

RESEARCH ETHICS

Assessment of the ethical review process for non-pharmacological multicentre studies in Germany on the basis of a randomised surgical trial

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Objective: To examine the current ethical review process (ERP) of ethics committees in a non-pharmacological trial from the perspective of a clinical investigator.

Design: Prospective collection of data at the Study Centre of the German Surgical Society on the duration, costs and administrative effort of the ERP of a randomised controlled multicentre surgical INSECT Trial (INterrupted or continuous Slowly absorbable sutures—Evaluation of abdominal Closure Techniques Trial, ISRCTN 24023541) between November 2003 and May 2005.

Setting: Germany.

Participants: 18 ethics committees, including the ethics committee handling the primary approval, responsible overall for 32 clinical sites throughout Germany. 8 ethics committees were located at university medical schools (MSU) and 10 at medical chambers. Duration was measured as days between submission and receipt of final approval, costs in euros and administrative effort by calculation of the product of the total number of different types of documents and the mean number of copies required (primary approval acting as the reference standard).

Results: The duration of the ERP ranged from 1 to 176 (median 31) days. The median duration was 26 days at MSUs compared with 34 days at medical chambers. The total cost was €2947. 1 of 8 ethics committees at universities (€250) and 8 of 10 at medical chambers charged a median fee of €162 (mean €269.70). The administrative effort for primary approval was 30. Four ethics committees required a higher administrative effort for secondary approval (37, 39, 42 and 104).

Conclusion: The ERP for non-pharmacological multicentre trials in Germany needs improvement. The administrative process has to be standardised: the application forms and the number and content of the documents required should be identical or at least similar. The fees charged vary considerably and are obviously too high for committees located at medical chambers. However, the duration of the ERP was, with some exceptions, excellent. A centralised ethics committee in Germany for multicentre trials such as the INSECT Trial can simplify the ERP for clinical investigators in and outside the country.

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The INSECT Trial (INterrupted or continuous Slowly absorbable sutures—Evaluation of abdominal Closure Techniques) is a multicentre, intraoperatively randomised controlled trial for the Study Centre of the German Surgical Society comparing three different standardised surgical techniques for abdominal wall closure in patients with elective primary midline laparotomy. The primary end point in this study is the occurrence of an incisional hernia in 1 year.^{1 2}

Interventions include abdominal closure using continuous sutures with different, medium-term, absorbable, single-filament material (PDS; Ethicon, New Jersey, USA or MonoPlus; BBD Aesculap GmbH, Tuttlingen, Germany) and with short-term absorbable, plaited-filament material (Vicryl; Ethicon). The estimated number of 600 subjects (200 per group) is based on the most recent meta-analysis, which could not identify a clear-cut advantage for any of the techniques used in the trial.³

To ensure equal surgical treatment in all centres, all participating surgeons initially underwent an instruction course. In addition, all centres recruited subsequently also received standardised training on the basis of in vivo and in vitro educational material and practice sessions. Each centre had to obtain approval from the responsible ethics committee before participating in the trial, irrespective of any other prior decision by another ethics committee, according to the current practice and guidelines in Germany. The first or primary approval of a study was processed at the Study Centre of the

German Surgical Society, Department of Surgery, University of Heidelberg Medical School, Heidelberg, Germany. All other sites would have to use this approval letter to obtain a decision from their local ethics committee (secondary approval) for non-pharmacological trials in Germany.

In general, two major groups of ethics committees are relevant in Germany: university medical schools of universities (MSU) have their own institutions, which are responsible for all medical doctors at the departments and all affiliated teaching hospitals. Medical chambers are the official association of all medical doctors in Germany, forming a federal system (like the states of Germany). All doctors not affiliated with a medical school who would like to participate in a study have to ask the ethics committee of the medical chamber responsible for their region for a decision before they enrol a patient. The structure of the committees varies, but in general medical doctors, statisticians, lawyers and patient advocates are members. These committees review the supplied material for a study regarding ethical and scientific aspects and decide whether a trial can start or whether a revision is necessary before approval or recommend not conducting a study.

Abbreviations: ERP, ethical review process; INSECT Trial, INterrupted or continuous Slowly absorbable sutures—Evaluation of abdominal Closure Techniques trial; MSU, university medical schools

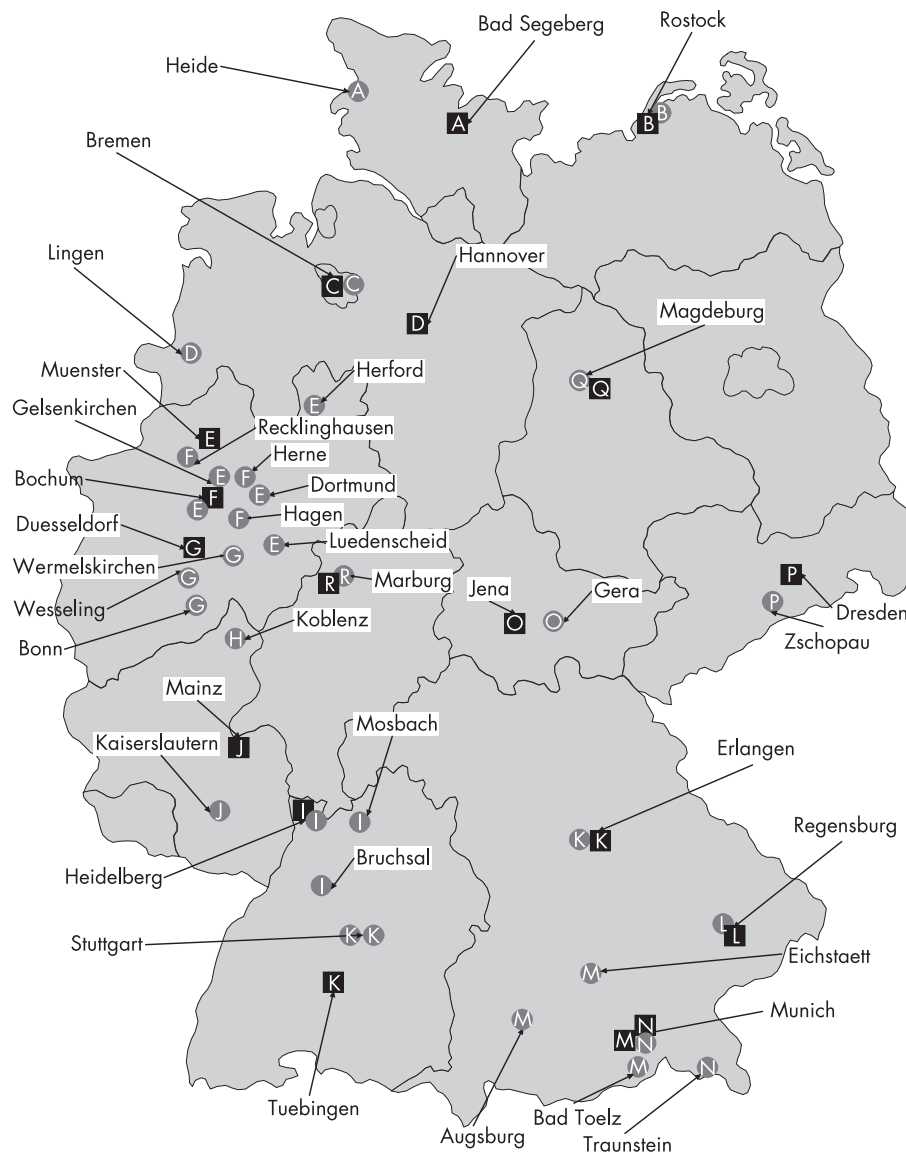


Figure 1 Map of Germany showing surgical sites (circles) and corresponding (letters) ethics committees (squares) participating in the INSECT (INterrupted or continuous Slowly absorbable sutures—Evaluation of abdominal Closure Techniques) Trial.

Until now, no data are available on the costs, time and paperwork of the ethical review process (ERP) of multicentre, non-pharmacological trials in Germany. The Directive of the European Union on Clinical Trials (2001/20/EG) was introduced by the German Drug Law in 2004, which changed the process for pharmaceutical trials considerably.⁴

This study assessed the efficiency of the ethics committees by using qualitative and quantitative indicators.

METHODS

The ERP for the INSECT Trial between 19 November 2003 and 6 May 2005, which was the date of receipt of the last secondary approval, was the basis for this study.

To provide an in-depth analysis of the efficiency of the ERP, three dimensions were quantified: duration, costs and administrative effort. While analysing the diverse dimensions, emphasis was placed on the differences between the ERP in MSU and medical chambers.

The quantitative indicator for the duration was the time (in days) between the date of submission of the documents and the

date of receipt of the approval, including all revisions as requested by the ethics committees. The quantitative indicator for the dimension costs was the fee (in euros) charged. The mean and median were calculated on the basis of these data.

To better define the dimension administrative effort of the ERP, the total number of different types of documents was multiplied by the mean number of copies required by each institutions committee. The administrative effort invested in the ERP for the primary approval at the MSU Heidelberg served as a reference standard for all others. In addition, the type and number of queries raised by the ethics committees were evaluated.

RESULTS

The first hearing of the study protocol was held before the ethics committee in Heidelberg on 8 December 2003. The written decision requiring a revised protocol and changes to the patient information leaflet was received on 10 December 2003. Primary approval was attained on 20 January 2004. After a meeting with representatives of all participating clinical sites on 5 and 6 March 2004, the process of obtaining the secondary

Table 1 Duration, costs and number of queries raised within the ethical review process of the INSECT Trial

Ethics committee (ET)	Centre	Duration (days) for primary, secondary and subsequent votes*	Cost (€)	Queries raised
EC at MSU	n = 14			
Medical College Hannover	Lingen	34	—	O
MSU Bochum	Herne	17	—	—
	Hagen	(30)	—	—
	Recklinghausen	(16)	—	—
MSU Marburg	Marburg	29	—	PI
MSU Heidelberg	Heidelberg	61	—	PI, O
(primary approval)	Mosbach	(7)	—	—
	Bruchsal	(6)	—	—
MSU Tübingen	Stuttgart RBK	14	—	—
	Stuttgart	(5)	—	—
	Marienhospital	(5)	—	—
MSU Erlangen	Erlangen	22	250	—
MSU Regensburg	Regensburg	1	—	—
MSU Munich	Traunstein	61	—	PI
	Großhadern	(11)	—	—
EC at MC	n = 18			
MC Schleswig-Holstein	Heide	14	275	—
MC Bremen	Bremen	12	75	P
MC Mecklenburg-Vorpommern	Rostock	33	—	—
MC Saxonia	Zschopau	17	350	—
MC Sachsen-Anhalt	Magdeburg	45	500	—
MC Thuringen	Gera	34	150	—
MC Westfalia-Lippe	Gelsenkirchen	8	174	—
(joint EC with the MSU Munster)	Herford	(6)	—	—
	Dortmund	(5)	—	—
	Luedenscheid	(7)	—	O
	Bochum	(2)	—	—
MC North Rhine	Wermelskirchen	176	1073	O
	Gerresheim Bonn	(11)	—	—
MC Rhineland-Palatinate	Kaiserslautern	45	100	PI, O
MC Bavaria	Augsburg	112	—	O
	Eichstätt	(10)	—	—
	Bad Toelz	(1)	—	—

INSECT Trial, Interrupted or continuous Slowly absorbable sutures—Evaluation of abdominal Closure Techniques trial; MC, medical chamber; MSU, university medical schools; P, study protocol; PI, patients' information sheet; O, others (eg, case report form).

*Duration for primary votes is denoted in normal writing, secondary votes are given in italics and subsequent votes in parentheses.

approvals was initiated. The application was submitted to 17 ethics committees, which, in total, were responsible for 29 centres (table 1, fig 1). The last secondary approval was attained from the MSU Marburg on 5 May 2005.

Duration

Table 1 and fig 2 list the duration of the ERP for the primary and the 17 secondary approvals. The total range was from 1 day in Regensburg to 176 days in North Rhine (mean 41, median

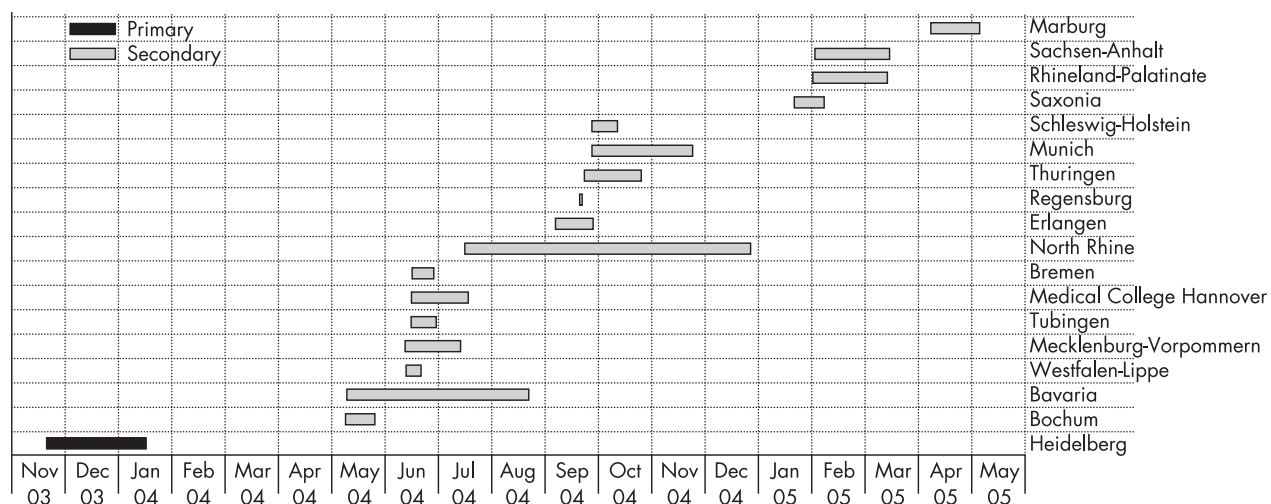


Figure 2 Duration of the ethical review process (primary and secondary approvals) of the INSECT (INterrupted or continuous Slowly absorbable sutures—Evaluation of abdominal Closure Techniques) Trial, November 2003 to May 2005.

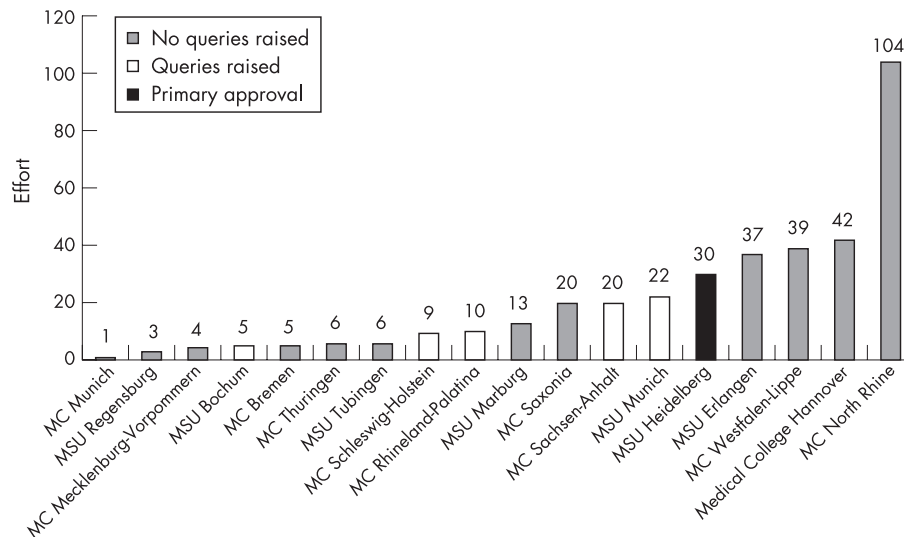


Figure 3 Administrative effort per ethical review process for the primary and secondary approvals of the INSECT (INterrupted or continuous Slowly absorbable sutures—Evaluation of abdominal Closure Techniques) Trial. MC, medical chamber; MSU, university medical schools.

31 days). The duration for eight medical schools ranged between 1 and 61 days (mean 30, median 26 days) and that for the 10 medical chambers between 8 and 176 days (mean 50, median 34 days).

Costs of the ethical review process

Table 1 lists the costs for each ERP. The primary approval in Heidelberg was free of charge. Overall, 9 of the 17 (53%) secondary approvals resulted in costs of €2947: 1 of 7 medical schools (€250) and 8 of 10 medical chambers (mean €269.70, median €162.00) charged fees.

Administrative effort

Figure 3 shows the administrative effort for the secondary approval. Heidelberg required four different types of documents: the study protocol, a summary of the protocol, the patients' information leaflet with the informed consent form and the application form.

The mean number of copies per document that needed to be handed in was 7.5. As a result, the amount of paperwork required added up to a reference value of 30. In regard to further inquiries by the ethics committee, queries were raised in 8 of the 17 (47%) ERPs for the secondary decisions. Table 1 lists the queries depending on whether they were related to the study protocol, the patients' information sheet or other aspects such as case report form or curriculum vitae of the leading investigator for a clinical site. Only one of these was related to the study protocol but was resolved after providing further scientific material requiring no amendments at the end. All other questions required minor changes but had no substantial effect on ethical or scientific aspects of the trial.

The net effect of a particular type of query on the administrative effort is difficult to estimate. Therefore this listing in fig 3 should merely be considered additional information.

DISCUSSION

The overall complexity of an ERP for a multicentre, non-pharmacological study has neither been adequately analysed nor published in the literature, to our knowledge. On the basis of the data from the ERP of the INSECT Trial, it can be concluded that the duration of this process is reasonable but

the administrative efforts and costs are rather variable, depending on the different participating committees.²

The median duration from submission to approval was 31 days. This did not cause a delay in the start of the trial and recruitment of patients at most clinical sites. With the implementation of the European Union directive 2001/20/EG in Germany in August 2004, in the form of the 12th amendment of the German Drug Law, the role of ethics committees in pharmacological studies has changed significantly.⁴ As regulated by a section in this law, a time limit of 60 days is set for the ERP⁵ (also see http://bundesrecht.juris.de/anig_1976_42.html ZwölftesGesetzArzneimittelgesetz.pdf). To improve the transparency of the ERP, the study sponsor is now obliged to hand in, besides the EudraCT number, all relevant documents relating to the clinical trial, such as the protocol, the patients' information sheet, information on the investigators and the criteria for the selection and eligibility of the participating trial centres. If clinical sites for multicentre studies are located in regions with different ethics committees, the ethics committee for the site of the principal investigator is the final authority. When looking at the secondary approvals of the INSECT Trial, only 3 of 17 ethics committees needed longer than 60 days for the ERP. This is even more remarkable, when taking into consideration that the above-mentioned regulations so far apply only to pharmacological trials, but not to non-pharmacological trials such as surgical, behavioural or other trials. Our data call for further efforts by the outliers to optimise their review process.

Some differences in the costs of the ERP were found in this study. With the exception of the University of Regensburg, all other secondary approvals at the university level were free of charge. In contrast, the ethics committees at medical chambers often charged fees that differed considerably (ranging from zero to €1073). The total cost of €2947 (2% of the whole budget for the INSECT Trial) for the approvals, given the effect of changes to the study material and the workload at the coordinating trial centre, is not acceptable. It is a major concern that one third of the costs were related to one institution. ERP costs are not currently fully transparent and only some ethics committees provide information regarding their fees on their homepages. The method used to calculate these fees is totally unknown and we were not able to find any standard on how this is done. In addition, it is not

acceptable for investigator-driven trials without substantial funding by industry or other institutions that most of the medical chambers do charge whereas most universities do not. Investigators may decide to select clinical sites eligible for participation in a trial on costs for approvals, which would cause substantial selection bias.

Less administrative effort was in general necessary to obtain the secondary than the primary approval, as expected. Only 4 of the 17 ethics committees (Erlangen, Westfalen-Lippe, North Rhine and Hannover) required more effort and paperwork.

The heterogeneity in the ERP of the INSECT Trial may be related to the different composition and locations of the ethics committees. In 2004, the Association of Medical Ethics Committees of Germany developed and passed reference regulations for the member ethics committees to improve their structure (<http://www.ak-med-ethik-komm.de>). The implementation of these recommendations by the individual ethics committees is currently in progress. The effect of the organisational and personnel structure of ethics committees on the ERP of non-pharmacological studies will then need further assessment.

Until now, only a few studies on the assessment of the ERP for multicentre pharmacological studies have been published, which allow some comparisons. Unfortunately, none of these studies was conducted in Germany. In a prospective study in 2004, 62 ethics committees in Spain were evaluated regarding the implementation of the European Union directive 2001/20/EG.⁶ They had a median number of 14 members and examined a total of 187 applications for 114 study centres. The median time from the application to the final approval was 62 days. In 55% of all applications, queries were raised (307 queries from 41 ethics committees). Of all queries, 40% were related to the protocol and 38% to the patients' information sheet. Ethics committees that charged fees had a shorter ERP than did not. The authors of the study concluded that the implementation of the European Union directive and the ERP in general still need improvement, especially regarding the communication of the decisions through the ethics committee.

These findings are in contrast with those of our study. Only one query was related to the protocol and four to the patients' information leaflet or consent form (table 1). Large multicentre randomised controlled trials in surgery are rare and therefore this may be a new challenge for committees that mostly review pharmacological trials. Special attention and strategies are mandatory to keep treatments in surgery equal for patients in all groups, which is achieved in the INSECT Trial with training courses, educational material and treatment manuals for all surgeons.² Also the ethics committee with the highest fee had the longest ERP time.

Past experience from the UK shows that specialised multicentre research ethics committees can reduce the duration, cost and the administrative effort of the ERP in multicentre trials.^{7, 8} Since their introduction in 1997, through research governance, to various legislative reforms of research practice, including the clinical trials regulations of 2004, ethical review in the UK has changed considerably.⁹ Instituted in March 2004, the Central Office for Research Ethics Committees supports, manages and trains ethics committees and their members. It also provides the forms that need to be completed to obtain approval from an ethics committee. The current experience with this system from the perspective of the clinical researcher is that of a more complex application causing an obstruction rather than supporting research.¹⁰

Within Germany and also throughout Europe, much emphasis is placed on the ERP for pharmaceutical trials, whereas other treatment options such as surgery and their specific corresponding clinical trials are just evolving. Patients problems do

not stop at borders within and between states, and neither do the corresponding multicentre trials. The important independent ethical reviews of these trials need further efforts on harmonisation in application and concentration on ethics by all participating institutions.

CONCLUSION

This study shows the heterogeneity of the ERP of non-pharmacological multicentre trials in Germany. In the INSECT Trial the fees varied considerably, ranging from nothing to more than €1000. The administrative process would benefit from standardisation of the application forms and the number, as well as the design and content, of the required documents. However, the duration of the ERPs was, with some exceptions, excellent.

Reliable planning of non-pharmacological multicentre trials in the national and the international setting is impaired by the existing system of ethical review throughout Europe, especially in Germany. It is necessary to establish multicentre research ethics committees, where they do not exist already, to provide independent ethical reviews in all member states of the European Union.

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