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ORIGINAL ARTICLE

# Ethical procedures and patient consent differ in Europe

Ulrike M. Stamer, Nadja Naef, Rouven Porz, Frank Stuber, Brigitte Leva, Winfried Meissner and Dominique Fletcher, euCPSP Study Group

**BACKGROUND** Research ethics approvals, procedures and requirements for institutional research ethics committees vary considerably by country and by type of organisation.

**OBJECTIVE** To evaluate the requirements and procedures of research ethics committees, details of patient information and informed consent based on a multicentre European trial.

**DESIGN** Survey of European hospitals participating in the prospective observational study on chronic postsurgical pain (euCPSP) using electronic questionnaires.

**SETTING** Twenty-four hospitals in 11 European countries.

**PARTICIPANTS** From the 24 hospitals, 23 local investigators responded; 23 answers were analysed.

**OUTCOME MEASURES** Comparison of research ethics procedures and committee requirements from the perspective of clinical researchers. Comparison of the institutions' procedures regarding patient information and consent. Description of further details such as costs and the duration of the approval process.

**RESULTS** The approval process lasted from less than 2 weeks up to more than 2 months with financial fees varying between 0 and 575 €. In 20 hospitals, a patient information sheet of variable length (half page up to two pages) was provided. Requirements for patients' informed consent differed. Written informed consent was mandatory at 12, oral at 10 and no form of consent at one hospital. Details such as enough time for consideration, possibility for withdrawal and risks/benefits of participation were provided in 25 to 30% of the institutions.

**CONCLUSION** There is a considerable variation in the administrative requirements for approval procedures by research ethics committees in Europe. This results in variation of the extent of information and consent procedures for the patients involved.

**TRIAL REGISTRATION** euCPSP in Clinicaltrials.gov identifier: NCT01467102; PAIN-OUT in Clinicaltrials.gov identifier: NCT02083835.

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## Introduction

The European observational study on chronic postsurgical pain (euCPSP) is a multicentre, prospective, noninterventional trial to assess the incidence of CPSP in Europe and to evaluate contributing risk factors by considering patients' characteristics, type of surgery and anaesthetic procedure. The basis for this study is the European acute pain registry PAIN OUT (Improvement of postoperative PAIN OUTcome), which is now established in some 50 hospitals within and outside Europe, with ongoing dissemination. The core of this project is a web-based registry, wherein each participant can enter pain-related outcome data of patients, including surgical and anaesthetic-related variables and the results of a standardised, validated patient outcome questionnaire from the first postoperative day.[1]

The euCPSP study was planned as an extension of PAIN OUT and offers an additional feature, namely two electronic patient questionnaires filled in 6 and 12 months after surgery[2] that request information about persistent postsurgical pain. This study is sponsored by the European Society of Anaesthesiology (ESA) within its Clinical Trial Network (http://www.esahq.org/research/clinical-trial-network).[3,4] The primary idea of this ESA network was to foster clinical research using large observational epidemiological studies and patient

From the Department of Anaesthesiology and Pain Medicine, Inselspital and Department of Clinical Research (UMS, NN, FS), Unit for Clinical Ethics, Inselspital, University of Bern, Bern, Switzerland (RP), Clinical Trial Network, European Society of Anaesthesiology, ESA Office Bruxelles, Brussels, Belgium (BL), Department of Anaesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany (WM), and Service d'Anesthésie Réanimation, Hôpital Raymond Poincaré, Garches, France (DF)

Correspondence to Ulrike M. Stamer, Department of Anaesthesiology and Pain Medicine, Inselspital, University of Bern, Freiburgstr, 3010 Bern, Switzerland
Tel: +41 316329995; fax: +41 316320554; e-mail: ulrike.stamer@dkf.unibe.ch

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recruitment from all over Europe to collect data that are helpful for improving patient care.[4] Observational studies were favoured for cost-effectiveness. They did not necessarily require an official sponsor and allowed for a simple, straightforward organisation without the need for patient insurance, approval by state regulatory authorities or the requirement to obtain a possible waiver for patient consent by the respective ethics committees.[4]

During the first meeting of all the local investigators, however, it transpired that ethical approval for euCPSP was not a straightforward procedure at each hospital and additional requirements had to be met in some institutions, which prolonged the process considerably. We had assumed that all ethics committees' processes would be based on research ethics guidelines such as the Nuremberg Code and the Helsinki Declaration, but we found that this is not the case.

Differences regarding ethical requirements and application details have been reported previously.[5,6] Our focus was to analyse differences in bureaucratic processes and the requirements of research ethics committees as an extension of the euCPSP study. Knowledge about possible differences and obstacles might be helpful when clinical researchers plan future European multicentre studies. Thus, the aim of this study was to explore the procedures for research ethics approval, organisational requirements and methods of patient information and consent in participating European hospitals

## Materials and methods

At the 2011 ESA congress in Amsterdam, the euCPSP study was launched. At this investigator meeting, the issues surrounding research ethics approval were discussed. The idea of a survey on local procedures and bureaucratic requirements regarding patient information and consent for euCPSP in the different European study centres was subsequently proposed. In autumn 2012, when all centres were already recruiting patients, the 24 local investigators were asked to fill in a questionnaire asking for details about their research ethics approval process. The link to this electronic survey was provided via an e-mail sent by the ESA office in Brussels. A draft of the questionnaire was distributed to the coauthors for discussion and then reworked. Subsequently, it was sent to colleagues for completion with the request to identify any inconsistency, ambiguity or incomprehensible wording. The final version of the questionnaire was then set up with SurveyMonkey (https://de.surveymonkey.com) and could be accessed by the project leaders of the participating hospitals. Several reminders were mailed to nonresponding hospitals to assure answers from all participants. The survey consisted of 18 questions and one additional field for entering free text comments at the end of the questionnaire.

The main issues addressed by the survey of the euCPSP participants regarding ethical procedures were:

(1) type of research ethics committee (local/regional/national);
(2) duration of the administrative procedure and necessity of a revised version of the application for approval and costs;
(3) need for a study amendment considering telephonic interviews of the patients;
(4) approach to the patient information process, whether oral/written (if written then details about the patient information sheet);
(5) type of informed consent given by the patient (oral/written).

In addition, participating investigators from the euCPSP study were asked to mail a copy of their patient information sheet and consent form to the ESA office. Differences between these documents were compared between study centres. If written forms were available, the following issues were examined: explanation of benefits and risks for the patients if participating in the study; the provision of sufficient time for the patient to consider his/her participation; opportunity to ask additional questions; the patients' right to withdraw from the study at any point in time; anonymisation of patient data; and details of data management and safety.

Confidentiality was promised to local investigators in order not to offend those centres with less elaborate ethical procedures.

For analysis, the data were imported into STATISTICA 10 (Stat Soft, Inc. Tulsa, Oklahoma, USA). A descriptive statistical analysis was performed. Of primary interest was the method of patient information and whether informed consent was mandatory for this observational trial.

## Results

### Participating hospitals

Of the 24 participating hospitals, 23 completed the questionnaire. The nonresponding institution only enrolled a few patients in the euCPSP study and subsequently prematurely terminated its participation. Responding hospitals were located in 11 European countries with five in Switzerland, three in Germany, two each in Belgium, Italy, Romania, Spain, the UK and Ukraine, and one each in France, Ireland and Moldova. Of the hospitals, 18 were university hospitals, two were university-affiliated teaching hospitals and two were community hospitals.

### Necessity for ethical approval

For 21 of the 23 hospitals, some kind of research ethical approval was mandatory, whereas no specific ethics review was necessary in only two centres. Twenty (83%) study centres sought a positive decision from their responsible ethics committee or institutional review board, which was a local (12), regional (six) or national (one) institution (one additional institution did not answer this question). In addition, in four of these study



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centres, the respective health/regulatory state authority had to be involved in the procedure. In one centre, only an assessment by the respective health/regulatory state authority was performed.

In eight countries, more than one hospital took part in euCPSP. About half of the investigators were asked by the research ethics committee to give detailed information about which other hospitals also planned to participate or were already participating in euCPSP. In nine hospitals, an approval of another committee from the same country could abbreviate the centre's own procedure for gaining research approval. Investigators were also asked whether a positive ethical decision from a foreign centre could theoretically abbreviate the ethical procedure in their own institution; this was the case for four research ethics committees.

#### Duration of approval process and financial costs

In most institutions ($n = 9$), the review process for the research proposal lasted up to 8 weeks. The shortest period reported was 2 weeks, although a duration of more than 2 months was reported by three participating sites. Eight participants had to submit a revised version of their research proposal to meet the requirements of the research ethics committee in charge. The main reasons for such resubmissions were as follows: changes requested in the patient information sheet and consent form ($n = 3$); specification of how patients were to be selected ($n = 1$); lack of information about patients' insurance ($n = 1$); and details regarding financing of the study ($n = 1$).

Aspects of data protection and the location of the data server had to be made transparent for 10 committees. These committees requested specific information and some clearly stated that a web-based database was acceptable only if the data server was located in a country in which data protection was considered to be as high as in the country where the data were collected. However, 12 participants did not have to give any information on these issues to their respective research ethics committees. At some institutions, there were no costs for approval, and at others that had to submit newly designed patient information sheets and consent forms and an additional amendment, fees varied between 300 and 575 €.

#### Amendment of the study protocol

After about 7 months of the ongoing euCPSP study, additional telephonic interviews were introduced as an alternative to electronic online questionnaires for the 6 and 12-month follow-up interviews. Fourteen hospitals used this additional option to gather data on patients' chronic pain after surgery. Of these institutions, all but two had to submit an amendment to their ethics committee.

#### Patient information and informed consent

In most institutions, written information sheets explaining the aims and scope of the study were provided to the patients (Fig. 1). These sheets varied considerably in length. At nine hospitals [from Switzerland (four), Germany (three), Italy (one) and the Netherlands (one)], ethics committees required a newly designed information sheet with a length of between one and two pages. These documents were formatted according to templates aiming at interventional studies provided by the respective ethics committees. Four hospitals did not provide their patient information sheets, but stated that the text comprised about half a page, which corresponds to the original PAIN OUT document.

On all information sheets, the patients were informed that their participation was voluntary and that data would be made anonymous. Further details of the written patient information sheets considering sufficient time for consideration, adequate time to ask questions relating to the study, withdrawal from the study, benefits and risks of study participation as well as confidentiality of the data are summarised in Table 1.

From the perspective of the respective research ethics committee, oral consent was perceived to be sufficient at 10 institutions, whereas one local investigator indicated in the questionnaire that neither written nor oral consent was mandatory. Patients' written informed consent was obtained in the other 12 departments (Fig. 1; Table 1).

## Discussion

Each euCPSP participating hospital was obliged to obtain approval for the study from the local research ethics committee at its site. In this European observational study on chronic postsurgical pain, ethical requirements differed considerably from one institution to another.

For randomised clinical trials, similar practices have been described previously. Duley *et al.*[7] criticised the need for multiple ethical approvals for multicentre studies and commented that the increased ethical regulations and guidelines were becoming barriers to the design and conduct of such trials. A considerable variety of requirements and issues raised by 14 institutional review boards was also reported for a multicentre 'minimal risk' genetic study.[8]

For the present trials, several reasons for these differences are likely to have contributed. The application for ethical approval submitted by the local investigators might have differed or the evaluation of the respective ethics committees might not have been consistent. Research ethics committees did not unanimously accept the nature of a prospective observational trial based on a registry. Half of the researchers had to introduce a more detailed and elaborate written patient information and informed consent form than originally planned. On the basis of our experience in the present study, the varying


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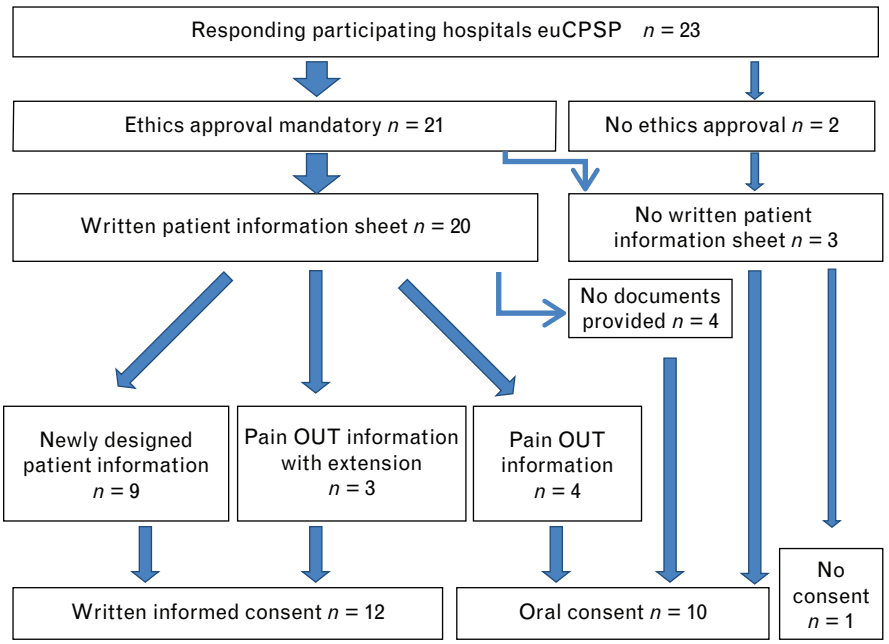
**Fig. 1**




Flow chart of responding hospitals participating in the European observational study on chronic postsurgical pain and their procedures for patient information and consent.

research ethics procedures and requirements can be divided into three different bureaucratic approaches (Table 1).

The basic procedure was that the existing PAIN OUT information sheet was sufficient and only oral consent was necessary. One might speculate that the respective ethics committees assessed the project simply as a registry for quality control with no scientific perspective. This procedure is well recognised in some European countries.[6] Bisgaard *et al.*[9] stated in their observational study on outcome and utilisation of intensive care resources after elective aortic surgery that neither formal ethical approval nor patient consent was required in Denmark; only approval by the Danish Data Protection Agency was necessary.[9] This emphasises the intention of the ESA CTN that noninterventional studies with a low risk should be easy to perform, allowing the recruitment of large patient cohorts representing everyday clinical practice without the artificial environment of a (double-blinded) randomised control trial (RCT). However, euCPSP was different due to the addition of the 6 and

**Table 1 Details of written patient information and informed consent**

| | Basic procedure PAIN OUT information | Full procedure PAIN OUT information with extension | Extended procedure New patient information & consent |
|---|---|---|---|
| Number of institutions | 8 | 3 | 9 |
| Anonymity | 8 | 3 | 9 |
| Voluntary participation | 8 | 3 | 9 |
| Withdrawal possible | 0 | 0 | 8 |
| Time for consideration | 0 | 0 | 5 |
| Time to ask questions | 0 | 1 | 6 |
| Benefits of the study | 0 | 0 | 6 |
| Risks of the study | 0 | 0 | 5 |
| Confidentiality of data | 0 | 0 | 5 |
| Possible audit of records or inspection by EC | 0 | 0 | 5 |
| Data safety | 0 | 0 | 3 |
| Oral consent only | 8 | 0 | 0 |
| Written consent | 0 | 3 | 9 |

Twenty hospitals provided information. The other 3 hospitals did not provide a written patient information sheet. EC, ethics committee.



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12-monthly follow-up questionnaires, which is a feature not included in routine patient assessment. This was not considered as an issue requiring written consent at the institutions with a basic procedure.

The full procedure consisted of an additional written informed consent form and (in the majority of cases) only a very few additions to the existing PAIN OUT information sheet. This version conforms to the requirements of research projects evaluating data from a registry. The new Swiss Human Research Act in force since 2014 clearly states that a scientific analysis of registry data with subsequent publication needs patients' written informed consent.

In the extended procedure, the existing PAIN OUT information was insufficient and a new patient information sheet and written informed consent form had to be designed. At these institutions, a template for a patient information and informed consent sheet for a prospective observational trial was not available, so the investigators had to use the templates designed for (randomised) clinical drug studies. These are comprehensive and contain paragraphs deemed to be unsuitable for an observational trial. In general, in this group of more elaborate ethics procedures, a fee had to be paid for approval by the ethics committee. Costs of up to 575 € in addition to the expenditure required for patient information and written consent are a major obstacle for some institutions to participate in such prospective observational trials. It has to be questioned whether this laborious procedure comparable to interventional studies is reasonable or might rather impede research based on registries or low-risk observational trials.

Furthermore, assessments of the technique of data anonymisation could have been inconsistent. In PAIN OUT, a unique code is created for each data entry, which is equivalent to strict anonymisation. This anonymisation process is also mentioned in the standard PAIN OUT information sheet. In departments in which individually designed patient information sheets were used, some further details seemed to be necessary. One concern was the storage of patients' e-mail addresses and telephone numbers for the follow-up interviews 6 and 12 months after surgery. Both items were stored separately from the euCPSP database. Thus, anonymisation was not complete, but was rather a form of pseudonymisation.

Clearly, these were not purely bureaucratic requirements but different interpretations of what was perceived as the ethical risk of the study. For data safety, some research ethics committees requested a country from the western part of Europe to host the database. This implies that possibly not all participating countries were categorised as 'safe', which in itself is an intriguing but clearly debatable judgement for a research ethics committee to make. One might question whether this categorisation of 'computer safety' and 'data protection' should really be in the purview of a research ethics committee.

In another ESA CTN study (European Surgical Outcome Study, EUSOS; http://www.esahq.org/research/clinical-trial-network), the requirements for patient information also varied considerably by country and institution.[10] In one country, centres were exempt from research ethics approval because the study was deemed to be a clinical audit; in others, formal research ethics approval had to be applied for. A written informed consent for EUSOS, however, was mandatory only in Finland.[10]

From a more general perspective, these variations may be comprehended as the professionalisation of an institutionalised form of ethics, which is a quite recent development within European healthcare systems.[11] This could explain why different European research ethics committees and review boards still operate in varying ways. The institutionalisation of ethics not only takes place within the context of research but also in different forms of clinical ethics support or national ethical advisory boards. Still, there is a strong conceptual difference between clinical ethics/national ethics boards and research ethics committees.[11] The work of clinical ethics support systems and national advisory boards is uniquely and exclusively supportive and advisory, whereas the work of research ethics committees results in decisions for or against conducting a research project. This conceptual difference inevitably results in a strong dependency of the researcher on the local research ethics committee. From the perspective of the clinical researcher, this dependency may appear rather arbitrary, because the procedures and requirements differ between European ethics committees, as demonstrated by this analysis. These inconsistencies considerably inhibit collaborative research in Europe.

In the future, the possibility of a unique centralised European research ethics approval process for multicentre European studies needs to be discussed. As multinational clinical research is hampered by the fragmentation of health and legislative systems, the European Clinical Research Infrastructures Network (ECRIN) will provide future coordination of research centres and make multinational clinical research more transparent (http://www.ecrin.org/). Another initiative is the report of the European Forum for Good Clinical Practice (EFGCP) on the procedure for the ethical review of protocols for clinical research projects in Europe and beyond. (http://www.efgcp.be/EFGCPRReports.asp?L1=5&L2=1).[12] However, the focus is still predominately on interventional trials. Prospective, multicentre, observational studies are in need of an adapted procedure more specific to this type of research. As risks for patients are low or even negligible, and benefits for researchers and clinicians might be high, this noninterventional research needs different considerations compared with interventional trials. Glasziou and Chalmers[13] provocatively mentioned the term 'ethics review roulette' and stated that although ethical standards are clearly essential for all type



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of evaluations, the notion that 'one size of ethics review fits all types of evaluation' should be rejected. Hopefully, the European efforts will enable comparable conditions for research ethics procedures and patient informed consent in the future. This would simplify the planning and performance of this kind of international multicentre study and would not evoke the feeling of being arbitrarily judged by different standards and bureaucratic approaches.

## Conclusion

Research ethics procedures and organisational requirements differed considerably among participating hospitals for this prospective observational study. Hopefully for all clinical researchers, future legislative and research ethics requirements will be harmonised within Europe to overcome these differences.

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