

Position paper "Cost development for clinical trials in Germany"

Summary

Currently, Germany is well prepared in principle and is internationally competitive as a location for conducting clinical trials. This is demonstrated by its No. 1 rank in Europe and No. 2 worldwide (behind the United States) in clinical trials. However, this good position of Germany as a research location is jeopardized by compensation claims for non-transparent structural costs associated with clinical trials (often falsely summarized under the generic term of "overhead cost" – a surcharge on billable services in accordance with the Physicians' Fee Schedule) that are put forward time and again by large clinics/university clinics. The consequence of shifting clinical trials to countries with a more favorable cost-quality ratio would be that patients in Germany will be delayed in gaining access to new therapeutic opportunities and that physicians would only get experience with new therapies at a later date.

Apart from the aspects summarized under the term "overhead costs," additional developments and claims that also directly concern the costs or practical feasibility of clinical trials were observable over the past few years as well. This includes the increasingly desired conclusion of multi-agreements for the implementation of a single trial at a trial institution, which shifts distribution problems within the (large) institutions toward the outside.

From the vfa's point of view, the basis for financing/cost reimbursement during a clinical trial should always be oriented on the "fair market value." In connection with compensation for the service rendered by a trial center, the principle of "quid pro quo" must be ensured, not least in order to avoid any semblance of corruptive conduct, which could arise in case of compensation without a provable, adequate service in return. In this situation, lump-sum compensation is inappropriate unless a direct reference to the clinical trial can clearly be made. The claim for a fixed percentage "overhead" that is not verifiable is equally inadequate.

Below, these topics are explained, the basic aspects of the cost review for clinical trials are represented, and the calculation approaches for an appropriate compensation of the research service rendered – oriented on the actual work and expense – are shown.

Introduction/Basic situation

Seite 2/18

The implementation of patient-oriented clinical trials is of outstanding significance. Clinical research is a necessary prerequisite for the successful development and launch of new pharmaceuticals and therapy forms and represents a key foundation of evidence-based medical care. Clinical trials improve the quality of medical treatments and create the necessary prerequisites and therefore decision-making certainty for the efficient use of medicinal products.

- Germany is currently well prepared

For a few years now, Germany has been well prepared in principle as a location for conducting clinical trials. Especially the grant programs of the Federal Ministry of Education and Research (BMBF) for the establishment of Coordination Centers for Clinical Trials (KKS) and subsequently the promotion of clinical trial centers have contributed to strengthening Germany's competitiveness as a location. In addition, the approval process of applications for clinical trials, which was introduced EU-wide in 2004 and is conducted in Germany by the superior federal authorities, the Federal Institute for Drugs and Medical Devices (BfArM) and the Paul Ehrlich Institute (PEI), proceeds appropriately, timely and scientifically soundly.

The assessment system for multi-center trials by a lead ethics committee, which has also been effective since 2004, has proven successful overall, even if there is some need for improvement in terms of details (additional harmonization of requirements of the individual ethics committees, elimination of bureaucratic requirements).

Germany, currently the third largest market for the pharmaceutical industry worldwide, basically has a good general framework for efficient, patient-oriented research. With 2.3 medical specialists for every 1,000 residents, Germany has the highest specialist density compared to other industrial nations, a circumstance that represents good general conditions for clinical trials. Germany's relatively high population density and the associated above-average number of patients in an environment of excellently equipped health care institutions, such as university clinics, represents another good prerequisite for patient-oriented research.

These factors have contributed to the fact that, in reference to the number of clinical trials conducted, Germany has ranked first in Europe and second worldwide after the United States since 2007. Furthermore, Germany ranks second internationally with a total of 7,359 trial locations after the United States (49,472) but clearly ahead of its other international or EU competitors (France (4,628);

Canada (4,186); Italy (3,246); UK (2,866) – Sources: Clinical Trial Magnifier 02/2011; vfa evaluation based on www.clinicaltrials.gov).

Seite 3/18

- The cost discussion jeopardizes the competitiveness of Germany as a location for clinical trials

However, according to the recent experience of our member companies, this good position is at risk to be jeopardized by compensation claims for **structural costs for clinical trials** (often falsely summarized under the generic term of “**overhead costs**”), which are put forward time and again especially by large clinics/university clinics.

Currently, compensation surcharges of up to 60% are claimed as so-called “overhead costs,” which are to be paid in addition to compensation for the research service actually rendered. In doing so, this claim is typically put forward without proving any connection to costs actually incurred based on the implementation of a clinical trial. The member companies of the vfa view these claims more and more as a competitive disadvantage for the execution of clinical trials in Germany. Furthermore, it must be considered that such claims, which exceed pure cost coverage of participation in a trial, must be viewed very critically, since this may result in relevant corruption law aspects, if the “quid pro quo” principle is not observed.

Apart from the aspects listed under the concept of “overhead costs”, additional developments and demands have been observed over the past few years that also directly concern the cost discussion or the practical feasibility of clinical trials. This includes also the increasingly upcoming call for conclusion of multiple agreements for the implementation of a single study at one trial location, which shifts distribution problems (of the internal distribution of the compensation paid) within the large institutions toward the outside. Furthermore, claims for initiation costs (often also designated as “set-up” costs) and contributions in terms of subsidies (“cross-financing”) are increasingly seen, and centralized cost directories of individual interest groups/areas (e.g. clinic pharmacies) are being developed.

Below, these topics are addressed, the basic aspects of the cost review for clinical trials are represented, and the calculation approaches for an appropriate compensation of the service as part of clinical trials rendered – oriented on the actual work and expense – are shown.

Basic aspects in the cost review of clinical trials

Seite 4/18

- Principle of "fair market value"

Fair market value is a philosophical concept that goes back to Thomas Aquinas, who spoke of a "fair price." It includes both the aspect of fairness and that of the market, so that two partly contradictory principles are represented here.

First, it includes a market component that is defined by supply and demand: If a trial is particularly important and all available trial locations are needed, the providers would be in a strong position – the sponsor would be at their mercy; if, in turn, the sponsor offers an attractive treatment option in the form of a highly innovative substance he could select the trial institution(s) and insist on a very low fee for the trial physician. This market aspect is (should be) domesticated by the "dictate" of fairness for both sides.

However, the dictate of fairness also means that the overall compensation paid, relating to a trial and "per" patient, should be comparable/identical in an economic region such as Germany and should not be distorted by additional costs, e.g. so-called overhead costs. As a consequence, this also means that the sum of the maximum overall compensation fee per patient should remain constant, even if several contracts within the same clinical trial are concluded.

- Cost "coverage"

The overall compensation in a clinical trial is meant to cover the costs incurred by the specific clinical trial. This can e.g. be derived from the German National Hospital Rate Ordinance ("Krankenhausentgeltgesetz" – KHEntG). On the other hand, this also means that the typical treatment measures ("standard of care") should not have to be paid by the sponsor (again). There is no consensus as to whether or how infrastructure costs can or should be included. Typically, these are already covered by the cost calculation of the clinic as part of its health care mandate or are to a certain extent included pro-rated in the rates used for calculating fees (based on time expense or according to a catalog/Physicians' Fee Schedule (GOÄ). As a result, the principle of cost coverage should basically be applied not just to industry-sponsored trials (see below).

To what extent the implementation of clinical trials should be allowed to result in net profits for the trial institution is a fundamental, theoretical question. With the same compensation fee, one trial institution may barely cover its costs, because e.g. deductions (also known as "overhead") must be paid to the clinic

administration, while another trial institution may record profits due to optimized processes.

Seite 5/18

- Appropriate proportion of service and compensation

Apart from the principles of transparency and “no tie-ins” (pharmaceutical prescriptions, procurement measures, etc.), the principle of reciprocity applies, i.e. each service must be proportionate to its compensation. A compensation fee that by far exceeds the real costs of the trial institution could be interpreted as accepting a bribe. The Physicians’ Fee Schedule (GOÄ) or commercially available benchmark data for fees for medical interventions could serve as orientation for an appropriate compensation for the trial site. For example, in this context and in terms of the Physicians’ Fee Schedule, several legal experts have multiplied the rate by a factor of 2.3 for technical services and by 3.5 for personally rendered services and used this for potential orientation. Occasionally, demands require in addition to the compensation fee the sponsors to finance non-physician medical staff (e.g. a “study nurse”). Even if the services of the trial institution are correctly represented in fee billing, this could violate the “quid pro quo” and the fair market value principles, if this results e.g. in double billing. In addition, separate or additional contracts relating to the clinical trial should be avoided as much as possible.

For commercial sponsors of clinical trials who do not observe the “quid pro quo” principle, this may also result in violations against basic approaches stipulated in the FSA “Healthcare Professionals” Code. Section 18 para. 1 No. 6 of this code states that *“remuneration must be exclusively monetary and must be in an proportionate to the service rendered.”* Non-observance of the “quid pro quo” principle could therefore constitute a violation against the Code, which would result in sanctions. The FSA Code has the objective of safeguarding an ethically flawless collaboration of pharmaceutical companies with physicians, pharmacists and other members of the medical expert circles – this also includes collaboration as part of clinical trials (see also Section 18 para. 1 of the FSA Code). With approval by the Federal Cartel Office, the FSA “Healthcare Professionals” Code was recognized on April 8, 2004, as a rule on competition. As a result, commercial sponsors are obligated to adhere to the “quid pro quo” principle.

- Avoidance of false incentives

Procurement of external funding to trial institutions (if it is specifically desired and even represents a job-related task) that is also partly supported by additional matched grants could lead to a situation in which a monetary incentive is created to include patients in trials “by any means” in order to fill the external

funding account. Especially for high percentage surcharges on paid fees for services rendered, such a false incentive would be possible.

Seite 6/18

- Clinical trials are not suitable as a basis for cross-financing of a clinic's other research activities

Fees paid as part of commercial trials are not meant to secure "cross-financing" of insufficiently funded investigator-sponsored trials (ISTs); otherwise, this would represent an indication of excessive cost claims by the trial institution.

- Impact on competitiveness

Trial physician fees have a significant impact on the competitiveness of a location. Considerable increases in the cost of implementation of clinical trials in Germany could lead to other locations for clinical research being favored. The example of Great Britain, where "reforms" of the Labour government and discussions regarding overhead fees led to dramatic cost increases in clinical development, has shown how quickly a country can lose its No. 1 ranking.

Possible fee calculation methods

If we take a look at the trial center's required expenses for the correct implementation of a clinical trial, the question arises as to which of the measures to be executed would be necessary **anyway** as part of the typical treatment and what measures need to be implemented specifically in connection with the clinical trial. The trial physician fee refers to services rendered **in addition** to the regular treatment; there is no compensation for costs that would also be incurred without participation in the clinical trial. The distinction between "anyway" and "in addition" is typically easy to make and should be stipulated by the sponsor in compliance with the legal framework. Ethical questions also play a role in this respect; e.g. a thorax X-ray exam that is performed "anyway" will certainly not be performed a second time in order to receive the corresponding trial-based compensation.

As a result, this raises the question of what should be the basis for a fair, appropriate and legally correct compensation for the services rendered as part of clinical trials. In this respect, it should also be considered that only the same amount per patient can be paid for each center as a maximum overall compensation fee (the upper limit per patient must be uniform and appropriate). Different options for calculating this compensation can be used:

1. Procedure-based;

Seite 7/18

2. Expense-based;

a. Based on the time expended;

b. Based on consumption.

1.) If we take path 1 with the **procedure-based compensation**, what lends itself as calculation basis – among others – is the catalog of services based on which medical services are billed to the health funds/patients (Physicians' Fee Schedule (GOÄ) in its current version). In this respect, it must be considered that the basic billing amount in question can be adjusted by different multiplication factors. The Physicians' Fee Schedule can serve as orientation for an appropriate trial physician fee. In most cases, the rate is multiplied by a factor of 2.3; as part of the trial participation, this can also be multiplied by 3.5 or 5, if medical examinations have been justified as being difficult, lengthy or expensive and this special expense is required in accordance with the trial protocol. Alternatively, commercially available benchmark data for fees for medical interventions which can be applied internationally to clinical trials, can also be used for procedure-based compensation.

Services billed in this way include all services rendered to or with the patient, e.g. consultation (patient education), taking blood samples, physical and machine-aided diagnosis, ECG, etc. as well as the generation of required study-specific documentation (medical certificates, reports). As a result, the patient education consultation as well as the explanation and evaluation of questionnaires can be calculated based on the Physicians' Fee schedule.

When using a procedure-based approach, the question arises for the specific billing *"for each fully documented patient"* as to how service compensation can be calculated in the case of incomplete visits or after a screening exam without subsequent recruitment. The following applies once again: Only a service actually rendered can and may be remunerated. It may be required to divide the compensation for each visit into individual services and to only compensate for the service rendered in each case. It should be determined beforehand how services are to be compensated as part of the patient screening, if the patient cannot be included in the trial after the completed screening. However, a false incentive due to generous remuneration of screening services should be avoided, just like insufficient compensation for an actually incurred screening expense.

Costs for in-patient treatment at a clinic are to be borne by the sponsor, if they are specifically required by the trial protocol and are needed for the purpose of a correct and safe conduct of a clinical trial but would be non-essential in the case of non-participation in the clinical trial. Compensation will be oriented on the daily rate of the clinic.

Seite 8/18

2.) **Expense-oriented compensation** is meaningful, if required study-related services must be remunerated that cannot be represented by the Physicians' Fee Schedule. This can be billed by the hour or by determining consumption. However, this seemingly easy approach can lead to under- or over-coverage, if the study-related activity later turns out to be significantly different from the original assumption made during the planning stage. An hourly compensation must be documented in a reproducible manner, i.e. lump sums of hours (e.g. "time expense: 1,000 hours") are not acceptable if this is not traceable as associated to a specific trial. The documentation of the service hours actually spent requires a high administrative expense on the part of both the trial center and the sponsor.

2.a) Another option would be to compensate for work time for each service, based on which different qualifications in the trial group can be represented separately and remunerated with the corresponding adjustments. Such an approach requires detailed accounting of the service rendered by the different functions and the work time determined for the service, which causes a high administrative expense. Whether the service was actually rendered by the function in question is difficult to verify for the sponsor. For the trial center, this billing model appears attractive, if there is an opportunity to spend less time than planned on an individual service and therefore more services can be rendered during the same time period. For the sponsor, this is a question of verifiability; from the quality assurance perspective, an incentive in term of work time savings should also be questioned in principle.

Fee billing based on assumed time expense per service is frequently used in connection with scientific consulting services or during the implementation of feasibility studies. In order to be able to calculate these fees reproducibly and with certainty, assumptions from experience values in consideration of stipulated general conditions from the Physicians' Fee Schedule (fees for consulting services) and the FSA Code are used. An internally approved procedure, possibly with a defined fee scale, can make compliance with the "quid pro quo" principle easier and simultaneously ensure comparability and consistency in the international comparison within the company.

2. b) In addition to the patient- and treatment-specific expense, other costs must be taken into consideration which can best be

taken into account as a flat rate, such as electricity, phone/fax, Internet, office supplies and the usage of other existing materials/equipment as well as potential internal transportation costs for patients, e.g. to a diagnostic center, if X-rays are taken there.

Seite 9/18

Such infrastructure costs can only be estimated, since documentation and verifiability of individual bills would represent an inappropriately large effort. In reference to these costs, a lump sum for "structural or overhead costs" is increasingly being demanded during fee negotiations. However, the "quid pro quo" principle must also be adhered to in terms of structural costs. Estimated sums must be provable and verifiable and be adequately proportionate to the duration of the clinical trial. The assessed costs should be realistic and plausible and correspond to the local market prices. Cost claims that are not appropriately justifiable and do not correspond to an adequate proportion in terms of the "quid pro quo" principle cannot be lodged. Furthermore, compensation from clinical research is not suitable for cross-financing of any type, since in clinical research a service is rendered. So a clinical trial must therefore be clearly distinguished from general research projects that tend to be more of a collaborative nature.

What must also be critically assessed are costs billed for premises and equipment usage. This includes e.g. rooms for patient care but also rooms made available for clinical monitors. The former are available in the clinic's infrastructure anyway and will be used in both the everyday clinical setting and in the implementation of clinical trials. The latter must be made available to the sponsor; however, this raises the question as to what the billing could look like, since trials are typically conducted in parallel with multiple sponsors and the costs must therefore be split. Again, there must be compliance with the "quid pro quo" principle and a reference to the duration of the clinical trial must be representable. Lump sums for potentially estimated values that are not reproducible remain unacceptable as long as there is no clear trial reference and the principle of an appropriate "quid pro quo" is not observed.

To the cost of consumption, expenses for additional measures for recruiting trial participants must also be added. If the center individually conducts such recruitment measures, these costs, which also include generating information materials as well as compensation for consultations by the ethics committee, are typically paid by the trial center and not reimbursed by the sponsor. However, if these additional measures for recruiting trial participants are managed by the sponsor in a centralized manner or coordinated with the sponsor (and approved by the ethics committees), as may be required e.g. for rare diseases, the costs incurred at each trial center will be reimbursed by the sponsor.

Costs incurred in connection with the archiving of trial documents can typically be represented in a transparent manner. The number of file folders to be stored can be recorded in meters of shelf space; the resulting file volume, the duration of archiving and the rental cost of the space in question can be put in relation to each other and costs can be calculated. Frequently, the legally stipulated period for archiving patient documents is shorter than the required storage period for documents from clinical trials, which results in higher archiving costs than expected by many trial centers. Especially when using external providers, unexpectedly high costs can be incurred. However, archiving costs are typically part of the general costs of trial implementation and should therefore be viewed as covered by the trial physician's fee.

Current problem areas

a. Trial preparation/initiation costs ("set-up" costs)

Over the past few years, a compensation model has become established in which fees are paid per trial patient treated. In this model, the provision of partial services can be taken into account easily and consistently. The service, which is described in detail in the trial protocol and divided over different trial visits, is compared to the corresponding fee for a doctor's visit. This approach is appropriate, since it meets the anti-corruption requirements (*with the four principles of "documentation, transparency, equivalence, and separation"*), and makes the actual object of the contract, i.e. the treatment of patients as part of a clinical trial, the focus of the mutual agreement for the contractual partners.

Over the past few years, expenses associated with the preparation of a clinical trial have increased significantly. This applies to both the trial center and the sponsor. Compensation for these initiation/set-up expenses is basically made through the per-case compensation paid. This fee must be billed in such a manner as to take into account not just medically indicated services but specifically also additional expenses caused by clinical research activity (e.g. documentation measures, collaboration in the field of monitoring, training).

In this situation, a lump-sum compensation or compensation in accordance with a catalog submitted by the trial center that is not oriented on the services to be rendered in a specific clinical trial is not appropriate.

However, under certain constellations, there is a possibility (also in compliance with the requirements of the FSA Code) to incorporate a compensation clause for the expenses incurred during the

initiation of a clinical trial in the contract. The trial center will be compensated for expenses, if inclusion of patients is not possible due to a shortcoming for which the trial physician bears no responsibility. This usually applies when the sponsor cancels the trial or a trial is not approved. Other than that, the measures before and after the clinical trial that are required for trial implementation must be viewed as typically covered by the fee paid per patient treated. The advantage of an approach that is oriented on the treatment objective is that the contractually agreed services and compensation remain clearly recognizable for both contractual partners.

Seite 11/18

b. Structural costs / "overhead"

Especially large clinics/university clinics – by referring to structural costs – demand additional payments on top of the trial physician's fee (often under the generic term of "overhead costs"). They justify these claims with the argument that the executing clinic renders an otherwise not required medical service in connection with the clinical trial, which means that – from the clinic administration's point of view – essential service elements remain unaccounted for in compensation. Examples of structural costs include e.g. building depreciation, electricity and other supply costs, administrative and archiving expenses, etc. These are typically charged as a flat percentage surcharge on the fee (charges currently amount to as much as 60% in overhead costs to be paid in addition to the remuneration of the actually rendered research service).

In most cases, this claim is put forward by the large clinics/university clinics without specific proof or a possible reference of this claim to the costs actually incurred through the implementation of a clinical trial. The member companies of the vfa view this critically, since such compensation exceeds cost coverage of the participation in a trial and this could give the impression of corruptive conduct, because the "quid pro quo" principle may not be observed in a verifiable manner. A "profit margin" for clinical trials, which is also demanded time and again, must be rejected as well – read about the problem of subsidies in the following section.

Demands for "overhead" payments without reference to the services rendered specifically as part of the clinical trial are unacceptable, make the conclusion of contracts for clinical research projects more difficult and delay or prevent the implementation of clinical trials at specific trial centers in Germany. This causes damage for Germany as a trial location as a whole. Germany risks to become less attractive for clinical research, if the start of trial implementation were to be postponed due to lengthier discussions on contract design as compared to other EU countries.

Inappropriate claims without any reference to trial specific services will make the implementation of clinical trials at German university clinics unnecessarily more difficult and result in unjustified cost increases.

Seite 12/18

From the vfa's point of view, the following aspects are not taken into account when so-called "overhead" surcharges are claimed:

The calculation of compensation fees during the preparation by the sponsor is usually already made in such a way that all costs incurred are taken into account appropriately – this is an obligation of the sponsor. Compensation is made not just for the medical service itself but all other services related to the conduct of the trial. The compensation rates provided in the Physicians' Fee Schedule are assessed in such a manner that fixed and variable costs are taken into account for the most part – after all, they must also cover structural costs for physicians operating in a private medical practice. If it can be proven that services as part of a doctor's visit during a trial represent a larger expense than would be the case during patient treatment (e.g. generation of multiple ECG printouts for each derivation event), the basic rate from the Physicians' Fee Schedule can be increased by applying a multiplication factor.

The demand for compensation of so-called "overhead" costs must be rejected, if costs incurred as part of the conduct of a specific clinical trial cannot actually be justified. **The principle of an appropriate fee for service ratio ("quid pro quo") must not be bypassed.**

As already mentioned, services can be rendered in certain areas whose compensation value can only be approximated. However, the principle of an appropriate "quid pro quo" ratio must still be applied and must be verifiable in each case. Compensation must be in a provable relation to the duration of the corresponding activity in connection with the clinical trial at the trial center in question. Remuneration that is not appropriately justifiable does not represent an adequate "quid pro quo" ratio and can therefore not be claimed. If a non-verifiable percentage coupling is used as the calculation basis for "*overhead costs*," additional payments in a considerable amount could be claimed but - depending on the individual case – no adequate, documentable service in return can be associated to this overhead costs demanded. Also a percentage coupling does not allow to take trial specificities into account.

Nowadays, lump-sum or percentage-based structural costs are even charged for the implementation of non-interventional trials, even though a treatment routine that is performed anyway is only documented additionally as part of the trial. This can also create unacceptable distortions in compensation. If provision of a medical

service is not explicitly planned as part of the normal therapy, "trial-related structural costs" cannot be incurred at all and can therefore not be billed or compensated by the sponsor of the non-interventional trials (since there would be no compliance with the "quid pro quo" principle in such cases). In these cases, compensation can only refer to the documentation service for the trial and for the low structural costs incurred in the context of a specific clinical trial. However, these would be regularly covered by the compensation rates provided.

c. The problem of subsidies

As mentioned in the previous section on structural costs ("over-head"), university clinics/clinics often justify their claim for overhead with a reference to the Official Journal of the EU (2006/C323/01), *"Community Framework for State Aid for Research and Development and Innovation"* (Section 3.2.1. Research on behalf of undertakings (Contract research or research services)). According to this framework, the university clinic/clinic would be entitled to a "profit margin" they should not forgo. The vfa believes this is incorrect.

The reference to the Official Journal of the EU, *"Community Framework for State Aid for Research and Development and Innovation"* (Section 3.2.1.) cannot be applied to the situation of clinical trials, since this framework only serves the purpose of ascertaining whether government subsidies are given or not. Entitlement to a profit margin cannot be derived from them, specifically not from Section 3.2.1, since this framework does not justify claims but are merely meant to create legal certainty and transparency for the decision-making process within the EU Commission (comp. Section 1.1 of the Official Journal).

The university clinics point out on a "missing market price" and to Section 3.2.1 No. 2 of the Official Journey, but this reference misses the target. It reads as follows:

"...When a research organisation carries out such a contract (Note: contract research or research services on behalf of companies), there will normally be no State aid passed to the undertaking through the research organisation, if one of the following conditions is fulfilled:

1. the research organization provides its service at market price; or

2. if there is no market price, the research organisation provides its service at a price which reflects its full costs plus a reasonable margin."

In this respect, it must be considered that the clinical research represents a service by the participating trial center, which must be assessed and treated differently than general research collaborations.

As a result, an “appropriate profit margin” – regardless of the lack of applicability of the notifications in the Official Journal – could only be claimed if there is no market price. However, since possibilities for calculation and orientation benchmarks for adequate compensation exist, which could be viewed as a market price, this reference does not apply.

Furthermore, from the vfa’s perspective, the demand for a “profit margin” is not compatible with the principle of an appropriate “quid pro quo.” In contrast to basic research, clinical research is not suited for cross-financing of other internal research projects or to gain additional funding for the institution. Over the past few years, the pharmaceutical industry has imposed on itself strict regulations for the collaboration with healthcare professionals (see e.g. the FSA “Healthcare Professionals” Code). Section 18 para. 6 for the collaboration with healthcare professionals requires the principle of an adequate “quid pro quo.” If a sponsor from the environment of the pharmaceutical industry does not comply with this voluntary commitment (and e.g. meets the demand for a “profit margin”), this could also possibly represent a code violation, which will be penalized accordingly.

In addition, remuneration for a trial beyond the principle of an appropriate “quid pro quo” would also be scientifically questionable since it could encourage accusations regarding the “purchase of positive results of clinical trials,” which are put forward time and again in the public discussion. Therefore, it would also be important in the interest of the participating trial centers/physicians to comply with the “quid pro quo” principle and to only claim costs as part of clinical trials that have a clear and verifiable connection to the trial project at hand.

- d. Multiple contracts due to unclear internal relationships – additional administrative expenses

Up until a few years ago, it was customary to conclude a single, trial-specific contract between the industrial sponsor and the trial center. However, more and more frequently, clinic administrations act as representatives of the institution and therefore as contractual partners and recipients of compensation. The executing and medically responsible trial physician is therefore merely a co-signer of the agreement. This is appropriate, since it takes into account the clinic physician’s status as an employee of his institution yet also creates transparency for all parties involved.

For a few years, it has been observed that individual contracts are now increasingly being demanded by clinics/university clinics as separate contracts from the actual main agreement. This specifically concerns the services of laboratories and pharmacies but also special groups of medical experts participating in the implementation of clinical trials (e.g. radiologists, nuclear medical specialists, dermatologists). This is amazing in that all participants involved in the clinical trial under the joint roof of their institution (which concludes the contract), so that a single agreement comprising all services can be concluded. In this respect, it must be emphasized that, from the sponsor's perspective, the institution as the contractual partner executes the clinical trial and renders an overall service. The conclusion of individual agreements ultimately leads to a situation in which the distribution of the compensation fee to be internally made within the clinic/university clinic is shifted from its internal relationship into the external relationship with the sponsor. This has consequences for all parties involved:

- The administrative expense increases considerably for both the sponsor and the institution, since significantly more individual agreements must be negotiated, created, processed and managed.
- Potential internal, unresolved conflicts of the institution in connection with the implementation of clinical trials are shifted to the sponsor, who is therefore pushed into the role of a mediator.
- Uncertainties and misunderstandings between the sponsor, third-party funding agencies and legal departments as well as the implementing specialist departments of the clinic/university clinic cause considerable additional expenses.
- The start of study projects is postponed, because the individual negotiations and the conclusion of all contracts take a lot of time.
- The generation of joint, bilaterally negotiated standard agreements between the sponsor and the clinic/university clinic is made considerably more difficult.
- Overall, this increases expenses and therefore also the costs for the implementation of the clinical trial – and consumes a lot of time of all involved parties.

How the compensation paid by the sponsor is to be distributed within the clinic/university clinic should be settled internally at the clinic – this is not a task of the sponsor. The assessment of whether the clinic/university clinic wishes to execute the clinical

trial for the compensation offered by the sponsor would also have to be made internally. However, an in-house office at the clinic that assesses the economic justifiability of the compensation foreseen for a clinical trial does not exist at most clinics.

Seite 16/18

- e. Ideas regarding service fees, e.g. for hospital pharmacists

The above-mentioned, additionally required expense based on multiple contracts is even increased, if – apart from the demands of individual clinics/university clinics – nationwide interdisciplinary publications present their own ideas regarding the service fees of individual interest groups (see e.g. by the hospital pharmacists in *“Recommendations of the German Association of Hospital Pharmacists (ADKA) Committee on Clinical Trials and the Working Group of Head Pharmacists at German University Clinics (LAUD) on the billing of hospital pharmacy services during clinical trials”*).

According to the sponsors' experience, it has become apparent in practice that this counteracts a joint approach within an institution more than it is helpful. It is regrettable that these ideas regarding service fees are typically compiled without the participation of or hearing with the key potential contractual partners. While the basic idea of a standardized approach should be welcomed in principle, these approaches are very one-sided and do not contribute to making things easier. The opposite is true: In some cases, the authors, who have compiled (their own) ideas about service fees, show amazement at the reactions of the sponsors of clinical trials. The sponsors reject approaches involving independent compensation of individual services as part of clinical trials, both in terms of content and procedure, and pursue standardized agreements with the clinic administrations.

The vfa's position

Clinical trials are an indispensable prerequisite for the development and launch of new pharmaceuticals and therapies. They represent the foundation of evidence-based medical care. Germany is currently an important and attractive location for the implementation of clinical trials. However, according to the current experience of our member companies, Germany's good position as a research location could be jeopardized by compensation demands for unverifiable **structural costs, in addition to the service-based remuneration of clinical trials** (often falsely referred to under the generic term of **“overhead costs,”** primarily by large clinics/ university clinics), since this would result in a competitive disadvantage as compared to other locations.

From the vfa's perspective, the following basic principles must be observed in the cost reimbursement for clinical trials:

Seite 17/18

- "Fair market value" should always represent the basis for financing/cost reimbursement as part of a clinical trial.
- The services and compensation to be rendered between sponsors and trial centers should be described in a single contract, which includes the shares of the different departments or divisions (e.g. clinic pharmacies) in the provision of the services.
- Complete compensation for the service rendered by a trial center must be ensured – the participation in clinical trials can and must not represent a "subsidized undertaking" for the clinics.
- Compensation for the service rendered must be compatible with the "quid pro quo" principle – fee for service.
- Compensation should be as closely oriented on the documented services provided during the conduct of a specific clinical trial as possible. Unless a direct connection to the clinical trial is verifiable, lump-sum payments are unsuitable and the demand for an unverifiable, fixed percentage "overhead" is inappropriate, because an appropriate fee for service ("quid pro quo") cannot be ensured.
- A profit margin in the compensation for clinical research is questionable, also from an ethical standpoint. It is therefore also in the interest of the participating trial centers/physicians to observe the principle of an appropriate fee for service ("quid pro quo") and to claim only costs that are specific to the clinical trial and that have a clear and verifiable connection to the conduct of a specific clinical trial project.
- The compensation for clinical trials as part of pharmaceutical development is not suited for the cross-financing of other (internal) research projects. Neither is it appropriate to fill financial gaps at clinics/trial centers.

In the interest of all parties involved - pharmaceutical industry, CROs (contract research organizations), physicians, university clinics/clinics or doctor's practices and in particular also the patients - these principles should be observed by all parties involved. Otherwise, there is the risk that Germany's competitiveness may be adversely affected, which would also have negative impacts for patients, physicians and clinics.

The vfa has a strong interest in continuing to position Germany as an attractive trial location in the international competition and to safeguard the high standards and quality that have already been achieved. In this context, the appropriate financing of clinical trials, oriented on a principle of adequate "quid pro quo," is indispensable.

Seite 18/18

As of: October 18th, 2013