Langenbecks Arch Surg (2005) 390: 171–177
DOI 10.1007/s00423-005-0547-6

Hanns-Peter Knaebel
Markus K. Diener
Moritz N. Wente
Hartwig Bauer
Markus W. Büchler
Matthias Rothmund
Christoph M. Seiler

The Study Centre of the German Surgical Society—rationale and current status

Received: 1 November 2004
Accepted: 27 January 2005
Published online: 22 February 2005

H.-P. Knaebel · M. K. Diener ·
M. N. Wente · M. W. Büchler ·
C. M. Seiler (✉)
Study Centre of the German Surgical Society, Department of Surgery,
University of Heidelberg Medical School,
Im Neuenheimer Feld 110,
69120 Heidelberg, Germany
e-mail: christoph_seiler@med.uni-heidelberg.de
Tel.: +49-6221-566986
Fax: +49-6221-566988

H. Bauer
German Surgical Society,
Berlin, Germany

M. Rothmund
Department of Surgery,
University of Marburg,
Marburg, Germany

Abstract *Background:* The concept of evidence-based medicine was introduced into surgery in the mid-1990s, initially focussing on the integration of best research evidence, surgeons' expertise and patients' value. The lack of relevant external evidence [randomised controlled trials (RCTs), systematic reviews] in favour of surgical procedures has led to the need for a new approach in clinical research. *Design:* Development and implementation of the Study Centre of the German Surgical Society (SDGC) in order to design, perform and analyse multicentre randomised controlled trials in surgery. *Results:* The German Surgical Society has recently initiated four surgical RCTs within the SDGC in order to improve the national infrastructure for clinical research and its international scientific standing. All surgical trials focus on procedures in various fields (thyroid and parathyroid diseases, pancreatic surgery, abdominal wall closure) and are designed to fit the specific needs of each study (blinding of patients and assessors, ranking of endpoints, patients' perspective). Additionally, in a nationwide survey of 1,274 surgical departments in Germany, 307 replied, of which 237 (19%) were willing to participate in multicentre projects. *Conclusion:* Evidence-based medicine has changed surgical practice, leading to an increase in demand for RCTs and requiring a new infrastructure in surgical departments and scientific societies.

Keywords Study centre · Randomised controlled trial · Evidence-based medicine · Surgery

Introduction

Since the beginning of the 1990s, the German Surgical Society [Deutsche Gesellschaft für Chirurgie (DGCH)] has aimed to meet demands for more evidence-based medicine (EBM) in the field of surgery by engaging itself in the creation and promotion of guidelines in collaboration with the Association of the Scientific Medical Societies in Germany (AWMF, representing 143 national societies). Yet, the applicability of surgical guidelines is rather low, and a lack of high-level evidence in many fields of surgery was detected. In the published surgical literature, only 3.4% of all publications present results of a randomised controlled trial (RCT). Only 15% of these compare surgical techniques; the others are dedicated to pharmaceutical substances [1].

History of randomised controlled trials

Forty years ago, Goligher et al. [2] performed the first RCT in surgery and compared different treatment options for duodenal ulcer disease. Unfortunately, since then, there has been no substantial increase in generating evidence in surgery by performing more RCTs. The investigation of RCTs in the British Journal of Surgery revealed only a slight increase in the frequency between 1965 and 1985 (0% in 1965 and 9% in 1985) [3].

Subsequently, Solomon and McLeod [4] analysed the different types of clinical trials published between 1980 and 1990 in three major surgical journals and found that over 80% of the published trials were retrospective case series and case reports. Horton [5] analysed the first issues of nine surgical journals in 1996 and reported that just 7% of the articles dealt with data derived from RCTs. In addition, an analysis of methodological standards of surgical trials published in ten leading journals between 1988 and 1994 revealed that more than 50% of the trials did not fulfil high methodological standards, such as reporting randomisation technique, sample-size calculation or unbiased outcome assessment as claimed in the CONSORT statement [6]. Consequently, one might conclude that there should be a concentrated increase of high-quality RCTs in surgery to preserve and develop good patient care. Thus, it is necessary to overcome the difficulties in pursuing surgical trials.

Challenges of randomised controlled trials in surgery

The need for evidence-based therapy has been increasingly recognised, but EBM has still not been implemented in surgery, and the quantity and quality of RCTs remain limited in the field [7]. The RCT is regarded as the reference trial design to compare different medical therapies, with the promise of minimising chance and bias. As technology expands and health care resources contract, there is a rising pressure on surgeons to assess surgical procedures in rigorously designed and conducted clinical studies [8]. Why are surgeons less enthusiastic in adopting the RCT design? This reluctance appears to be due to very specific difficulties in, and pitfalls of, surgical RCTs. The basic principles of performing an RCT, as defined in the CONSORT statement [9], evoke a set of challenging methodological issues in surgical RCTs [10].

Standardisation and reliability Standardisation is viewed by many as the main limiting factor of surgical RCTs [11]. In pharmaceutical trials, patients receive standardised treatments, independent of any special skill of the physicians involved. In contrast, surgeons may vary in their experience with a specific surgical technique [12]. Moreover, different perioperative and postoperative standards have to be taken into account and recognised as a source of bias [13]. Standardisation is also endangered by the number of surgeons included in a trial, as many surgeons cause a greater variability in the performance of the surgical procedure. On the other hand, a sufficient number of participating surgeons or centres is necessary to achieve a greater generalisability [11]. Obviously, variations in operating techniques and operative findings are common and may influence the outcome. Several strategies have been adopted to create a certain minimum of standardisation: first, the number of participating centres and surgeons has to be limited and their expertise ranked (e.g. participation is limited to surgeons with a sufficient number of documented procedures/high-volume centres). Second, prior to the trial, consensus on the specific techniques and their variations has to be ensured in definitions, manuals and teaching sessions [14]. Third, surgical procedures have to be monitored and documented during the trial (e.g. videotapes, photographic documentation, case report forms). Fourth, patients have to be stratified by the surgeon in order to generate balanced groups [11, 13, 15]. In conclusion, a certain amount of standardisation is paramount to maintain reliability of the results.

Randomisation In surgical trials, the so called "random order operations design" is the most common technique to allocate patients to different treatment groups. In such a design, an envelope or a telephone call decides, at a certain stage in an operation, which way the surgeon is to proceed [13]. Randomisation is considered the most appropriate method to reduce selection bias in clinical research. The random allocation of patients causes, in general, an equal distribution of known and unknown risk factors in the groups at the beginning of the trial [16, 17]. However, the difficulties are obvious: some physicians may be unwilling to randomise a patient, on the basis of their subjective feeling that one treatment may be superior, even if this is based on questionable evidence [18]. Furthermore, some surgeons may even be uncomfortable with performing a procedure under investigation, because they might not be as familiar with the technique as they should be. At that point, randomisation reduces the decision making of a surgeon to tossing a coin which is necessary in order to answer a number of relevant open questions.

Start of a surgical trial The issue of randomisation leads to the topic of the optimal timing of a surgical trial. Chalmers [19] stated that the first patient undergoing a new surgical procedure should be randomised. However, assuming a learning curve, to include these early patients would certainly bias the results against the new procedure [11]. The question of the optimal time to test a procedure in an RCT cannot be answered yet. Whenever a new technique requires training, most investigators would be unable to randomise the first patient [13]. Nevertheless, whenever the efficacy of a procedure is uncertain, an RCT is justified, but one should keep in mind that this "test of efficacy" leads to further trials, as a new technique tends to be "fine tuned" after its first implementation ("test of effectiveness") [12]. Hence, the maxim "evaluate early and evaluate often" has been stated by Mowatt et al. [20].

Blinding Another source of bias in surgical trials is the blinding of patients and observers, as already described by many authors [12–16]. Blinding is dependent on the question under investigation. A good example of successful and relevant blinding in a surgical trial has been shown by Majeed et al. [21], using the same wound dressing in patients who had undergone laparoscopic or small-incision

cholecystectomy. When subjective outcomes are to be measured, blinding is a must to reduce observational bias. When the patient and the outcome assessor are blind to the nature of the operation, it is possible for a quasi-double blind design to be achieved, even in surgical trials [13, 16, 22].

Sham surgery, placebos and ethics The placebo effect in surgery is a difficult issue, for practical and ethical reasons. In surgical trials, a true placebo arm would mean a sham operation. The use of sham operations, as performed by Dimond et al. [23] in 1958, is only justifiable within controlled trials. Therefore, sham surgery is only applicable under very special circumstances that represent a minority of all surgical questions to be investigated [24].

Applying and updating the evidence Once the pitfalls of RCTs in surgery are overcome, the evidence created faces challenges to its integration into clinical practice. The generation of relevant evidence in the field of surgery will require considerable effort, to ensure that the translation of knowledge will improve clinical expertise and decision making. Therefore, the methods and practice of EBM have to be integrated into undergraduate and postgraduate teaching. Recently, in their meta-analysis of 23 studies, Coomarasamy and Khan [25] assessed the effects of EBM teaching on various outcomes in postgraduates. These investigations found better results from clinically integrated teaching of EBM than from stand-alone courses (improvement in skills, attitudes and behaviour). This fact emphasises the necessity to make the generated evidence accessible and to promote its consecutive execution. In view of the rapidly growing amount of clinical literature and the time one requires to search and read relevant articles, the need for a reasonable synthesis of evidence is mandatory. One method that can provide surgeons with relevant literature is the setting up of systematic reviews and meta-analyses. Easily accessible and updated high-quality reviews (such as systematic reviews of the Cochrane Collaboration: http://www.cochrane.de) will help to disseminate evidence to a widespread audience. Additionally, special review sections in medical journals should routinely discuss the latest and most relevant evidence. We have to bear in mind that the pure creation of evidence does not ensure its reasonable transmission into day-to-day clinical practice. Rather, we are forced to develop strategies to bridge the gap between evolving knowledge and clinical practice.

National differences in clinical research

From 1996 to 1998, the Lancet published a series of articles comparing the status of clinical research in various European countries. Germany was described as a country with poor participation in clinical trials and a poor prognosis for clinical research in the future. Many Germans may be reluctant to participate in clinical trials for the fear of being treated as "laboratory animals." Furthermore, the lack of vision in its decisive structural changes would inhibit further development in clinical research [26]. In absolute values, Germany, France and the UK had the most clinical trials running, but in relation to their population, the Scandinavian countries were clearly in a league of their own.

Thus, several other obstacles explain why Central Europe, and especially Germany. have fallen behind in clinical research. First, funding is almost exclusively dedicated to basic research. The closer the research is moving towards the patient, the harder it is to obtain external or public funding for a clinical trial project [27]. Second, the current practice of surgery is not compatible with the application of modern evidence-based decision making and therapeutic principles. The attempt to give each patient the best individual treatment creates a mentality averse to randomisation and subsequently systemisation, the essence of medicine in the Anglo–American world [26]. Third, the rapidity with which medical development is currently outdating itself within a few years makes it quite difficult to design a high-quality RCT for many open questions. Finally, the over-regulation of clinical research in Europe, which is now being imposed by the new European Union (EU) directive, makes clinical trials an "endangered species" in Germany. The new EU directive aims "to harmonise the regulation of clinical trials across the EU" and is well suited to commercial research. At the same time, this directive severely jeopardises clinical research in academic institutions because the hurdles might be too high to be crossed [28].

The future of evidence-based surgery

In order for evidence-based surgery to be made feasible for surgeons at all levels of care, the main goal can only be to generate the missing external evidence by conducting well-planned clinical studies within the boundaries of daily clinical routine. If it is kept in mind that only 24% of all surgical procedures are evidence-based [29], surgery should not solve the dilemma by stepping down its demands to the expert opinion level of evidence in order to increase the percentage of evidence-based procedures.

Besides the international efforts of the Cochrane Collaboration to combine the available knowledge into systematic reviews, which are clearly the basis for well-planned clinical trials, surgeons have to build up networks locally, nationwide, and internationally. A good example of such an initiative is the American College of Surgeons Oncology Group (ACOSOG; http://www.acosog.org). ACOSOG focuses on oncological studies involving surgical procedures. Structured in organ-site groups, it acts as a nationwide management service for surgical studies in the USA.

Surgeons have no time to wait for external evidence. If they learn to treat patients on the basis of clear-cut study protocols, they will be more familiar with reading and assessing articles in order to practise evidence-based surgery. How each individual department will generate evidence

depends on its setting and background. Several options are possible, for example: (1) participating in trials where patients are treated following a protocol without responsibility for study development or results analysis; or (2) creating protocols in cooperation with colleagues and playing an active role as a principal investigator in a trial.

Today, the complexity of RCTs will nearly always require an interdisciplinary team to perform trials in accordance with sound guidelines of clinical practice. These teams should include at least a study manager, a data manager, a biostatistician, a monitor and, finally, a surgeon. In addition, an independent data monitoring and safety committee should be established. In order to create more external evidence, each effort is valuable to close the existing gap. For surgeons who believe in science as the basis of their clinical practice, this remains the major challenge now and in the future.

Study Centre of the German Surgical Society

In 2003, the German Surgical Society [Deutsche Gesellschaft für Chirurgie (DGCH)] resolved to improve coordination of multicentric surgical trials in Germany; the Society's Steering Committee committed itself to establishing a Study Centre of the German Surgical Society [Studienzentrum der Deutschen Gesellschaft für Chirurgie (SDGC); http://www.sdgc.de] [30]. Simultaneously, the German Ministry of Education and Research [Bundesministerium für Bildung und Forschung (BMBF)] decided to fund a programme for clinical trials in order to enhance clinical research in Germany. Surgery was found to be in special need of supportive measures to live up to the international standards set by other countries such as the UK, the Scandinavian countries and the Netherlands. In the framework of the decisions mentioned above, the German Surgical Society and the Medical Faculty of the University of Heidelberg, with their infrastructure, successfully applied for funding of a national study centre (SDGC) (see Fig. 1). The motivation of German surgeons to participate in surgical trials was investigated through a nationwide survey. There were 1,274 survey questionnaires sent out, and a total of 307 surgical departments (24%) answered the questionnaire, with 237 (19%) committing to participate in clinical trials (see Table 1). Only 130 out of 237 hospital had prior experience with clinical trials. The major interest of the hospitals were as follows: surgical oncology (n=233), laparoscopy (n=217), general surgery (n=211),

Table 1 Results of a national survey (mailed August 2003, answered by December 2003)

Parameter	Number	Percent
Total number of hospitals	1,274	100
Returned questionnaires	275	22
Willing to participate in clinical trials	237	19
Undecided	48	4
Not interested in clinical trials	22	72

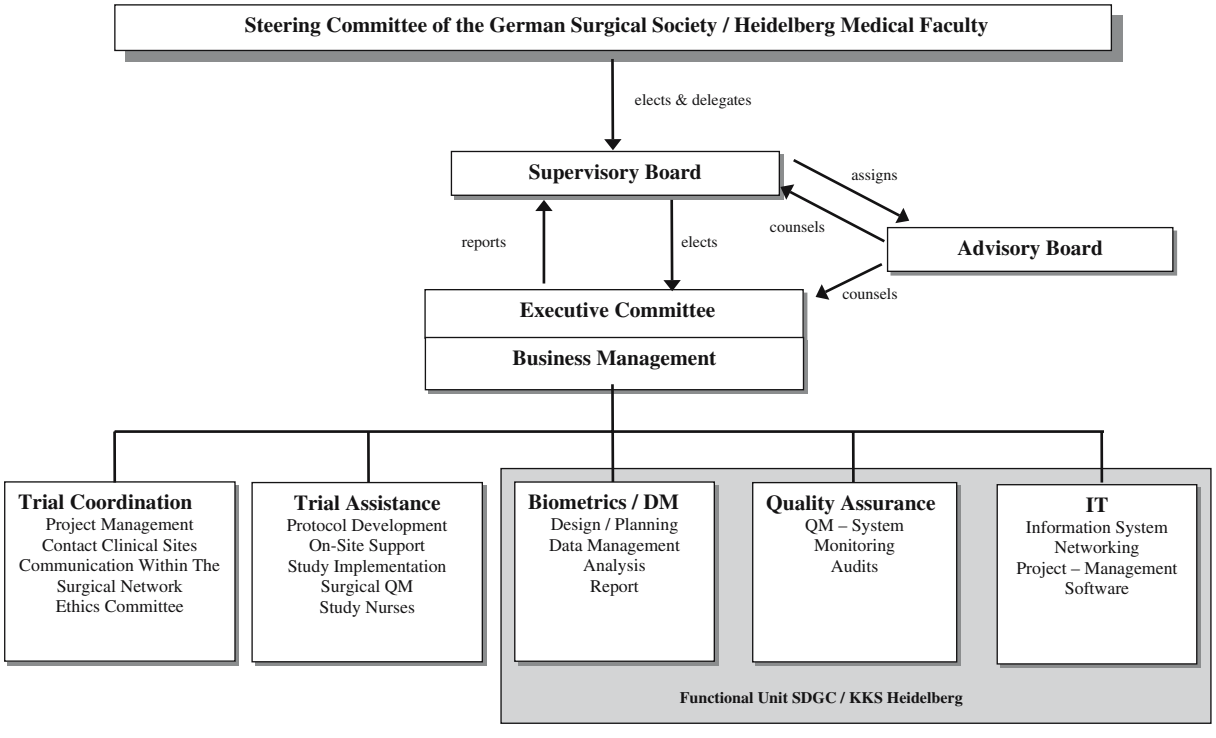

Fig. 1 Structure of the Study Centre of the German Surgical Society. *KKS* Coordination Centre for Clinical Trials

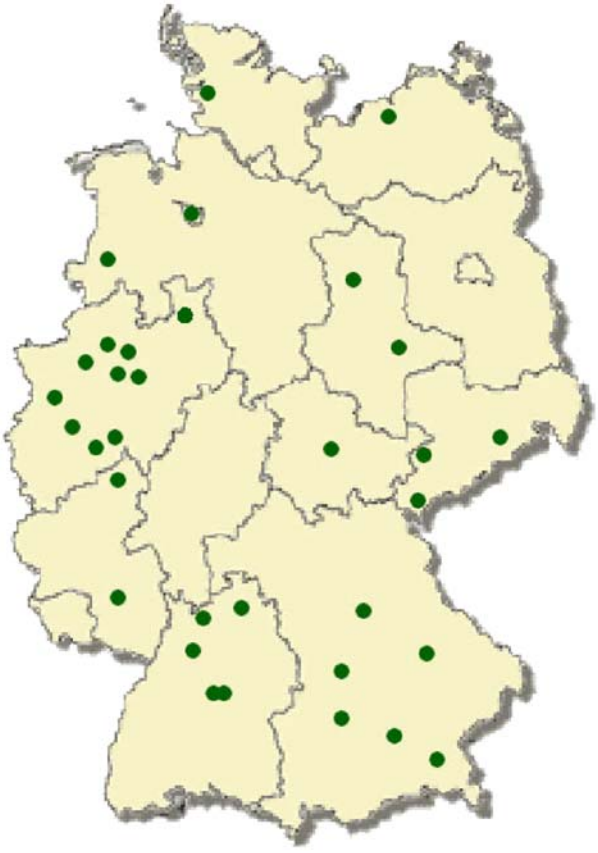

Fig. 2 Map of Germany with currently active surgical departments recruiting patients into SDGC trials

surgical gastroenterology (n=190) and endocrine surgery (n=142).

Clearly, a national study centre, as set up here, can only flourish and grow in recognition when closely collaborating with clinical sites. A still increasing number of various participating hospitals spread out all over Germany guarantee the proximity to clinical routine and to the patient (see Fig. 2). In addition, there is an ongoing discussion about the set-up of other institutions within the existing framework that focus on special topics such as oncology.

Study design in surgical trials of the SDGC

Relevant endpoints in surgical trials can be chosen from the different perspectives of patients, surgeons, the health care system and others. Dependent on this concept a trial can be designed, taking into account further aspects (e.g. efficacy versus effectiveness, blinding, placebo) for generating a valid and reproducible result. All factors have a major influence on the performance of a trial.

Trials of the SDGC are registered after approval by the independent ethics committee review board of the University of Heidelberg and are given an International Standard Randomised Controlled Trial Number (ISRCTN; http://www.controlled-trials.com) (see Table 2). The protocols are published so that subsequently undetectable changes can be prevented and transparent study conditions achieved [22]. All published results can be reviewed and discrepancies with the initial study protocol have to be discussed. Following the CONSORT statement, a flow chart of the trial should be included in such a design paper so that expected and observed patient numbers in the specific trial can be compared [9]. Unfortunately, most journals still do not include a full protocol section, ignoring the numerous advantages of such a strategy. An example of a short communication that informs surgeons about trials is the German journal *Der Chirurg* [31].

Consequently, all study protocols finalised by the SDGC follow the ICH-GCP guidelines to ensure good clinical practice and to meet transparent international standards. Independent data and surgical monitoring is established for all trials to guarantee the validity of the generated data.

The first effectiveness trial of the SDGC is INSECT (interrupted or continuous slowly absorbable sutures—evaluation of abdominal closure techniques; ISRCTN 24023541). A major argument against the existing external evidence (systematic reviews) is the question of whether a lower incidence of abdominal hernias can be achieved by

Table 2 Clinical trials of the SDGC (*INSECT* interrupted or continuous slowly absorbable sutures—evaluation of abdominal closure techniques, *CLIVIT* clips versus ligatures in thyroid surgery—a randomised controlled trial, *DISPACT* distal pancreatectomy—a randomised controlled trial to compare two different surgical techniques, *TOPAR* secondary hyperparathyroidism: does total parathyroidectomy alone lead to a lower rate of recurrence than total parathyroidectomy with autotransplantation? A randomised controlled multicentre trial)

Trial	ISRCTN	Topic	Status
INSECT	24023541	Abdominal wall closure Running vs interrupted technique	Recruiting
CLIVIT	96901396	Thyroid surgery—clips vs ligation	Recruiting
DISPACT	In progress	Pancreatic surgery Closure of pancreatic remnant after distal pancreatectomy	Starts 2005
TOPAR	In progress	Parathyroid surgery Autotransplantation vs none after total parathyroidectomy	Starts 2005

continuous suturing of the abdominal wall. A study group was formed from a representative range of German hospitals (30 centres) to conduct this study. The challenge of standardising the surgical techniques in these departments was met by a study meeting, prior to the start of the trial, to teach and review the performance of the surgeons (auditorium, visual presentation), and practically (laboratory conditions).

Another example of an SDGC trial is the upcoming efficacy study DISPACT (distal pancreatectomy—a randomised controlled trial to compare two different surgical techniques), which will investigate two different, commonly used techniques for the closure of the pancreatic remnant in order to reduce the rate of pancreatic fistulas after distal pancreatectomy. Owing to the rarity of pancreatic operations and the necessity of specialised (high-volume) centres with experience in pancreatic surgery, a multicentre and multinational approach will be chosen.

Evidence-based surgery—is the future bright?

The German Surgical Society aims to generate more high-level evidence from well-designed clinical trials, meaning, in particular, from randomised controlled trials. If one examines this commitment and the measures taken, it is obvious that evidence-based medicine has changed surgical practice. Yet, solid clinical evidence-based data is still lacking. Conducting good clinical trials for most relevant clinical questions can only be performed with a multicentre approach.

Currently, the national view demands an approach towards implementing national standards of surgical care. Nevertheless, in the future, a national view on surgical issues will be too narrow, and a European view, and sometimes even a worldwide view, will have to be taken. Owing to the limited human and financial resources, international collaborations will have to be strengthened to achieve faster results in clinical research.

Collaboration with different national and international surgical departments is a demanding task for a surgeon's diplomacy and requires the will to compromise in order for a mutually agreed goal to be reached. As prejudices in some people's minds suggest, it is not generally the strength of surgeons always to give in to somebody else's opinion or even be frank and tell the unmasked clinical truth [32]. However, because modern surgery requires teamwork, modern surgeons are being forced to modify their habits. Therefore, the Study Centre of the German Surgical Society (SDGC) aims to develop and strengthen international cooperation.

References

1. Uhl W, Wente MN, Buchler MW (2000) Surgical clinical studies and their practical realization. Chirurg 71:615–625
2. Goligher JC, Pulvertaft CN, Watkinson G (1964) Controlled trial of vagotomy and gastro-enterostomy, vagotomy and antrectomy, and subtotal gastrectomy in elective treatment of duodenal ulcer. BMJ 5381:455–460
3. Pollock AV (1989) The rise and fall of the random controlled trial in surgery. Theor Surg 4:163–170
4. Solomon MJ, McLeod RS (1993) Clinical studies in surgical journals—have we improved? Dis Colon Rectum 36:43–48
5. Horton R (1996) Surgical research or comic opera: questions, but few answers. Lancet 347:984–985
6. Hall JC, Mills B, Nguyen H, Hall JL (1996) Methodologic standards in surgical trials. Surgery 119:466–472
7. Solomon MJ, Laxamana A, Devore L, McLeod RS (1994) Randomized controlled trials in surgery. Surgery 115:707–712
8. Meakins JL (2002) Innovation in surgery: the rules of evidence. Am J Surg 183:399–405
9. Moher D, Schulz KF, Altman DG (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet 357:1191–1194
10. Stirrat GM, Farrow SC, Farndon J, Dwyer N (1992) The challenge of evaluating surgical procedures. Ann R Coll Surg Engl 74:80–84
11. McLeod RS, Wright JG, Solomon MJ, Hu X, Walters BC, Lossing A (1996) Randomized controlled trials in surgery: issues and problems. Surgery 119:483–486
12. McLeod RS (1999) Issues in surgical randomized controlled trials. World J Surg 23:1210–1214
13. van der Linden W (1980) Pitfalls in randomized surgical trials. Surgery 87:258–262
14. Wente MN, Seiler CM, Uhl W, Buchler MW (2003) Perspectives of evidence-based surgery. Dig Surg 20:263–269
15. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D (2002) Randomised trials in surgery: problems and possible solutions. BMJ 324:1448–1451
16. Lilford R, Braunholtz D, Harris J, Gill T (2004) Trials in surgery. Br J Surg 91:6–16
17. Treasure T, MacRae KD (1998) Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups; minimisation does. BMJ 317:362–363
18. Taylor KM, Margolese RG, Soskolne CL (1984) Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. N Engl J Med 310:1363–1367
19. Chalmers TC (1975) Randomization of the first patient. Med Clin North Am 59:1035–1038
20. Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L (1997) When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies. Health Technol Assess 1:1–149
21. Majeed AW, Troy G, Nicholl JP, Smythe A, Reed MW, Stoddard CJ, Peacock J, Johnson AG (1996) Randomised, prospective, single-blind comparison of laparoscopic versus small-incision cholecystectomy. Lancet 347:989–994

22. Reidel MA, Knaebel HP, Seiler CM, Knauer C, Motsch J, Victor N, Buchler MW (2003) Postsurgical pain outcome of vertical and transverse abdominal incision: design of a randomized controlled equivalence trial [ISRCTN 60734227]. BMC Surg 3:9
23. Dimond EG, Kittle CF, Crockett JE (1958) Evaluation of internal mammary artery ligation and sham procedure in angina pectoris. Circulation 18:712–715
24. Edwards SJ, Lilford RJ, Hewison J (1998) The ethics of randomised controlled trials from the perspectives of patients, the public, and healthcare professionals. BMJ 317:1209–1212
25. Coomarasamy A, Khan KS (2004) What is the evidence that postgraduate teaching in evidence based medicine changes anything? A systematic review. BMJ 329:1017
26. Selbmann HK, Flohl R, Volk HD, Rothmund M, Reinauer H, Konze-Thomas B, Troidl H, Lorenz W (1996) Country profile: Germany. Lancet 348:1631–1639
27. Lovett B, Sawyer W, Houghton J, Taylor I (2000) Systematic review of the methodological quality of randomized controlled trials of the surgical excision of cancer (abstract). Eur J Surg Oncol 26:840
28. Canter PH, Ernst E (2004) Clinical trials and tribulations. J R Soc Med 97:101–102
29. Howes N, Chagla L, Thorpe M, McCulloch P (1997) Surgical practice is evidence based. Br J Surg 84:1220–1223
30. Rothmund M (2004) Studienzentrum der Deutschen Gesellschaft für Chirurgie. Mitt Dtsch Ges Chir 01:34–35
31. Schwenk W (2004) The LAPDIV-CAMIC Study. Multicenter prospective randomized study of short-term and intermediate-term outcome of laparoscopic and conventional sigmoid resection in diverticular disease. Chirurg 75:706–707
32. Pitches D, Burls A, Fry-Smith A (2003) How to make a silk purse from a sow's ear—a comprehensive review of strategies to optimise data for corrupt managers and incompetent clinicians. BMJ 327:1436–1439