dutch); list of accredited ECs available

Country	English information on EC procedure available?	URL(s), if applicable (only provided if relevant English information available)	Quality/quantity of information provided	Contact details provided?	Responsiveness to inquiry	Application in English accepted?	Application possible based on available information	Remarks
Norway	yes	http://www.etikkom.no http://www.etikk.no/	poor	yes	good	no	no	Info from National Committee for Research Ethics; no details on EC application requirements available; templates of ICF available; deadlines for submissions to EC provided; national application form required in Norwegian language
Poland	yes	http://www.bioetyka.am.wroc.pl/ang/index.html	poor	yes	good	no	no	Some English information obtained from EC at at Wroclaw Medical University; Polish application form required (template available)
Portugal	no	n/a	not assessable	yes	poor	unknown	no	No information in English available
Slovakia*	yes	http://www.sukl.sk/en	poor	yes	good	yes	yes	No relevant information from website available; CA website provides only information on CTA procedure; according to e-mail response application to EC has to follow EU guidance
Slovenia*	yes	http://www.kme-nmec.si/	good	yes	good	yes	yes	Info obtained from National Medical Ethics Committee; checklist for application documents available; English EU application form accepted; dates of submission deadlines provided
Spain	no	n/a	not assessable	yes	poor	unknown	no	No information in English available

Country	English information on EC procedure available?	URL(s), if applicable (only provided if relevant English information available)	Quality/quantity of information provided	Contact details provided?	Responsiveness to inquiry	Application in English accepted?	Application possible based on available information	Remarks
Sweden	yes	http://www.epn.se/start/application.aspx	good	yes	n/a	no	no	Info obtained from Board for Ethics Review; extensive information available in English incl. contact details of regional ECs; national application form required (in Swedish), English version with comments available
UK*	yes	http://www.nres.npsa.nhs.uk/home/	excellent	yes	n/a	yes	Yes	info obtained from the National Research Ethics Service; extensive and detailed information available on the EC application process; a national online application system has to be used for applications to both CA and EC in parallel (IRAS)

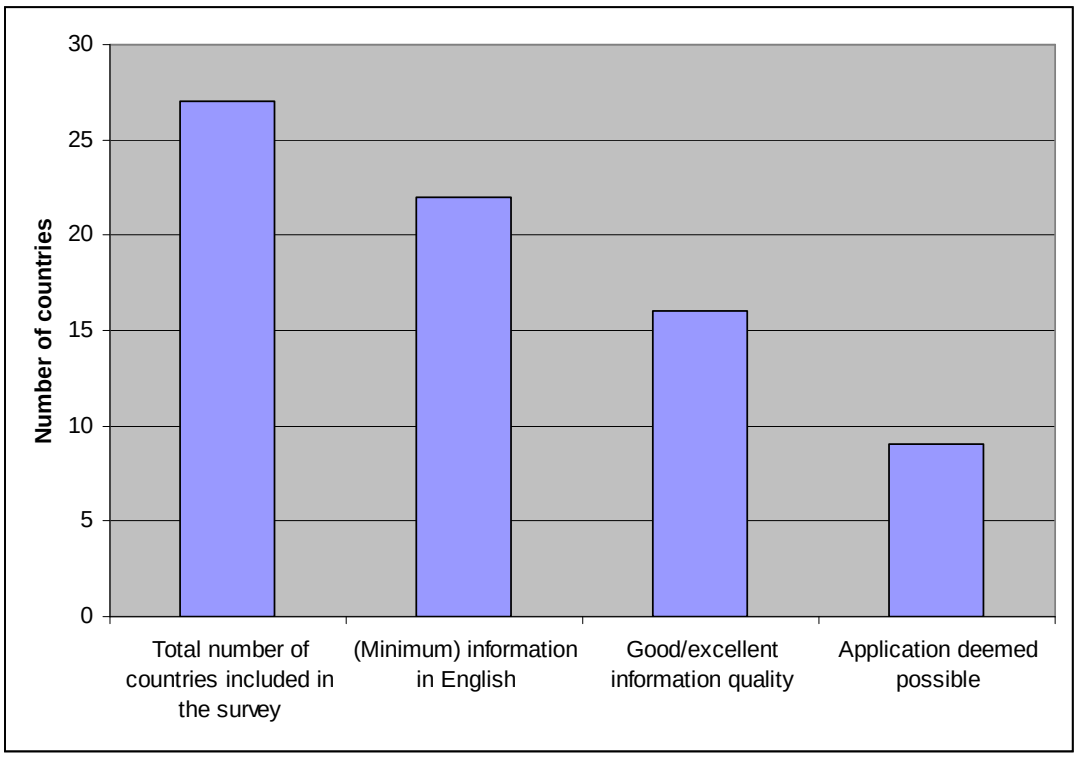
* Countries where an application has been considered possible based on the available information

With the EC systems differing from country to country, the information on the application procedures are occasionally published by various different institutions. In some countries a central EC is the main source of information (e.g. Cyprus, Denmark, Finland, Greece, Ireland, Lithuania, Malta, Norway, Slovenia, Sweden, UK) whereas in others the CA provides the relevant instructions (Belgium, Czech Republic, Estonia, Hungary, Latvia, Netherlands, Slovakia).

The survey shows that for more than three-quarters of the countries (22 out of 27; ≈81%) a minimum of relevant information is in fact available in English whereas the amount of information and level of detail differ significantly. It is noted that the responsible institutions in Spain actually offer English versions for some of their websites. However, the content is not available in English so that even basic details on EC procedures could not be found. Consequently, it was classified as “no English information available”. A number of English websites were under construction, e.g. in Belgium.

Quite a few countries with English websites provide detailed information. As can be seen in the table, Denmark, Hungary, Iceland, Italy, Malta, Netherlands and UK were identified as the countries with the most significant level of information. Comprehensive information on the entire system of ethical review can be found for these MSs as well as detailed instructions on the EC application processes and corresponding documentation requirements. Consequently, these countries were rated as “excellent” in this regard. Information of good quality is available in further nine countries, i.e. in total an acceptable level of information is available in 16 countries (59%) which, however also includes Germany providing good information quality in German language only. For the other countries either no information in English could be found (5;19 %) or the available details were of poor quality or quantity (7, ≈26 %).

Figure 2.2.1-1: Characteristic results of country survey of EC information



This estimation has been exclusively based on information available in English. This means that in cases of marginal information in English sufficient details may still be available in local language. This is at least true for Germany and Austria for which some relevant information and instructions could be found due to fact that the author is a German native speaker. For both countries a lot of information is available in German language. It should be kept in mind that the structures of the websites differ occasionally from country to country and, therefore, it was sometimes hard to discover the relevant information, either because of an illogical user guidance or a lack of an appropriate internal search engine. Accordingly, some countries might have been assessed as "poor" just because the relevant page could not be found even though the relevant source may have been present.

From the above mentioned countries with the best information quality, Hungary, Malta and the UK are among those countries where one central institution is usually responsible for handling applications for ethical review of clinical trials.

In Iceland there is also some kind of central EC institution (the *'National Bioethics Committee'*) although it is not the one and only EC responsible for handling applications for clinical trials. From the remaining countries with central ECs, relatively good information is available for Cyprus, Estonia and Slovenia whilst Greece, Portugal and Slovakia do provide either no or only weak information (in English). On the other hand, Denmark, Iceland, Italy, Latvia and the Netherlands are examples of countries with an excellent or good level of information accessible through a single repository although they do not have a central EC. Nevertheless, it may be deduced that there is some kind of positive correlation between the existence of a central EC and the level of published information and guidance on the application procedure (see figures 2.2.1-2 and 2.2.1-3 below).

Figure 2.2.1-2: Characteristic findings of the country survey split by type of countries (by absolute numbers)

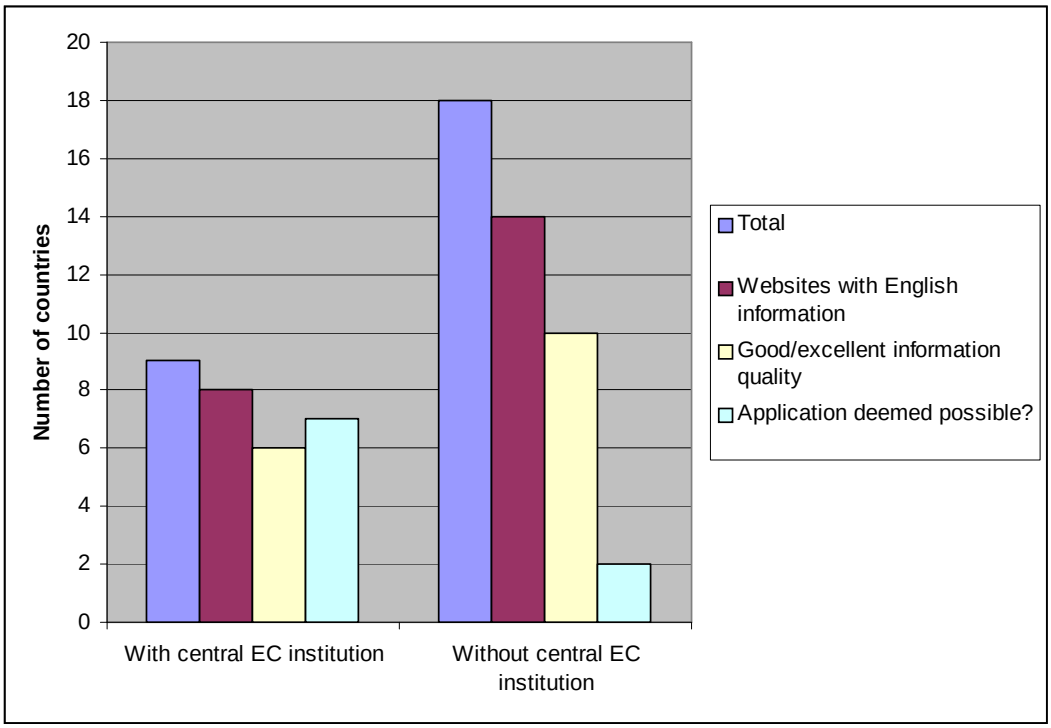
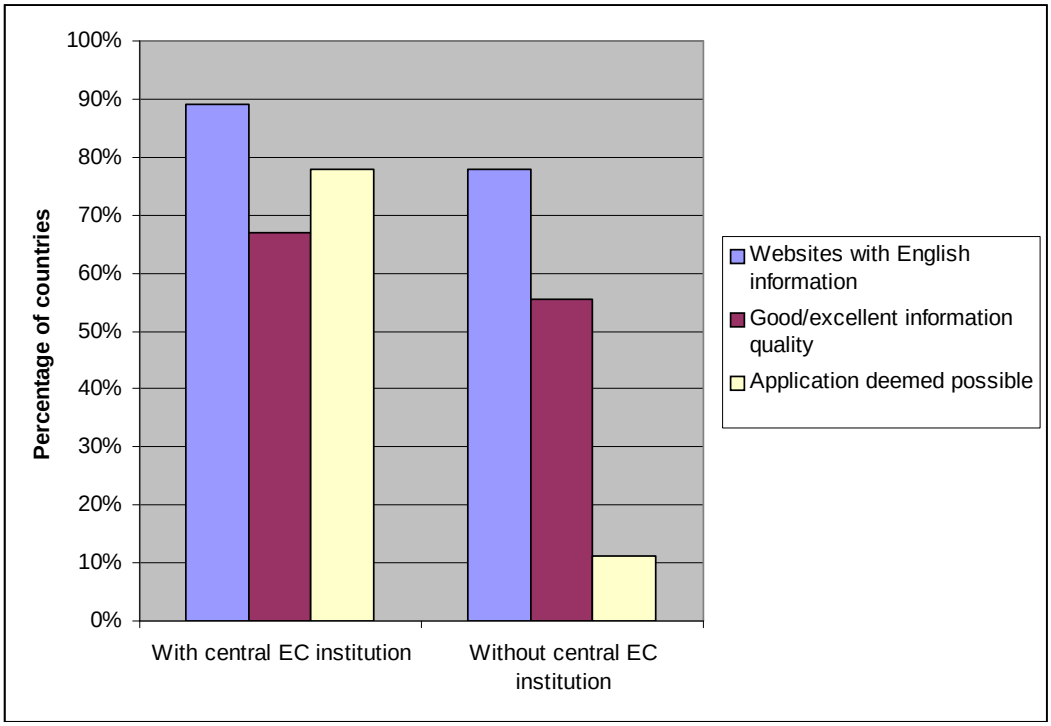


Figure 2.2.1-3: Characteristic findings of the country survey split by type of countries (by percentages)



If available at all, the relevant information is often either directly accessible on the websites or outlined in separate embedded guidance documents for download. A number of countries provide the relevant instructions in the form of (check) lists, namely Austria, Finland, Iceland, Ireland, Italy, Lithuania, Malta, Slovenia, and UK; sometimes the lists are even in line with the format of the tabulation of country requirements as presented in the detailed guidance ENTR/CT2. By contrast, the information is rather difficult to locate in other cases. National laws and decrees have been identified as relevant sources for EC applications requirements in a number of countries, i.e. where the pertinent laws are very specific and comprehensive. In fact, in some countries English translations of relevant national laws are available (Denmark, Estonia, Hungary, Iceland, Italy, Latvia and Lithuania).

The responsiveness to an inquiry was just based on whether a response was given at any time before the completion of the thesis (July 2009), and if so it was graded as “good”. Responses were usually received within one day up to two weeks. The exceptions were Iceland and Cyprus with a time-lag of more than three weeks. Unfortunately, the overall responsiveness to the (e-mail) inquiries can be considered poor since out of the 17 contacted institutions or persons only eight responded at all (47 %). Additional helpful details on the application process were in fact obtained from Austria, Cyprus, Finland, Iceland, Italy and Slovakia. The remaining answers did not yield much beneficial information as they mainly referred to general guidance or to those websites that had already been examined before or to local ECs (Belgium). The reply from Norway pointed to the fact that the national ethics committees will launch a new application form in accordance with a new Norwegian act on health research.

With regard to the acceptance of the applications in English language, it should be pointed out first that for the non-English countries certain documents like patient information and informed consent form are usually required in the local language whereas general study documents like

the study protocol or the IB are acceptable in English. It is obvious that those documents to be handed out to patients (e.g. SIS/ICF, patient card) or local advertisement material will have to be made available in the respective local language anyway. The essential information provided in the (basic) study documents (protocol, IB etc.) documents will be more or less identical across all countries and, hence, their acceptance in English language may represent some degree of harmonisation. As shown in table 2.2.1-1 and figure 2.2.1-1, based on the present survey only nine (33%) of the investigated countries do in fact accept applications in English, namely Cyprus, Estonia, Hungary, Ireland, Latvia, Malta, Slovakia, Slovenia und UK.

Except for Latvia, Malta, Slovakia and Slovenia all countries require specific national application forms, most of which have to be prepared in the respective national language. The countries with application forms in the national language are: Austria, Denmark, Finland, Germany, Iceland, Lithuania, the Netherlands, Norway, Poland, Italy and Sweden. In contrast, the national forms required in Cyprus and Estonia should or may be completed in English. Of course, in Ireland and UK the national forms are in English as the official language, thus this linguistic aspect does not play a role.

The review demonstrates that the proposed EU application form as proposed in attachment 4 to the ENTR/CT2 guideline is accepted only by Latvia, Malta, Slovakia and Slovenia, i.e. in only 15 % of the countries. In Germany, the *'Permanent Working Party of German Research Ethics Committees'* has developed a German version of that application form; this can be downloaded form their website and should be used by for the application to the EC(s).

The ultimate goal of the investigation at hand was to collect as much information as possible on the different EC application requirements and to find out whether it might be possible for foreign applicants to file complete applications without the knowledge of the local but just the English language. It was found that this objective mainly depends on two determining factors: First, does available information enable the applicant to discover how to compile a complete application? Second, will the application be accepted in English language and is it required to prepare a national application form in local language? For the purpose of this survey an application was deemed impossible in case specific linguistic expertise is compulsory to complete the application. On the basis of these considerations the results indicate that a proper application should be possible in nine countries and these are exactly those countries which have been identified as the ones that accept an English application: Cyprus, Estonia, Hungary, Ireland, Latvia, Malta, Slovakia, Slovenia und UK.

For ease of review those countries with a positive rating have been highlighted with a green background in table 2.2.1-1. It should be noted that apart from these countries excellent or good quality information is also made available by other countries and institutions; however the demand for an application in local language and a specific application form, respectively, eventually lead to a negative rating in this regard. As a matter of fact, it appears that without the linguistic barrier sponsors could be in a position to realise complete applications in Denmark, Finland, Germany, Iceland, Lithuania, Netherlands and Sweden. This finding confirms the high relevance of that linguistic aspect for the present assessment.

2.3 Review of country-specific requirements and comparison with specifications of the detailed guidance ENTR/CT2

The objective of the present section is to evaluate in more detail the procedures for applications for ethical review of clinical trials in order to get a more comprehensive picture of the situation in the different countries. Furthermore, it was intended to investigate to which extent the purpose of the detailed guidance ENTR/CT2, to provide advice to applicants on submissions to ECs in the MSs, has been achieved. In that context the practical relevance of that guideline has been assessed. To this end, the requirements identified during the survey of websites were compared against the country-specifications as outlined in attachment 1 of the detailed guidance ENTR/CT2.

Only those countries have been considered for this section for which sufficient information could be collected during the survey described in section 2.2; these are: Austria, Cyprus, Denmark, Estonia, Finland, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Slovenia, Sweden and UK. For Slovakia no actual comparison could be carried out as no instructions could be gathered from a website. On the other hand, a prompt response was received to an inquiry by e-mail, and this in fact revealed that the requirements are completely in accordance with the detailed guidance; hence it is assumed that there are virtually no deviations. As regards Poland the results may be considered preliminary since the review was based on the information obtained from just one local EC which might not actually represent the country-wide perspective.

For ease of review a separate tabulation has been prepared for each of the countries whereas the format of the tabulations follows the style of the country tabulation in the detailed guidance ENTR/CT2. The respective tabulations are presented in Annex 3 in alphabetical order. Each country table contains two columns, one for the country requirements as specified in the detailed guidance, and another one with requirements as derived from the aforementioned website survey. For each country relevant remarks on the findings are provided in this section, as appropriate.

It should be noted that the information from the survey was sometimes gathered from various kinds of sources. As already mentioned, some countries have published well-structured checklists whilst in other cases the relevant details and instructions are fairly spread across different web pages, chapters or even several different documents. Therefore, it was not always possible to find some information on certain items which are, however, compulsory according to the tabulation in the ENTR/CT2 guideline. In such cases, the respective data fields were left blank in the columns on the right hand side (containing information from the survey). It may be assumed though that the questionable items are actually not required for the initial EC application.

For any discrepancies between the findings from the web survey and the specifications of the guideline the respective fields have been highlighted in yellow and the text in **bold** and *italic* type, however in cases of actual contradictory entries only. For example, if a particular element is required as per the detailed guidance but a counterpart could not be found during the investigation then this was not marked, considering that this could just not be found. It may therefore occur that there are more deviations in reality than actually highlighted.

As already mentioned, apart from the process of obtaining CA approval and a favourable EC opinion, the Directive imposes further requirements associated with the actual conduct of a clinical trial, i.e. during the post-approval or maintenance period. In this respect, notifications of (substantial) amendments, safety reporting and notifications of the end of a clinical trial are the main elements. Since the respective provisions should have been implemented EU-wide these aspects have additionally been taken into account for this examination in order to further evaluate the degree of harmonisation across the EU countries. It has been tried to collect the relevant information during the website survey, and the findings have been included in the country overviews below, as appropriate.

Although no or only marginal information is available in English language, Germany has also been included in this review. It may serve as an example of a country with limited information in English but with comprehensive instructions in the local language. This might again be helpful to estimate whether the relevant information on EC application procedures is in fact not available at all or only not on the pages in English.

2.3.1 Overview of results

2.3.1.1 Initial applications to ECs

The country tables in Annex 3 demonstrate a good conformity for 11 countries, i.e. for those where in fact no deviations were found: Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Malta, Norway, Poland, Sweden and UK. Only very few deviations became obvious for Cyprus, Germany, Lithuania, Netherlands and Slovenia. The most deviations were found for Austria, Hungary and Italy. The reason for the high deviation rates in Hungary and Italy are the IMP related documents which are required as per the instructions obtained from the respective websites. This appears comprehensible inasmuch as there is a kind of combined application to the CA and the EC in each of these countries. In Hungary all applications for clinical trials have to be submitted exclusively to the CA (NIP) who then passes a copy of the relevant parts of the application to the EC after their initial assessment.

The survey revealed that in contrast to what is specified in the country tables of the ENTR/CT2 guideline, certain IMP-related items seem to be required for the EC applications in Austria, Cyprus, Germany (in addition to Hungary and Italy, see above). This is astonishing given that the Directive constitutes that the data relating to quality of the IMPs should be subject to review by the CAs.

Furthermore, the review displays that in addition to the requirements mentioned in the ENTR/CT2 guideline, there are particular country-specific documents required in almost each country. For example, quite a number of countries require specific statements or permits from the directors or the management boards of the (proposed) study sites. Also the documents intended for collection of data (e.g. CRF, questionnaires) are expected frequently. Overall, the amount and kinds of country-specific requirements varies significantly across the countries, similar to the wide range of information quality and quantity as published on the websites in the different MSs.

As mentioned before in section 2.2, specific national application forms - primarily in the local language - are required for EC applications in the majority of countries. In addition, some

countries have meanwhile installed specific online application systems for registration of clinical trials or to generate the national application forms, respectively. These are Denmark, Italy, Netherlands and UK. The systems in Italy and the UK are even connected to the EudraCT database. This means that applicants do not have to use the EudraCT system for the preparation of the application form whereas data entered into the national systems will be transferred to EudraCT by the respective CAs accordingly.

On the other hand, it is interesting that in the vast majority of countries the EudraCT application form does not seem to be required for applications to the ECs. That form is primarily needed for the CTAs, i.e. the applications to the CAs, however it is also designed in the way that a corresponding version for submission to ECs can be generated. Moreover, the detailed guidance ENTR/CT2 defines this form as the first module ('Module 1') which should be used for applications to EC. According to the findings of this review the EudraCT application form is only required for EC submissions in Germany, Hungary, Iceland and the Netherlands. For Italy an Italian version of the EudraCT form has to be completed by the applicant. Similar to the EudraCT website, that form can be generated via the Italian online application system (OsSC).

Overall, it must be stated that quite a lot of discrepancies to current online information have become obvious. Moreover, the guideline has been published more than three years ago, so it is quite obvious that the instructions given are not up to date any more.

2.3.1.2 Amendment notifications

Since the Directive has been implemented by all EU/EEA countries it could be expected that the definitions and provisions for notification to and/or approval by ECs are essentially equal across Europe. Indeed, the present survey confirms that at least for the investigated countries the definitions and timelines more or less meet the common specifications. Nevertheless, some differences became apparent as to how ECs want amendments to be handled. Some ECs wish to be informed of all amendments, substantial or non-substantial, whereas others wish to be notified only of those substantial amendments which actually impact the ethical review by the EC. Finland explicitly requires only *substantial* amendments to be notified to the EC for review.

There are sometimes different approaches in terms of the format of the notification. Although the detailed guidance ENTR/CT1 proposes a harmonised notification form for (substantial) amendments, a number of countries have established their own forms and templates, namely Austria, Cyprus, Estonia, Ireland, Italy and Poland. Furthermore, Austria, Ireland, Italy and Poland require the notifications to be completed in the national language. Notably, Italy and Poland have implemented national versions of the standard EU form in their respective language. Cyprus has a national form (in English) specifically for cases of changes to the clinical trial protocol. In Estonia, amendment notifications may be made in free form, i.e. without using a specific format.

No details could be found for Latvia, Norway, Slovenia and Sweden; hence it may be assumed that the standard requirements and procedures are applicable in these countries. With regard to the procedures in Iceland, a discrepancy has become obvious between the EFGCP report and the web survey. Despite the fact that the provisions for amendments as laid down in the Icelandic law on clinical trials are in accordance with the common EU rules, the EFGCP report

specifies that “all amendments must be sent to the ethics committee, which assesses their impact.”

2.3.1.3 Safety reporting (SUSAR/ASR)

The Directive as well as the associated detailed guidance ENTR/CT3 require SUSARs to be reported to CAs and ECs at the same time. Indeed, this review confirmed that all of the countries for which sufficient information could be obtained have constituted appropriate safety reporting requirements in their national legislation. In terms of SUSAR reporting to ECs, however, some countries have implemented specific procedures: national forms have been established in Austria, Cyprus, Ireland, Norway and the Netherlands. Moreover, for Austria, Cyprus, Germany and the Netherlands some additional instructions on the reporting procedures to the EC have been found which obviously means some advantages for sponsors. A novel approach is taken by Denmark and Norway: whilst Denmark has already established that SUSARs have to be reported exclusively to the CA, the same procedure is going to be implemented in Norway as well. According to the information collected, the CIOMS form is definitely accepted for SUSAR reporting in Austria, Estonia and the Netherlands. However, it may be assumed that this standard form is also acceptable in other countries, particularly where no specific forms are available.

In Germany a consultation group has been established to discuss and possibly revise the current provisions due to the enormous workload for ECs in connection with the handling and processing of SUSAR reports (cf section 2.1.2).

Finland and UK have also diminished the amount of SUSAR reports to the EC since they require only those SUSARs which have occurred in clinical trials conducted in their respective territories, and which have been reviewed by the respective EC. No individual reports from foreign countries have to be submitted to the ECs which also reduces the reporting workload for the sponsor.

In Italy, a new Ministerial Decree defining the safety reporting requirements is currently being developed.

In addition to the Annual Safety Reports which can be considered obligatory in each country, specific safety reports are required in Austria and UK. In Austria sponsors are required to submit so-called annual interim reports accompanied by the respective notification form (so-called ‘*Berichtsformular’)* of the ‘*Forum of Austrian Ethics Committees’.* Apparently, this is necessary to obtain a renewal of the EC’s vote. The due dates of the annual safety reports (triggered by the first authorisation of the trial in the EU) and of the annual interim report (triggered by the issue date of the vote) are normally different. The UK requires commercial sponsors to prepare semi-annual safety reports in addition to the standard ASRs.

No particular details on SUSAR and ASR requirements could be found in this survey for Lithuania, Malta, Poland and Sweden. It may therefore be assumed that the standard European provisions apply.

In Cyprus, it is the responsibility of the Local Principal Investigator to report SUSARs to the EC meaning a deviation from the common EU rules according to which “the sponsor should report

all the relevant safety information […] to the concerned competent authorities and to the Ethics Committee concerned" [6].

With regard to Estonia and Slovenia some discrepancies were found between the information presented in the EFGCP report and the corresponding requirements found during the website survey. For Slovenia the survey revealed that the provisions are in accordance with the Directive whereas the EFGCP reports states that SUSARs have to be reported only if "it may be considered by the sponsor/CRO or the responsible investigator that the risk to the participants could exceed the anticipated or acceptable level, or that the originally estimated risk / benefit ratio is changed unfavourably."

According to the EFGCP report, SUSARs have to be reported at least quarterly to the EC in Estonia. In contrast, the website survey showed accordance with the rules of the Directive, i.e. each SUSAR would be subject to expedited reporting to EC and CA.

Overall, the present examination has shown that the basic safety reporting elements as defined in the Directive are established in all EU countries. However, some particularities and deviations from the standard procedures have been observed for a number of countries. It seems therefore that there is currently no real harmonisation in terms of safety reporting in clinical trials.

2.3.1.4 End-of-study notifications

The findings of the survey show that at least for the following countries Denmark, Estonia, Finland, Germany, Iceland, Latvia, Malta and the UK the requirements for notifying EC(s) of the end of a clinical trial are in accordance with the general rules laid down by the Directive. In principle, this is also true for Hungary, however, like for the initial application the declaration has to be submitted only to the CA and not to the EC. For Austria, Latvia, Norway, Poland, Slovenia and Sweden no specific information could be found, hence it may only be expected that the requirements are in line with the EU standards.

Whilst the standard form as provided in Annex 3 of the ENTR/CT1 guideline has to be used in the majority of countries, Cyprus, Ireland, Italy and Poland have developed specific notification forms. The Polish and Italian forms are basically national language versions of the standard EU form.

2.3.2 Results by country

In this particular section specific information and remarks are presented for each of the MSs considered for the comparison exercise. The links of the country websites referred to in this section are specified in table 2.2.1-1. The countries have been grouped by certain categories, depending on the respective systems that are in place for the ethical review of clinical trials or how the single opinion will be granted, respectively. Based on similarities of the systems and procedures the following categories were chosen:

- Countries with a central institution responsible for the application
  (e.g. where only one central EC is responsible for the assessment of all clinical trials)
- Countries with a central EC institution and additional local/regional ECs
  (The responsibility of the central EC or a local EC for issuing the single opinion depends

on the type of study, e.g. mono- or multi-centre study, or the central EC institution itself decides which EC will actually be responsible for the review)

- Countries with a real single EC opinion on clinical trials without the involvement of local ECs
  (the selection of the responsible EC depends on the location of the National Coordinating Investigator, or the sponsor or investigator may choose one out of several recognised EC in the country)
- Countries with a main EC opinion plus site-related assessments by local ECs
  (the selection of the responsible EC depends on the location of the National Coordinating Investigator, or in the case of the UK, the main reviewing EC will be assigned by the central allocation system.)

2.3.2.1 Countries with a central institution responsible for the application

2.3.2.1.1 Cyprus

Initial applications:

A checklist of required documents is provided in a national template which is normally used by the Ethics Committee (available in English). The required documents as specified in the online guidance column were taken from that document. The application to the EC should be submitted by completing the respective application forms which are available on the National Bioethics Committee website. All relevant documents outlined in the forms have to be included in the submission. A template of the ICF is available in English language.

Amendments:

Specific national forms should be used for the notifications. Templates are available on the Cyprus National Bioethics Committee (CNBC) website.

Safety reporting:

No specific information could be found on the searched websites. Additional information was obtained from CNBC in response to an e-mail request. According to a specific guidance document the Local Principal Investigator (LPI) is responsible for submitting all the relevant details on any SUSAR occurring in a participant in a centre in Cyprus. A specific form has to be used which is available on the CNBC´s website. For SUSARs occurring outside Cyprus the LPI is responsible for reporting to the CNBC using a summarised table, not through the CIOMS forms. The investigator has to give a risk-benefit assessment concerning the safety of the study participants.

However, according to a decision of the Committee confirmed on 22/01/2008 the Committee will not assess any SUSARs that are submitted after that date.

End-of study declaration:

Specific national forms should be used for the notifications. Templates are available for download on the National Bioethics Committee website.

2.3.2.1.2 Estonia

Initial applications:

The requirements outlined in the online guidance column were derived from the *'Rules of procedure of medical ethics committee for clinical trials'*, established on the basis of subsection 92 (8) of the Medicinal Products Act. Additionally, the application form appended to that Regulation has been considered. The regulation specifies that other documents may be required at the written request of the EC.

Amendments:

The procedure is specified in the guidance document *'Conditions and procedure for conducting clinical trials'*. Amendments should be notified to ECs in writing in "free form", i.e. no specific form is required. The timelines for review are defined as 35 days, thus in line with the EU legislation.

Safety reporting:

International standards on safety reporting apply. SUSAR reporting shall occur in accordance with ICH guideline E2A (by using a CIOMS form). Reporting to both CA and EC is mandatory as defined in the guidance document *'Conditions and procedure for conducting clinical trials'*. Annual Safety Reports are required as usual.

End-of-study declaration:

The notification has to be made by the Coordinating or Principle Investigator, in accordance with the timelines defined in the Directive.

2.3.2.1.3 Hungary

Initial applications:

The requirements specified in the online guidance column were derived from a checklist that is annexed to the Decree No. 35/2005 outlining the documentation needed for the application to the National Institute of Pharmacy (NIP). The NIP (the Hungarian CA) will forward a copy of the complete application to the EC without delay, thus no separate application to the EC is necessary.

Amendments:

The definitions and review timelines are in line with the specifications of the Directive.

Safety reporting:

SUSAR reporting requirements are in accordance with the specifications of the Directive. No specific information on ASR could be obtained.

End-of-study declaration:

The notification has to be made in line with the Directive's provisions but only to the CA who will inform the responsible EC within 8 days.

2.3.2.1.4 Malta

Initial applications:

The requirements specified in the online guidance column were derived from a guidance document published by the Maltese Health Ethics Committee. The document contains a

checklist of required documentation for the EC. The European guidelines and the proposed application form may be used; hence the application is possible in English language.

Amendments:
The definitions of amendments are in line with the specifications of the Directive.

Safety Reporting:
No specific information could be obtained.

End-of-study declaration:
The definitions, requirements and forms are in accordance with the EU legislation.

2.3.2.1.5 Slovenia

Initial applications:
The requirements specified in the online guidance column were derived from a checklist for the application for ethical review of a clinical trial to the *'National Medical Ethics Committee'* (NMEC). In addition to the above, a number of items are also mentioned in that checklist; however, as these will usually be included in or covered by other basic study documents anyway they have not been listed explicitly (e.g. "*where control group is envisaged, how will their interests and right to proper medical care be assured, arrangements for confidentiality of personal data and the right to privacy"*). The EU application form as appended to the ENTR/CT2 guideline is accepted.

Amendments:
No specific information could be obtained.

Safety reporting:
SUSAR and ASR reporting is required to NMEC, in accordance with the Directive's standards.

End-of-study declaration:
No specific information could be obtained.

2.3.2.2 Countries with a central EC and local/regional EC

2.3.2.2.1 Finland

Initial applications:
The requirements specified in the online guidance column were derived from the guidance document *'Operating Procedures for the Subcommittee on Medical Research Ethics'*.

Amendments:
The definitions are in accordance with the Directive whilst reference is made to the corresponding European guidelines. ECs have to be notified of substantial amendments only.

Safety reporting:
Due to limited capacities for safety assessment the Subcommittee on Medical Research Ethics (TUKJIA) should be informed only about those SUSARs which have occurred in clinical trials conducted in Finland and which have been reviewed by TUKJIA. Moreover, no individual reports from foreign countries have to be submitted to the EC. Annual Safety Reports are required in accordance with EU legislation.

End-of-study declaration:
The requirements are in accordance with the provisions specified in the Directive.

2.3.2.2.2 Iceland

Initial applications:
A comparison against the country table of the ENTR/CT2 guideline could not be carried out as that table does not contain any details for Iceland. The requirements specified in the online guidance column were derived from a checklist for the application which is usually used and completed by a member of the National Bioethics Committee (NBC) staff. Furthermore, some information was obtained from the national Clinical Trials Regulation.

Amendments:
The definitions and review timelines are in line with the specifications of the Directive.

Safety reporting:
SUSAR and ASR requirements are in accordance with the specifications of the Directive.

End-of-study declaration:
The notification has to be made in accordance with the standard EU procedures.

2.3.2.2.3 Lithuania

Initial applications:
The requirements specified in the online guidance column were gathered from a checklist of documents to be submitted to the Lithuanian Bioethics Committee. That list is available for download from the website of the Committee. A national application form has to be completed in Lithuanian and English.

End-of-study declaration:
No specific information could be obtained.

Safety Reporting:
No specific information could be obtained.

End-of-study declaration:
No specific information could be obtained.

2.3.2.3 Countries with a real single EC opinion on clinical trials

2.3.2.3.1 Denmark

Initial applications:
The requirements specified in the online guidance column were derived from a guidance document published on the website of the Danish National Committee on Biomedical Research Ethics (*'Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics'*). A specific national online application form has to be completed in Danish language, that system is accessible via the above mentioned website, along with a completion guide in English.

Amendments:
The requirements are laid down in the Danish *'Act on a Biomedical Research Ethics Committee System and the Processing of Biomedical Research Projects'* and are in accordance with the corresponding provisions of the Directive.

Safety reporting:
The reporting requirements are also specified in the Danish *'Act on a Biomedical Research Ethics Committee System and the Processing of Biomedical Research Projects'*.

Expedited reporting of SUSARs shall be made exclusively to the Danish Medicines Agency which is the CA. ASRs have to be submitted to the EC by either the sponsor or the investigator in line with the usual requirements.

End-of-study declaration:
The notification requirements are specified in the above mentioned Danish law; these are in accordance with the corresponding provisions of the Directive.

2.3.2.3.2 Ireland

Initial applications:
The requirements specified in the online guidance column were derived from a checklist published on the website of the *'Department of Health and Children'* (DOHC).

Amendments:
The definitions are in line with the Directive. A specific amendment notification form should be used; a template is available on the DOHC website.

Safety reporting:
SUSAR reporting requirements are in accordance with the Directive. A specific reporting form should be used; a template is available on the DOHC website.

End-of-study declaration:
The requirements are in line with the EU legislation. Again, a specific notification form is available for download from the DOHC website.

2.3.2.3.3 Latvia

Initial applications:
The requirements specified in the online guidance column were derived from the national Clinical Trial Regulation of which an English version is available on the website of the State Agency of Medicines, the CA. The EU application form (attachment to ENTR/CT2) may be used.

Amendments:
The definitions are specified in the national Clinical Trial Regulation; it is referred to the corresponding notification form of the European Commission. Non-substantial amendments (e.g. administrative issues) should also be notified in writing to the EC and CA; however, an opinion or authorisation is not required.

Safety Reporting:
The definitions and timelines are specified in the national Clinical Trial Regulation and are in accordance with the EU legislation. Reporting has to be made through the EudraVigilance system.

End-of-study declaration:
The definitions are specified in the national Clinical Trial Regulation; again, they are in accordance with the EU legislation. It is referenced to the corresponding form proposed by the European Commission (Annex 3 to guideline ENTR/CT1).

2.3.2.3.4 The Netherlands

Initial applications:
The requirements specified in the online guidance column were derived from the website of the CCMO which usually acts as the CA for clinical trials. In cases of medical research within particular areas like gene therapy, xenotransplantation, heroin addiction etc., the CCMO acts as the responsible (central) EC. The application documentation has to be presented in a particular structure. The EudraCT application form is mandatory in addition to the national online application form *('ABR-form')* which has to be completed in Dutch language. It is possible that the reviewing EC can add something to or amend the list of required documents, therefore close communication with the EC will be crucial. The identical set of documentation needs to be submitted to the EC and the CA whilst the CA will only perform a marginal review of the application.

Amendment notifications:
The definitions, requirements and forms are in accordance with EU legislation. However, all amendments will be primarily assessed by the accredited EC. The CA will confirm the receipt of the amendment notification, which can be interpreted as *'no grounds for non-acceptance'* [11].

Safety reporting:
The definitions and requirements are in accordance with EU legislation and reference is made to the detailed guidance ENTR/CT3. A specific form in Dutch language should be used for reporting of SUSARs though this is not mandatory (a template is available on the CCMO website). Alternatively, CIOMS or MedWatch forms may be used.

End-of-study declaration:
The definitions, requirements and forms are in accordance with EU legislation. Additionally, a specific form published by CCMO is required (in Dutch language).

2.3.2.3.5 Norway

Initial applications:
The requirements specified in the online guidance column were derived from the website of the National Ethics Committees and from guidelines on completion of the national application form.

Amendments:
No specific information could be obtained.

Safety reporting:
According to first-hand information from the EC, the requirements for SUSAR reporting are going be changed in the way that SUSARs do not have to be reported to the EC whilst receipt and assessment of SUSARs will be the sole responsibility of the CA. ASRs have to be submitted to the CA for review by using a specific form which is available on the CA website.

End-of-study declaration:
No specific information could be obtained.

2.3.2.3.6 Sweden

Initial applications:
The requirements specified in the online guidance column were derived from the website of the *'Board for Ethics Review'* as well as from a guidance document on EC procedures. Also the items outlined in the compulsory national application form (to be completed in Swedish) were taken into account.

Amendments:
No specific information could be obtained.

Safety reporting:
No specific information could be obtained.

End-of-study declaration:
No specific information could be obtained.

2.3.2.4 Countries with a main EC opinion plus review by local ECs

2.3.2.4.1 Austria

Initial applications:
The documentation as specified in the online guidance column has been derived from a checklist of required documents (so-called '*CHECK LIST J – Muster für Ethikkommission'*) which is available for download from the website of the Austrian Forum of ECs. The application to the EC should be submitted by completing the national application form in German language which is available on the above website as well.

Amendments:
A specific national form (in German language) should be used for the notifications. The templates are available on the website of the Austrian Forum of ECs, along with guidance on the completion of the forms.

Safety reporting:
Safety reporting requirements are in accordance with the specifications of the Directive. A specific notification form is available for download from the above website. Alternatively, CIOMS or MedWatch forms are accepted for reporting of SUSARs and SAEs, as applicable. A guidance document with detailed instructions on safety reporting to Austrian Ethics Committees is available in English language. Annual Safety Reports have to be submitted in accordance with the EU legislation; however, sponsors are also obliged to submit annual interim reports by using the so-called *'Berichtsformular'* of the Forum in order to get a renewal of the vote for the study.

End-of study declaration:
No specific information could be found.

2.3.2.4.2 Germany

Initial applications:

The requirements specified in the online guidance column were gathered from a checklist published on the website of the *'Permanent Working Party of German Research Ethics Committees'*.

Amendments:

The requirements are laid down in the German GCP-Ordinance (*'GCP-Verordnung'*) and are in accordance with the corresponding provisions of the Directive.

Safety reporting:

The requirements for reporting of SUSARs and submissions of ASRs are also specified in the GCP-Ordinance, again in line with the Directive. A guidance document with additional instructions on the procedure of SUSAR reporting to ECs is published on the Working Party website (in German language only).

End-of-study declaration:

The notification requirements are specified in the GCP-Ordinance and are in accordance with the respective provisions of the Directive.

2.3.2.4.3 Italy

Initial applications:

The requirements specified in the online guidance column were derived from a checklist available on the website of the Italian National Monitoring Centre for Clinical Trials *('Osservatorio Nationale sulla Sperimentazione Clinica dei Medicinali Osservatorio – OsSC')* which is established at the Italian Medicines Agency. That checklist is structured in the similar order as the country table in the attachment 1 of the detailed guidance ENTR/CT2. It distinguishes between requirements for the application to the central EC and the local EC whereas some pieces are exclusively required for the central EC and others only for the local EC. In the country tabulation in Annex 3 the respective items are marked accordingly.

For the comparison at hand the maximum of required documents has been taken into account, no matter if the respective items are mandatory for the local or the central EC. The national application form represents an Italian version of the EudraCT application form that is annexed to the detailed guidance ENTR/CT1. The Italian form has to be generated by entering the requested data into the national clinical trials database (OsSC) and subsequently printing and saving the application form. The use of that electronic (online) registration system is mandatory for applications for clinical trials in Italy; on the other hand a separate data entry into the EudraCT database will not be necessary as the data are transferred from OsSC into EudraCT.

Amendments

The definitions are in line with the specifications of the Directive. A national notification form in Italian language should be used which also represents an Italian version of the European amendment notification form. A template is provided in an annex to the Italian Ministerial decree of 21 December 2007.

Safety reporting

For SUSARs and ASRs a new Ministerial Decree which will be regulating these aspects is under preparation.

End-of-study declaration

The notification has to be made in line with the provisions specified in the Directive. A specific notification form in Italian language should be used.

2.3.2.4.4 Poland

Initial applications:

The requirements specified in the online guidance column were derived from the website of the *'Commission of Bioethics at Wroclaw Medical University'*. This may, therefore, just serve as an example for the application requirements to a Polish EC and may not be applicable for all EC applications in Poland in general.

Amendment notifications:

No specific information could be obtained. It is known, however, from practical experience with CTAs that there is a national notification form in Polish language. That form can be found as an appendix to the Polish decree on clinical trials with medicinal products; it is available on the CA website (see Annex 2).

Safety Reporting:

No specific information could be obtained.

End-of-study declaration:

No specific information could be obtained. It is known, however, that there is a national notification from in Polish language (cf. Amendment notifications above).

2.3.2.4.5 United Kingdom

Initial applications:

The requirements specified in the online guidance column were taken from a checklist as attached to the NHS Research Ethics Committee Application Form which is available for download from the NRES website (see Annex 2). Additionally, some items have been derived from corresponding sections of that application form, as appropriate. It should be noted that a new system for applications for clinical trials to both EC and CA has been established in the UK in 2008. The so-called *'Integrated Research Application System'* (IRAS) was launched on 29 January 2008 with the intention "to have a central system that collates all information needed for various regulatory bodies' permissions and approvals to conduct clinical trials and other health and social care research in the UK".

Since April 2009 it is mandatory for researchers wishing to create new applications for ethical review to use IRAS. As study-related data will be shared between IRAS and the EudraCT database all the information about a study can be entered through IRAS in one place. That means that once a EudraCT number has been obtained from the EudraCT system it is possible to use only IRAS to complete the whole EudraCT dataset and to save the application in the required format. It is also possible to generate the application form to the MHRA in the appropriate format directly from IRAS.

Amendments:
Extensive guidance on classifications of amendments and their notification procedures as well as different scenarios are provided on the NRES website. The legal requirements are in accordance with the provisions of the Directive and the standard EU notification of amendment form should be used.

Safety reporting
The definitions and specifications for reporting SUSARs and ASRs are basically in accordance with the corresponding provisions of the Directive and the detailed guidance ENTR/CT3, respectively. Specific guidance on safety reporting procedures for clinical trials is provided on the NRES website containing detailed instructions on the procedures for the various kinds of safety reports. Compared to the standard EU requirements SUSAR reporting is simplified. The main REC should routinely receive only expedited reports of all SUSARs occurring in the UK in the trial for which the main REC gave a favourable opinion. In addition to the ASR commercial sponsors are required to submit six-monthly safety reports on the safety of subjects in all clinical trials for which the sponsor is responsible worldwide, with a global line listing of SUSARs occurring in these trials in the reporting period. For trials conducted in the UK only, six-monthly reports are not required.

End-of-study declaration
Again, extensive information on the requirements and procedures can be found on the NRES website. The legal requirements are in accordance with the Directive. As for amendment notifications, the standard EU form for declaration of the end of a trial should be used.

3. DISCUSSION

The Clinical Trials Directive 2001/20/EC introduced a number of measures with the intention to harmonise the ethical review of clinical trials with medicinal products. Amongst others, it imposed on MSs to establish the legal basis for an EC system and to implement various specifications for the review and assessment of clinical trial dossiers by ECs. This harmonisation approach was intended to reduce the administrative burden to set up particularly multi-centre and multi-national clinical trials whilst reducing the time to study commencement.

It was found by the EFGCP Ethics Working Party that despite the harmonisation efforts the ethical review processes vary widely across the Member States [6], due to the differences how the Directive was implemented in each MS. Also representatives from the stakeholder groups have highlighted the current differences in the organisations of ECs between the MSs. It was even found that there is no real single opinion in some MSs [3]. As a consequence, the EFGCP has summarised the different EC procedures and particularities for most European countries while focusing on a number of relevant aspects, including the general functioning of the systems, the application procedures, safety-monitoring etc.

The EFGCP report and the European Commission detailed guidance ENTR/CT2 represent useful references to applicants. However, due to the differing requirements between the countries, it will remain important for applicants to have easy access to current information on the different requirements in order to adequately fulfil the demands. It was therefore the intention

of this master thesis to explore the availability and level of relevant information made publicly available by ECs and related organisations in the EU countries.

In the first instance it was found useful to analyse the EFGCP report, thereby categorising countries in order to estimate the complexity of the EC systems and application procedures as well as the level of concordance with essential provisions implied by the Directive. The selected parameters for this categorization are certainly not equally important, therefore the overview should be regarded as a rough estimate only. Nevertheless, the factor “availability of information” has been considered to be of major importance for the application processes. Hence, in the next step it was tried to collect as much country-specific details as possible on EC application procedures and to analyse them.

Thereby, it was focused on internet sources since nowadays the internet can be considered generally as the primary source for up-to-date information. In this respect the EFGCP report was useful as well as it already contains a number of pertinent web-links. Additionally, an internet search was conducted for further sources of information. During the survey it became obvious that some links mentioned in the EFGCP report were not active any more, hence the overview in Annex 2 represents a comprehensive updated list of relevant sources. It is acknowledged though that some of the presented links might change again in the future, due to the permanently evolving nature of internet sources.

This thesis is considered to be the first investigation that comprehensively investigated and compiled publicly available information on EC application requirements for EU and EEA countries. The aim was not only to explore the existence of relevant information but also to evaluate the level of detail, so both quantitative and qualitative aspects have been taken into consideration. Ultimately, it was strived to assess whether it may be (theoretically) possible to file a valid application for ethical review by relying exclusively on the information made available. This assessment was particularly based on the perspective of foreign applicants who do not have specific linguistic expertise in the target country other than knowledge of the English language. Consequently, a stringent condition was applied for the evaluation, i.e. an application was deemed impossible in case specific linguistic expertise is necessary to complete the application. This is reasonable given the fact that research and innovation are central areas of activities of the European Union [12]. The European Commission proposes a strategy that aims to allow Europe to benefit from the positive potential of life sciences and biotechnology [13]. Therefore, one might expect that within the Community essential regulatory requirements for research projects are available in English as the common scientific language.

It is obvious that the above European policy is constrained if the understanding of national requirements for clinical research is hampered for foreign applicants, simply due to linguistic barriers. In such cases, it will be inevitable for foreign sponsors to resort to local consultants, e.g. CROs with an office in the country of interest, resulting in an increase of complexity and costs for a given research project. As a consequence, sponsors might be forced to cancel their research ambitions in certain countries despite the fact that a number of patients with possibly severe and/or hitherto untreated diseases would possibly benefit from potentially effective medications by participation in a clinical study. In addition, this is contradictory to the objective of the Directive, namely to reduce the administrative burden.

On the other hand, it is acknowledged that lay persons with a sometimes limited understanding of English are regularly members of ECs, and it might be difficult for them to fully understand the essentials of a given clinical study if the information is not provided in their national language.

In terms of the linguistic aspect the same rating scale has already been applied by a previous investigation on the availability of information on requirements for applications for Clinical Trial Authorizations (CTA) in the EU Member States [14]. Insofar, the present examination may also be considered supplementary to that work from an ethical perspective.

The results of the investigation demonstrate that the level of information on the EC application procedures is just as heterogeneous as the different EC systems themselves. Whilst the overall amount of information is considerable, only a few sources actually provided the full set of desired information. Mostly, the essential details were located in various different sources, sometimes directly on the websites and sometimes in embedded documents like checklists which have been found to be very comfortable. Also national laws and regulations contain the relevant information in some cases. Though collection of details from legal texts is sometimes difficult and time-consuming, it provides first-hand information on recent legal provisions.

Although it has been aimed at finding and collecting as much information as possible there might still be some sources that were overlooked. Nonetheless, it is believed that the results adequately reflect the real situation, considering that applicants should be given easy access to the relevant sources ensuring that the required information can be obtained without major obstacles. A basic, general knowledge and understanding of functions of websites and how to locate information on the internet remains essential though.

The present investigation demonstrates that it might in fact be possible to complete EC applications in English in nine countries. These include six countries where English is not an official language, raising the question why this might not be possible in other non-English speaking countries alike. As described in section 2.2.1, it may be assumed that without the linguistic barrier an application would probably be possible in additional seven countries. It is noted at this point that a definite and valid statement can not be made. To provide more reliable predications this would have to be substantiated by real applications which would obviously have gone beyond the scope of the present thesis. Such evaluation could be subject to further investigations, e.g. by comparing the results against retrospective experiences from real EC applications.

False negative assessments might have occurred due to the inability to find the relevant information on the websites as mentioned above. However, the probability can be considered relatively low as the English contents of the websites are usually limited and therefore are not very difficult to screen thoroughly. Moreover, if the ultimate information was just not found despite the thorough review the quality of the website probably had to be rated poor anyway (see above). Thus, a negative assessment can be considered more valid in the context of this survey. Anyhow, it should be taken into consideration that the above estimations as to whether an application might be feasible are also influenced by subjective perception to some degree. In addition, the present assessment has not taken into account any formalistic aspects (e.g. numbers of copies, electronic copies etc.) though these may be relevant as well.

Despite its limitations the present investigation clearly demonstrates that it is currently not possible for clinical trial sponsors to collect all relevant information and instructions needed to apply for ethical review of clinical trials in all EU countries. This statement is true at least if one has to rely on information in English language. Even through direct contact with the relevant institutions an application is considered feasible only for one third of the countries investigated here. Nevertheless, the present examination may serve sponsors and applicants as another helpful reference to understand the different procedures and it may be interpreted as an addendum to the EFGCP report.

With regard to the detailed guidance ENTR/CT2, it might be assumed that sponsors just need to go back to this document when preparing for an EC application within the EU since it was prepared by the European Commission as the essential guideline on applications to ECs. In this respect, another aim of this thesis was to investigate the validity and reliability of the country requirements specified in the guidance, while particularly taking into account the findings of the above mentioned website survey. Where possible, the application requirements gathered from the survey were compared country by country against those specified in the guideline. These comparisons revealed that additional documentation is required for almost all countries (89%). Furthermore, at least one deviation between these two sources was found for 42% of the investigated countries.

Another interesting finding of the country review was that the common template for an EC application form as proposed by the guideline seems to be utilised in only very few countries, i.e. in only four (15%) of those 19 countries included in the comparison (Latvia, Malta, Slovakia and Slovenia). In the remaining countries specific forms are to be completed by applicants. Furthermore, the EudraCT application form (defined as '*Module 1*' in the detailed guidance) seems to play only a minor role for the EC applications, given the fact that it is required in Germany, Hungary, Iceland and the Netherlands only. It is noted that from the author's practical experience the EudraCT form is also required for EC applications in France and Spain, for example, however this could not be verified in the present investigation due to linguistic limitations.

The rationale for the need for a country-specific application form remains questionable. The various sections of the proposed common application form ('Module 2') cover all relevant issues that would have to be subject of an ethical review. Also it has obviously been prepared under collaboration of all MSs, hence an EU-wide acceptance could be expected. Though it appears reasonable that at least some essential details are requested in local language, a harmonisation across the MSs is lacking in this regard.

Although the detailed guidance provides useful general information on the EC application processes at least the practical relevance of the country requirements tabulation appears limited, given the above results. It can certainly not be regarded as the ultimate source of information for EC applications. Also there are a number of gaps in the tabulation of country requirements which demonstrates that even the European Commission was not able to fully collect all necessary details from certain countries. The overall significance of the detailed guideline may therefore be questioned. Definitely, an update of the tabulation of country-specific application requirements is indispensable.

The sometimes numerous discrepancies between the specifications within the detailed guidance and respective online instructions clearly point to the need to make all relevant information publicly available in English language, whilst keeping them up to date. Otherwise applicants are always required to collect and verify current requirements when arranging for a clinical trial in a certain country. As discussed before, easy access to comprehensive information is reality only in very few EU countries, at least from the perspective of foreign stakeholders with knowledge of the English language only.

Since the introduction of the Directive, various examinations and initiatives have shown that the objective of simplification and harmonisation has not been fully achieved, especially since there are still significant differences in the different national requirements for applications to the CAs and ECs [3, 15]. Although it is appreciated that through the legal establishment of GCP valid study designs, qualified data management, analysis, monitoring and, ultimately, more valid data and protection of study participants are promoted [16], the administrative burden for applicants has significantly increased. This particularly affects non-commercial clinical trials [17]. Also the Directive “appears not to shorten the duration of regulatory procedures for clinical trial initiation” [18].

For the regulatory review of clinical trials, the principle of a Voluntary Harmonisation Procedure (VHP) has been introduced under coordination of the Clinical Trials Facilitation Group (CTFG) [19]. It is understood that in contrast to CA reviews an ethical review of a clinical trial is more influenced by country-specific particularities to a certain degree (e.g. due to cultural, historical and also personal notions), however the fundamental ethical principles should be identical across the nations. Hence it might be worthwhile to consider and discuss on a European EC level whether a similar harmonisation procedure for the ethical review could be beneficial as well.

The ICREL project, a recently completed initiative aiming at measuring the direct and indirect impact of the Directive and related EU legislation revealed that whilst there was no negative impact on the number of CTAs submitted by commercial sponsors, a slight negative impact for non-commercial sponsors was observed, resulting in a reduced number of CTAs. Overall, the times required for approval of the protocol and the approval of substantial amendments increased by more than 30 %. [20]

With respect to the ethical review procedures the present work basically confirms that the administrative demands for sponsors are extensive, in particular when planning for multi-national clinical trials across Europe. The spectrum of the EC systems as such as well as the specific application requirements is still very broad across the MSs, thus we are still far from an EU-wide harmonisation. The findings from the present investigations are well in line with the conclusions of previous examinations (see above). In terms of timelines, currently a significant amount of time has to be spent for elaborating country-specific requirements, in addition to the time for compiling the application documentation and the whole EC review process. The present work has proven that this can be extremely time-consuming and that for the vast majority of EU countries it is simply impossible to fulfil the respective demands without going back to consultancies.

A possible solution for the dilemma could be the establishment of one single repository located at an appropriate European institution. Unfortunately, there is no formally established network at the EU level for ECs, like the Heads of Medicines Agencies (HMA), the network of the National CAs [21]. It might be a reasonable (interim) solution to use the platform of the HMA as a central location for making all necessary EC application requirements available in English language (e.g. along with the CTA country requirements). The Research Biosociety portal of the European Commission [22] might also be an alternative location for this.

A long-term goal should be an established single list of requirements to be included in the applications whilst this list should be compulsory for both applicants and ECs. In line with the provisions of the Directive, the requirements should focus on aspects pertinent to GCP, and given that GCP represents a global notion it should be possible to realise such an idea in the future.

Originally, the principles of the harmonisation of clinical trial requirements favour protection of subjects and high-quality research in the EU, thereby contributing to a beneficial research environment in the EU and ultimately bringing innovative medicines to patients as quickly as possible. However, given the diversity of the EC procedures and the findings presented in this thesis, one might think that these aspects were disregarded to some extend in favour of an increase in administrative obstacles.

With regard to information on handling of amendments, safety-reporting and end-of study notifications, the present survey showed that specific information on amendments is not provided regularly whereas the relevant provisions are mostly defined in the respective national legislations. It was confirmed for most of the countries, however, that the definitions and timelines are fairly in accordance with the common EU specifications. Nevertheless, some differences and discrepancies were noted, e.g. how amendments have to be managed and notified, respectively; hence this confirms the recently highlighted concerns of both commercial and non-commercial sponsors about the different interpretation of the definition of a substantial amendment between MSs [3].

The situation is similar for the safety reporting procedures. Whereas the provisions of the Directive have been implemented in most cases, there are a number of countries for which particular procedures could be noticed, e.g. the need for using specific forms for reporting of SUSARs. Actually, the Directive requires SUSARs to be reported to the respective CAs and ECs at the same time, however, it has been found that some countries deviate from that principle, e.g. by limiting the reporting to just domestic cases or by bundling of cases over a certain period of time. Furthermore, in some countries the reporting of SUSARs to EC has been abandoned whilst maintaining the sole reporting to the CA. Apparently, it was determined that the clinical and practical relevance of reporting SUSARs to both institutions in parallel does not seem to be reasonable. Also, ECs do often not have the capacities to handle and assess the sometimes vast number of reports that are submitted. Another important problem is the fact that many cases (SAEs) have been considered as SUSARs because incorrect assessment principles have been applied, resulting in over-reporting [8]. Overall, it appears reasonable to limit the reporting of SUSARs to the responsible CAs as they may perform a more comprehensive safety assessment, particularly due to their connection to the EudraVigilance database.

4. CONCLUSION AND OUTLOOK

Despite the commendable objective of the Clinical Trials Directive to simplify and harmonise the administrative provisions governing clinical trials with medicinal products it has been shown by a number of recent investigations and discussions that this goal has not been achieved yet, particularly with regard to the procedures for ethical review.

The extensive report prepared by the EFGCP Ethics Working Party demonstrates the great variety of the EC systems and ethical review processes and corresponding application procedures across the European countries. The findings of extensive surveys described and analyzed in this master thesis confirm this notion and, even more important, have shown that the amount and quality of publicly available information on the different EC (application) procedures vary significantly between the investigated EU/EEA countries.

Furthermore, it was found that the detailed tabulation of country-specific requirements as included in the detailed guidance ENTR/CT2 is not adequate to provide applicants with the comprehensive information. It is therefore concluded that the relevance of that guideline is limited in this respect whilst it is useful only for learning about the application and post-approval processes in general. It can certainly not serve as the ultimate reference document for applications for ethical review of clinical trials.

The findings described above call for the necessity to have easy and unrestricted access to essential information in order to enable applicants to comply with current EC requirements in the different MSs. To that effect, the evaluation of the information content of EC websites revealed that full availability of all required information is not reality in all countries, at least when focussing on information in English language. It could be shown that recent information on the requirements for applications to ECs have been made available in English language in 63% of the Member States.

Indeed, sufficient information is provided in some of the non-native English countries, thus it appears appropriate to postulate that other MSs should make the relevant details publicly available as well, specifically in English language as the common denominator. Of course, the information should be kept up to date, reliable and binding for both applicants and EC institutions.

Based on the results presented in this thesis, it was estimated that a complete and valid application for ethical review seems possible in only nine countries, under the premise that the applicant does not have any specific linguistic knowledge other than English. This leads to the conclusion that without specific linguistic expertise it is currently not possible for foreign applicants to undertake the EC applications in most of the EU countries. As a consequence, currently the only realistic way to complete such process is to go back to consultancies/CROs with specific knowledge about the procedures in the desired countries. This might in turn prevent sponsors from undertaking their studies in certain countries, thereby raising ethical questions about patients not being given the opportunity to participate in clinical studies with possibly effective medicinal products. Moreover, the development and marketing authorization of such products may be delayed which may also have public health-related as well as economic implications.

With regard to regulatory approval for clinical trials (CTA) the Voluntary Harmonisation Procedure (VHP) that has been introduced in 2009 under coordination of the CTFG can be regarded as a seminal initiative for an improvement of the situation. It appears worthwhile to consider a similar initiative for the ethical review of clinical trials as well. However, as a pre-requisite a coordinating body with representation from country EC organisations would have to be established on the European level.

In view of the significant difficulties to collect the necessary information from EC websites in the different countries it is proposed to set up a unique repository located at an appropriate institution at the EU level, e.g. the HMA website or the Research Biosociety portal of the European Commission. The principles of GCP are globally applicable (at least as far as the ICH regions are concerned), and thus are respected by all members of the Community. To that effect, a long-term goal for further harmonisation of the EC application process should be the establishment of a definite set of documentation requirements that will be respected by all MSs. In view of the basic aim of the Directive to implement GCP-principles into national legislation, it should be desired to focus on the actual principles of this harmonised approach, with the ultimate goal of protection of study subjects and ensuring high-quality clinical research.

5. SUMMARY

The Clinical Trials Directive 2001/20/EC that has been implemented in all EU Member States had significant implications on clinical trials with medicinal products within the Community. Amongst others it has affected the ethical review of clinical trials by introducing various provisions for the procedures for obtaining favourable opinions. By this harmonised approach it was intended to simplify the administrative provisions for setting up particularly multi-centre and multi-national clinical trials and, thereby to reduce the time to commencement. However, an EU directive allows different interpretations to be made by Member States when implementing it into national legislation, and accordingly significant differences between the countries were the result. Applicants are therefore still confronted with significant problems to comply with country-specific requirements, particularly when planning multi-national studies.

Given the various EC systems and corresponding application requirements it is crucial for sponsors to have unrestricted and easy access to up-to-date information on the conditions in the different countries. Therefore, the main aim of this thesis was to investigate which level of details on such requirements are available for the EU/EEA countries in the internet and additionally to assess whether a foreign applicant with just English language skills might be able to complete a valid application for ethical review in the respective countries. For that survey the report of the EFGCP Ethics Working Party which summarised the different EC procedures and particularities for most of the European countries was taken as a starting point. The results revealed that actual information on the application requirements have been made available in English language in about 63% of the Member States and that, based on the available details, a complete and valid application for ethical review seems possible in only nine countries.

Furthermore, a country-by-country comparison of the application requirements obtained from the website survey against those specified in the corresponding country tabulation of the European detailed guidance on EC procedures (ENTR/CT2) was carried out. This yielded a number of deviations and therefore the validity and reliability of the country tabulation in the detailed guidance is called into question. On the other hand, this confirms again the high importance for applicants to have unrestricted access to current EC application requirements in the different countries as mentioned above.

The findings of the examinations described in this master thesis clearly confirm that one of the main objectives of the Clinical Trials Directive, namely to harmonise the procedures for ethical review of clinical trials and to reduce the administrative burden, has still not been achieved. Furthermore, it has become obvious that even though a considerable amount of information on the EC application requirements are available in English in a number of European countries, it is currently not possible for foreign applicants to fully undertake the EC applications in most of them. In fact, nowadays the only way to complete the ethical review process successfully is to go back to consultancies/CROs with specific knowledge about the conditions in the desired countries.

Given the fundamental principles of the EU with its common market, the current situation is dissatisfactory as the conduct of clinical trials may be negatively affected in some EU countries. As a consequence, interested patients might not be given the opportunity to participate in studies with promising new drug treatments, thereby raising ethical questions again. Moreover,

the development of new medicinal products might be delayed. To improve the situation, it is necessary that all relevant EC application requirements should be made available in an unrestricted and structured way by all countries. Finally, the harmonised principles of GCP and underlying ethical considerations call for a further EU-wide harmonisation of requirements for ethical review of clinical trials with medicinal products.

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ANNEXES

Annex 1 – Index of questions applied by the EFGCP report

1. What laws or regulations apply to an application for conducting a clinical trial?
2. Which government, legal or authoritative body or bodies is or are responsible for the establishment and/or accreditation of (research) ethics committees for IMPs, and for their supervision and quality? Are there different (research) ethics committees reviewing other projects?
3. What is the process for achieving clinical trial authorisation from the competent authority?
4. What is the process for obtaining ethical review of a clinical trial protocol by a competent authority?
5. Is there a single organisation to which to apply for ethical review of a clinical trial for an investigational medicinal product, regardless of whether this is for a single site or multiple sites?
6. What is the website for the organisation that issues guidelines on the ethical review of a clinical trial for an investigational medicinal product?
7. Is there a procedural interaction between the national or local competent authority and the (research) ethics committee during the approval process?
8. Does the application to the EC and to the competent authority have to be submitted in parallel, or, if not, in which order?
9. How many (research) ethics committees are there in each country?
10. How are the ECs funded? Do they charge fees? If yes what is their scale of fees?
11. Who is responsible for submitting the request for ethical review to the competent ethics committee for single-site and for multi-site clinical trials?
12. How is a “single opinion” achieved for multi-site studies?
13. How many members serve on an EC?
14. How many members constitute a quorum?
15. How are EC members appointed?
16. How is the independence of members ensured?
17. How are conflicts of interest of EC members avoided?
18. What backgrounds and/or qualifications of members are actively sought?
19. How do ECs obtain specialist expertise?
20. What are the training requirements for members of ECs?

21. What training programmes are available for EC members?

22. What are the timelines for the assessment of single- and multi-site studies?

23. How are substantial amendments submitted during the review process dealt with?

24. How does an EC assess the suitability of investigators and of sites?

25. How are the requirements for (research) ethics committees to review the contractual or financial arrangements in clinical trials for both investigators and hospitals handled?

26. How are the requirements for ethics committees to review the compensation arrangements for study subjects handled?

27. Is there an ongoing quality assurance process (e.g. audits, inspections, internal SOP) for (research) ethics committees?

28. Is there an appeal mechanism?

29. How do ECs deal with SUSAR reports and Annual Safety Reports?

30. How are ‘substantial amendments’ defined?

31. What are the indemnity insurance requirements for research projects?

32. What are the indemnity insurance requirements for ethics committee members themselves?

33. How is informed consent obtained from vulnerable subjects who are potentially to be involved in a clinical trial?

34. How do ECs assess the progress and outcome of research projects that they have approved?

35. How does the EC ensure reception of the Annual Safety Report and the Summary of the Final Report of a research project that it has approved?

Annex 2 – Overview of websites with information on EC application process in EU/EEA countries

Country	Specific website providing EC application guidance	Other sources of information
Austria	Not available	http://www.ages.at The website of the Austrian Ministry for Health, Family and Youth (*Bundesministerium fur Gesundheit, Familie und Jugend*) http://www.bmgfj.gv.at http://ethikkommissionen.at http://www.vscr.at The website of the Vienna School of Clinical Research (VSCR)
Belgium	Not available	http://www.health.fgov.be The website of the Medicines Directorate-General of the Federal Public Service: Health, Food Chain Safety and Environment (which is the competent authority) http://www.health.fgov.be/bioeth The website of the Belgian Advisory Committee for Bioethics http://www.ordomedic.be The website of the Belgian "*Ordre des Médecins*" http://www.fagg-afmps.be/en/ The website of the Federal Agency for Medicines and Health Products
Bulgaria	Not available	http://www.bda.bg/?lang=en The website of the Bulgarian Drug Agency, in English
Cyprus	http://www.bioethics.gov.cy/Law/cnbc/cnbc.nsf/DMLindex_en/DMLindex_en?OpenDocument The website of the Cyprus Bioethics Committee.	http://www.pio.gov.cy The website of the Cyprus Medicines Authority http://www.moh.gov.cy The website of the Ministry of Health

Czech Republic	Not available	http://www.sukl.cz The website of SÚKL, the competent authority http://www.forumek.cz/ The Czech Forum of Ethics Committees (Czech language only)
Denmark	http://www.cvk.sum.dk/da-DK/English.aspx The website for the Danish National Committee on Biomedical Research Ethics	http://www.dkma.dk The website of the Lægemiddelstyrelsen, competent authority http://www.retsinfo.dk The website where the latest Medicines Act, L7 is available http://www.etiskraad.dk/sw293.asp The website of the Danish Council of Ethics
Estonia	http://www.sam.ee http://www.ravimiamet.ee/222 The websites of the State Agency of Medicines	http://www.sm.ee The website of the Ministry of Social Affairs. http://www.ut.ee/eetikakeskus/download/ethics-committees The website of Tartu University
Finland	http://www.etene.org/e/tukija/index.shtml The websites of the National Advisory Board on Health Care Ethics	http://www.finlex.fi/en/laki/kaannokset/1999/en19990488 Website of the Medical Research Act http://www.stm.fi The website for the Ministry of Social Affairs and Health http://www.nam.fi The website of the National Agency for Medicines (*Lääkelaitos*). http://www.tenk.fi/index.htm The website of The National Advisory Board on Research Ethics

France	Not available	http://philpez.chez-alice.fr/listing.html The website with the list of competent regional ethics committees (CPP) (French only!) The list of CPP is also available at http://www.recherche-biomedicale.sante.gouv.fr/ (French only!) http://www.afssaps.sante.fr The website of the Afssaps, the competent authority http://www.ccne-ethique.fr/?langue=2 The website of the national consultative Ethics Committee http://www.inserm.fr/en/index.html The website of Inserm, the French public research body entirely dedicated to human health
Germany	Not available	http://www.ak-med-ethik-komm.de The website of the "Permanent Working Party of German Research Ethics Committees"(Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland) http://www.ethikrat.org The website of the National Council for Ethics http://www.bundesaerztekammer.de The website of the German Medical Association http://www.bmgs.bund.de The website of the Federal Ministry for Health http://www.bfarm.de The website of the Federal Institute for Drugs and Medical Devices (Competent Authority)

Greece	http://www.bioethics.gr	http://www.eof.gr The website of the competent authority, the Ethnicos Organismos Pharmacon (EOF)
Hungary	http://www.ogyi.hu/main_page/ The website of the National Institute of Pharmacy, which is the competent authority for clinical trials in Hungary and also the website of the Committee for Clinical Pharmacology and Ethics of the Medical Research Council.	n/a
Iceland	http://www.visindasidanefnd.is/Default.aspx?id=18&cmd=menu The website of the National Bioethics Committee	http://eng.heilbrigdisraduneyti.is/laws-and-regulations/Regulations/ Regulation on clinical trials of medicinal products in humans no.443/2004 http://www.personuvernd.is/information-in-english/greinar//nr/438 Data protection act no. 77/2000 http://www.personuvernd.is/information-in-english/greinar//nr/441 Rule no. 698/2004 on the obligation to notify and processing which requires a permit http://www.personuvernd.is/information-in-english/greinar//nr/442 Rule no. 299/2001 on security of personal data http://eng.forsaetisraduneyti.is/acts-of-law/nr/17 The website of the administrative procedures act no. 37/1993
Ireland	http://www.dohc.ie/omoi/clinical_trials/ The website of the Department of Health and Children	http://www.imb.ie The website of the Irish Medicines Board. http://www.dohc.ie/issues/clinical_trials_2004 The website where the standard application form (Form 1) to be used for all applications to an EC can be found. http://www.dohc.ie/issues/clinical_trials_2004/ethics_committees.html The website with the list of recognised ethics committees in Ireland

Italy	https://oss-sper-clin.agenziafarmaco.it/faq/FAQ_ING.htm#accesso#accesso The website of the National Monitoring Centre for Clinical Trials (run by the *Agenzia Italiana del Farmaco*)	http://www.ministerosalute.it The website of the Italian Ministry for Health (*Ministero della Salute*) http://www.palazzochigi.it/bioetica The website of the National Bioethics Committee (*Comitato Nazionale per la Bioetica*) http://www.unich.it/fnace The website of the National Federation of Ethics Committees (*Federazione Nazionale dei Comitati di Etica*) http://www.iss.it/scf1 The website of the National Institute of Health (*Istituto Superiore di Sanità*)
Latvia	http://www.vza.gov.lv The website of the State Agency of Medicines	http://www.ttc.lv/New/lv/tulkojumi/E0050.doc The website where an English translation of the law is available
Lithuania	http://bioetika.sam.lt/index.php?1462798423 The website of the Lithuanian Bioethics Committee	http://www.vvkt.lt The website of the State Medicines Control Agency (SMCA), the competent authority
Malta	http://www.sahha.gov.mt/pages.aspx?page=134 The website of the Health Ethics Committee	http://www.doi.gov.mt The website where the Regulations can be accessed. http://www.medicinesauthority.gov.mt The website of the Maltese Medicines Authority
The Netherlands	http://ccmo-online.nl The website of the Central Committee on Research Involving Human Subjects (CCMO) http://www.ccmo-online.nl/hipe/uploads/downloads_cati/Instruction%20manual%20versie%202.pdf The website where the instruction manual for applications for clinical trials can be found.	http://www.cbg-meb.nl The website of *College ter Beoordeling van Geneesmiddelen* (CBG), the Dutch competent authority http://www.ceg.nl/cgi-bin/orga.pl?id=58 The website of the Dutch Society of Research Ethics Committees (NVMETC) https://toetsingonline.ccmo.nl The website (*ToetsingOnline*) where the electronic SUSAR-form will be found and which is currently operational for submissions to the CCMO and accredited METCs.

Norway	http://www.etikkom.no The website of the three national ethics committees including the National Committee for Medical Research Ethics. http://www.etikk.no/	http://www.legemiddelverket.no The website of the Norwegian Medicines Agency (*Legemiddelverk*), the competent authority http://www.lovdata.no/for/sf/ho/xo-20030924-1202.html The website of the Norwegian Regulation relating to clinical trials on medicinal products for human use (Norwegian only) http://www.ub.uio.no/ujur/ulovdata/lov-20060630-056-eng.pdf The Norwegian Regulation relating to clinical trials on medicinal products for human use
Poland	http://www.mz.gov.pl/wwwmzold/index?ml=en The website of the Ministry of Health (providing some guidance on ethical review of a clinical trial for an investigational medicinal product)	http://www.urpl.gov.pl The website of the competent authority http://www.nil.org.pl/xml/nil/wladze/str_zl/zjazd7/kel Guidelines on Scientific Research and Biomedical Experiments http://www.bioetyka.am.wroc.pl/ang/ The website of the Bioethics Commission at Wroclaw Medical University
Portugal	http://www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/CEIC Guidelines on submitting an application to the National Research Ethics Committee http://www.ceic.pt The website of the National Research Ethics Committee	http://www.infarmed.pt The website of the *Instituto Nacional de Farmacia e do Medicamento* (INFARMED), which is the Portugese Regulatory Agency
Slovakia	http://www.sukl.sk The website for the SIDC, the competent authority.	http://www.health.gov.sk The website of the Slovak Ministry of Health
Slovenia	http://www.kme-nmec.si/ The (new) website of the National Medical Ethics Committee (NMEC)	http://www.jazmp.si The website of the competent authority http://mz.gov.si The website of the Agency of the Republic of Slovenia for Medicinal Products and Medical Devices (*Ministrstvo za zdravje*)

Spain	Not available	http://www.agemed.es The website of the Spanish Medicines Agency, the competent authority http://www.msc.es The website of the Spanish Ministry of Health.
Sweden	http://www.epn.se The website where the application form to the relevant EC (Board for Ethics Review) is available http://www.forskningsetikprovning.se	http://www.lakemedelsverket.se http://www.mpa.se The website of the Medical Products Agency (*Lakemedelsverket*)
UK	http://www.nres.npsa.nhs.uk/home The website of the National Research Service (NRES) https://www.myresearchproject.org.uk/Signin.aspx The website of the Integrated Research Application System (IRAS) http://www.ukcrn.org.uk/index/clinical/csp.html The website of the National Institute for Health Research (NIHR) Coordinated System for gaining NHS Permission (CSP)	http://mhra.gov.uk The website of the Medicines and Healthcare Regulatory Agency.

Annex 3 – Tabulations of country requirements for initial applications to ECs

Austria

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	Yes
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	Yes
1.5	Copy of ethics committee opinion in the MS concerned when available		No
1.6	Copy of any scientific advice	Yes	Yes
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes
1.8	Will accept application to EC in English	Yes	No
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	Yes	Yes
3.4	Ethical assessment made by the principal/coordinating investigator	***No***	***Yes***
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	No
4.3	Simplified IMPD for known products.	No	No
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	Yes
4.5	Outline of all active trials with the same IMP	***Yes***	***No***
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	***Yes***	***No***
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	No
	4.7.2 Certification of GMP status of active biological substance	***Yes***	***No***
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	No
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	No
4.9	Viral safety information and data	***Yes***	***No***
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	No
4.11	TSE Certificate when applicable	***Yes***	***No***
4.12	Examples of the label in the national language	No	No

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site	Yes	Yes
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	***Yes***	***No***
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	***No***	***Yes***
7	**Additional country-specific documents**		
	n/a		

Cyprus

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		
1.2	Covering letter	Yes	
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	No	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English		Yes
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	Yes	
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	***No***	***Yes***
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	***No***	***Yes***
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	Yes	Yes
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	Yes	Yes
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	***No***	***Yes***
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site		Yes
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	Yes	Yes
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	
7	**Additional country-specific documents**		
	n/a		

Denmark

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		
1.2	Covering letter	No	
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	No	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English		No
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	No	
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	No	
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	No	
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	No	
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	No	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	Electronically completed notification form		Yes
	Documentation of the identity of the applicant		Yes
	A statement that the chief investigator has a profession acknowledged for performance of research or that he is involved in actual research work.		Yes
	Copy of application to CA		Yes
	Documentation of the notifier's medical or dental training (certificate of graduation or authorization		Yes
	Description of procedures for communicating oral information to participants		Yes
	Protocol version in Danish language (meeting Danish legal requirements)		Yes
	Protocol summary for lay persons		Yes
	Questionnaires		Yes

Estonia

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		Yes
1.2	Covering letter	Yes	
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	No	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English	Yes	Yes
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	Yes
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	No	
6.6	Agreement between the investigators and the trial sites	Yes	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	Case report form (CRF)		Yes

Finland

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		
1.2	Covering letter	Yes	
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English	No	No
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	No	
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	No	
6.6	Agreement between the investigators and the trial sites	No	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	information on how the consent will be obtained		Yes
	other material to be given to the subject (CRFs, patient diaries etc		Yes
	description of the personal data file (523/1999) in accordance with 10 § of the Personal Data Act		Yes
	statement by the person in charge of the investigation on the quality of trial facilities and equipment of the trial sites		Yes
	statement on the suitability of the person in charge of the investigation and the responsible investigators at other trial sites		Yes
	The sponsor of the trial shall have a contact person in Finland for communication related to the application procedure		Yes
	rationale for the trial in cases where subjects who are not able to give their informed consent are included		Yes

Germany

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		Yes
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	Yes
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English		No
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator	No	
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	***No***	***Yes***
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	Yes	

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects		Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	Yes	Yes
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	Information on professions of investigators who are no physicians		Yes
	Justification for adequate gender distribution of participants		Yes
	Information on negative opinions of responsible ECs or rejections of competent authorities of other member states		Yes
	Confirmation of instruction of subjects about data processing		Yes
	Declaration on inclusion of persons depending on sponsor if applicable		Yes
	Information on possible economic interests of investigators in connection with the IMPs		Yes
	Information on suitability of sites		Yes
	Description of procedure to avoid that patients will participate in other clinical trials at the same time		Yes
	Description of examination procedures deviating from normal clinical practice		Yes
	Declaration on data protection		Yes
	List of participating ECs (for multi-centre trials)		Yes

Hungary

1	General	ENTR/CT2	Online guidance*
1.1	Receipt of confirmation of EudraCT number	Yes	Yes
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	No	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		Yes
1.8	Will accept application to EC in English	Yes	Yes
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	Yes	Yes
3.4	Ethical assessment made by the principal/coordinating investigator	No	
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	***No***	***Yes***
4.3	Simplified IMPD for known products.	***No***	***Yes***
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	***No***	***Yes***
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	***No***	***Yes***
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	***No***	***Yes***
	4.7.2 Certification of GMP status of active biological substance	***No***	***Yes***
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	***No***	***Yes***
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	***No***	***Yes***
4.9	Viral safety information and data	***No***	***Yes***
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	***No***	***Yes***
4.11	TSE Certificate when applicable	***No***	***Yes***
4.12	Examples of the label in the national language	***No***	***Yes***

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site		Yes
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	Yes	Yes
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	Disk with XML file for EudraCT		yes
	Protocol signature page signed by the investigators		yes
	Age of subjects exactly		yes
	Permission of the director of the hospital		yes
	letter of intent by the principal investigator regarding compliance with protocol, GCP, CA and EC stipulations		yes
	statement of admission by the head of the care provider		yes

Iceland

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		
1.2	Covering letter		
1.3	Application form		Yes (national and EudraCT)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions		
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English		No
2			
2.1	Informed consent form		Yes
2.2	Subject information leaflet		Yes
2.3	Arrangements for recruitment of subjects		
3			
3.1	Protocol with all current amendments		Yes
3.2	Summary of the protocol in the national language		Yes
3.3	Peer review of trial when available		
3.4	Ethical assessment made by the principal/coordinating investigator		
4			
4.1	Investigator's brochure		
4.2	Investigational Medicinal Product Dossier (IMPD)		Yes
4.3	Simplified IMPD for known products.		
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community		Yes
4.5	Outline of all active trials with the same IMP		
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation		
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality		
	4.7.2 Certification of GMP status of active biological substance		
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive		
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected		
4.9	Viral safety information and data		
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals		
4.11	TSE Certificate when applicable		
4.12	Examples of the label in the national language		

5			
5.1	Facilities for the trial		
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)		
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)		
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial		Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor		
6.3	Compensations to investigators		
6.4	Compensations to subjects		
6.5	Agreement between the sponsor and the trial site		
6.6	Agreement between the investigators and the trial sites		
6.7	Certificate of agreement between sponsor and investigator when not in the protocol		Yes
7	**Additional country-specific documents**		
	Copy of application to CA (IMCA)		Yes
	Application to be signed by Principle Investigator		Yes
	Application to be signed by Head of Institute		Yes
	Application to be signed by sponsor		Yes
	Training program for staff		Yes

Ireland

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes (National)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English		Yes
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	
3.3	Peer review of trial when available	Yes	
3.4	Ethical assessment made by the principal/coordinating investigator	No	
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	
4.5	Outline of all active trials with the same IMP	Yes	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	Yes	
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	
6.4	Compensations to subjects	Yes	
6.5	Agreement between the sponsor and the trial site	Yes	
6.6	Agreement between the investigators and the trial sites	Yes	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	
7	**Additional country-specific documents**		
	Site-specific assessment form for each site		Yes
	Summary, synopsis or diagram of protocol in non-technical language		Yes
	Details of any Data Monitoring Committee		Yes
	Sample diary card / patient card		Yes
	(non) validated questionnaires		Yes
	Advertisement material for research participants		Yes
	Letter of invitation for participants		Yes

Italy

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	Yes
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes (National)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	Yes[1]
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice	***No***	***Yes***[1]
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes
1.8	Will accept application to EC in English	No	No
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	***No***	***Yes***
3.4	Ethical assessment made by the principal/coordinating investigator	***No***	***Yes***
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	***No***	***Yes***[1]
4.3	Simplified IMPD for known products.	***No***	***Yes***[1]
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	Yes
4.5	Outline of all active trials with the same IMP	Yes	Yes
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	Yes	Yes[1]
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	Yes	Yes[1]
	4.7.2 Certification of GMP status of active biological substance	***No***	***Yes***[1]
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	Yes	Yes[1]
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	***No***	***Yes***[1]
4.9	Viral safety information and data	***No***	***Yes***[1]
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	Yes	Yes[1]
4.11	TSE Certificate when applicable	Yes	Yes[1]
4.12	Examples of the label in the national language	Yes	Yes[1]

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site	***No***	***Yes***
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	No	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	Material to distribute to patients		Yes
	Previous clinical trials and data about clinical use, if not in IB		Yes[2]
	Overall Risk-Benefit assessment if not in IB		Yes[2]
	AIFA (Italian CA) summarizing letters		Yes[1]

1 required for central EC only

2 required for local ECs only

Latvia

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	Yes
1.2	Covering letter	Yes	
1.3	Application form	Yes	Yes
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	No	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes
1.8	Will accept application to EC in English	Yes	Yes
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	No	
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator	No	
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	No	
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	Yes	
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site	Yes	Yes
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	No	
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	No	
6.6	Agreement between the investigators and the trial sites	No	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	CVs of sub-investigators		Yes
	agreement of the administration of the medical establishment		Yes

Lithuania

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	Yes
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	Yes
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes
1.8	Will accept application to EC in English	***Yes***	***No***
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	Yes	Yes
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	Yes	
4.3	Simplified IMPD for known products.	Yes	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	Yes
4.5	Outline of all active trials with the same IMP	***No***	***Yes***
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	Yes	Yes
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	Yes	Yes

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	
6.4	Compensations to subjects	Yes	
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	Yes	Yes
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	
7	**Additional country-specific documents**		
	National application form (in Lithuanian and English)		Yes
	National cover page		Yes
	Authorization (license) of health care institution (trial site)		Yes
	Statement of head of trial site that the institution is authorised and has relevant facilities to conduct all the procedures anticipated in the trial protocol.		Yes

Malta

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	Yes
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes
1.8	Will accept application to EC in English	Yes	Yes
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	No	No
3.3	Peer review of trial when available	Yes	Yes
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	
4.5	Outline of all active trials with the same IMP	Yes	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	Yes	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	Yes	
4.12	Examples of the label in the national language	Yes	Yes

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site	Yes	Yes
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	Yes	Yes
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	Yes
7	**Additional country-specific documents**		
	Submission checklist completed		Yes
	Proof of fees payment		Yes
	CD-ROM with electronic copies of all documents		Yes
	Proof of establishment of the sponsor or its legal representative in the Community		Yes
	Informed consent letter of authorisation holder when cross-referencing is made		Yes
	All available contact numbers of investigators		Yes
	The intention of the sponsor / investigator on whether to continue to supply the product or other therapies, for example, supportive therapy, after the trial ends together with the time periods and conditions involved		Yes
	Letter signed by Head of department(s)/ Consultant(s) concerned when patients / relatives and / or records of their department are involved.		Yes

The Netherlands

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	Yes
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	Yes
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice	Yes	Yes
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	Yes
1.8	Will accept application to EC in English	Yes	
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	Yes	Yes
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	Yes	Yes
4.3	Simplified IMPD for known products.	Yes	Yes
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	Yes
4.5	Outline of all active trials with the same IMP	Yes	Yes
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	Yes	Yes
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	Yes	Yes
	4.7.2 Certification of GMP status of active biological substance	Yes	Yes
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	Yes	Yes
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	Yes	Yes
4.9	Viral safety information and data	Yes	Yes
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	Yes	Yes
4.11	TSE Certificate when applicable	Yes	Yes
4.12	Examples of the label in the national language	Yes	Yes

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site	***No***	***Yes***
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Upon request	Yes
6.6	Agreement between the investigators and the trial sites	Upon request	Yes
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Upon request	
7	**Additional country-specific documents**		
	National application form ('ABR-form'; via online system)		Yes
	Questionnaires, patient diary, patient card etc.		Yes
	Independent doctor(s) résumé(s)		Yes
	Local feasibility declaration form the Board of Directors/Management per centre		Yes

Norway

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	
1.2	Covering letter	Yes	
1.3	Application form	Yes	Yes
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions		Yes
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English		No
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	No	
3.3	Peer review of trial when available	Yes	
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)		
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community		
4.5	Outline of all active trials with the same IMP	Yes	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	No	
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	Yes
6.6	Agreement between the investigators and the trial sites	Yes	Yes
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	Yes
7	**Additional country-specific documents**		
	questionnaire or other instruments for obtaining information (if applicable)		Yes
	Cope of notification to the Norwegian Medicines Agency		Yes

Poland

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	Yes	
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	
1.5	Copy of ethics committee opinion in the MS concerned when available	n/a	
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes	
1.8	Will accept application to EC in English	No	No
2	**Subject related**		
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	
3	**Protocol related**		
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator		
4	**IMP related**		
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	Yes	
4.3	Simplified IMPD for known products.	Yes	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	
4.5	Outline of all active trials with the same IMP	Yes	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	Yes	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	Yes	
	4.7.2 Certification of GMP status of active biological substance	Yes	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	Yes	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	Yes	
4.9	Viral safety information and data	Yes	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	Yes	
4.11	TSE Certificate when applicable	Yes	
4.12	Examples of the label in the national language	Yes	

5	**Facilities & staff related**		
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site	Yes	Yes
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	
6.4	Compensations to subjects	Yes	
6.5	Agreement between the sponsor and the trial site	Yes	
6.6	Agreement between the investigators and the trial sites	Yes	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	
7	**Additional country-specific documents**		
	In case of multi-national trials, names of institutions in countries where trial is to be conducted		Yes
	PI's commitment to obtain consent from subjects		Yes
	Model form of patient's acceptance of insurance terms		Yes
	Model of patient's statement on data processing		Yes
	List of expected therapeutic/scientific benefits of the trial and benefits for the participants		Yes
	Sponsor's agreement to accept invoices without signature		Yes

Slovenia

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		
1.2	Covering letter	Yes	
1.3	Application form		
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	No	
1.5	Copy of ethics committee opinion in the MS concerned when available		
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English		Yes
2			
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3			
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	Yes	
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4			
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)		
4.3	Simplified IMPD for known products.	Yes	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	
4.5	Outline of all active trials with the same IMP		
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5			
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	Yes
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	***No***	***Yes***
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	
6.6	Agreement between the investigators and the trial sites	No	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	The name and professional qualifications of the doctor responsible for safety of human subjects in the study		Yes
	Safety arrangements (usually specified in protocol and/or IB)		Yes
	Arrangements for confidentiality of personal data and the right to privacy		Yes
	Any previous ethical review by the same or other ethics committee for the same or related research.		Yes
	Statement by the Head of the institution or department where the study is to be conducted that he / she agrees to the study being conducted		Yes
	Statement of the responsible investigator that he / she would adhere to the principles of the Helsinki Declaration, the Oviedo Convention on Human Rights and Biomedicine and the Slovene Code of Medical Deontology. Declaration of the existing or potential conflict of interests.		Yes

Sweden

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number	No	
1.2	Covering letter	Yes	
1.3	Application form	Yes	Yes (national)
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	
1.5	Copy of ethics committee opinion in the MS concerned when available	n/a	
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		Yes
1.8	Will accept application to EC in English		No
2	**Subject related**		
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes
3	**Protocol related**		
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes
3.3	Peer review of trial when available	No	
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	
4	**IMP related**		
4.1	Investigator's brochure	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	
4.3	Simplified IMPD for known products.	No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	Yes	Yes
4.5	Outline of all active trials with the same IMP	No	
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	
	4.7.2 Certification of GMP status of active biological substance	No	
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	
4.9	Viral safety information and data	No	
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals		
4.11	TSE Certificate when applicable	No	
4.12	Examples of the label in the national language	No	

5	**Facilities & staff related**		
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	Yes
6.4	Compensations to subjects	Yes	Yes
6.5	Agreement between the sponsor and the trial site	Yes	
6.6	Agreement between the investigators and the trial sites	No	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	Protocol summary in lay language		Yes
	Questionnaires		Yes
	Certificate from operations manager concerning resources at site		Yes

United Kingdom

1	General	ENTR/CT2	Online guidance
1.1	Receipt of confirmation of EudraCT number		
1.2	Covering letter	Yes	Yes
1.3	Application form	Yes	Yes
1.4	List of Competent Authorities within the Community to which the Application has been submitted and details of decisions	Yes	
1.5	Copy of ethics committee opinion in the MS concerned when available	n/a	n/a
1.6	Copy of any scientific advice		
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor		
1.8	Will accept application to EC in English	n/a	n/a
2	**Subject related**		
2.1	Informed consent form	Yes	Yes
2.2	Subject information leaflet	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	If applicable
3	**Protocol related**		
3.1	Protocol with all current amendments	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	If applicable
3.3	Peer review of trial when available	Yes	If applicable
3.4	Ethical assessment made by the principal/coordinating investigator	Yes	Yes
4	**IMP related**		
4.1	Investigator's brochure	Yes	If applicable
4.2	Investigational Medicinal Product Dossier (IMPD)	No	No
4.3	Simplified IMPD for known products.	No	No
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community	No	No
4.5	Outline of all active trials with the same IMP	No	No
4.6	If IMP manufactured in EU and if no marketing authorisation in EU		No
	4.6.1 Copy of the manufacturing authorisation referred to in Art. 13(1) of the Directive stating the scope of this authorisation	No	No
4.7	If IMP not manufactured in EU and if no marketing authorisation in EU		
	4.7.1 Certification of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP or that each production batch has undergone all relevant analyses, test or checks necessary to confirm its quality	No	No
	4.7.2 Certification of GMP status of active biological substance	No	No
	4.7.3 Copy of the importer's manufacturing authorisation as referred to in Art. 13(1) of the Directive	No	No
4.8	Certificate of analysis for test product in exceptional cases		
	4.8.1 where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	No
4.9	Viral safety information and data	No	No
4.10	Applicable authorisations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	No
4.11	TSE Certificate when applicable	No	No
4.12	Examples of the label in the national language	No	No

5	**Facilities & staff related**		
5.1	Facilities for the trial	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes
5.3	CV of each investigator responsible for the conduct of a trial in a site in the MS concerned (principal investigator)	Yes	No
5.4	Information about supporting staff in each site		
6	**Finance related**		
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes
6.3	Compensations to investigators	Yes	
6.4	Compensations to subjects		Yes
6.5	Agreement between the sponsor and the trial site	Yes	
6.6	Agreement between the investigators and the trial sites		
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	
7	**Additional country-specific documents**		
	Specific (national) application form		Yes
	Site−Specific Information Form (for SSA)		If applicable
	GP/Consultant information sheets or letters		Yes
	Letter from sponsor		If applicable
	Letter from statistician		If applicable
	Letter from funder		If applicable
	Details of any Data Monitoring Committee		If applicable
	Sample diary card/patient card		If applicable
	Validated questionnaire		If applicable
	Non−validated questionnaire		If applicable