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Making or Losing Money with Participation in Clinical Trials: A Decision Analysis

Volker R. Jacobs

Frauenklinik, Technische Universität München, Germany

Key Words
Clinical study · Study management · Economics · Cost covering · Decision analysis · Flow chart · Model

Summary
Background: There is increasing demand and quality-driven pressure from professional organizations for physicians and health care providers to increase participation in clinical studies. But this can have a severe financial impact on the institution, so costs should be identified and calculated in advance. **Method:** In a diagram, the decision-making process to participate in clinical trials based on economic and budget impact is reviewed and analyzed in detail. **Results:** This flow chart describes how cost-effective participation in clinical trials is determined. Since its implementation, all trials in our institution have been cost covering. **Conclusions:** All service and care required within the studies must be distinguished as either medically necessary or study related. Costs for the first category have to be covered by the health care system, but in case of the second category by the study sponsor. The institution's own costs for study-related services should be known and deducted from the study income to determine the actual study gains. Subsidizing studies from tight clinic budgets is difficult in times of rationed medicine and should be avoided. Non-cost-covering clinical studies should be renegotiated with the sponsor until cost effectiveness is reached. Otherwise, a rejection of study participation for financial reasons should be seriously considered. The design of cost-covering clinical trials supports better recruitment for studies.

Schlüsselwörter
Klinische Studie · Studienmanagement · Wirtschaftlichkeit · Kostendeckung · Entscheidungsanalyse · Flussdiagramm · Modell

Zusammenfassung
Hintergrund: Es gibt steigende Anforderungen und qualitätsorientierten Druck von Berufsorganisationen auf Ärzte und Gesundheitsinstitutionen, die Teilnahme von Patienten in klinischen Studien zu steigern. Aber dies kann erhebliche finanzielle Folgen für die Institution haben, so dass die Kosten genau bekannt und im Voraus berechnet werden sollten. **Methode:** Anhand eines Diagramms wird der Entscheidungsprozess zur Teilnahme an klinischen Studien basierend auf ökonomischen Aspekten und Budgetfolgen dargestellt und im Detail analysiert. **Ergebnisse:** Ein Flussdiagramm beschreibt, wie eine kostendeckende Teilnahme an klinischen Studien bestimmt werden kann. Alle Studienteilnahmen in unserer Klinik sind seit der Implementierung kostendeckend. **Schlussfolgerungen:** Alle Dienstleistungen, die innerhalb einer Studie durchgeführt werden, sollten in medizinisch notwendige oder studiennotwendige Kosten unterschieden werden. Erstere sollten durch das Gesundheitssystem, Letztere aber durch den Studiensponsor abgedeckt werden. Die eigenen studienbezogenen Kosten der Institution sollten bekannt und von den Studieneinnahmen abgezogen werden, um die tatsächlichen Studieneinnahmen zu erhalten. Die Subvention klinischer Studien von knappen Klinikbudgets ist schwierig in Zeiten rationierter Medizin und sollte vermieden werden. Nicht kostendeckende Studien sollten mit dem Sponsor bis zur Kostendeckung nachverhandelt werden. Anderenfalls sollte eine Ablehnung der Studienteilnahme aus finanziellen Gründen ernsthaft erwogen werden. Die Gewährleistung von kostendeckenden klinischen Studien unterstützt ein verbessertes Einbringen von Studienpatienten.

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Fax +49 761 4 52 07 14
Information@Karger.de
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PD Dr. med. Volker R. Jacobs, MBA
Frauenklinik
Technische Universität München
Ismaninger Str. 22, 81675 München, Germany
Tel. +49 89 4140-5425, Fax -4831
volkerjacobs@hotmail.com

Introduction

Oncological therapies in clinical trials, especially when performed at state-of-the-art level with innovative (= often expensive) medication, can be very costly and imply financial risks like off-label use among many others, resulting in insufficient reimbursement for any provider of therapy. Active oncological cost management [1] of standard oncological care can determine costs and risks for the health care provider in advance and can be used to optimize for cost reduction without sacrificing standard of care [2, 3].

Clinical studies contain – besides the core target of improving medical care – multiple aspects, from ethical issues to conflicts of interest [4–6], responsibility and integrity of research [7] or financing the costs [8–10], which have to be addressed and solved before initiating any trial. With rising cost awareness, the management for research projects [11] in form of clinical studies is becoming increasingly relevant but is more complicated to solve because study sponsors assume that medical care has to be paid by the health care system. The health care system, on the opposite, often insists that clinical studies have to be paid completely by the study sponsors [12]. The health care provider with an oncological unit is caught in the middle and might face a potential economic loss due to participation in clinical trials [13]. The social law in Germany contributed to this confusion [14], but this issue has been solved in the meantime: Participation in clinical trials has to be reimbursed analogously to standard oncological clinical care [15]. However, not everything is paid for by health insurances and sickness funds. As a consequence, clinical trials have to be evaluated analogously to standard oncological care for their cost coverage and budget impact from the providers' perspective [16, 17].

For many clinical trials, it is not self-evident that a potential participation is cost covering for the health care institution. Financial study benefits are often more obvious, but study-related costs at the same time are often nebulous or remain undetermined due to the fact that they are hidden, unknown and finally likely to be covered in the clinic budget. Although economic reasons might and shall not be the exclusive base for the decision to participate in clinical trials, in times of limited resources, at least cost coverage of any study protocol should be evaluated and calculated in advance, to be included and used as a base in the decision-making process.

Therefore, before signing and submitting any new study protocols to the authorized ethics commission, or in some institutions the Internal Review Board (IRB), the financial impact for the institution should be exactly determined to avoid potential losses for the institution. The calculation of all costs and determination of the cost coverage of any participation in clinical trials are primarily the responsibility of the principal investigator (PI) of a study. In case of insufficient funding, usually the head of a department or clinic needs to give his/her approval, too. Since economic knowledge and financial data are often not available among physicians, all resources in the institution should be asked to contribute all necessary data and information for the cost evaluation of clinical trials.

In the following, a successfully implemented decision analysis flow chart for economic performance of and cost-effective participation in clinical trials in a German university setting, which reduces financial risks and limits the budget impact for the health care provider, is presented and discussed.

Method

All relevant clinical study protocols covering mainly breast and ovarian cancer at the Frauenklinik (OB/GYN) at the Technische Universität München, Munich, Germany, over more than 5 years from 2003 up to now, were prospectively and retrospectively evaluated and analyzed. Most of the studies were analyzed in cooperation with the Münchner Studienzentrum [18], a specialized study center for managing clinical trials, and several hospital departments involved (administration, controlling, reimbursement, purchase, clinical pharmacy, etc.), identifying all study-related prices and economic aspects. Based on this information and experience, a universally valid and transferable decision-making flow chart (fig. 1) was developed, which since then has been permanently used as a mandatory process for economic approval before participating in any clinical study.

Results

The decision-making process for analyzing costs and reimbursement for clinical studies is initiated by receiving the complete study protocol (fig. 1, #1). A synopsis, overview or summary cannot substitute for the full study protocol for sufficient and exact study cost evaluation.

The next step is the comprehensive analysis of the protocol regarding all financial aspects (#2). Since not all physicians have the necessary business and economic knowledge, support from within the institution like expert knowledge from a study center, study nurses, hospital administration, e.g. controlling, reimbursement, pharmacy, accounting, etc., should be integrated. Ideally, a competent clinical study center is available covering all aspects (#3).

In the next step (#4), for each single service listed in the study protocol, it is necessary to distinguish between study-related or medical treatment-related costs. Study-related costs have to be paid by the study sponsor, medical treatment-related costs from the patients' health insurance. Although it is sometimes not easy to distinguish between both, it should be obvious that tumor markers once a week or computed tomography (CT) scans every 2 weeks to determine the size of a tumor lesion are not included in a standard of care and cannot be covered by the health care system.

In step 5 (#5), all study-related costs are quantified with focus on cost drivers like expensive medication and imaging, interventions, etc. To simplify calculations, marginal costs can be estimated and services calculated based on averaging flat rates.

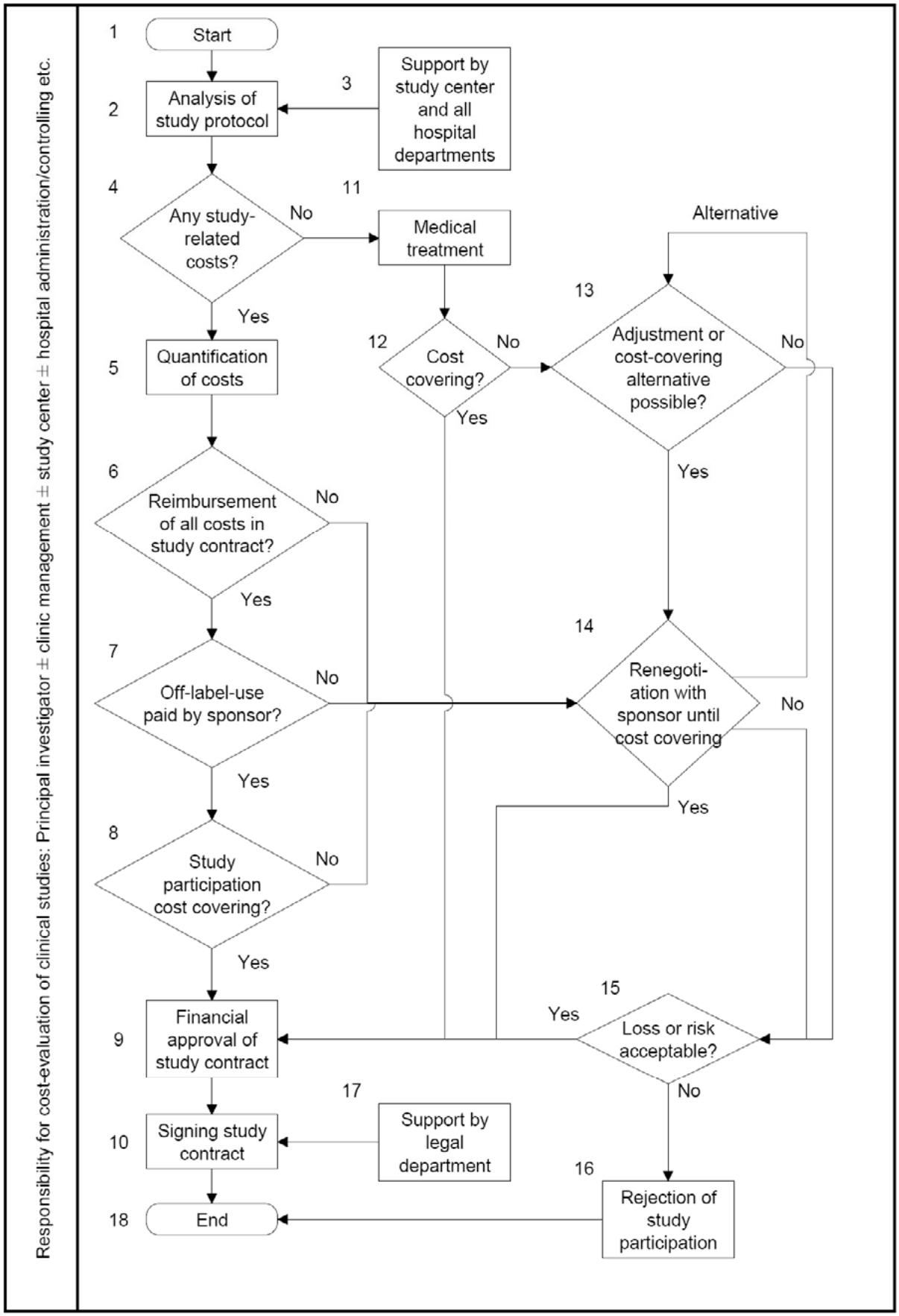

Fig. 1. Decision-making diagram for or against participation in clinical trials based on the economic evaluation of clinical studies from the health care provider's perspective.

After calculation of the hospital-specific study costs, three main important questions should be addressed:

- Are all study-related costs adequately reimbursed in the study contract (#6)?
- Is off-label use of any medication in one or both or all study arms paid by the sponsor (#7)?
- Is participation in this clinical study overall cost covering for the institution (#8)?

If the answer to all three questions is Yes, financial approval is given (#9) and the process can continue with finalizing and signing the study contract (#10), preferably with support from the legal department (#17), and proceed with submission to the ethics commission or IRB, if applicable. The evaluation process is then finalized (#18).

But if at least one of these three questions (#7–9) is answered with No, this should lead to a renegotiation with the study center and/or sponsor to find an acceptable solution to reach approximate cost coverage (#14). If a cost-covering solution is found with written documentation – e.g. as amendment in the contract – the process continues with financial approval (#9). If a renegotiation with the study center and/or sponsor is unsuccessful, there are two possibilities: The first one is: Creative adjustments (#13) within the institution are identified, e.g. adjustment of the protocol for cost reduction, cross-financing from a third party, or shifting costs outside the institution which can lead to cost coverage. The alternative is to accept or reject covering the financial loss and/or implemented risks by the institution (#15). If the financial loss and/or risks are accepted, financial approval is given (#9). If they are not acceptable, a rejection of the study participation should seriously be considered (#16) and – if done so – the financial study evaluation is terminated (#18).

In rare cases that study protocols are just observing and do not require any additional study-related costs, all treatment is considered as regular medical treatment (#11). However, any medical treatment has to be evaluated analogously for cost coverage (#12) for the institution as well, resulting in either financial approval (#9) or creative adjustments (#13), which in some cases again need appropriate protocol amendments (#14). However, even regular medical treatment within or without study protocols can occasionally be not cost covering for a hospital's oncology unit, potentially resulting in a referral to a different institution or physician's office for continuing medical therapy at the same quality-assured level of care.

Discussion

Starting in 2003, this decision-making model (fig. 1) has been implemented in our institution, a university-based gyneco-oncological day case unit, and has been enforced over the last 5+ years. All study protocols have to be evaluated accordingly and in advance. This model is universal and valid also for other entities than just oncology units within similar economic environments and conditions. In the beginning, most of the existing study contracts (~75%) that were retrospectively evaluated were insufficiently sponsored and not cost covering. Typical examples for insufficient sponsoring were, e.g., only 50% of off-label use medication (= every second therapy paid in the experimental arm), a study nurse paid instead of at least twice the costs of the off-label use in the experimental arm, study sponsored with 25% of costs off-label use medication, etc. In all these cases, the off-label use was paid from the hospital's own budget without reimbursement by any health insurance. In one case, the therapy of study patients was even subsidized by the clinic in five-figure per patient. Since then, we have renegotiated insufficiently sponsored contracts based on our objective calculations, stopped recruiting new study patients if renegotiation was unsuccessful and have repeatedly rejected under-reimbursed study contracts. From our experience, professional organization-sponsored studies are more likely to expect participation in under-reimbursed clinical studies than industry-sponsored ones. As example, there are organization-sponsored studies that actually offered up to only ~25% coverage of the study-related cost and the sponsor was upset when such a cost plan had to be rejected. If these studies pretend to be cost covering as calculated by the sponsors, comprehensive transparency of the study budget and allocation of financial resources and the beneficiary could support this. Clinical studies would definitely benefit from an increased support by professional medical organizations for cost-covering clinical trial budgets.

The proposed decision-making flow chart diagram (fig. 1) shall help to determine financial cost coverage and give a standardized pathway structure for internal evaluation for or against participation in clinical trials. However, there might be other reasons to participate, like scientific reputation and personal prestige, clinic marketing, obligation to science, increasing innovative therapy options for patients, networking, etc., which could be rare but necessary exemptions from the paramount of cost-covering clinical trials. In these cases, a loss due to participation in clinical studies might be acceptable but has to be paid from the clinic's budget. Physicians are increasingly realizing that performance and rather intensive work for clinical trials comes additionally to normal clinical work and therefore should be paid adequately and accordingly. Clinical studies are often very time consuming and costly in resources; so if no cost coverage is reached but instead the study sponsor himself is actively subsidized for performing a study with the clinic's own budget and work force, any trial participation can become questionable. The result is that either physicians are not paid for study-related overtime or a financial loss due to expensive resources consumption can lead to compensation by reducing physicians' jobs. Therefore, PIs and their health care institution should have the right, and even the obligation, in times of rationed medicine to reject insufficiently sponsored clinical trials, since their task is to provide health care and not to subsidize the

development of new innovative care for the society or industry or other third-party interests without any economic benefits from this investment.

In contrast to incremental costs between standard medical care and clinical trials [19–21], which might be of interest for health insurances and politicians and can only be calculated specifically for each study concept, this paper focuses on a universal model of the actual study-related costs and its cost-covering reimbursement from the providers' perspective. The decision diagram (fig. 1) encourages a fair and adequate budget negotiation of study budgets with sponsors [13]. Manager competence for research [11] with in-depth knowledge of calculating research-related costs is becoming increasingly important for researchers. But cost calculations especially for clinical studies require by far more than just personnel costs and material expenses [11, 22].

Economic and quality aspects in health care are often in contrast, also regarding clinical trials. In the meantime, the percentage of study participation serves as a surrogate marker for quality, which can be seen controversially, especially if not adequately reimbursed. The German Society for Senology (DGS) requirement for recertification of breast centers after 3 years is that 20% of all primary breast cancers are recruited for clinical trials with ethics commission approval [23]. However, physicians should not feel pushed to fulfill quality requirements at maximum percentage rates, but should carefully weigh up quality aspects against potential financial losses due to clinical study participation.

The decision about all costs, calculations, and budgets of clinical trials is, surprisingly, still made by physicians – at least at this institution – and not by the hospital administration. The reason is that physicians have, personally and within their professional group, to carry the financial risk of clinical studies. The hospital administration just takes overhead, i.e. a percentage of the overall study income. Therefore, the responsibility to identify and negotiate cost-covering trials is in general with the PI of a study. He/she should be encouraged to evaluate clinical trials economically from the provider's perspective regarding the clinic's budget impact. A problem might be that the PI can potentially be biased due to a conflict of interest between simultaneously being a physician, a scientist, a professional organization member, a study board member, etc., resulting in a personal interest in clinical studies. His/her duty is often complicated by a lack of economic information and knowledge, the general limited cost transparency in health care and a potential bias to underestimate the actual costs and to shift study-related costs into the clinic budget to increase the potential income gain from the study.

The intention of this decision-making model and the target for study calculations should not be to maximize profits but at least to break even with additional study costs. However, too few study contracts include an actual profitable margin up to now. Although financial benefits in a study contract suggest an income through participation in a clinical trial, all study-related costs have to be deducted before the actual income is gained. Income numbers in a study contract can be misleading because they do not reflect the actual income of a study. All study-related costs have to be subtracted before the actual income results. The gain of any study protocol can only be determined after finishing the study, which in some studies with long-term follow up and controls can take up to 5–10 years. Inflation and compensation for long-term study contracts should also be considered. Therefore, fixed-prices flat rate reimbursement in study contracts often does not reflect the actual costs [13] and should be carefully evaluated.

Optimal reimbursement in clinical study contracts is negotiated among equal partners and lists all study-related services and identifies the institution-specific costs for these services. Physicians and health care providers cannot blame the industry or study sponsors for designing non-cost-covering clinical trials if they themselves do not even know their own costs. Therefore, all specialties involved in a study in any way have to be identified, e.g. the gyneco-oncologist, radiologist, pathologist, pharmacist, the study center and nurses, the laboratory physicians, etc., and each single service required according to the study protocol like physical examination, imaging, laboratory, ECG, etc. For each single service, the actual and objective institution-individual price should be determined. These data should be at hand at the controlling department of each clinic. Individual contracts with each specialty providing service within the study protocol are desirable. Separate contracts are made within the same institution with each single department because study-related costs are income realized outside the limited budget and therefore of interest for each department. Additional costs like overhead are institution specific and have to be added on top. A profit margin for the PI and the institution should be negotiated, which should not be used as financial safety net to cover more or less unexpected losses during the clinical study. Flat rate reimbursements per patient upfront covering all costs for the entire length of study up to 5–10 years are not in the interested of physicians and hospitals, especially when economic parameters change over time or are not known in advance. In long-term studies, inflation and cost changes over time should also be addressed in the clinical study contract, and options for renegotiations to reach decent and adequate as well as cost-covering payment for studies should be implemented. Decent reimbursement for participation in clinical trials can encourage health care providers to take part and support better recruitment rates of study patients.

Conflict of Interest

This project is independent from any sponsor and was self-financed. The author has no conflict of interest.

References

1 Jacobs VR, Thoedtmann J, Brunner B, Kiechle M: An economic model to reduce the cost of chemotherapy for gynecologic cancer. Int J Fertil Womens Med 2004;49:274–277.

2 Jacobs VR, Thödtmann J, Brunner B, Kiechle M: Modell eines aktiven Kostenmanagements gynäkoonkologischer Therapien zur Reduktion der Medikamentenkosten um 58,7% innerhalb eines Jahres. [Model of an active cost management of gynecooncological therapies for reduction of medication costs by 58.7% within one year.] Geburtshilfe Frauenheilkd 2005;65:46–55.

3 Jacobs VR, Thoedtmann J, Euler U, Paepke S, Fischer T, Harbeck N, Kiechle M: Physician-based active cost management of oncological therapies reducing pharmaceutical costs by 83.4% in two years without leaving standard of care. Onkologie 2005;28: 441–445.

4 Greco D, Diniz NM: Conflicts of interest in research involving human beings. J Int Bioethique 2008;19: 143–154, 202–203.

5 Tereskerz PM: Research accountability and financial conflicts of interest in industry-sponsored clinical research: a review. Account Res 2003;10:137–158.

6 Tereskerz PM, Moreno J: Ten steps to developing a national agenda to address financial conflicts of interest in industry sponsored clinical research. Account Res 2005;12:139–155.

7 American Society of Clinical Oncology (ASCO): American Society of Clinical Oncology policy statement: oversight of clinical research. J Clin Oncol 2003;21:2377–2386.

8 Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, Orlewska E, Watkins J, Trueman P: Principles of good practice for budget impact analysis: report of the ISPOR Task Force on good research practices – budget impact analysis. Value Health 2007;10:336–347.

9 Neumann PJ: Budget impact analysis gets some respect. Value Health 2007;10:324–325.

10 Fireman BH, Fehrenbacher L, Gruskin EP, Ray GT: Cost of care for patients in cancer clinical trials. J Natl Cancer Inst 2000;92:136–142.

11 Steurer J, Bachmann LM: Management eines Forschungsprojektes. [Managerial considerations in research]. Ther Umsch 2007;64:683–686.

12 Antman K: Reimbursement issues facing patients, providers, and payers. Cancer 1993;72(suppl 9):2842–2845.

13 Beal K, Dean J, Chen J, Dragaon E, Saulino A, Collard CD: Budget negotiation for industry-sponsored clinical trials. Anesth Analg 2004;99:173–176.

14 Jacobs VR: Das aktuelle Bundessozialgerichtsurteil zur Studienfinanzierung: Onkologische Studien in Deutschland vor dem finanziellen Ende? [The recent decision of the German Federal Social Court regarding funding of studies: will oncological studies in Germany be terminated for financial reasons?]. Onkologie 2004;27:589–590.

15 Krankenhausentgeltgesetz (KHEntgG) [Hospital Payment Law], *www.g-drg.de/cms/index.php/inek_site_de/Rechtsgrundlagen/Gesetze_und_Verordnungen/Krankenhausentgeltgesetz_KHEntgG* (06.03.2009).

16 Jacobs VR: Cost planning for oncological therapies from the clinic's point of view regarding clinical care and studies. 1. COMBATing Breast Cancer Conference, Frankfurt, 21.–22. November 2008. Geburtshilfe Frauenheikd 2008;68:1226–1228.

17 Jacobs VR: Wirtschaftliche Durchführung von klinischen Studien aus Sicht der Universitäts-/Frauenklinik [Economic performance of clinical studies from the university/OB/GYN clinic perspective]; in Harbeck N (Hrsg): Das frühe Mammakarzinom. [Early Breast Cancer]. Bremen, Uni-Med Verlag, 2008, pp 114–119.

18 Münchner Studienzentrum [Munich Study Center], *www.muenchner-studienzentrum.de* (06.03.2009).

19 Wagner JL, Alberts SR, Sloan JA, Cha S, Killian J, O'Connell MJ, van Grevenhof P, Lindman J, Chute CG: Incremental costs of enrolling patients in clinical trials: a population-based study. J Natl Cancer Inst 1999;91:847–853.

20 Bennett CL, Stinson TJ, Vogel V, Robertson L, Leedy D, O'Brien P, Hobbs J, Sutton T, Ruckdeschel JC, Chirikos TN, Weiner RS, Ramsey MM, Wicha MS: Evaluating the financial impact of clinical trials in oncology: results from a pilot study from the Association of American Cancer Institutes/Northwestern University clinical trials costs and charges project. J Clin Oncol 2000;18:2805–2810.

21 Bennett CL, Adams JR, Knox KS, Kelahan AM, Silver SM, Bailes JS: Clinical trials: are they a good buy? J Clin Oncol 2001;19:4330–4339.

22 Jacobs VR: Kostendeckende Durchführung von klinischen Studien. [Cost-covering performance of clinical studies]. German Breast Group (GBG), Annual Meeting 2009, February 19–20, Frankfurt, Germany.

23 Deutsche Gesellschaft für Senologie (DGS) [German Society for Senology]: Erhebungsbogen für Brustzentren: Anteil Studienpatienten, S. 14 [Survey for breast centers. Proportion of study patients, p. 14], *www.senologie.org/download/word/_fab-erhebungsbogen-B1(31.08,2006).doc* (06.03.2009).