



The influence of the EU directive on the quality of non-commercial clinical trials in Sweden

- **Has the quality in non-commercial clinical trials in Sweden changed after the EU harmonization?**

**Degree project including research proposal, 45hp
Karolinska Institutet
Stockholm 2009**

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Abstract

There are two paradigms on how the implementation of the EU directive has affected non-commercial clinical trials. One is that the EU directive brings unnecessary registrations and acquires time and resources from scientific production, leading to a quality decrease. The other is that the quality in clinical trials has increased now because the requirements are clearer and function as guidelines. The aim of this study is to identify how the quality has been influenced in non-commercial clinical studies, after the amendment 2004 in the Swedish legalization based on the EU directive (2001/20/EC). In order to investigate this, a questionnaire was sent to 400 people involved in clinical trials at Karolinska University Hospital and interviews were held with 8 of these respondents. Furthermore, the medical products agency and independent ethics committee were also interviewed. The study demonstrates that after the implementation of the new EU directive on non-commercial clinical trials there is more consciousness about the requirements with better results in some moments and improved quality in non-commercial clinical trials.

Abbreviations

CRF	Case Report Form
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
KTA	Karolinska Trial Alliance
KUH	Karolinska University Hospital
LVFS	Läkemedelverkets Författningssamling
MPA	Medical Products Agency
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person

Table of Contents

Abstract	2
1 Introduction	5
2 Background	6
2.1 Quality in clinical trials	6
2.2 The EU directive and the regulatory authorities	6
2.4 Protection of trial subjects	6
2.5 Changes the EU directive has brought to clinical trials in Sweden	6
3 Aim.....	7
4 Methods.....	7
4.1 Questionnaire	7
4.2 Interviews	8
4.3 Evaluation of the patient information.....	9
5 Results	9
5.1 Results from the questionnaire	9
5.2 Results from the interviews.....	14
5.3 Evaluation of the patient information.....	22
6 Discussion	23
6.1 Reflection over the methods.....	23
6.2 Analysis of the result.....	24
6.4 Future studies	29
7 Conclusion.....	29
8 Acknowledgement.....	29
9 References	30
Appendix 1 – Questionnaire.....	31
Appendix 2 – Value table.....	39
Appendix 3 – Interview forms	44
Appendix 4 – Patient information form	50

1 Introduction

The EU directive in clinical trials (2001/20/EC) came into force in 2004, with the objectives to harmonise the EU regulatory environment and simplify the trial application process in the member states [1]. Regarding the quality of clinical trials, the EU directive states that there must be observed quality requirements for designing, conducting, recording and reporting clinical trials on medicinal products for human use. In this manner the rights, safety and well-being of trial subjects are protected and the results from the clinical trials are reliable [2]. In other words the declaration of Helsinki is to be followed.

In the EU there are commercial clinical studies, where the drug industry is the sponsor and non-commercial clinical studies, where the investigator is the sponsor [3]. The non-commercial clinical research in Europe has changed after the new directive and has created concerns for the academic researchers, for the reason that it implies increased costs and bureaucracy in clinical trials [1, 4]. Some believe that the EU directive has increased the protection of the trial subject's furthermore, improved the quality in clinical trials because of the strict system of rules [5]. Others believe that it has proven to be counterproductive since the administrative work has become huge [6]. Observers as Markus Hartmann, an independent consultant on medical and regulatory affairs based in Trier, remark that the directive has failed to deliver, meaning that the harmonisation is not achieved and that there are not many positive effects for safety [1, 6]. These problems could be the reasons why the Swedish MPA discovered that the non-commercial clinical studies decreased with 20 percent between 2004 and 2005, after the implementation of the new EU directive [4]. The decrease of the non-commercial clinical studies is still current today, 2007 [7].

At a glance, the EU directive should lead to a decrease of unoriginal or badly conducted clinical trials, to increase the trial subject's safety and to speed up the development of drug treatments [8]. Meaning that with the implementation of the new directive, an increase of quality in both commercial and non-commercial fields should be ascertain [6]. However, it is likely to have the opposite effect by reducing the amount of clinical trials that public-funding bodies can afford to support and the amount of patients enrolled in each study. Thus, this does not imply well for academic research in Europe or indeed for improvement of health and quality of life [8]. Since earlier studies has shown that the quantity of non-commercial clinical studies was impaired , it is of interest to identify how the quality has been influenced in the non-commercial clinical studies, after the amendment 2004 in the EU directive.

2 Background

2.1 Quality in clinical trials

GCP is an ethical and a quality standard for clinical trials that is related to the design, conduct and analysis of the clinical trial, its clinical relevance and the validity of the results from the clinical trial [9]. To maintain good quality in clinical trials, they have to be scientifically sound and be described in a clear detailed protocol that is approved by the regulatory authorities and followed during the study [10].

2.2 The EU directive and the regulatory authorities

The regulatory authorities insist that clinical trials must be performed according to the guideline GCP, which reaffirms the Declaration of Helsinki. Furthermore the new EU directive is based on ICH-GCP [11].

In Sweden the medical products agency (MPA) evaluate documentation and quality requirement on the medicinal products used in clinical trials based on a risk-benefit valuation. The evaluation follow the common EU system of rules with consideration to factors as the type of material, patient group, disease and the exposure length [12].

2.4 Protection of trial subjects

The Declaration of Helsinki declares a high standard of protection for trial subjects which the EU directive reaffirms. Nevertheless, new requirements were introduced by the changes in the EU directive, which states that the trial subjects should be provided with an independent contact point for the purposes of obtaining further information [2, 13].

2.5 Changes the EU directive has brought to clinical trials in Sweden

The important changes that the EU directive has brought are specific requirements in the information and the informed consent to the trial subjects, particular protection to under-age children and communicatively handicapped. Furthermore, the sponsor has an obligation to assist the patients in the clinical trials with medical products without costs. Non-intervention studies do not need approval from the MPA. Another new change is that every clinical trial has to have an unique European Union drug regulating authorities clinical trials (EudraCT) number to be identified with and all the applications are made in a common form where the EudraCT number is given. The EudraCT is obtained from the European medicines agency (EMA) through the sponsor. The reasons to these changes are to facilitate the work and the communication between the different competent authorities in Europe. There is an increased responsibility to the sponsor regarding the adverse event report because all serious adverse

events that are both unexpected and at least possible related to the study products, so called suspected unexpected serious adverse reaction (SUSAR) have to be reported to a common database [11]. Other modifications are the time limitations for the MPA in the processing of the application and the report procedures. With the changes of the EU directive, all involved in clinical trials has to have documented GCP education and all the trials have to be monitored [13, 14]. A further change is the common application format to all ethics committees and ethics committees will have a time limit in which to issue their opinions [11].

3 Aim

The aim of the study is to clarify if the implementation of the new EU directive on clinical trials (2001/20/EC) into Swedish law 2004 has influenced the quality in non-commercial clinical studies. The Karolinska University Hospital will be used as a representative sample of Sweden. Furthermore, as an additional measurement of quality, this work will use patient information's from non-commercial clinical trials. Consequently, the secondary aim will be to study how the patient safety has been influenced by the new EU directive on clinical trials.

4 Methods

The methodology of acquiring the empirical data to reach the aims is based on quantitative and qualitative methods, thereby a questionnaire and individual deep interviews have to be used. The quantitative method gives a general picture of the clinical trials, in addition the magnitude and distribution in a bigger population. The qualitative research method was performed with a combination of semi structured and open targeted questions.

The information received in the study is divided in primary and secondary information. The primary data was gathered from the questionnaire along with individual deep interviews with people involved in clinical trials at KUH, the MPA and IEC. The secondary data was acquired through other established sources like scientific articles, literature and the internet.

4.1 Questionnaire

The questionnaire and accompanying letter were specially designed for this study and were quality audited by four people involved in clinical trials before it was sent. The questionnaire was sent through KUH internal post to 400 investigators and involved in non-commercial clinical studies at the KUH. The respondents got two weeks to respond the questionnaire and send it back to KTA through the internal post. The questionnaire was in Swedish and constructed with closed questions together with structured answering alternatives and open structured questions [16]. The questions comprise general information regarding the

respondent, experiences of clinical trials, knowledge about GCP and the system of rules. General questions about quality, comparing questions to measure differences before and after 2004 in different moments of a clinical trial and questions about the patient information.

The questions that are responded through a ten graded scale or through multiple reply alternatives will be quantitative analyzed and graphically presented, while the open questions will be qualitative analyzed (Appendix 1).

4.2 Interviews

Before the interviews were implemented an interview template was made with questions that answer the aim of the study. Most of the questions were a further development of the questions in the questionnaire to have a deeper insight to the answers (Appendix 3). The interviews were in Swedish, approximately one hour long and notes were done during the interviews.

From the respondents that showed interest in participating through the questionnaire, 10 respondents were randomly selected to the individual interview. To investigate if the quality has increased or decreased after the amendment 2004 of the new EU directive, people that has been involved in clinical studies before and after 2004, was investigated.

Furthermore, the same interview template but with modest modifications was used for the interview with the MPA and IEC (Appendix 3). The respondents from the MPA, was selected because of their knowledge of the area that is being studied and for their availability to participate in an interview. The purpose with interviewing with the MPA was to get deeper insight in clinical trials and the quality in Sweden. The MPA and IEC can provide the authorities opinion regarding these questions and a different point of view compared to the respondents from KUH.

The interviews respondents:

- From the KUH, three investigators, two unit commanders, one study-coordinator and two research nurses. The interview was implemented at KUH.
- From the MPA, Gunnar Danielsson that is drug inspector and Ingrid Wallenbäck that is branch head in clinical trials. The interview was implemented at the MPA.
- From the IEC, Pierre Lafolie that is a scientific secretary at IEC.

The results from the interviews were compiled from the notes, in relationship to each question and according to Giorgis phenomenological analysis model [15].

4.3 Evaluation of the patient information

In the aspect of how the patient protection has been influenced by the EU directive, patient information will be studied as an additional measurement of quality and patient protection. The patient information from 20 non-commercial clinical trials will be accessible from the Swedish MPA. Then an evaluation and a comparison will be done between the patient information from clinical studies obtained from 2003 and 2008, with help of a form from IEC (Appendix 4).

5 Results

5.1 Results from the questionnaire

The questionnaire study showed that from the 400 questionnaires that were sent out to investigators and involved in non commercial clinical trials at Karolinska University Hospital, 83 answers got through. This gives a reply frequency of 20, 8%.

General information

Of the people who answered the questionnaire 48% were investigators, 37% were research nurses and 15% had other functions.

The major part of the respondents, 74 (89%) had documented GCP and 9 (11%) did not have it. 62% of the respondents considered to have good knowledge in GCP, 34% considered to have moderate knowledge and 4% have bad knowledge. The prime way they got GCP education was through other ways than from a company or KTA (Appendix 2).

Experiences of clinical trials

Most of the respondents had participated in clinical trials before and after 2004 (81%). The respondents that had not participated in clinical trials before and after 2004 (19%) were not further analyzed on the questions where a comparison between before and after 2004 was made, since they can't answer the aim of the study (Appendix 2).

Concerning the influence of the EU directive in the quality of clinical trials, 57% of the respondents thought that the quality had increased after the implementation of the EU directive 2004. Furthermore 27% considered no difference in quality, 15% did not know and 1% considered a quality decrease after the implementation of the EU directive (Fig. 1).

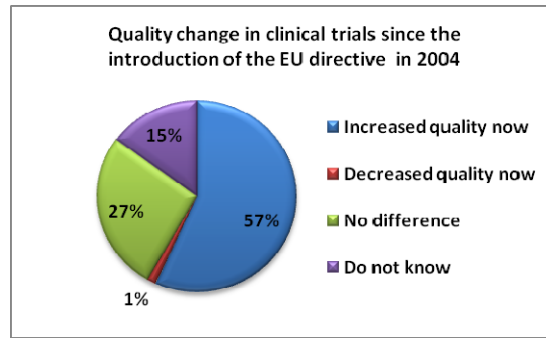


Figure 1. An overview of the respondent's reply concerning the quality influence in clinical trials after the implementation of the EU directive. A large amount, 57% considered an increased quality after the implementation, 27 % no difference, 15% of the respondents did not know and 1% considered a decrease in quality.

Quality in clinical trials

In order to analyze the respondents view on the importance of quality in clinical trials they had to draw a parallel in a scale from 1 to 10. Where the number ten means that quality is very important in clinical trials and the number one, quality is not important. 71% stated ten, 21% nine, 7% eight and 1% stated seven in the scale (Appendix 2).

Concerning the question about who has the responsibility for the quality in a clinical trial, the most frequent answer was that the principal investigator has formally the highest responsibility and informally, the coordinator and the monitor. The next recurrent answer was that all concerned in the study has the responsibility and the third most common reply was that the responsibility is sheared between the investigator and sponsor.

Regarding the question how improved quality in a clinical trial can be reached, the most common reply was to have qualified persons (QP) in the clinical trial through more education and understanding for GCP. The second frequent reply was to have a well prepared protocol and study design according to GCP, before the study starts. The third most repeated answer was to have a good communication and cooperation between the responsible and the people involved and furthermore to have more time and money to clinical trials. Moreover to eliminate the EU directive from 2004 since this is most about unnecessary registrations and reports and thereby acquire time and resources from true safety work and scientific production.

Moments before the clinical trial

Most of the respondents that had documented knowledge of GCP, considered to recognize the declaration of Helsinki, ICH-GCP, EU directive and LVFS (Läkemedelverkets Författningssamling). However, more respondents recognized the declaration of Helsinki compared to LVFS (Fig 2). The respondents that did not have documented GCP, recognized

the declaration of Helsinki and almost half of the respondents recognized ICH-GCP and EU directive. Two-thirds recognized the LVFS (Fig 3)

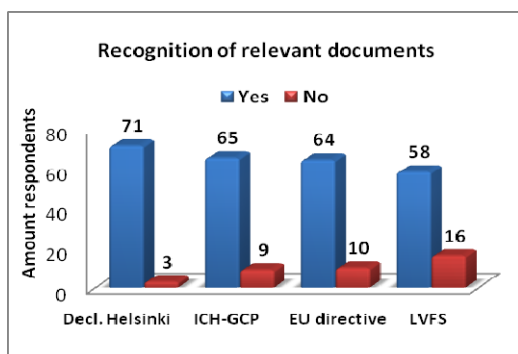


Figure 2. An illustration on the knowledge of the respondents with documented GCP. The most recognized was the declaration of Helsinki with 71 respondents and the least recognized was the LVFS.

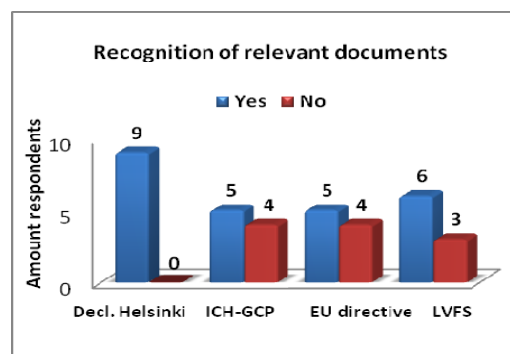


Figure 3 An illustration on the knowledge of the respondents without documented GCP. There is a higher recognition to the declaration of Helsinki compared to ICH-GCP and EU directive.

Regarding the application process to the MPA and IEC, and the relationship to the quality, 31 respondents replied that there is a quality increase in the clinical trials. 18 respondents considered that the application process had not influenced the quality at all, 16 respondents did not know and 2 considered a quality decrease (Fig 4).

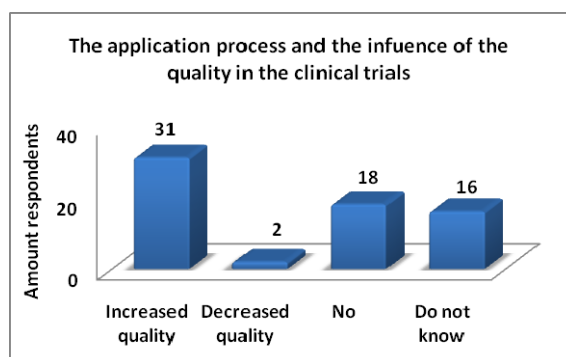


Figure 4. An illustration on the relationship between the application process and the quality in clinical trials. 31 respondents considered a quality increase, 18 respondents stated that the application process had not influenced the quality at all, 16 respondents did not know and 2 considered a quality decrease.

On the question if there is a difference in how the sponsor supplies knowledge about the clinical trials after 2004, the majority, 32 respondents considered that there is a difference and the explanation was because they are more conscious about the increased requirements and the need for quality. Thereby it is a higher pressure on the GCP education to the involved, more details and instructions and it is more extensive and structured now. 26 respondents replied that there were no difference and 3 respondents did not know (Appendix 2).

Moments during the clinical trial

In the questionnaire the respondents had to state if there is a difference in the monitoring before compared to after 2004. The result is illustrated in figure 5, where the majority replied that there is a difference, 20 respondents did not consider a difference and 15 did not know (Fig 5).

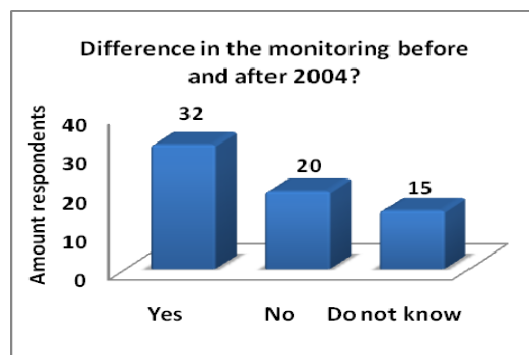


Figure 5 An illustration of the respondents reply about if there is a difference in the monitoring before and after 2004. Most of the respondents, 32, replied that there is a difference. 20 did not consider a difference and 15 respondents did not know.

Regarding the question about who reads the monitoring report now compared to before, most of the respondents did not reply and the few data that is given is difficult to analyze and it is not valid to use.

On the question about the use of case report form (CRF) in clinical trials, the majority of the respondents (55) answered that there were no difference in the use and 12 respondents answered that they use CRF now and not before (Appendix 2).

On the subject of the differences in drug management 39 respondents did not consider a difference in the drug management. 25 respondents said that there was a difference and the reasons was because it is more structured and more documentation now. The marking is more clear and extensive and there is more control concerning the storage and distribution. Another frequent type of replies considered that it is too much unnecessary routines, more centralized and complicated orders and that it is in general more expensive. 3 respondents did not know if there was a difference now compared to before (Appendix 2).

As regards the difference in the amount adverse event reporting now compared to before, 29 respondents considered no difference in the reporting. 21 respondents did not know if there was a difference, 16 considered more reports now and 1 respondent wrote that there were more reporting before (Appendix 2).

In the questionnaire the respondents was requested to state if there were a difference in the amount of audit before compared to after 2004. Most of the respondents replied that they did not know. 25 respondents stated no difference and 15 respondents considered more audit now compared to before (Appendix 2).

On the question concerning if there is a change in the note-to-file writing, 33 respondents considered no difference, 18 stated that it is more note-to-file writing now compared to before, 15 did not know and 1 respondent considered less writing now (Appendix 2).

Regarding the question about the knowledge if the laboratory that did the analyses to the trial was certified by SWEDAC, 50 respondents replied yes, 26 did not know and 6 respondents said no (Appendix 2).

On the subject if the trial subjects has a better safety now compared to before 2004, most of the respondents considered no difference, 15 stated that it is better now, 12 did not know and 2 respondents said it was better before (Fig 6)



Figure 6. The illustration shows the respondents experience concerning the trial subjects safety now compared to before. The majority, 38 answered no difference, 15 respondents stated that it is better now, 12 did not know and 2 stated that it was better before.

Moments after the clinical trial

On the following question about the time for report of the study results, 37 respondents did not know. 15 stated that it is longer now, 11 said that there is no difference and 4 respondents stated that it was longer before (Appendix 2).

Regarding the archiving of clinical trials before compared to after 2004, 62 respondents replied that they archived before and after, 3 stated only after 2004 and 2 respondents did not know (Appendix 2).

Regards to the difference in the amount of trials being publicized most of the respondents stated no difference before compared to after 2004. 15 considered more publicized trials before than now, 13 did not know and 9 said it was more after 2004 (Fig 7).

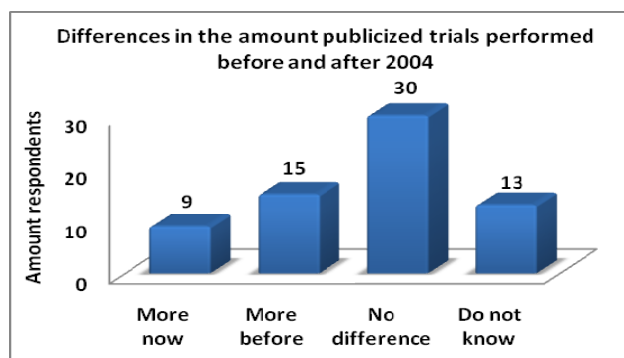


Figure 7. An overview of the replies regarding if there is a difference in the amount of performed publicized trials before compared to after 2004. Most of the respondents, 30 stated that there is no difference, 15 considered more publicized trials before, 13 did not know and 9 respondents replied that it is more now.

5.2 Results from the interviews

There were 20 persons that replied in the questionnaire that they were interested in participating in a following interview. From these, 10 respondents were randomly selected to do the interview. Unfortunately, two respondents could not be reached, resulting in an interview with eight persons.

The data from the interviews with eight respondents from KUH, two respondents from the MPA and one from the IEC are compiled according to each question. Additional questions that were particular made for the MPA are compiled separately subsequently.

5.2.1 Is there a difference in performing a clinical trial today compared to before 2004?

All of the respondents said that there was a difference with the performance of a clinical trial before and after 2004. They motivated that there are more control, structured rules, monitoring, safety reports and administration burden along with clearer guidelines. This leads to an increased importance that the requirements are followed since the requirements on quality assurance and security has increased. At the same time it is more time-consuming and difficult to get resources to make quality assurance of the clinical trial, which leads to smaller projects. However, two-eighths opined that knowledge, time and resources are needed to manage the difficulties and perform a clinical trial.

The respondents from the MPA considered a small difference in the execution of a clinical trial now compared to before 2004. It is the same system of rules that is used today but there are modest difficulties in the administration and bureaucracy components.

5.2.2 Is there a quality difference in Sweden's non-commercial clinical trials after the implementation of the EU directive 2004?

Half of the respondents did not notice any difference in the quality. One of these did not know if the quality of studies has improved, but sure that the input of the EU directive had not lead to decreased quality. Although, the system of rules is improved and they are followed orderly, it is difficult to state that the quality in clinical trials has become better, according to the respondent. Three respondents considered that the quality in clinical trials has improved because of all the requirements that have been implemented. Furthermore, one respondent did not consider that the quality in clinical trials has improved, with the motivation that quality is a good thing, but investigations that retain in small details will at the end focus on wrong things. According to the respondent, the implementation of the EU directive has made it more difficult to start a clinical trial with the result of a decrease in the amount of non-commercial clinical trials.

The respondents from the MPA replied that they have not looked into how the implementation has influenced the quality of non-commercial clinical trials. According to the MPA, there is no clear difference in the quality of clinical trials, since Sweden always have had high quality standards and compliance in following the system of rules. The requirements are more clear and easier to follow. Thus, it is impossible to say if the quality has become better now compared to before, since it is almost the same requirements on the investigator as before. The amateurish has become more informed about the system of rules but the professionals have always been working with high quality.

Another opinion that was given from the MPA, was that many investigators have the belief and attitude that it is more difficult, demanding and more administration now compared to before, although the system of rules has become more clear, pronounced and informative.

5.2.3 Is it a quality problem if the sponsor is the same person as the investigator?

Half of the respondents said that it is not a quality problem that the sponsor is the same person as the principal investigator as long as the clinical trial is professional arranged. The other half considered that it is a quality problem, since two different persons can acknowledge a problem from different point of views.

The MPA replied that if the sponsor is the same person as the investigator, it could bring problems, mainly in the administration area. However, these are not huge problems considered that most of the non-commercial clinical trials, almost 99% have a sponsor/investigator and it works.

5.2.4 Has the changes in the application process to the MPA and IEC after 2004, influenced the quality in clinical trials?

Half of the respondents thought that the changes of the application process to the MPA and IEC has not influenced the quality in clinical trials. Three other respondents thought that the quality has increased because of the details and the complex of the requirements. One respondent said that the changes of the application process to the MPA and IEC has made the investigators more conscious about the requirements of a complete application.

The respondents from the MPA agreed that the application process has become more extended and time consuming to complete it. However, the procurement time is shorter with clearer question formulation on the clinical trial, leading to improved quality. Now there are more guidelines on what the application should contain, which makes it easier to understand what kind of information is required, but at the same time it could be interpreted as more complicated. This change should increase the quality in clinical trials but there is no data that supports this.

5.2.5 Is there a difference in the protocol approval from the MPA before compared to after 2004? In what way has the quality in clinical trials got affected?

Five of eight responders consider that there is a difference in the protocol approval from the MPA, with more protocols being rejected. It is more finical but at the same time it varies. One of these illustrated the importance of the comments that is achieved from the MPA which works as directions and leads to increased quality in the clinical trial. Another of these respondent stated that there are more papers and plights, without leading to improved quality. Three respondents did not see any difference since the implementation of the EU directive.

The respondents from the MPA stated that the process for protocol approval is more concentrated and standardized now and almost all clinical trials get approval. They did also consider a quality improvement in the protocol. If a clinical trial is rejected, it is never because of a single deviation but the entire overall of the study. The respondents pointed out that there is not a difference in the system of rules on how the protocol should be written and what it should contain now compared to before. The only difference is that the interpretation of the system of rules is clearer and furthermore that the MPA is stricter now. The protocols are more structured, better designed and better thought-out which brings better quality and a risk decrease.

The MPA considered that it is more an attitude the investigator and involved have about that the financing and the study protocol process are more time consuming and extensive, than the real truth. Since, the execution of the study protocol rarely occurs it is more of an impracticable issue.

5.2.6 Has the use of the investigator's file, sponsor's file and delegation list changed today compared to before 2004?

Half of the respondents said that there is no greater difference between the use of the files containing the essential documents before and after 2004, the only difference is that they have a bigger volume and are more accurate and complex now. Two respondents said that they have used the files before but that it works better now. Two respondents were uncertain if they had used the files before 2004.

5.2.7 Is there a difference in the monitoring before compared to after 2004 and how is the quality affected in clinical trials?

Six of eight responders said that there was a difference in the monitoring today compared to before 2004. The monitoring has become more extensive and occurs more frequently. There are more distinct requirements on the monitoring and the monitoring report, and it is more finical now. Five of these, believed that the change in the monitoring has increased the quality.

Two respondents experienced in general, no difference in the monitoring and that the monitoring quantity depends on the monitor and the weight of the trial. One respondent considered that the quality has decreased. According to the respondent, the high amount of monitoring that occurs now results in more control on that everything gets correct written and there is more details.

According to the respondents from the MPA, more studies have adequate monitoring today and that has increased the quality. The monitoring process has been clarified and it is better habituated now than before.

5.2.8 Is there a difference in the amount inspections today compared to before 2004?

Six of eight respondents stated that there is no difference, three of these have never been involved in an inspection. Two respondents had a few more inspections now compared to

before 2004 and they considered that it was probably related to the lower amount studies that were made before compared to now.

The MPA replied that, the EU directive has not done any changes in Sweden, however it has meant a big change in the amount of inspections abroad. Summarized, there is no difference in the amount of inspections now compared to before.

5.2.9 Is there a difference in the amount Audit today compared to before 2004?

Half of the respondents said that there was no difference in the amount of audits now compared to before. Two respondents said that they never had audits. Two said they had had more audits after 2004 but that it is related to the lower amount studies that were made before compared to now.

5.2.10 Is there a difference in the performance of the data evaluation today compared to before 2004?

Six-eighths considered that there is a difference in the data evaluation. It has become more IT based and electronic CRF are more frequently used. The changes facilitate that the data get correct written onto a form. The factor that obstructs the use of electronic CRF is the large dependence on a working IT structure. Another problem is that there are many different systems for data evaluation thereby it gets more time-consuming. Two of these, things that the quality is decreased in this area because of the problems the electronic CRF bring.

Two-eighths said that there is no difference in how data is evaluated before compared to after 2004 and one said that there is a difference but does not know if it is because of the input of the EU directive.

5.2.11 Is there a difference in the amount of published clinical trials performed before and after 2004?

Five-eighths considered that there was no difference in the amount publications of clinical trials before and after 2004.

Three-eighths thought that the amount publications have decreased after 2004. The reasons that were given were time limitation, the need of a large budget and that the study must be registered in a clinical database. Other barriers were that clinical trials are bigger and more complex today, leading to difficulties in finishing the study quickly. A decrease in the amount of clinical trials was also mentioned.

5.2.12 How can improved quality be approached in clinical trials?

Six-eighths of the respondents considered that better quality in clinical trials can be obtained by having a good knowledge about the system of rules and how to follow them, have an outstanding team with good collaboration, a large budget, more time and an excellent protocol. A well written protocol is easier to follow with fewer deviations as result. One of these, said that it would be good with regular GCP education to improve the quality in the clinical trials. Two other respondents considered that it is important to sharpening the requirements on the question formulation to the clinical trial to get better quality. The question formulation should have public welfare versus commercial interests and it would also be good with fewer details.

The respondents from the MPA considered that improved quality can be reached by following the system of rules and administer the rules with commonsense.

5.2.13 Is there a good quality system today that maintains the quality in clinical trial compared to before 2004?

Six respondents answered that there is better quality system now compared to before 2004 and that the quality system can be found in GCP, SOP and instructions. Two other respondents considered that there is good quality system now compared to before 2004, in reaching data but not concerning the protocol and data processing.

The MPA answered that the GCP concept is a good quality system, to apply GXP in clinical trials and all the other system of rules that are relevant. There are a lot of quality aspects but it is about having a common sense and to follow them.

5.2.14 How is the quality in the moments before, during and after a clinical trial today compared to before 2004?

Half of the respondents considered that some moments in a clinical trial has better quality now but are in general more complex. The parts that are more complex are the financing, application process and the study protocol which is more time-consuming and extensive. Also the moments after which includes, that includes data processing, handle of data and statistics. Concerning the recruitment of the patients it is almost the same as before. The quality in the adverse event report has increased because of a bigger control, more monitoring and a clear description on what you should report. Furthermore, the monitoring and drug management

has better quality now, since the drug management is more structured and the monitoring is more clear and extensive.

Three - eighths considered that all the moments are in general better and safer today than before 2004, but need to accomplish more in the moments after. The financial part is better now, there are better CRF, databases, analyse plan, adverse event report and also more and better monitoring. But need to work more on the data management and statistics.

One respondent considered that clinical trials are in general more complex now than before, and has thereby caused a quality decrease in clinical trials. The main contributory factors that have decreased the quality are the patient information, recruitment of the patients and the moments after the clinical trial. According to the respondent, the patient information has too many details and is too extensive, which results in a risk that the patient will not remember what they have signed on. The recruitment of the patients is more complex now with higher requirements on the patients to fit the inclusion and exclusion criteria's. This leads to a study in a subpopulation and the results will not be applicable in the normal population. The other factor that has decreased the quality is the data processing, handle of data and statistics, because there is a bad oversee of the data.

5.2.15 Has the recruitment procedure of the trial subjects changed after the implementation of the EU directive 2004?

Five-eighths considered no difference in the recruitment of the patients before and after 2004. Three respondents said that there was a difference in the recruitment procedure since the implementation of the EU directive. Today a SOP for recruitment of patients is more frequently used, there is a bigger base and thereby more mixed people to the study. Another difference that was pointed out was that before the implementation of the EU directive on clinical trials an oral approval from the patient was enough. Now the patient has to give a written informed consent, which is considered better and safer for the patient.

5.2.16 Has the approval of the patient information from the IEC changed after 2004?

Almost all of the respondents consider no difference in the approval of the patient information to the IEC. One respondent said that there was more details now and thereby more difficult to embrace it.

According to the IEC the procedure has changed. Now it is regulated in the law regulated in the ethical trial law. However, the content and details are the same as before.

5.2.17 Do the trial subjects have better safety today compared to before 2004?

Five-eighths considered no difference in the trial subject's safety and security compared to before. The aim has always been to give the trial subjects good safety and security.

Three of the respondents consider that the trial subjects have better safety now for the reason that it is more particular, details and it is easier to see connections. Another aspect that was given was that the safety report is more distinct, better and also the conscious of the system of rules is better. The patients are better informed, both written and orally which brings more security and safety for the patient.

The MPA replied that the trial subjects have better safety but it is not because of the EU directive. However, there is a progress in the development. The knowledge is raising leading to a safer participation in a clinical trial, which leads to improved safety. The safety has developed, it is safer now but it is never 100% safe in a clinical trial.

According to the IEC there is no difference in the trial subject's safety in a clinical trial. However, now there is a penalty responsibility, six months in prison, if you do research without permissions.

5.2.18 Do you experience that the patient information is the same now compared to before 2004? If there are changes, how has that affected the quality?

According to the MPA the patient information cannot be longer than five pages. The patient information should contain significant information in order to not drown the important fact in unimportant facts. Extremely elongated patient information decreases the quality, since it make it impossible to the trial subjects to get the significant information.

The IEC have not observed any main changes in the patient information. The patient information in non-commercial clinical trials is still as short as before and the commercial clinical trials are still as extensive as before.

5.2.19 Compilation of the interview with the MPA

This is a presentation of the additional question that was specifically asked to the MPA.

What parameters do the MPA have to measure quality?

The respondents considered that that there should be a GCP statement in the protocol and in the study report to follow up that this has been followed. However, GCP is the quality

parameter and it is a question of interpretation if the project is GCP compatible or not. LVFS and the declaration of Helsinki should also be followed to obtain quality in the study.

Is there a difference in the amount clinical trials now compared to before?

Both the respondents said that there is no major change in the amount clinical trials now compared to before.

Is improved quality acquired through following the system of rules exactly?

The respondents said that improved quality is reached through having knowledge of the system of rules, administer it with a commonsense and not follow them slavishly. Then there are different interpretations on the system of rules which could affect the quality. An example is the over interpretation of the system of rules with the aim to get better quality in the study, but with the risk to concentrate on the wrong things.

5.3 Evaluation of the patient information

As a measurement of quality and the patient protection, a comparison of the patient information from 2003 and 2008 was done. The evaluation showed no major difference but still a change could be observed. The ten patient information obtained from 2008 were more structured with headlines that makes it easier for the reader to read and understand, compared to the patient information obtained from 2003. All of the patient information obtained from 2008 follow and uses the same headlines that are suggested in the form from the IEC. Only three patient information's from 2003 have headlines, seven of ten have the content in a concurrent text, which makes it difficult for the reader. There were two patient information from 2008 that did not mention what the risks were with the study. The majority of the patient information obtained from 2003 are in general very superficial in the description of the study. Six of ten patient information obtained from 2003 describe the procedure of the study very briefly, do not mention how the samples will be managed, the volume of the blood sample, where the blood samples were stored and one of these do not mention the aim. All the patient information from 2008 was between three and four pages compared to the patient information's from 2003 that were between two and three pages.

6 Discussion

6.1 Reflection over the methods

By using a quantitative and a qualitative method, the validity of the study increases. The advantage with the questionnaire is that a big number of respondents can be reached, standardized replies are reached and it is possible to evaluate the data with quantitative and statistical methods. The advantages with structured answering alternatives in the questionnaire are that the questions are easy to answer and it is easy to compile the collected data. The disadvantage is that the reply alternatives do not always reflect the respondents' opinion and could lead to false or default answers [17]. That is why the questionnaire has four reply alternatives where the last alternative is "Do not know". The disadvantage with a questionnaire is that the answers usually get short, difficult to interpret and it is not possible to ask consequence questions. Furthermore, it was not time effective to send 400 questionnaires through the internal post. The advantage with the interviews is that valuable information about their experiences and properties can be reached, that can be difficult to get from a written questionnaire. With the semi structured and open targeted questions in the qualitative method, it is possible to control the interview in a specified question area and ask consequence questions. This gives higher validity since the probability to find the truest information increases [15]. The disadvantage was that the interview was done with a small amount people, which bring difficulties to achieve a representative selection where the opinions can be applied in a bigger population.

Nevertheless, it was not a high reply frequency to the questionnaire, which could have been caused by many different factors. One factor is the selection framework which was not optimal since there is no register on the investigators and individuals that perform clinical trials at the KUH. Thus, the list of this study was composed of different lists, with investigators, research nurses and those who had typed agreements with KUH. These lists were old and not updated, meaning that many respondents were not available. A further factor that could have affected the reply frequency is the access to the people which is a very busy group. In addition a reminder could not be sent for the reason that all mail addresses were not available. The low reply frequency has to be taken in consideration during the analysis of the results.

There are some aspects to take in consideration during analyzing of the results from the questionnaire and interviews. Regarding the question about who reads the monitoring report now compared to before and the therapy area question, most of the respondents did not reply

and the few data that is given is difficult to analyze and it is not valid to use. In addition, even if there was a repetition that the questions concerns non-commercial clinical trials, it is possible that the respondents have answered after commercial clinical trials. In the questionnaire, the question 4.2 should have had reply alternatives instead of being an open question to make it easier to handle the data. A lot of replies do not fit the question or perhaps the wording of the question should have changed. On the questions were the respondents have replied that they do not know as question 5.1, the assumption was made that these questions were misunderstood.

The evaluation and comparison of the patient information was done to get an overview and a broad and general picture of an object prepared before and after 2004. A disadvantage with this is that it is not that credible to compare patient information from different kind of studies. Furthermore, a competent person should also have compared to increase the credibility.

6.2 Analysis of the result

After the compilation of the answers from the questionnaires and the interviews, the data was used to distinguish if the quality has improved or declined after the amendment 2004 of the new EU directive. Even if the new EU directive in clinical trials has not implied a large alteration in Sweden, it has brought some changes in some areas. This will be considerate in the analysis of the result. There are some areas with quality changes that are elucidated in this study. The areas are the obligation to have documented GCP education, the monitoring process, the application and protocol approval from the MPA, the sponsor, the data evaluation, the patient information and the trial subject's safety. The areas that did not show a greater difference after the implementation of the EU directive are, the recruitment of the trial subjects, the drug management, the amount of publicized clinical trials, the amount of adverse event reporting, note to file writing and the archiving. This differences or non differences will be further discussed in each area.

The differences in the quality impact of the clinical trials after the implementation of the EU directive.

Although the difficulties and bureaucracy indicated by the respondents, 57 % of the respondents from the questionnaire considered a quality increase after the implementation of the EU directive. This result is not reflected in the interviews, where three-eighths from the KUH interviews considered a quality increase. Though, half of the KUH interview respondents and 27% of the questionnaire respondents did not notice any difference in the quality compared to before 2004. This result relates to the MPA reflections concerning that

there is no clear difference in the quality of clinical trials because Sweden always had good quality but that they are more conscious about the system of rules now because the stricter requirements. However, it is interesting that the majority of the respondents from the interview answered that there is a better quality system today while only three of eight respondents stated a quality improvement. Theoretical, a good quality system should lead to improvement in quality of the clinical trials.

The majority of the interview respondents from the KUH stated that all the moments has in general better quality today than before 2004 but are in general more complex, however the moments after a clinical trial needs to be more accomplished. The parts that have a quality improvement are the monitoring, the adverse event reporting and the drug management. This is because of a better structure, clearer descriptions and a bigger control. The parts that are more extensive today are the financing, application process, study protocol, data management and statistics. Nevertheless, a minority of the respondents considered that clinical trials are in general more complex now than before, and has thereby caused a quality decrease in clinical trials. This could be related to what the MPA opined about that many investigators have the belief and attitude that it is more difficult compared to before, although the system of rules is more clear, pronounced and informative.

There is a discrepancy in the interview replies concerning the quality in clinical trials before compared to after 2004. Since, the majority stated no difference in the quality after the implementation of the EU directive but on the same time that all the moments in a clinical trial has in general better quality today compared to before 2004.

There is an interesting point that 71% of the respondents stated in the questionnaire that the quality is very important in clinical trials, by selecting the maximum number alternative. This could either be seen as negative or a positive result. A negative result since all the respondents did not select the maximum number alternative saying that superior quality is not the aim of everyone and thereby do not have a high priority and importance for good quality. Or as a positive result since all the respondents selected numbers over five meaning that quality is important to everyone but not the most important in a clinical trial. Where the safety of the trial subjects, the monitoring or other things are more important. This correlates to the statement the MPA did about different interpretations on the system of rules that can affect the quality, as over interpretation of the system of rules with the risk to concentrate on the wrong things.

How to get improved quality in clinical trials

According to the respondents from KUH, improved quality can be reached by having a QP with good GCP knowledge. Followed by good communication in the team and a well prepared study protocol according to GCP. Other factor for a quality improvement is to have more time and resources to the clinical trial (Fig 8). Some considered that it is important to sharpening the requirements on the question formulation to improve the quality in clinical trials. The MPA said that, there are requirements on the question formulation to the study written in ICH-GCP and the MPA controls that a protocol contains a relevant scientific question formulation.

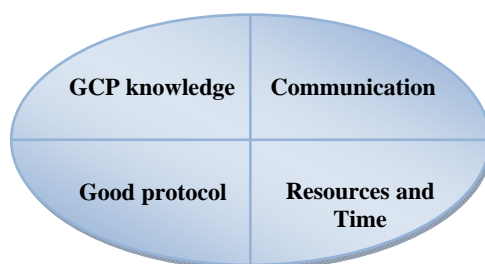


Figure 8. The picture shows the factors that are needed for improvement of a quality system in clinical trials according to the KUH respondents.

There was an interest subject about the relationship between improved quality and orderly following the system of rules. The MPA explained that improved quality in clinical trials is not reached by only following the system of rules orderly and slavishly, but by having knowledge of the system of rules and administer them with a commonsense. Good research means that a clinical trial should answer the aiming question and that the answer is credible. Even if the system of rules is followed into the smallest detail it cannot always guarantee improved and high quality in clinical trials.

Quality and the application process to the MPA

The application process to the MPA is considered to be more complex than before according to an earlier study [4]. However, the majority replied in the questionnaire that there is a quality increase in clinical trials because of the changes in the application process which is illustrated in figure 4. This result is not reflected in the interviews, where only three-eighths stated increased quality and half of the respondents considered no difference in the quality. The MPA said that there are more guidelines on what the application should contain to get more completed applications. The changes could be interpreted as more complicated now compared to before, but this requires more reflection when the applications are written and they get more correct written which improves the quality.

Quality and the protocol approval

The most common findings by the MPA during an inspection are deviations from the study protocol. With a good written protocol, fewer deviations are made and thereby better quality is achieved in the clinical trial. Nevertheless, the interview respondents from the KUH had an overwhelming view that there is a difference in the protocol approval from the MPA, since the change of the EU directive. There were divided views on the differences, some said that it was more difficult with decreased quality and other said that the MPA gives directions that lead to increased quality in the clinical trial. The MPA considered an improved quality in the protocol now and that it is more a feeling the investigator and involved has about that it is more difficult, than the real truth.

Documented GCP education

An important headstone the EU directive has implemented is that clinical trials should have QP with documented GCP education involved in the clinical trial. In this study 74 of 83 respondents had documented GCP and from these, 62% considered to have good knowledge in GCP. An important question to rise is what happened to the rest of the respondents and why do they not consider having good knowledge in GCP despite having documented GCP? It could be an uncertainty that makes them doubt on their GCP knowledge.

From the questionnaire the majority of the respondents with documented GCP recognized the relevant documents. However, more respondents recognized the declaration of Helsinki compared to the LVFS which is illustrated in figure 2. As many respondents elucidated, it would be good with updates of the GCP education to fresh up the knowledge, get new knowledge furthermore to overcome the uncertainty. Thus, increased GCP knowledge through education, the quality in clinical trials increases throughout the people involved in it.

The monitoring

The majority of the KUH respondents from the interview and the questionnaire stated that there is a difference in the monitoring today compared to before 2004, which can be seen in figure 5. The reasons that was given was that the monitoring has become more extensive, finical, frequently and have more distinct requirements on the monitoring than before, which has increased the quality. The MPA had the same view as the KUH respondents. Regarding the question about who reads the monitoring report now compared to before, most of the respondents did not reply and the few data that was given is not valid to analyze.

The patient information and the safety of the trial subjects

The comparison of the patient information obtained before and after the implementation of the EU directive, showed few differences in quality. The differences concerning the structure and the standardization could be because there is a common form now from the IEC that suggest how the patient information should be written and what it should contain. There were one before 2004 but it was simple, not so developed and detailed as the one now. In the aspect of how the patient protection and quality has been influenced by the EU directive, the patient information is better written, structured and with enough information for the trial subject to understand the study. This demonstrates an increase in quality and the safety of the trial subjects.

The KUH respondents from the interview stated no difference in the recruitment of the patients and the approval of the patient information to the IEC before and after 2004. This could be because they always had good recruitment of the trial subject or as the IEC stated that the procedure has changed but has the same content as before. According to the KUH respondents, the aim has always been to give the trial subject good safety and thereby the majority did not consider a difference compared to before, which can be seen in figure 6.

There is a difference in the results from the KUH respondents and the evaluation of the patient information. This has a relationship to that it is easier to see a change from an external angle than from the place where the change is. Fact can be reached through comparing material obtained from before and after 2004, which in this case showed an increase in quality and the safety of the trial subjects.

Sponsor issues

There was a disagreement on the question about if it is a quality problem that the sponsor is the same person as the principal investigator. Half of the KUH respondents stated that it is not a quality problem as long as the clinical trial is professional arranged. The other half considered a quality problem, since it is easier to see a problem if it is two different persons.

The MPA stated that it could bring problems in the administration area if it is the same person but not huge problems.

Concerning how the sponsor supply knowledge about the clinical trial, the majority of the respondents considered that it is better now and it is because they are more conscious about the increased requirements and need of high quality. About the sponsors file, there is no greater difference in the use of the sponsor files before and after 2004, according to the KUH respondents.

Areas without apparent differences after the implementation of the EU directive

Several results in different moments did not show a clear difference after the implementation of the EU directive. These includes the areas how the CRF is used in clinical trials, the drug management, the amount adverse event reporting, note to file writing, the approval of the patient information, archiving of the clinical trial, the amount of audit, the inspections and amount of publicized clinical trials which can be seen in figure 7. This result could be that Sweden always has had good quality and thereby no clear difference in quality. Another explanation could be that the implementation of the EU directive in 2004, have not noticeable affected these moments or could be that it have affected but is still not obvious and visible to the people involved in the clinical trials.

6.4 Future studies

Future studies could be to investigate how the EU directive has affected the quality in other countries, where the monitoring was not that common in clinical trials as England or France. Another study could be to analyze how other countries in Europe interpret the new system of rules that the EU directive in clinical trials has brought and if it differs from Sweden's interpretation. Further to study if the EU directive (2001/20/EC) that came into force in 2004 has harmonized the EU regulatory environment and simplified the trial application process in the member states as it was aimed to.

7 Conclusion

The study demonstrates that the implementation of the new EU directive on clinical trials into Swedish law 2004 has in general improved the quality in non-commercial clinical trials. This result is supported by the additional measurement of quality, the evaluation of the patient information which also showed that the safety of the trial subjects is better. The main areas that showed a quality increase is the monitoring, application process and patient information. Also, an increased GCP knowledge and that the sponsor supply better with knowledge.

8 Acknowledgement

I would like to thank all the respondents from the KUH that participated in the study through the questionnaire and the interviews furthermore the MPA and IEC for the interview contribution. I would also thank my supervisor Peter, for the constructive advice throughout the study as well as Anna and Elin for input and support all the way through.

9 References

1. Hoey R. The EU Clinical Trials Directive: 3 years on. *The Lancet*. 2007, May 26 Vol 369; 1777-8
2. European Parliament and Council of the European Union (2001) Directive 2001/20/EC of the European Parliament and the Council of 4 Apr 2001. OJ L 121: 34-44. Available: http://eudract.emea.eu.int/docs/Dir2001-20_en.pdf. Accessed 5 Sep 2008 [2008-09-01]
3. Är akademiska läkemedelsstudier möjliga? *Onkologi i Sverige*. nr 5-06, 1-59. Available: http://www.onkologiisverige.se/virtupload/onkologi/content/4/OIS5_2006.pdf [2008-09-01]
4. Alvehag E. Clinical Trials at Karolinska University Hospital – Problems and possibilities from an academic investigator’s perspective. 2007
5. Pincock S. Consent rule in EU clinical trial directive triggers concern. *The Lancet*. 2004, 6 March. Vol 363; 785
6. Hartmann M, Hartmann-Vareilles F. The clinical Trials Directive: How is it affecting Europe’s non-commercial research? *Plos clin trials*. 2006 June e13 1-5
7. Världsklass! Åtgärdsplan för den kliniska forskningen. Statens offentliga utredningar SOU 2008:7. 1-271. Available: <http://www.sweden.gov.se/content/1/c6/09/79/05/3881eb4a.pdf> [2008-09-05]
8. Pincock S. Consent rule in EU clinical trial directive triggers concern. *The Lancet*. 2004, 6 March. Vol 363; 785
9. Jüni P, Altman DG, Egger M. Assessing the quality of controlled clinical trials. In: Egger M, Davey Smith G, Altman DG, eds. *Systematic reviews in health care: meta-analysis in context* 2nd ed. London: BMJ Books, 2001
10. ICH harmonized Tripartite Guideline. (1996). www.ich.org
11. Binns R and Driscoll B. the clinical trials Directive – a new regulatory regime for Europe? *Pharmaceutical Science & Technology Today*. 2000, 1 April, Vol 3: 113-4.
12. Läkemedelsverket. Available: http://www.lakemedelsverket.se/Tpl/NormalPage_5687.aspx [2008-09-03]
13. Strandberg, K. (2005). Kan vi behålla försprånget? *Läkartidningen* Nr 12. värdetabell
14. Andersson, K., Agrell, B. (2004). EU:s direktiv inom klinisk forskning: Varken till fördel eller nackdel för Sverige. *Pharma industry*, Nr 4.
15. Malterud K. *Kvalitativa metoder i medicinsk forskning*. Studentlitteratur: Lund 1998, 88-100.
16. Eriksson & Wiedersheim-Paul 1999:89
17. Kumar et al.1999:312ff

Appendix 1 – Questionnaire

Accompanying letter to the questionnaire

2008-11-14

This is a study on how the new EU directive influences the quality on the non-commercial clinical trials.

This questionnaire is a part of a degree project from the Master program in Biomedicine at Karolinska Institutet in cooperation with the Karolinska Trial Alliance. The purpose with this study is to examine how the new EU directive that was introduced in 2004 in clinical studies has affected the quality on non-commercial clinical trials in Sweden. To examine this, questionnaires are sent out to investigators and people involved at the Karolinska University Hospital.

The questionnaire will be followed by a short interview for a deeper insight. If you would like to participate in a short interview, write it on the questionnaire. If you only have experience from clinical trials before or after 2004, please answer what is possible.

The participation is voluntary and the gathered information will be treated anonymously.

When you have answered the questionnaire, please send it in the following envelope trough the intern post of Karolinska, at latest *November 28, 2008*.

If you have any questions, please contact me at the mail below.

Thank you for your participation!

Agneta Cruz Galdo
Mail: agneta.cruz-galdo.867@student.ki.se
Karolinska Institutet

Peter Westerling, Dr Med. Sc
Handledare
Karolinska Trial Alliance

Detta är en studie om hur det nya EU direktivet påverkar kvalitet i de akademiska kliniska prövningarna.

Enkäten är en del av ett examensarbete som görs inom Mastersprogrammet i biomedicin på Karolinska Institutet i samarbete med Karolinska Trial Alliance. Syftet med studien är att undersöka hur det nya EU direktivet som infördes 2004, i kliniska studier, har påverkat kvalitet i de akademiska kliniska prövningarna i Sverige. För att undersöka detta så skickas denna enkät till prövare och involverade på Karolinska Universitetssjukhuset.

Enkäten kommer att följas upp med en kort intervju för att få en djupare inblick. Om du skulle vilja medverka i en intervju, skriv ner det på enkäten. Om du enbart har erfarenheter från kliniska studier innan eller efter 2004, så vänligen fyll i det som är applicerbart ändå.

Deltagandet är frivillig och uppgifterna som lämnas in kommer att behandlas anonymt.

När du har fyllt i enkäten, lägg den i det lilla ifyllda kuvertet och skicka den via Karolinskas Internpost, senast den **28 november 2008**.

Har du några frågor, så är Du välkommen att kontakta mig på nedanstående mail.

Tack för din medverkan!

Agneta Cruz Galdo

Mail: agneta.cruz-galdo.867@student.ki.se

Karolinska Institutet

Peter Westerling, Dr Med. Sc

Handledare

Karolinska Trial Alliance

1. General information

1.1 Name (optional):

1.2 What therapy area do you work in?

1.3 Do you have documented GCP education? Yes No

1.4 What is your normal role in clinical trials?

1.5 How have you mainly learned GCP?

Through a company

Through a course in another place

Through a course at KTA

Another:

1.6 How is your knowledge in GCP? Good Moderate Bad

2. Experiences of clinical trials

2.1 Have you participated in clinical trials before and after 2004?

Before2004

After 2004

Before and after

Nothing

2.2 Do you experience a quality change in clinical trials since the introduction of the EU directive 2004?

Increased quality now

No difference

Decreased quality now

Do not know

2.3 Have you participated in non-commercial clinical trials? Yes No

2.4 Have you participated in commercial clinical trials? Yes No

2.5 How important is quality for you in a clinical trial from 1-10? (Box in your answer,

where 1=little and 10 = Very much)

1 2 3 4 5 6 7 8 9 10

2.6 Who has the responsibility for quality in a clinical trial according to you?

.....

2.7 How can improved quality be reached in a clinical trial according to you?

.....

.....

3. Moments before the clinical trial

- 3.1 Do you recognize the Declaration of Helsinki? Yes No
The ICH-GCP? Yes No
The EU directive in clinical trials? Yes No
The MPAs body of law in clinical trials? Yes No

3.2 Has the application process to the MPA and IEC influenced the quality in clinical trials, after 2004?

- Yes, increased quality No
 Yes, decreased quality Do not know

3.3 Is there a difference in how the Sponsor supplies knowledge about the clinical trials after 2004? Yes No

3.4 If yes on question 3.3, what is the difference?

.....
.....

2. Moments during the clinical trial

4.1 Is there a difference in the monitoring before and after 2004?

- Yes No Do not know

4.2 What role has the one that reads the monitoring report now and before 2004?

Now:

Before:.....

4.3 Is there a difference in how CRF is used in clinical trials before and after 2004?

- Have CRF now CRF before and after 2004
 Had CRF before Never had CRF

4.4 Is there a difference in the drug management before and after 2004?

- Yes No Do not know

4.5 If yes on question 4.4, what is the difference?

.....
.....

4.6 Is there a difference in the amount side-effect reporting before and after 2004?

- More now No difference
 More before Do not know

4.7 Is there a difference in the amount audit before and after 2004?

- More now No difference
 More before Do not know

4.8 Has your note-to-file writing changed after 2004?

- More now No difference
 Less now Do not know

4.9 Do you know if the laboratory that did analyzes to the clinical trial is certified by SWEDAC?

- Yes No Do not know

4.10 Do you experience that the trial subjects have better safety now compared to before 2004?

- Better now 2004 No difference
 Better before 2004 Do not know

3. Moments after the clinical trial

5.1 Do you consider that the time for reporting of the study result to the authorities has changed before and after 2004?

- Longer now No difference
 Longer before Do not know

5.2 Did you archive the trial both before and after 2004?

- Only before Both before and after
 Only after Do not know

5.3 Is there a difference in the amount publicized trials you have performed before and after 2004?

- More now No difference
 More before Do not know

Would you like to contribute in a follow-up interview? Yes No

If yes, state contact information:

1. Allmän information (The original)

1.1 Namn (frivilligt):

1.2 Inom vilket terapiområde arbetar Du?

1.3 Har du dokumenterat GCP utbildning? Ja Nej

1.4 Vad är Din vanligaste funktion i prövningar?

1.5 Hur har du huvudsakligen lärt dig GCP?

Via ett företag

Via en kurs på annat ställe?

Via en kurs på KTA

Annat:

1.6 Hur är dina kunskaper inom GCP? Goda Måttliga Dåliga

2. Erfarenhet av kliniska prövningar

2.1 Har du deltagit i kliniska prövningar före och efter 2004?

Endast före 2004

Endast efter 2004

Före och efter

Vet ej

2.2 Upplever du någon förändring av kvalitet kliniska prövningar efter införandet av EU direktivet 2004?

Ökad kvalitet nu jämfört med före 2004

Ingen skillnad

Minskad kvalitet nu jämfört med före 2004

Vet ej

2.3 Har du deltagit i Akademiska prövningar?

Ja Nej

2.4 Har du deltagit i Företagsinitierade prövningar?

Ja Nej

2.5 Hur viktigt är kvalitet för dig i kliniska prövningar från skala 1-10? (Ringa in ditt

svar, där 1=Lite och 10 = Mycket)

1 2 3 4 5 6 7 8 9 10

2.6 Vem har ansvaret för kvalitet i en klinisk prövning enligt din åsikt?

.....

2.7 Hur kan man få bättre kvalitet i en klinisk prövning enligt din åsikt?

.....

3. Moment innan prövningen

- 3.1 Känner du till Helsingforsdeklarationen? Ja Nej
ICH-GCP? Ja Nej
EU-direktivet i kliniska prövningar? Ja Nej
Läkemedelsverkets författningssamling i kliniska prövningar? Ja Nej

3.2 Tycker du att ansökningsprocessen till LV och EPN påverkat kvalitet i de kliniska prövningar, efter 2004?

- Ja, kvalitet har ökat Nej
 Ja, kvalitet har minskat Vet ej

3.3 Finns det någon skillnad på hur den som är Sponsor förmedlar kunskap om kliniska prövningen nu jämfört med innan 2004? Ja Nej

3.4 Om ja på fråga 3.3, vad är skillnaden?

.....
.....

4. Moment under prövningen

4.1 Upplever du att det finns en skillnad i monitoringen före och efter 2004?

- Ja Nej Vet ej

4.2 Vilken funktion har den som läser monitoreringsrapporten nu och innan 2004?

Nu:

Innan:

4.3 Finns det någon skillnad på hur CRF används i prövningar före och efter 2004?

- Har CRF nu men hade inte före 2004 Har CRF både före och efter 2004
 Hade CRF före 2004 men inte nu Har inte haft CRF före/efter 2004

4.4 Upplever du att det finns en skillnad på läkemedelshanteringen före och efter 2004? Ja Nej Vet ej

4.5 Om ja på fråga 4.4, vilken skillnad?

.....
.....

4.6 Upplever du att det finns en skillnad i antal biverkningsrapportering nu jämfört med före 2004?

- Fler nu än före 2004 Ingen skillnad
 Fler före 2004 Vet ej

4.7 Är det en skillnad i antal Audit före och efter 2004?

- Fler nu än före 2004 Ingen skillnad
 Fler före 2004 Vet ej

4.8 Har ditt "Note to File" skrivande förändrats efter 2004?

- Skriver mer nu än före 2004 Ingen skillnad
 Skriver mindre nu före 2004 Vet ej

4.9 Känner du till om laboratoriet som tog/tar hand om laboratorieanalyserna till provningarna är certifierad av SWEDAC?

- Ja Nej Vet ej

4.10 Upplever du att försökspersoner/patienter har bättre säkerhet nu jämfört med före 2004?

- Bättre nu än före 2004 Ingen skillnad
 Bättre före 2004 Vet ej

5. Moment efter provningen

5.1 Anser du att tiden för rapportering av studieresultat till myndigheterna har förändrats före och efter 2004?

- Längre tid nu än innan 2004 Ingen skillnad
 Längre tid före 2004 Vet ej

5.2 Arkiverade ni provningen både före och efter 2004?

- Endast före 2004 Arkiverade både före och efter
 Endast efter 2004 Vet ej

5.3 Finns det någon skillnad på mängden publicerade provningar som du utfört före och efter 2004?

- Fler nu än innan 2004 Ingen skillnad
 Fler före 2004 Vet ej

Skulle du kunna tänka dig att medverka i en uppföljande intervju? Ja Nej

Om ja, uppge kontaktuppgifter:

Appendix 2 – Value table

1.3 Do you have documented GCP education?				
Yes	No			
74	9			

Amount answers:	
83/400 =	20.8%

1.4 What is your normal role in clinical trials?				
Do not have GCP	Investigator	Other		
	6	3		

1.4 What is your normal role in clinical trials?				
Have GCP	Investigator	Investigator nurse	Other	
	34	28	12	

1.5 How have you mainly learned GCP?				
Company	KTA	Other		
32	33	48		

1.6 How is your knowledge in GCP?			
(No)	Good	Moderate	Bad
	1	6	2

(Yes)	Good	Moderate	Bad
	48	21	1

2.1 Have you participated in clinical trials before and after 2004?				
Before 2004	After 2004	Before/after	Nothing	
8	8	67		

2.2 Do you experience a quality change in clinical trials since the introduction of the EU directive 2004?				
Increased	Decreased	No difference	Do not know	
38	1	18	10	

2.3 Have you participated in non-commercial clinical trials?				
Before/after	Yes	No		
	59	8		

2.4 Have you participated in commercial clinical trials?				
Before/after	Yes	No		
	62	5		

2.5 How important is quality for you in a clinical trial from 1-10?				
Ten	Nine	Eight	Seven	
59	17	6	1	

3.1 Do you recognize the Declaration of Helsinki?				
Do not have GCP	Yes	No	Have GCP	Yes
	9	0		71
	5	4		65
	5	4		64
	6	3		58
				3
				9
				10
				16

3.2 Has the application process to the MPA and IEC influenced the quality in clinical trials, after 2004?							
Before	Increased	Decreased	No	Do not know			
	1	1		6			
After	Increased	Decreased	No	Do not know			
	2			6			
Before/after	Increased	Decreased	No	Do not know			
	31	2	18	16			
	3.2 Before/after, increased Q			Increased	Decreased	No	Do not know
			24	1	5	8	
	3.2 Before/after, decreased Q			Increased	Decreased	No	Do not know
					1		
	3.2 Before/after, no difference			Increased	Decreased	No	Do not know
			6		9	3	
	3.2 Before/after, do not know			Increased	Decreased	No	Do not know
			1	1	3	5	

3.3 Is there a difference in how the Sponsor supplies knowledge about the clinical trials after 2004?						
Before	Yes	No				
		3				
After	Yes	No				
		2				
Before/aft	Yes	No	Do not know			
	32	26	3			
	3.3 Before/aft -increas			Yes	No	Do not know
			27	11	2	
	3.3 Before/aft -decrea			Yes	No	Do not know
			1		6 did not reply	
	3.3 Before/aft -no diffe			Yes	No	Do not know
			3	14		
	3.3 Before/aft - do not			Yes	No	Do not know
			1	1	1	

4.1 Is there a difference in the monitoring before and after 2004?						
Before	Yes	No	Do not know			
	0	1	7			
After	Yes	No	Do not know			
	2	0	6			
Before/aft	Yes	No	Do not know			
	32	20	15			
	4.1 Before/aft -increas			Yes	No	Do not know
			23	6	9	
	4.1 Before/aft -decrea			Yes	No	Do not know
			1			
	4.1 Before/aft -no diffe			Yes	No	Do not know
			7	8	3	

	4.1 Before/aft - do not	Yes	No	Do not know		
		1	6	3		

4.3 Is there a difference in how CRF is used in clinical trials before and after 2004?						
Before	CRF now	CRF before	Both	Never had		
	0	4	2	2		
After	CRF now	CRF before	Both	Never had	Vet ej, de gjorde egen ruta	
	2	0	1	0	5	
Before/aft	CRF now	CRF before	Both	Never had		
	12	0	55	0		
	4.3 Before/aft - increased	CRF now	CRF before	Both	Never had	
		7		31		
	4.3 Before/aft - decreased	CRF now	CRF before	Both	Never had	
				1		
	4.3 Before/aft - no difference	CRF now	CRF before	Both	Never had	
		2		16		
	4.3 Before/aft - do not know	CRF now	CRF before	Both	Never had	
		3		7		

4.4 Is there a difference in drug management before and after 2004?						
Before	Yes	No	Do not know			
	2	3	3			
After	Yes	No	Do not know			
	4	1	3			
Before/aft	Yes	No	Do not know			
	25	39	3			
	4.4 Before/aft - increased	Yes	No	Do not know		
		19	17	2		
	4.4 Before/aft - decreased	Yes	No	Do not know		
		1	0	0		
	4.4 Before/aft - no difference	Yes	No	Do not know		
		4	13	1		
	4.4 Before/aft - do not know	Yes	No	Do not know		
		1	9	0		

4.6 Is there a difference in the amount side-effect reporting before and after 2004?						
Before	More now	More before	No difference	Do not know		
	2	0	1	5		
After	More now	More before	No difference	Do not know		
	3	0	2	3		
Before/aft	More now	More before	No difference	Do not know		
	16	1	29	21		
	4.6 Bef/aft - increased	More now	More before	No difference	Do not know	
		11	1	13	13	

	4.6 Bef/aft -decreased	More now	More befo	No differer	Do not know		
		0	0	1	0		
	4.6 Bef/aft -no differer	More now	More befo	No differer	Do not know		
		2	0	12	4		
	4.6 Bef/aft - do not kn	More now	More befo	No differer	Do not know		
		3	0	3	4		

4.7 Is there a difference in the amount audit before and after 2004?							
Before	More now	More befo	No differer	Do not know			
	0	0	0	8			
After	More now	More befo	No differer	Do not know			
	0	0	2	6			
Before/aft	More now	More befo	No differer	Do not know			
	15	0	25	27			
	4.7 Bef/aft -increased	More now	More befo	No differer	Do not know		
		9	0	14	15		
	4.7 Bef/aft -decreased	More now	More befo	No differer	Do not know		
		1	0	0	0		
	4.7 Bef/aft -no differer	More now	More befo	No differer	Do not know		
		4	0	8	6		
	4.7 Bef/aft - do not kn	More now	More befo	No differer	Do not know		
		1	0	3	6		

4.8 Has your note-to-file writing changed after 2004?							
Before	More now	Less now	No differer	Do not know			
	0	0	1	7			
After	More now	Less now	No differer	Do not know			
	0	0	2	6			
Before/aft	More now	Less now	No differer	Do not know			
	18	1	33	15			
	4.8 Bef/aft -increased	More now	Less now	No differer	Do not know		
		16	1	12	9		
	4.8 Bef/aft -decreased	More now	Less now	No differer	Do not know		
		0	0	1	0		
	4.8 Bef/aft -no differer	More now	Less now	No differer	Do not know		
		2	0	13	3		
	4.8 Bef/aft - do not kn	More now	Less now	No differer	Do not know		
		0	0	7	3		

4.9 Do you know if the laboratory that did the analyzes to the clinical trial is certified by SWEDAC?							
Yes	No	Do not know					
50	6	26					

4.10 Do you experience that the trial subjects have better safety now compared to before 2004?							
Before	Better now	Better befo	No differer	Do not know			
	1		3	4			
After	Better now	Better befo	No differer	Do not know			
	2		1	5			

Before/aft	Better now	Better bef	No differer	Do not know			
	15	2	38	12			
4.10 Bef/aft -increased	Better now	Better bef	No differer	Do not know			
			14	1	16	7	
4.10 Bef/aft -decrease	Better now	Better bef	No differer	Do not know			
				1			
4.10 Bef/aft -no differer	Better now	Better bef	No differer	Do not know			
					16	2	
4.10 Bef/aft - do not k	Better now	Better bef	No differer	Do not know			
			1		6	3	

5.1 Do you consider that the time for reporting of the study result to the authorities has changed before and after 2004?								
Before	Longer now	Longer bef	No differer	Do not know				
	0	1	2	5				
After	Longer now	Longer bef	No differer	Do not know				
	0	0	1	7				
Before/aft	Longer now	Longer bef	No differer	Do not know				
	15	4	11	37				
5.1 Bef/aft -increased	Longer now	Longer bef	No differer	Do not know				
			9	4	4	21		
5.1 Bef/aft -decreased	Longer now	Longer bef	No differer	Do not know				
			1	0	0	0		
5.1 Bef/aft -no differer	Longer now	Longer bef	No differer	Do not know				
			5	0	4	9		
5.1 Bef/aft - do not kn	Longer now	Longer bef	No differer	Do not know				
			0	0	3	7		

5.2 Did you archive the trial both before and after 2004?								
Before	Only before	Only after	Before/Aft	Do not know				
	1	0	2	4				
After	Only before	Only after	Before/Aft	Do not know				
	0	0	4	4				
Before/aft	Only before	Only after	Before/Aft	Do not know				
	0	3	62	2				
5.1 Bef/aft -increased	Before	After	Before/ aft	Do not know				
			0	0	36	2		
5.1 Bef/aft -decreased	Before	After	Before/ aft	Do not know				
			0	0	1	0		
5.1 Bef/aft -no differer	Before	After	Before/ aft	Do not know				
			0	2	16	0		
5.1 Bef/aft - do not kn	Before	After	Before/ aft	Do not know				

5.3 Is there a difference in the amount publicized trials you have performed before and after 2004?						
Before	More now	More befo	No differer	Do not know		
	0	3	2	3		
After	More now	More befo	No differer	Do not know		
	1	0	1	6		
Before/aft	More now	More befo	No differer	Do not know		
	9	15	30	13		
	5.1 Bef/aft -increased	More now	More befo	No differer	Do not know	
			6	6	19	7
	5.1 Bef/aft -decreased	More now	More befo	No differer	Do not know	
			0	1	0	0
	5.1 Bef/aft -no differer	More now	More befo	No differer	Do not know	
			2	4	8	4
	5.1 Bef/aft - do not kn	More now	More befo	No differer	Do not know	
			1	4	3	2

Appendix 3 – Interview forms

Interview form to KUH

Experiences of clinical trials

- 1) Have you participated in non-commercial clinical trials before and after 2004?
- 2) Is there a difference in performing a clinical trial today compared to before 2004?
- 3) Is there a quality difference in Swedens non-commrcial clinical trials after the implementation of the EU directive 2004? Increased/ decreased and Why?
- 4) Is it a quality problem if the sponsor is the same person as the investigator?

Moments before the clinical trial

- 5) Has the changes in the application process to the MPA and IEC after 2004, influenced the quality in clinical trials? Increased/ decreased and Why?
- 6) Is there a difference in the protocol approval from the MPA before and after 2004? In what way has the quality in clinical trials got affected?

- 7) Has the use of the investigator folder, sponsor folder and delegation list changed today compared to before 2004?

Moments during the clinical trial

- 8) Is there a difference in the monitoring before and after 2004 and how is the quality affected in clinical trials?
- 9) Is there a difference in the amount inspections you had today compared to before 2004?
- 10) Is there a difference in the amount Audit you had today compared to before 2004?

Moments after the clinical trial

- 11) Is there a difference in the performance of the data evaluation today compared to before 2004?
- 12) Is there a difference in the amount published clinical trials that you have performed before and after 2004?

General questions about quality

- 13) How do you consider that improved quality can be approached in clinical trials?
- 14) Do you consider that there is good quality system today that maintains the quality in clinical trial?
- 15) How do you experience the quality in the moments before, during and after a clinical trial today compared to before 2004?

Patient information

- 16) Has the recruitment procedure of trial subjects changed after the implementation of the EU directive 2004?
- 17) Has the approval of the patient information from the IEC changed after 2004?
- 18) Does the trial subjects have better safety today compared to before 2004?

- 19) Do you experience that the patient information is the same now compared to before 2004? If there are changes, how has that affected the quality?

Intervjumall till KUH (The original)

Erfarenhet av kliniska prövningar

- 1) Har du deltagit i kliniska prövningar före och efter 2004?
- 2) Upplever du att det finns en skillnad med att utföra en klinisk prövning innan jämfört med efter 2004? Är det lättare eller svårare?
- 3) Upplever du någon förändring av kvalitet i kliniska prövningar efter införandet av EU direktivet 2004? Är den ökad/sänkt och varför isåfall?
- 4) Är det ett kvalitetsproblem att sponsor och prövare kan vara en och samma person?

Moment innan prövningen

- 5) Tycker du att ansökningsprocessen till LV och EPN påverkat kvalitet i de kliniska prövningar, efter 2004? Har kvalitet minskat/ökat och varför isåfall?
- 6) Upplever du att det finns en skillnad på protokoll godkännandet från LV innan och efter 2004? Tvungen att korrigera protokollet oftare/mindre?
- 7) Användandet av prövarpärm, sponsorpärm och delegeringslista före och efter 2004?

Moment under prövningen

- 8) Upplever du att det finns en skillnad i monitoreringen före och efter 2004 och hur är kvalitet i kliniska prövningar påverkad?
- 9) Finns det en skillnad i antal inspektioner LV gjort före och efter 2004?
- 10) Är det en skillnad i antal Audit före och efter 2004?

Moment efter prövningen

11) Upplever du att det finns en skillnad på hur data evalueringen utfördes innan och efter 2004?

12) Finns det en skillnad på mängden publicerade prövningar som ni utfört före och efter 2004?

Generella frågor om kvalitet

13) Hur anser du att man kan få bättre kvalitet kliniska prövningar?

14) Tycker du att det finns bra kvalitetssystem idag som upprätthåller kvalitet i studien?

15) Hur upplever du att kvalitet är i följande moment jämfört med innan 2004 – Innan, under, efter kliniska prövningen?

Patient informationen

16) Upplever du att rekryteringsprocessen av patienter har förändrats innan och efter 2004?

17) Upplever du att godkännandet av patient informationen till EPN har förändrats efter 2004?

18) Upplever du att försökspersoner/ patienter har bättre säkerhet nu jämfört med före 2004?

19) Upplever du att patient informationen är likadan nu jämfört med före 2004? Om det finns förändringar, hur har det påverkat kvaliteten?

Interview form to the MPA

1) What parameters do you have to measure quality?

2) Is there a difference in the amount clinical trials now compared to before?

3) Do you acquire improved quality through following the system of rules exactly?

4) Have you looked into how the implementation of the EU directive has influenced the quality in Sweden's non-commercial clinical trials and is there a change of the quality in clinical trials after the implementation of the EU directive?

Differences in the clinical trials

6) Is it a quality problem if the sponsor is the same person as the PI?

7) Is there a difference in the execution of a clinical trial now compared to before 2004? Is it more difficult or easier?

8) Has the changes in the application process to the MPA influenced the quality in clinical trials after 2004?

9) Is there a difference in the protocol approval from the MPA now compared to after 2004? In what way has the quality in clinical trials got affected?

10) Many respondents considered that it is more papers and details in the protocol to get it approved. In what way has the quality in clinical trials got affected?

11) It seems that the financing, the application process and the study protocol are more time consuming and extensive. How has the changes in these areas affected the quality?

12) Is there a difference in the monitoring before and after 2004 and how is the quality affected in clinical trials?

13) Is there a difference in the amount inspections the MPA has done before and after 2004?

15) How can improved quality in a clinical trial get approached?

16) Is there a good quality system that maintains the quality in clinical trials?

17) Do you experience that the patient information is the same now compared to before 2004?

18) Does the trial subjects have better safety in a clinical trial now compared to before?

Intervjumall till LV (The original)

- 1) Vilka parametrar används för att mäta kvaliteten?
- 2) Finns det en skillnad i mängden kliniska prövningar nu jämfört med före 2004?
- 3) Uppnår man bra kvalitet genom att exakt följa regelverken?
- 4) Har ni undersökt hur införandet av EU direktivet har påverkat kvalitet i de akademiska kliniska prövningarna? Isf finns det någon skillnad i kvalitet?

Differences in the clinical trials

- 6) Är det ett kvalitetsproblem om sponsorn är densamma som prövaren?
- 7) Finns det en skillnad i utförandet av en klinisk prövning nu jämfört med före 2004? Är det svårare eller enklare?
- 8) Har ändringarna i ansökningsprocessen till LV påverkat kvalitet i kliniska prövningar efter 2004?
- 9) Finns det en skillnad i protokoll godkännandet från LV före jämfört med efter 2004? Hur har kvaliteten i kliniska prövningar påverkats?
- 10) Många respondenter upplever att det är mera papper och detaljer i protokollen för att få det godkänt. Hur har det här påverkat kvalitet i kliniska prövningar?
- 11) Det tycks att finansieringen, ansökningsprocessen och studieprotokollet är mera tidskrävande och omfattande. Hur har dessa ändringar i de här områdena påverkat kvalitet?
- 12) Finns det en skillnad i monitoreringen före jämfört med efter 2004 och hur är kvaliteten i kliniska prövningar påverkad?
- 13) Finns det en skillnad i antalet inspektioner LV före jämfört med efter 2004?
- 15) Hur kan förbättrad kvalitet i kliniska prövningar uppnås?
- 16) Finns det ett bra kvalitetssystem som upprätthåller kvalitet i kliniska prövningar?

17) Upplever du att patient informationen är likadan idag jämfört med före 2004?

18) Upplever du att försökspersoner/ patienter har bättre säkerhet nu jämfört med före 2004?

Interview form to the IEC (The original)

1) Has the approval of the patient information from the IEC changed after 2004?

2) Has changes in the patient information affected the quality in clinical trials?

3) Does the trial subjects have better safety in a clinical trial now compared to before?

Appendix 4 – Patient information form

Forskningspersonsinformation (Original)

Forskningspersonsinformation

Formuläret ska innehålla all den information som en person rimligtvis kan behöva känna till för att kunna ta ställning till deltagande i ett forskningsprojekt, men inte mer.

Den skriftliga informationen är ett komplement till den information som ska ges muntligen.

Tillfälle tillfrågor ska alltid ges. Samtyckesformuläret kan vara separat men ska (i kopia) liksom informationsformuläret och eventuella bilagor behållas av forskningspersonen.

Det är viktigt att förshingsper sonsinformation ges på ett enkelt och tydligt språk och inte innehåller ord som kan upplevas som en påtychiing eller överord om studiens tänkbara värde. Informationen bör anpassas till personens ålder och förutsättningar i övrigt eller eventuell annan orsak till nedsatt beslutskompetens. Vid forskning med barn ska information riktas till såväl barnet (om läskunnigt) som till vårdnadshavaren. Informationen bör inte vara för lång och endast undantagsvis överstiga 3-5 A4- sidor. Om informationsbladet av olika skäl behöver vara betydligt längre bör en kortare version (1-2 A4-sidor) med den för forskningspersonen väsentligaste informationen (se nedan) ges med den längre versionen som bilaga. Detaljerad instruktion kan vid behov ges i bilaga.

Nedanstående är utformat för att passa både medicinsk och övrigforskning och får tillämpas i relevanta delar.

Rubriker enligt nedan kan underlätta läsbarheten:

Rubrik Kommentar

1. Bakgrund och syfte

2. Förfrågan om deltagande

3. Hur går studien till?

4. Biobanksprover

Ge en kort men tydlig beskrivning angående bakgrund och övergripande syfte med studien.

Här ska anges varför just den aktuella personen tillfrågas samt hur man fått tillgång till uppgifter om personen som gör att denne tillfrågas (t.ex. "vi har fått ditt namn ur folkbokföringsregistret").

Här beskrivs översiktligt ur forskningspersonens perspektiv, vad som kommer att krävas, vilka metoder

som kommer att användas, antal besök vid en mottagning, eventuella provtagningar, intervjuer, tester mm. Det ska tydligt framgå på vilket sätt undersökningsprocedurer skiljer sig från t.ex. en patients/klients rutinemässiga behandling. Det ska också framgå hur prover och analysresultat kommer att hanteras och om de kommer att sändas utomlands för analys eller förvaring. Om analyserna avser gener bör det framgå vilken eller vilka sjukdomar eller andra egenskaper man avser koppla till gener. Vid blodprovstagning bör provmängd tydligt framgå.

Om prover ska förvaras i en biobank bör det framgå hur och var proverna förvaras, att de är kodade så att de inte

5. *Vilka är riskerna?*

6. *Finns det några fördelar?*

7. *Hantering av data och sekretess.*

utan tillgång till en kodnyckel direkt kan hänföras till en individ och att de endast får användas på det sätt forskningspersonen givit sitt samtycke till. Det ska också framgå om prover som sparas kan komma att användas för framtida ännu ej planerad forskning. Att i sådant fall ny etisk prövning kommer att göras och att forskningspersonerna i vissa fall senare kan komma att kontaktas igen.

Här ska framgå om obehag, smärta eller andra biverkningar kan uppstå av en behandling. Även långtidseffekter ska beskrivas. Eventuella förutsebara känslomässiga effekter som kan uppstå och möjliga integritetskränkningar ska beröras. I förekommande fall ska också framgå hur de forskningsansvariga kommer att hantera problem som att procedurer avbryts, möjlighet till uppföljande samtal etc.

Här ska utan förskönande moment tydliggöras eventuella fördelar för patienten. När det gäller behandlingsforskning ska det tydliggöras att den nya behandlingens eventuella effekter (i sammanhanget) är okända eller måste verifieras.

Här ska framgå på vilket sätt data kommer att behandlas: Om data direkt eller indirekt kan spåras till enskild individ, eventuell datoriserad behandling, registerhantering. Det ska framgå om uppgifterna kommer att lämnas vidare till uppdragsgivare, t.ex. läkemedelsbolag eller till medarbetare vid annat universitet inom eller utom landet. Om personuppgifter används ska enligt personuppgiftslagen (1998:204) information ges om vem som är personuppgiftsansvarig (t.ex. "ansvarig för dina personuppgifter är Göteborgs universitet"), ändamålen med behandlingen av personuppgifterna samt all övrig information som behövs för att forskningspersonen ska kunna ta till vara sina rättigheter enligt personuppgiftslagen. Sådan information är uppgift om varifrån personuppgifterna hämtas, vilka uppgifter eller

kategorier av uppgifter som behandlas, forskningspersonens rätt att få ett registerutdrag och rätt att få rättelse av eventuellt felaktiga uppgifter. Referens till personuppgiftslagen bör anges. Formulering om sekretess bör lyda: "Dina svar och dina resultat kommer att behandlas så att inte obehöriga kan ta del av dem". Uppgift om hur studiens resultat kommer att presenteras och hur personidentiteten då skyddas bör också finnas.

8. *Hur får jag information om studiens resultat?*

9. *Försäkring, ersättning*

10. *Frivillighet*

11. *Ansvariga*

Här ska framgå på vilket sätt forskningspersonen kan få ta del av sina individuella data (egna analysresultat) eller resultat av hela studien (t.ex. publicering i patientföreningsskrift, muntlig information i grupp eller dylikt). Forskningspersonens möjlighet att slippa ta del av eventuella analysresultat kan också framgå.

Här ska anges om patientskadeförsäkring gäller eller om särskild försäkring tecknats för projektet. Vidare ska framgå om forskningspersonen har rätt att få ersättning för förlorad arbetsinkomst eller andra utgifter kopplade till projektet. Det ska också framgå att eventuell övrig kompensation är skattepliktig inkomst. Avslutningsvis ska tydliggöras att deltagande i forskningsprojekt är frivilligt och att man när som helst, utan särskild förklaring, har rätt att avbryta. Här kan också förtydligas vilka delar/uppgifter som då förstörs. Om prover tagits ska det framgå att forskningspersonen har rätt att begära att proverna förstörs eller märkes så att de inte längre är möjliga att spåra till den enskilde. Här ska framgå att om en forskningsperson som är patient/ klient inte vill delta eller vill avbryta kommer detta inte att påverka sedvanlig(t) behandling/ omhändertagande.

Under denna rubrik ska anges ansvariga för genomförandet av studien (forskningshuvudman, forskare och personuppgiftsansvarig) samt kontaktadress (telefonnummer, telefontid, e-post etc.) till en person som kan ge ytterligare information.

Samtyckesformulär Här ska tydliggöras att forskningspersonen har informerats, fått tillfälle att ställa frågor, fått dem besvarade och samtyckt till:

dels deltagande i studien, dels - i förekommande fall - till behandling av personuppgifter respektive lagring av prover i en biobank. Vid läkemedelsprövning ska samtycket även inkludera att annan (studiemonitor) får ta del av journaluppgifter för kontroll av data. Om studien innehåller olika delar ska det framgå att forskningspersonen kan välja att delta endast i vissa delar.