Detailed Recommendation on the Pharma Priority Area

Towards more harmonisation and single submission per Member State for Clinical Trial Application and Amendments (23)

EU PROJECT ON BASELINE MEASUREMENT AND REDUCTION OF ADMINISTRATIVE COSTS

26th June 2009

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An introduction to Administrative Burden reduction

This Recommendation is the culmination of a process of analysis using the EU Standard Cost Model methodology. This is an EU methodology for measuring administrative costs imposed by legislation – both existing and planned. This methodology is based on the Standard Cost Model (SCM) applied in several Member States. Adapted to EU needs and resources, the EU SCM takes into account the fact that EU legislation often replaces 27 different national legislations and thus decreases operating costs at EU level.

The EU SCM breaks down administrative costs imposed by legal acts into components that can be assessed with reasonable accuracy. Those costs are then further differentiated on the basis of 'business-as-usual' (BAU) costs, i.e. costs that a business would incur irrespective of whether there is an Information Obligation (IO), and those costs which are the direct result of regulation. The latter constitute the administrative burden.

The total administrative cost is calculated as P×Q, where:

- Q is the number of times per year (occurrences) that each Information Obligation has to be complied with multiplied by the number of businesses;
- P is the administrative cost per business of complying with the obligation. P is the sum of internal costs, consultancy costs, equipment costs and overheads.

For this project, data for calculation of the administrative cost was collected in a sample of businesses in a limited number of Member States (generally six). These are the 'Measurement Countries'. This data was supplemented by existing, applicable data from Member States which had previously carried out SCM measurement (the 'Baseline Countries'). The data for the remaining EU Member States (the 'Extrapolation Countries') was estimated through extrapolation.

The ensuing Recommendations have been defined as Type I and/or Type II. Distinguishing between Type I and Type II reduction opportunities is useful because this provides all parties involved with a clear view of the ownership of the reductions.

Type I reductions refer to changes at EU level (legal as well as changes to EU level implementing practices) and are clearly owned and adopted at EU level, though they may subsequently require transposition at national level.

Type II refers to changes at Member State level in the way transposition is approached and in implementing measures. They will deliver Improved/Good Practice in Member State transposition and implementation, and thus simplification of the business process at national level. Type II recommendations are clearly for adoption and implementation by the Member States.

For more information on the Action Programme for Reducing Administrative Burdens in the EU and the EU Standard Cost Model, see http://ec.europa.eu/enterprise/admin-burdens-reduction/home_en.htm.

Summary Table

Legislative act	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Art. 9 par.1; Art 9 par. 2
Information Obligation	1) "Request for authorisation to commence a clinical trial" 2) "Notification of substantial amendments to the protocol after the commencement of the trial"
Regulatory origin	EU Origin
Recommendation name	Towards more harmonisation and single submission per Member State for Clinical Trial Application and Amendments
Recommendation addressed to:	National institutions and EU- institutions
Scale of the Recommendation	Structural change
Target group - Businesses targeted by the information obligation(s)	All pharmaceutical companies are affected
Original population ('As-is')	IO 1) 20,619 IO 2) 17,049
Affected population ('To-be')	IO 1) 20,619 IO 2) 17,049
Specifically targeted at Small and Medium Sized Enterprises	No
Current administrative cost	IO 1) €78,336.600

	IO 3) €21,776.800
Current administrative burden	IO 1) €73,631.500 IO 2) €21,776.800
Current "business as usual" factor ('As-is')	IO 1) 6,01% IO 2) 0%
Future "business as usual" factor ('To-be')	IO 1) 8,01% IO 2) 0%
Expected administrative burden reduction in %	IO 1) 26,58% IO 2) 22,94%
Expected administrative burden reduction in euro	IO 1) €19.572.394 IO 2) €4.994.948
Source of the recommendation	Source of recommendation: Consortium

1. Background and underlying problem

1.1 Legal context

Directive 2001/20/EC[1] establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products. The Directive provides a framework for clinical trials on medicinal products in Europe, establishing a common legal and regulatory reference point for all Member States, responsible parties, and citizens.

Providing greater protection to subjects participating in clinical trials, ensuring quality of conduct and harmonising the regulation and conduct of clinical trials throughout Europe are important aims of the Clinical Trial Directive. Since 2001 this has improved significantly with Directive 2001/20 coming into force throughout the Member States.

In 2005 the European Commission published, in consultation with the Member States, more detailed guidance on:

- The format and contents of the IO 'Request for authorisation to commence a clinical trial' (named hereafter as 'Clinical Trial Authorisation Request') as well as the documentation to be submitted to support that request;
- The presentation and content of notifications of substantial proposed amendments to the protocol;
- The declaration of the end of the clinical trial.

This detailed guidance is intended to provide Recommendations on the format and content of the information that needs to be delivered.

[1] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0020:EN:HTML

1.2 Problem description

National differences blur European guidance

Guidance exists at European level on what to include in the content of the Clinical Trial Authorisation Request – the EudraCT database is well standardised, as well as the scientific information required. However, there are substantial additional differences at the level of Member States and Local Ethics Committees within Member States (for example, a detailed quality description of the investigators may be required. The specific requirements of various national ethics committees can also be hard to ascertain). As a result, companies spend a great deal of time retrieving the relevant information, modifying it, and writing the request.

The definition of a "substantial amendment" is far from clear and leaves pharmaceutical companies too much room for interpretation

Differences also exist in the definition and the assessment of "substantial amendments". The aim of the legislation was to allow the sponsor to notify the authorities only if a change has a substantial impact on how the clinical trial is conducted. However, there are many differences between Member States in the interpretation of what could be considered as a "substantial amendment". This leads to a situation whereby the company considers something as a substantial change more often than it actually should in order to avoid problems of non-compliance. This leads to a situation where more notifications are made than necessary.

Pharmaceutical companies are unclear about where to submit the reporting of requests and amendments.

Currently, we observe that companies submit all information to the national competent authorities (NCA) of the Member States concerned and to all local or regional Ethics Committees involved.

In conclusion more harmonisation regarding the content of the information requested at Member State level as well as simplifying the submission of information would certainly reduce the burden for companies.

The affected target group for this Recommendation is the pharmaceutical industry who is in the role of sponsor, i.e. the companies that take responsibility for the initiation, management and/or financing of a clinical trial. Both innovative as well as generic companies are affected, but as innovative companies are more heavily involved in Clinical Trials the impact is higher for this segment.

1.3 EU/Member State remit to act

Please note that the scope of this Recommendation is limited to the harmonisation of the content of the requested information for conducting clinical trials at Member State level, and providing solutions for the single submission of information per Member State in order to diminish the differences between the Member States.

Pharmaceutical businesses would ideally like a unified standard for clinical trials, with an approval process for multi-centre trials in more countries by a single competent authority and a single ethics committee which would then allow the trial to be run across the whole of the EAA. Although this would represent an extremely large reduction of administrative burden for businesses, the Consortium's Recommendation is not that far-reaching and respects the Member States' authority. Currently, each Member State has the authority to decide on the clinical trials that may be conducted in the Member State. This Recommendation respects the current autonomy of the Member States in making the final decision.

Therefore, the Consortium has come up with four different Recommendations. Some are Type 1 (EU remit to act) Recommendations and are considered as simple changes, while Type 2 (Member States remit to act) Recommendations may take longer to implement across all Member States.

- **Recommendation 1**: Review of the definition of "substantial amendment" in the legal act and improve guidelines by giving more instructions as to what could be considered 'substantial' (Type I Recommendation – EU remit to Act).

- **Recommendation 2**: Increase the harmonisation of content needed for Clinical Trial Authorisation Request by creating one single list of requirements per Member State

applicable for all NCA and ethics committees concerned (Joint Type 1/Type II Recommendation – EU/MS remit to Act)

- **Recommendation 3**: Enable a single submission of Clinical Trial Authorisation Requests and "substantial amendments" per Member State by submission to (1) the NCA, which will then dispatch to (2) national ethics committee and then to (3) local ethics committees (Type II Recommendation – MS remit to Act).

- **Recommendation 4**: Enable electronic submission of Clinical Trial Authorisation Requests and "substantial amendments". The Recommendation is to re-use administrative information, scanned documents, electronic signature (vs. digital) and to extend to all steps. (Type I Recommendation – EU remit to Act).

2. Reduction objective pursued and nature of the Recommendation

2.1 Recommendation 1: Review of the definition of substantial amendment

2.1.1 Objectives of the Recommendation 1

The objective of Recommendation 14 is to establish a clearer definition of "substantial amendments" in the legal act, including additional guidance with examples, to avoid multiple interpretation by the sponsor, national competent authority and Ethics Committees.

2.1.2 Description of Recommendation 1

Current situation: 'As-Is'

Amendments to the trial are regarded as "substantial" where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or,
- the quality or safety of any IMP used in the trial.

In all cases, an amendment is only to be regarded as "substantial" when any of the above criteria are met. Each amendment has to be evaluated on behalf of the sponsor as to whether the amendment will have a significant impact on the above areas.

The abovementioned definition of "substantial" leads in practice to many different interpretations. At Member State level and between Ethics Committees different interpretations are seen. It is the responsibility of the "sponsor" or any person acting on behalf of the sponsor to decide whether a change should be considered as substantial. Because of the different use of the criteria, generally more changes will be reported by the sponsor to ensure compliance with the legislation.

The problem lies in the definition of "significant impact". It is not clear what is considered as significant. Another reason lies in the fact that there is in general a risk-averse culture. Some sponsors have difficulty making decisions on which changes should be reported and which should not.

The topic of Clinical Trials and therefore also amendments to them are subject to cultural differences and interpretations. The current situation surrounding the reporting of amendments leads to several Member States initiatives providing more guidance.

France and Germany are currently working on guidance documents to help define which amendments should be considered as substantial. The UK provides clear examples based on the EU legislation and guidance. The examples mentioned above are good initiatives, but will lead to different approaches across the Member States.

Future situation: 'To-Be'

The Recommendation aims at two different targets:

1. Improvement of the definition of "significant impact" in the legal act.
2. Addition of an annex with a listing of examples of substantial amendments for each of the four categories to the "Detailed guidance for the Request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial, October 2005". As good practice for this, examples are available on the UK Medicines and Healthcare products Regulatory Agency (MHRA) website[2].

Due to the different characteristics of each clinical trial, the final judgement on whether or not an amendment should be considered as substantial should be made on a case by case basis. In the current situation this is the responsibility of the sponsor. It should remain so in future.

[2] http://www.mhra.gov.uk/index.htm

Good practice UK MHRA Website

On the website of the MHRA in the UK the sponsor is informed about the process of notifying substantial amendments. This website lists clear examples of amendments which would normally be considered as a "substantial amendment". The objective of this initiative is to give clear instructions, while avoiding too much reporting and keeping the responsibility for the final decision with the sponsor.

Examples of "substantial amendments" are grouped in the following categories on the MHRA website:

- Amendments related to protocol;
- Amendments related to trial arrangement;
- Amendments related to Investigational Medicinal Products (IMP);
- Changes to investigational medicinal product quality data;
- Changes to non-clinical pharmacology and toxicology data where this is relevant to the ongoing trials (i.e. altered risk/benefit assessment);
- Changes to clinical trial and human experience data where this is relevant to the ongoing trials (i.e. altered risk/benefit assessment).

A list of examples of "substantial amendments" per category as in the UK example could very well be used as a basis for a new annex in the "Detailed guidance for the request for authorisation of a clinical trial".

This Recommendation will have an impact on the number of substantial amendments that will be submitted as in the current situation, sponsors tend to report changes if they are in doubt. This would lead to a decrease in the number of "substantial amendments" reported.

2.2 Recommendation 2: Enhanced harmonisation of the content of Clinical Trial Authorisation Requests at MS level and across Member States".

2.2.1 Objectives Recommendation 2

The objective of Recommendation 2 is to harmonise at Member State level the information requested by all stakeholders, to avoid companies having to spend too much time to understand all the relevant ethics committees' requirements.

2.2.2 Description of Recommendation 2

Current situation: 'As-Is'

Detailed guidance on what to include in the content of the Clinical Trial Authorisation Request is available. For example, details are provided on the application form and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial. Additionally, for each Member State, there is a list of extra documentation required in addition to the basic request. However, guidance documents are in many cases no longer up-to-date. Additionally, across the Member States, Ethics Committees ask for different documentation, while, in some countries the submission process and application form differ between Local Ethics Committees. This is for example the case in Italy and Spain. In Germany, extensive notification procedures are in place at the federal level (in addition to the procedures with the competent authority). The situation as mentioned in Italy, Germany and Spain are just examples of situations which increase the burden for companies, but in fact most countries deal with these country-specific harmonisation problems.

Finally, the level of detail and language requirements for the same kind of information can differ between Member States. Although Member States have the right to ask for specific information the aim should be to harmonise at least the language specifications for the acceptance of the protocol in case of multi-centre trials, e.g. trials where multiple countries are involved. In some countries, for example in Spain, a translation of the protocol in Spanish is still required.

Future situation: 'To-Be'

A. Improvement in the current situation can be reached by the following initiatives at country level:

- Agreement and harmonisation across national competent authorities and central and local ethics committees about the information required for the Clinical Trial Authorisation Request. Additional local committees should avoid requesting further information.

- Detailed communication about the requirements on the NCA/Central Ethics Committees websites. A list of the information required is not enough; guidelines for specific content should also be provided:
- As much harmonisation as possible among the Member States about the way certain information should be sought. The level of harmonisation should at least be reached for multi-centre trials with acceptance of the protocol in English only..

B. Improvement in the current situation can be reached by the following initiatives at EU level by changing the EU legal act:

- The EU guidelines should describe the documents which may be submitted in English. The proposal is at least to do this for the Clinical Trial Protocol in case of multi-centre trials in more than one country
- The EC should provide stricter guidelines on the format and requirement of the core documents which are part of the request, such as the update of the Investigator's Brochure to avoid the many differences between countries. The EC has provided guidance as to the content and format of the Clinical Trial Application. However this still leaves room for too much interpretation and each country fills in the specific requirements in their own way.

Example of good practice in the Netherlands

The Netherlands is an example of a country where there is already harmonisation between the requirements of the national competent authority and the local ethics committees. The Ministry of Health, Welfare and Sports is the national competent authority. The Central Committee on Research inv. Human Subjects (CCMO) takes the role of the central ethics committee. Furthermore, the Netherlands has five regions with 30 accredited ethics committees. For some clinical studies, the Central Committee on Research inv. Human Subjects (CCMO) takes on the role of the accredited ethics committee.

The dossier that should be submitted to the Competent Authority is exactly the same as the one required by the accredited ethics committee. The requirements for the dossier, including detailed guidance, are described very clearly on the website of the central ethics committee.

Implementing this Recommendation successfully at Member State level, as well as improving the harmonisation within the Member State, will significantly reduce the time spent by companies to prepare the "Request for authorisation to commence a clinical trial". Time savings are also anticipated by identifying local ethics committee wishes, and therefore overall better guidance on country level.

2.3 Recommendation 3: Enable a single submission of Clinical Trial Authorisation Requests and "substantial amendments" per Member State

2.3.1 Objectives Recommendation 3

The objective of Recommendation 3 is to reduce the number of stakeholders involved where the companies need to submit information related to Clinical Trial Authorisation Requests and "substantial amendments".

2.3.2 Description of Recommendation 3

Current situation: as-is

In some countries it is unclear to which Ethics Committees pharmaceutical companies should submit their Clinical Trial Authorisation Request. Also, in many countries, the Clinical Trial Authorisation Request and substantial amendments should be submitted to the National Competent Authority and the multiple Ethics Committees in case of a multi-centre trial, which multiplies the administrative burden

Future situation: to-be

Improvement in the current situation can be achieved by the following initiatives on country level:

- Guarantee that all requests can be submitted to the National Competent Authority, which will in turn communicate to all Ethics Committees concerned in the Member State. A successful implementation of Recommendation 3 requires already an implementation of Recommendation 2.

The national competent authority will receive the Clinical Trial Authorisation Request from the company and sends this request to the Central Ethics Committee, which in turn informs all other Ethics Committees involved. The Central Ethics Committee takes the coordinating role towards the regional/local Ethics Committees. The process would be facilitated by already having a streamlined approval procedure for the Ethics Committee involved. The same situation will apply for submission of substantial amendments.

Industry prefers to have a good and effective contact with the National Competent Authority, preferably by having the National Competent Authority coordinating the interaction and the dialogue with the Ethics Committee. Examples of countries where there is already a good dialogue between the pharmaceutical companies and the National Competent Authority are Germany and France. Next to a good dialogue with the Industry have these Competent Authorities a good dialogue with the Ethics Committee.

This Recommendation has an impact on the time spent related to the submission of the request.

Examples of good practices in the Netherlands and Denmark

In terms of effective organisation between Ethics Committees are the Netherlands and Denmark good examples. Although in hereafter mentioned examples the company submits the application to both the National Competent Authority and the accredited Ethics Committee, the process in Denmark and the Netherlands can be seen already as a good example on how to simplify the reporting process.

<u>The Netherlands: only one assessment from one accredited ethics committee is required in multicenter trials</u>

In the Netherlands, there are 30 local ethics committees. Of note, only the assessment of one accredited ethics committee is required from a regulatory point of view for multicentre studies. The decision of one accredited Ethics Committee is sufficient and this means that other Ethics Committees in the Netherlands don't conduct this assessment again. However it's always possible that once the decision is reached the

management of a participating centre can (possibly after consulting its own MREC) decide not to participate in the research for other reasons (for example, feasibility).

This is a good starting point for further simplification of the submission process.

Denmark: one coordinating Ethics Committee

According to the Danish regulations the Clinical Trial Authorisation Request for a multi-centre trial should be submitted to the Regional Ethics Committee in the area where the leading investigator works, along with information about which other hospitals/clinics are involved in Denmark. This Regional Ethics Committee will then distribute the protocol to the other Regional Ethics Committees in the area where hospitals/clinics are involved in the trial. Other Regional Ethics Committees are asked for their opinion within 30 days. The Regional Ethics Committee to which the multi-centre project is submitted is responsible for final approval of the project, on behalf of all other Ethics Committees involved, and will take care of coordinating the various comments that are submitted from the other Regional Ethics Committees. This speeds up the approval process and simplifies the submission procedure for the company vs. countries where there is no communication between the various Ethics committees.

2.4 Recommendation 4: Enable an electronic submission of Clinical Trial Authorisation Requests and substantial amendments

2.4.1 Objectives Recommendation 4

The objective of Recommendation 4 is to allow the electronic submission of Clinical Trial Authorisation Requests at Member State Level[3].

[3] The scope of this Recommendation is based on enabling electronic submission on the level of an individual Member State and not on one portal that is being used by all Member States.

2.4.2 Description of Recommendation4

Current situation: 'as-is'

The Clinical Trial Authorisation Request contains several parts: 1. Covering letter, 2. EudraCT number and, application form, 3. several attachments (e.g. arrangement for recruiting subjects, protocol, IMP, investigator information, staff, finance).

Specific core information about the Clinical Trial is registered within the EU in the EudraCT database. The purpose of EudraCT is to achieve transparency within the EU and it doesn't aim to be the system to support full electronic submission for the full request.

Registering of this core information in EudraCT works as follows. Before submitting the request to the competent authorities, the company needs to obtain a unique EudraCT number from the EudraCT database. This number will identify the protocol for a trial whether conducted at a single site or at multiple sites in one or more Member States. After completing and checking the national requirements, the applicant should print the completed form and send it as part of the application to the competent authority of each Member State where the trial is to be conducted. The company has to save the core data set or the full application form data set, according to national requirements as an XML file and send a copy of this XML file, on a disk, with the request. The competent authority has the responsibility to enter the final data into the EudraCT database after validation of the request.

The above procedure means in practice that the submission of the full request will take place on paper and/or CD-ROM in most Member States. Most of the time the dossier needs to be submitted to the national competent authority and to all the Member States concerned.

Digital submission on CD-ROM

In some of the countries digital submission is possible, often on CD-ROM, for example in the Netherlands and the UK. Companies consider this already as a large improvement. The

Netherlands does not allow submission via e-mail yet because the covering letter still requires an authentic signature (original on paper).

The same situation applies for substantial amendments.

Future situation: to-be

Require online submission of Clinical Trial Authorisation Requests and substantial amendments.

To make this possible authentication and electronic signature are crucial elements. Online submission could not only be beneficial for pharmaceutical companies in reducing time spent and costs for sending the request or amendment, but could also facilitate worksharing between NCAs and Ethics Committees within the Member States. Requests can be easily taken from a central place and reviews and opinions can be shared.

An example of a good practice: new IT system in Spain

According to the Spanish ministry of Health, a new IT system designed to help ethics committees process clinical trial requests for medicines should be up and running March 09. After approval of the Ethics Committees in Spain the system will be implemented. This means full online submission of the request to commence a clinical trial, and substantial amendments in the future. Spanish authorities have been preparing this since 2006.

3. Impact

3.1 Impact Recommendation 1: Review of the definition of substantial amendment

The aim of Recommendation 1 is to establish a clearer definition of substantial amendments in the legal act, including additional guidance with examples, to avoid multiple interpretations by competent authority of the Member States and Ethics Committees. This Recommendation will affect the IO 'Notification of a substantial amendment'.

This Recommendation will have impact on the number of substantial amendments that will be submitted as in the current situation Sponsors report in case of any doubt the change. Through the implementation of Recommendation 1 the number of substantial changes reported will decrease.

3.1.1 Price

This Recommendation will not affect the time spent on the preparation of the substantial amendment,

3.1.2 Tariff

In the current situation ('as-is') the tariff is based on the dominant employee type 'professionals'. This Recommendation does not result in a change in the employee type carrying out the different activities. Therefore the dominant employee type will not change and the tariff will remain the same. Wage rates differ between countries (The average wage rate for Italy is for example seven times higher than that for Estonia).

3.1.3 Impact on population

The population is the number of substantial amendments submitted to the Member States. The expected impact of this Recommendation is a 20 percent reduction in the number of substantial amendments that will be submitted. Although there are differences between the Member States in way of working between Member States, it is too early to distinguish different reduction percentages per Member State (e.g. more or less than 20 percent reduction). This requires more in depth analysis for each Member State. On overall level an

average percentage of 20 percent reduction is expected, based on experiences during field measurements.

3.1.4 Average impact

Based on these assumptions the impact will be:

- 20% in 2008, equal to a reduction of € 4.4 million

Annex 1 presents the impact calculation of the Recommendations.

3.2 Impact Recommendation 2: Enhance the harmonisation of the content of Clinical Trial Authorisation Requests at MS level and across Member States

The objective of Recommendation 2 is to harmonise at Member State Level the required information by all stakeholders, to avoid that companies spend too much time in understanding all specific 'ethics committees' wishes. This Recommendation affects the IO 'Request for authorisation to commence a clinical trial'.

3.2.1 Mapping the business process of the IO 'Request for Authorisation to Commence a Clinical Trial' in line with the standard activities

To calculate the impact of Recommendation 2, it should be made clear which activities the Recommendation will affect. In case of more harmonisation of the requirements for a Clinical Trial Authorisation Request this will affect mainly two steps in the business process:

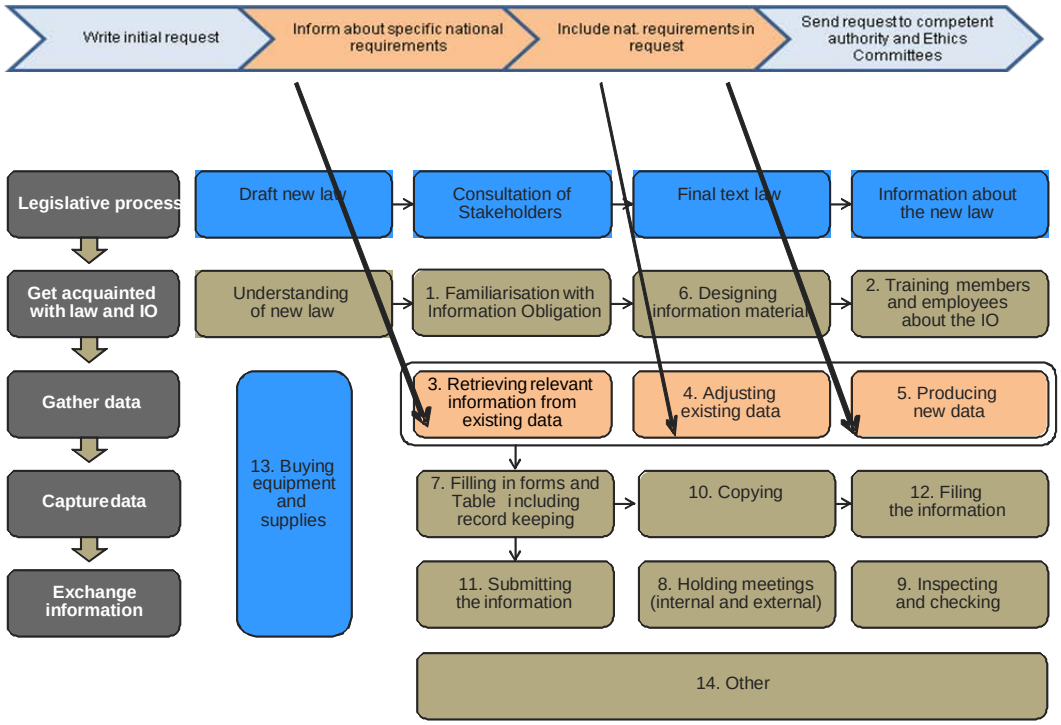
- Inform about specific national requirements
- Include the national requirements in the requests.

These two steps in the business process relate mainly to three activities in the standard cost model:

1. retrieving relevant information from existing data;
2. adjusting existing data;
3. producing new data.

This is illustrated hereafter.

Figure 1: Influence of Recommendation 2 on generic process based on SCM activities



By Capgemini/Deloitte/Ramboll Management.

3.2.2 Impact on time

Recommendation 2 aims for more harmonisation in the content and format of the Clinical Trial Authorisation Request. The Recommendation for harmonisation as described in chapter 2 is expected to decrease the time spent for each of the three activities by 30 percent. Uniformisation of the language requirements will reduce the amount of translation work. An increased harmonisation of the requested content at Member States Level (between national competent authority and Ethics Committees concerned) will significantly reduce the time needed for companies. It currently takes companies much time to ascertain what is the right information and the format of information to be delivered for each Member State, both at NCA and Ehtics Committee levels. The same situation applies to modifying the request to specific countries wishes.

3.2.3 Tariff

In the current situation ('as-is') situation the tariff is based on the dominant employee type 'professionals'. This Recommendation does not result in a change in the employee type carrying out the different activities. Therefore the dominant employee type will not change and the tariff will remain the same. Wage rates do differ between countries (see 3.1.2.).

3.2.4 Impact on population

The population is the number of Clinical Trial Authorisation Requests that are submitted to a country. This number will not change by this Recommendation

3.2.5 Average impact

Based on these assumptions the impact will be:

- 21% in 2008, equal to a reduction of € 15.2 million

By reducing the time spent under the three activities (described above) by 30 percent, the average time spent for this IO is expected to be reduced by 21 percent.

Annex 1 presents the impact calculation of the Recommendations.

3.3 Impact Recommendations 3 and 4: Enable a single submission and an electronic submission of Clinical Trial Authorisation Requests and substantial amendments per MS

The objective of Recommendations and 3 and 4 is to streamline the submission process by creating one single point of contact per Member State and enable electronic submission[4]. Recommendations 3 and 4 affect two IOs:

- Request for authorisation to commence a clinical trial
- Notification of a substantial amendment

[4] The scope of electronic submission is the submission on the level of an individual Member State.

3.3.1 Mapping the business process of the IOs 'Request for Authorisation to Commence a Clinical Trial' and 'Notification of a Substantial Amendment' in line with the standard activities

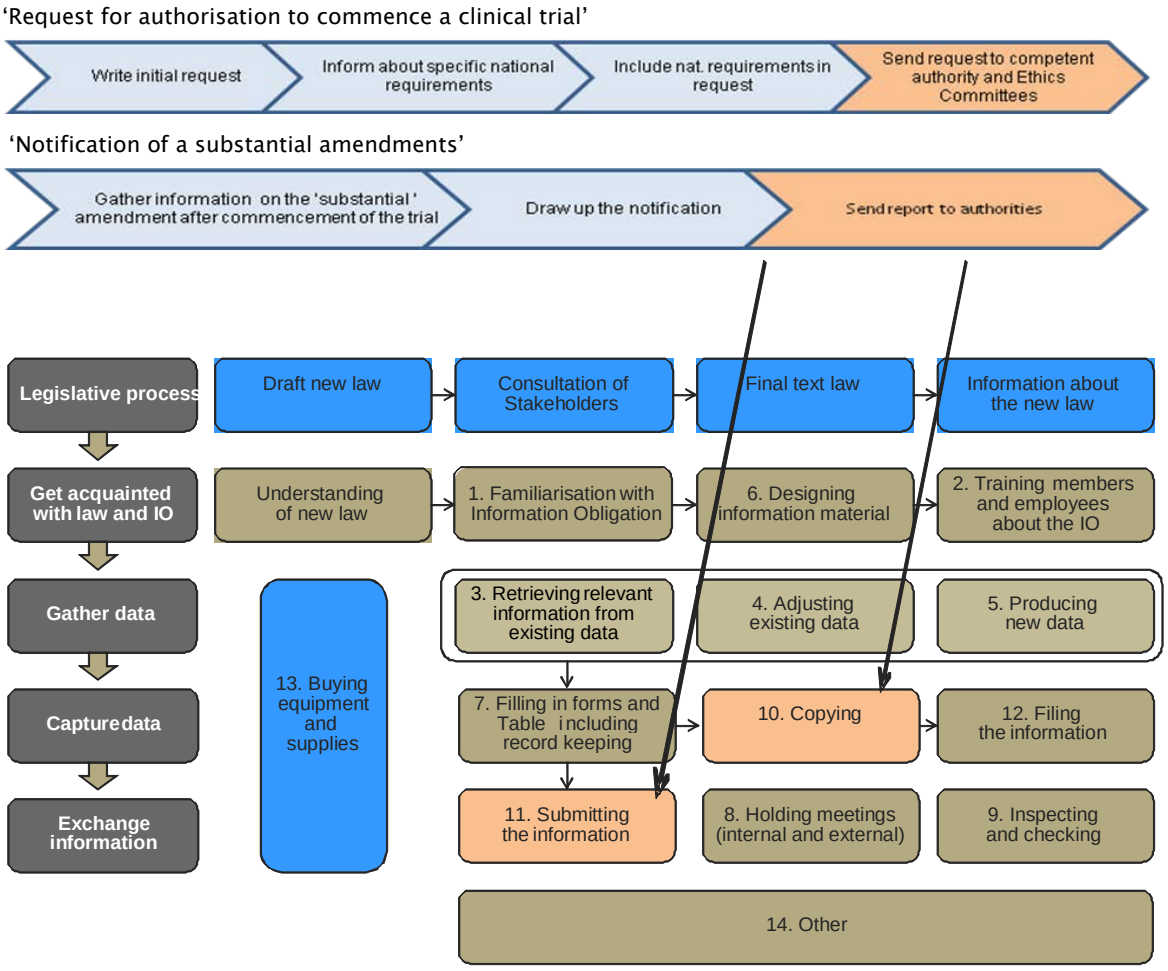
To calculate the impact of Recommendation 3 and 4, it should be made clear which activities the Recommendation will mostly affect. Recommendations 3 and 4 affect mainly one step in the business process:

- Send the request or amendment to the National Competent Authority and Ethics Committee.

These two steps in the business process relate mainly to two activities in the standard cost model:

1. Copying;
2. Submitting the information.

This is illustrated hereafter.



3.3.2 Impact on time

Recommendations 3 and 4 have both an impact on the time spent of the IOs 'Request for authorisation to commence a clinical trial' and 'Notification of substantial amendment'.

Impact on time Recommendation 3

Recommendation 3 aims to streamline the submission process by creating one single point for submission, namely the National Competent Authority, which will in turn communicate to all Ethics Committees concerned in the Member State. Impact of this Recommendation concerns a reduction of 30 percent of the activities 'Copying' and 'Submitting the information' for both IOs concerned.

Impact on time Recommendation 4

Recommendation 4 aims to support electronic submission of the full dossier for the IO 'Request for Authorisation to Commence a Clinical'. Impact of this Recommendation concerns a reduction of 30 percent of the activities 'Copying' and 'Submitting the information' for both concerned IOs. This means an extra reduction above the already achieved reduction by realising Recommendation 3.

3.3.3 Tariff

In the current situation ('as-is') the tariff is based on the dominant employee type 'professionals'. This Recommendation does not result in a change in the employee type carrying out the different activities. Therefore the dominant employee type will not change and the tariff will remain the same. Wage rates do differ between countries (see 3.1.2.)

3.3.4 Impact on population

The population is the number of Clinical Trial Authorisation Requests or substantial amendments that are submitted to a country. The fact that the request or amendment will be submitted in one country to the National Competent Authority and all Ethics Committees concerned is calculated in the P of the IO and not in the Q. The population represents the number of Clinical Trial Authorisation Requests or amendments submitted to one Member State. As an effect of this, both Recommendations will not affect the population but the time spent and therefore the price.

3.3.5 Average impact

In order to avoid any overlap in cost reduction calculations for the impact of Recommendations 3 and 4 with regards to the IO 'Notification of substantial amendments', it has been taken into account that Recommendation 1 has already led to a reduction in the number of substantial amendments notified (population). The reduction in population is 20 percent after implementation of Recommendation 1.

Recommendations 3 and 4 lead to a reduction in time spent and therefore to a reduction in Price (P) of the IOs concerned. The impact of this reduction in P for Recommendations 3 and 4 is for the IO 'Notification of substantial amendments' not calculated based on the

current number of substantial amendments submitted, but on the reduced number of amendments based on Recommendation 1 (80 percent of current population).

Average impact Recommendation 3

IO 'Request for authorisation to commence a clinical trial'

- 3% in 2008, equal to a reduction of € 2.2 million

IO 'Notification of substantial amendments '

- 1,47% in 2008, equal to a reduction of € 319.795,-

Average impact Recommendation 4

IO 'Request for authorisation to commence a clinical trial'

- 3% in 2008, equal to a reduction of € 2.2 million

IO 'Notification of substantial amendments '

- 1,47% in 2008, equal to a reduction of € 319.795,-

Annex 1 presents the impact calculation of the Recommendations.

4. *Implementability*

This chapter provides a high level description the investments needed for the implementation of the Recommendations. Furthermore the technological, legal, and process complexity is highlighted, as well as political opportunities and barriers. The last part of this chapter indicates the timeline of this Recommendation.

4.1 Investment costs

4.1.1 Public sector

Public sector investments Recommendation 1: Review of the definition of substantial amendment

This Recommendation concerns a review of additional definitions and examples in EC guidelines en specific country guidelines. Investment costs are low. Costs represent mainly the discussion process between EC and Member States about definitions.

Table 1: Public sector Investments for Reviewing of the definition of substantial amendment

Reviewing of the definition of substantial amendments requires activities with regards to: - Definition of scope - Identification of EC and MS responsibility in determining guidelines for definition of substantial amendments - Review and analysis of existing national definitions - Approach for review process - Development of proposals - Stakeholder consultations - Finalisation proposals - Implementation - Communication to all stakeholders Primary responsibility: EC and NCAs

Public sector investments Recommendation 2: Enhance the harmonisation of the content of Clinical Trial Authorisation Requests on MS level and across Member States

Further specification of EC Legislation and additional guidelines with regards to: - Standardisation of formats - Requirements core parts of the Clinical Trial Authorisation Request - Language requirements Primary responsibility: EC

This Recommendation concerns on the one hand further specification of EC Legislation and guidelines on aspects as standardisation formats and requirement of core parts of the request, standardisation of certain language requirements. Investments mainly concern the discussion process between EC and Member States about specifications, where the EC is in the lead.

On the other hand it requires further harmonisation on Member State Level between National Competent Authorities and Ethics Committees. Investment costs relate mainly to the discussion process between National Competent Authorities and Ethics Committees.

Table 2: Public Sector Investments for increasing the harmonisation of content for Clinical Trial Authorisation

Improvement of harmonization at MS level between specific requirements National Competent authorities and Ethics Committees Primary responsibility: NCA and Ethics Committees

Public sector investments Recommendation 3: Enable a single submission of Clinical Trial Authorisation Requests and substantial amendments per Member State

This Recommendation concerns an improved coordination at Member State Level between National Competent Authorities and Ethic Committees. Investments needed relate to the discussion process between National Competent Authorities and Ethics Committees for streamlining the process and establishing new procedures.

Table 3: Public sector Investments for Enabling a Single Submission of Clinical Trial Authorisation Requests and substantial amendments

Establishing a single point of contact requires activities with regards to: - Identification of possibilities for organising a single point of contact Clinical Trials Authorisation and Conduct Matters - Identification and redesign of the business processes, roles and responsibilities - Development of new organizational structure between NCA en Ethics Committees - Communication to all stakeholders Primary responsibility: NCA and Ethics Committees

Public sector investments Recommendation 4: Enable the electronic submission of Clinical Trial Authorisation Requests and substantial amendments per Member State

Enabling electronic submission can be organised in several ways. The simplest way is allowing companies to submit the request or amendments per e-mail. This requires alignment of the signature page with national legislation; e.g. a scanned cover letter with signature could be a possibility. More advanced roads for electronic submission would include the implementation of a web application or portal by countries.

In the long run the latter possibility is recommended as it would ease access for Ethics Committees to all relevant information and would allow the download of the information from the portal. Besides this portal could (depending on which functionalities are chosen) support the daily work of National Competent Authorities and Ethics Committees by providing: status information, datasharing, discussion forums. Datasharing is the key element of the coordination of assessment. Investments costs will depend on the functionalities chosen. E-mail submission of request or amendments will not require high investments. Web applications with basic functionalities are possible at a cost of €100.000 for one Member State, but depending on additional features (e.g. workflow, worksharing) costs will be significantly higher[5].

Factors that have an impact on the implementation costs for a web application, are:

- Requirements of the MS for the web application
- If a Competent Authority already has an ICT (web) application in place that could also potentially offer basic functionality for electronic submission of Clinical Trial Authorisation Request: this can reduce implementation costs

A more precise assessment of involved costs can be only performed once the various elements mentioned above have been ascertained for each Member State.

Table 4: Public sector Investments for Enabling a Electronic Submission of Clinical Trial Authorisation Requests and substantial amendments

Establishing functionality for electronic submission of Clinical Trial Authorisation Requests and substantial amendments requires activities with regards to: - Identification of possible solutions, ranging from using simple e-mail functionality to advanced web application - Identification of current ICT environment of NCA and options for extending functionality - Definition of requirements for web application

[5] Internal Consortium expert assessment

- Identification and redesign of the business processes, roles and responsibilities
- Development of new organisational structure between NCA en Ethics Committees
- Realisation of the webapplication
- Communication to all stakeholders

Primary responsibility: NCA

4.1.2 Private sector

Private sector investments Recommendations 1, 2, 3, and 4

All Recommendations would merely lead to benefits for Pharmaceutical Companies (Sponsors). No specific investments are required.

4.2 Complexity

Complexity Recommendation 1: review of the definition of substantial amendment and Recommendation 2: Increase the harmonisation content for Clinical Trial Authorisation Requests on MS level and across Member States

Recommendations 1 and 2 do not rely on complex technological solutions. The complexity mainly relates to the following factors:

- *Legal / Policy:* The extent to which EU legislation can be specified further. For instance, the actual progress made by the CTFG remains small, although the road towards harmonisation of national legislation is currently being examined by the Clinical Trials Facilitation Group).
- *Process:* Clinical Trials, including amendments, are subject to cultural differences and interpretations of ethic values and not only a matter of objective criteria. This makes the process to obtain further harmonisation between Member States challenging and it will require time to obtain a well concerted solution.

Complexity Recommendation 3: Enable a single submission of Clinical Trial Authorisation Requests and substantial amendments per Member State

Recommendation 3 requires a modification of the working process between National Competent Authorities and Ethics Committees. Depending on the current characteristics of the national healthcare system the required changes will be more or less complex. In general it means that, the more Ethics Committees are involved in a certain country, the more complex it will be to realise the modification needed.

Complexity Public sector investments Recommendation 4: Enable an electronic submission of Clinical Trial Authorisation Requests and substantial amendments per Member State

Recommendation 4 concerns an eGov solution, but doesn't require any complex technological solution. Also process and legal aspects are not expected to be challenging.

4.3 Political will / opportunities & barriers

Recommendation 1 and 2: the autonomy of Member States (and of the Ethics Committees within each Member State) with regards to detailed requirements for Clinical Trial requests is the main barrier for reaching harmonisation on the short term.

4.4 Time-frame

Time frame Recommendation 1: review of the definition of substantial amendment

This Recommendation concerns a review of additional definitions and examples in EC guidelines en specific country guidelines. Definition and implementation takes time. This is a structural change and the Recommendation could be implemented mid 2010.

Time-frame Recommendation 2: Increase the harmonisation content for Clinical Trial Authorisation Requests on MS level and across Member States

Getting more harmonisation on Member State Level is a structural change. The years 2009 and 2010 should be used for coming with proposals for harmonisation and deciding what

will be amended in EC Legal Act and what is part of harmonisation within Member States and Ethics Committees. Recommendations could be implemented in 2011-2012.

Time-frame Recommendation 3: Enable a single submission of Clinical Trial Authorisation Requests and substantial amendments per Member State

Establishing a single point of contact in Member States requires a different way of coordinating and working between the National Competent Authority and Ethics Committee and this requires a structural change.

Time-frame Public sector investments Recommendation4: Enable an electronic submission of Clinical Trial Authorisation Requests and substantial amendments per Member State

The time frame for implementation depends on the government solution that will be chosen. Electronic submission by e-mail could be implemented very easily and could be considered as a quick win. Establishment of a portal would take some longer time.

5. *Image*

The IOs 'Request for authorisation to commence a clinical trial' and 'Notification of substantial amendments' have a medium irritation score, based on the average of six statements and an average of six countries. Irritation is mainly related to many differences in requirements between the Member States, and within Member States between Ethics Committees, leading to unnecessary burdens. With the Recommendations in this impact fiche the cause of irritation is addressed by the reduction measures.

Annex 1 – Assumptions for impact calculations

5.1 Recommendation 1 - Review of the definition of substantial amendment

The aim of Recommendation 1 is to establish a clearer definition of substantial amendments in the legal act, including additional guidance with examples, to avoid multiple interpretations by competent authority of the Member States and Ethics Committees.

5.1.1 The effect of the Recommendation 1 on the price

Recommendation 1 has no impact on the price.

5.1.2 The effect of the Recommendation 1 on population

The population is the number of substantial amendments submitted to the Member States. The expected impact of this Recommendation is a 20 percent reduction in the number of substantial amendments that will be submitted. Although there are differences between the Member States in way of working between Member States, it goes too far in this stage to distinguish different reduction percentages per Member State (e.g. more or less than 20 percent reduction). This requires more in dept analysis for each Member State. On overall level an average percentage of 20 percent reduction is expected, based on experiences during field measurements. The table hereafter shows the impact for the six measurement countries.

Recommendation 1: Detailed calculation assumptions 2008 (€) for IO 'Notification of substantial amendments'

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
Austria	172,600	138,080	20%	34,520
Belgium	37,665	30,132	20%	7,533
Czech Republic	8,279	6,623	20%	1,656
Denmark	1,125,900	900,720	20%	225,180
Estonia	896	717	20%	179

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
Italy	287,000	229,600	20%	57,400
Netherlands	49,869	39,895	20%	9,974
Poland	6,900	5,520	20%	1,380
Portugal	75,278	60,222	20%	15,056
United Kingdom	7,397,570	5,918,056	20%	1,479,514

By Capgemini/Deloitte/Ramboll Management.

5.2 Recommendation 2 - Increase of the harmonisation content for Request for Information to Commence a Clinical Trials on MS level and across Member States

The objective of Recommendation 2 is to harmonise at Member State Level the required information by all stakeholders, to avoid that companies spend too much time in understanding all specific 'ethics committees' wishes. This Recommendation affects the IO 'Request for authorisation to commence a clinical trial'.

5.2.1 The effect of the Recommendation 2 on the price

The Recommendation for harmonisation as described in chapter 2 is expected to decrease the time spent for each of the three activities with 30 percent. Uniformisation of the language requirements will reduce the amount of translation work. An increased harmonisation of the requested content on Member States Level (between national competent authority and Ethics Committees concerned) will significantly reduce the time needed for companies. Now it takes companies much time to get for each country, and for all the Ethics Committees involved, the right information about required content and format. The same situation applies for modifying the request to specific countries wishes.

5.2.2 The effect of the Recommendation 2 on population

The population is the number of requests for authorisation to commence a clinical trial that is submitted to a country. This number will not change by this Recommendation.

The average reduction percentage for the EU 27 is 21 percent. For the measurement countries is the average reduction of this Recommendation 27 percent. For two of the

Baseline countries, Germany and UK, is the percentage lower, due to different mapping on activity level. The expected reduction for Poland is slightly higher as companies stated that the approval procedure is extremely complex as can also be seen in the time spent for the activities to be reduced.

Recommendation 2: Detailed calculation assumptions 2008 (€) for IO 'Request for authorisation to commence a clinical trial'.

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
Austria	1,657,205	1,240,832	25%	416,373
Belgium	4,805,879	3,508,292	27%	1,297,587
Czech Republic	422,947	308,751	27%	114,196
Denmark	3,532,882	2,645,245	25%	887,637
Estonia	40,763	29,757	27%	11,006
Germany	23,446,721	19,929,713	15%	3,517,008
Italy	7,535,185	5,500,685	27%	2,034,500
Netherlands	859,859	643,820	25%	216,040
Poland	684,848	438,303	36%	246,545
Portugal	231,559	171,353	26%	60,205
United Kingdom	14,115,297	11,856,849	16%	2,258,447

By Capgemini/Deloitte/Ramboll Management.

5.3 Recommendation 3

The objective of Recommendation 3 is to streamline the submission process by creating one single point of contact per Member State. Recommendation 3 affects two IOs:

- Request for authorisation to commence a clinical trial
- Notification of a substantial amendment

5.3.1 The effect of the Recommendation 3 on the price

Impact of this Recommendation concerns a reduction of 30 percent of the activities 'Copying' and 'Submitting the information' for both IOs concerned.

5.3.2 The effect of the Recommendation 3 on population

The population is the number of requests for authorisation to commence a clinical trial or substantial amendments that are submitted to a country. The fact that the request or amendment will be submitted in one country to the National Competent Authority and all Ethics Committees concerned is calculated in the P of the IO and not in the Q. The population represents the number of requests for authorisation to commence a clinical trial or amendments submitted to one Member State. As an effect of this, both Recommendations will not affect the population but the time spent and therefore the price.

5.3.3 Average impact

For the impact of Recommendation 3 with regards to the IO 'Notification of substantial amendments' it has been taken into account that Recommendation 1 has already led to a reduction in the number of substantial amendments notified (population). This is to avoid overlap in the reduction calculation. The reduction in population is 20 percent after implementation of Recommendation 1.

Recommendation 3 leads to a reduction in time spent and therefore to a reduction in Price (P) of the IOs concerned. The impact of this reduction in P for Recommendation 3 is for the IO 'Notification of substantial amendments' not calculated based on the current number of substantial amendments submitted, but on the reduced number of amendments based on Recommendation 1 (80 percent of current population).

Impact of this Recommendation concerns a reduction of 30 percent of the activities 'Copying' and 'Submitting the information' and leads for the IO 'Request for authorisation to commence a clinical trial' to a reduction of 3 percent in the Administrative Burden.

There are no considerable differences between the measurement countries. The Baseline countries were not taken into account, because these countries didn't apply the mapping on activity level in the same way.

Recommendation 3: Detailed calculation assumptions 2008 (€) for IO 'Request for authorisation to commence a clinical trial'.

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
Belgium	4,805,879	4,661,703	3%	144,176
Czech Republic	422,947	410,258	3%	12,688
Estonia	40,763	39,540	3%	1,223
Italy	7,535,185	7,309,129	3%	226,056
Poland	684,848	664,303	3%	20,545
Portugal	231,559	224,612	3%	6,947

By Capgemini/Deloitte/Ramboll Management.

'Copying' and 'Submitting the information' leads for the IO 'Notification of a substantial amendment' to a reduction of 1,47 percent in the Administrative Burden for EU 27. For the measurement countries the reduction is on average 2.4 percent. Austria shows a slightly higher percentage of reduction, based on the mapping on activity level. Germany, which has very high time spent for this IO, shows a much lower percentage of reduction, which can be explained by the fact that more time than in other countries is related to other activities than 'Copying' and 'Submitting'.

There are no considerable differences between the Measurement Countries. Not all Baseline countries were taken into account, because not all Baseline countries applied the mapping at activity level in the same way.

Recommendation 3: Detailed calculation assumptions 2008 (€) for IO 'Notification of substantial amendments'.

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
Austria	172,600	167,077	3.20%	5,523

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
Belgium	37,665	36,761	2.40%	904
Czech Republic	8,279	8,080	2.40%	199
Denmark	1,125,900	1,100,004	2.30%	25,896
Estonia	896	874	2.40%	22
Germany[6]	12,202,720	12,105,098	0.80%	97,622
Italy	287,000	280,112	2.40%	6,888
Netherlands	49,869	48,722	2.30%	1,147
Poland	6,900	6,734	2.40%	166
Portugal	75,278	73,471	2.40%	1,807

By Capgemini/Deloitte/Ramboll Management.

5.4 Recommendation 4

Recommendation 4 aims to support electronic submission of the full dossier for the IO 'Request for Authorisation to Commence a Clinical'. Recommendation 4 affects two IOs:

- Request for authorisation to commence a clinical trial
- Notification of a substantial amendment

5.4.1 The effect of the Recommendation 4 on the price

Impact of Recommendation 4 concerns a reduction of 30 percent of the activities 'Copying' and 'Submitting the information' for both concerned IOs. This means an extra reduction above the already achieved reduction by realising Recommendation 3.

[6] Total AC for Germany and UK for the IO 'Notification of Substantial Amendments' is much higher than in the other countries. This is explainable due to a relatively higher amount of headquarters in UK and Germany of Pharmaceutical companies, preparing most part of the amendments also for other countries.

5.4.2 The effect of Recommendation 3 on population

The population is the number of requests for authorisation to commence a clinical trial or substantial amendments that are submitted to a country. The fact that the request or amendment will be submitted in one country to the National Competent Authority and all Ethics Committees concerned is calculated in the P of the IO and not in the Q. The population represents the number of requests for authorisation to commence a clinical trial or amendments submitted to one Member State. As a result, these Recommendations will not affect the population but the time spent and therefore the price.

5.4.3 Average impact

For the impact of Recommendation 4 with regards to the IO 'Notification of substantial amendments' it has been taken into account that Recommendation 1 has already led to a reduction in the number of substantial amendments notified (population). This is to avoid overlap in calculated reduction. The reduction in population is 20 percent after implementation of Recommendation 1.

Recommendation 4 leads to a reduction in time spent and therefore to a reduction in Price (P) of the IOs concerned. The impact of this reduction in P for Recommendations 4 is for the IO 'Notification of substantial amendments' not calculated based on the current number of substantial amendments submitted, but on the reduced number of amendments based on Recommendation 1 (80 percent of current population).

Impact of this Recommendation concerns a reduction of 30 percent of the activities 'Copying' and 'Submitting the information' and leads for the IO 'Request for authorisation to commence a clinical trial' to a reduction of 3 percent in the Administrative Burden.

There are no considerable differences between the measurement countries. The Baseline countries were not taken into account, because these countries did not apply the mapping at activity level in the same way.

Recommendation 4: Detailed calculation assumptions 2008 (€) for IO 'Request for authorisation to commence a clinical trial'.

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
Belgium	4,805,879	4,661,703	3%	144,176
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By Capgemini/Deloitte/Ramboll Management.

'Copying' and 'Submitting the information' leads for the IO 'Notification of a substantial amendment' to a reduction of 1,47 percent in the Administrative Burden for EU 27. For the measurement countries the reduction is on average 2.4 percent. Austria shows a slightly higher percentage of reduction, based on the mapping on activity level. Germany, which has a very high time spent for this IO, shows a much lower percentage of reduction, which can be explained by the fact that more time than in other countries is related to other activities than 'Copying' and 'Submitting'.

There are no considerable differences between the measurement countries. Not all Baseline countries were taken into account, because not all Baseline countries applied the mapping on activity level in the same way.

Recommendation 4: Detailed calculation assumptions 2008 (€) for IO 'Notification of substantial amendments'.

Member State	Current Administrative Burden (in €)	New Administrative Burden (in €)	Reduction percentage	Reduction (in €)
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Netherlands	49,869	48,722	2.30%	1,147
Poland	6,900	6,734	2.40%	166
Portugal	75,278	73,471	2.40%	1,807

By Capgemini/Deloitte/Ramboll Management.

5.5 Total impact of the 4 Recommendations

The total impact of the Recommendations on the two IOs in scope is:

Expected administrative burden reduction in %	IO Request for authorisation to commence a clinical trial: 26,58% IO Notification of substantial amendments: 22,94%
Expected administrative burden reduction in euro	IO Request for authorisation to commence a clinical trial: 19.572.394 IO Notification of substantial amendments: 4.994.948

[7] Total AC for Germany and UK for the IO 'Notification of Substantial Amendments' is much higher than in the other countries. This is explainable due to a relatively higher amount of headquarters in UK and Germany of Pharmaceutical companies, preparing most part of the amendments also for other countries.