

Infrastructures and framework for the conduct of clinical trials in Germany

A review of the status quo in preparation for a European Clinical Research Infrastructures Network (ECRIN)

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Abbreviations: AkdÄ = Pharmaceutical Commission for the Medical Profession
AMG = Federal Drug Act
AWMF = Working Group of Scientific and Medical Professional Associations
BÄK = Federal Chamber of Physicians
BfArM = Federal Institute for Pharmaceutical and Medicinal Products
BMGS = Federal Ministry for Health and Social Affairs
BMBF = Federal Ministry for Education and Research
BPI = Federal Association of the Pharmaceutical Industry
BVMA = Federal Association of Medical Contract Research Organizations
CDISC = Clinical Data Interchange Standards Consortium
CRO = Contract Research Organization
DFG = German Research Foundation
ECRIN = European Clinical Research Infrastructures Network
GCP = Good Clinical Practice
KKS = Coordination Centre for Clinical Trials
KKS-AG = Working Federation of the Coordination Centre for Clinical Trials
MedDRA= Medical Dictionary for Regulatory Activities
MPG = Medicinal Products Act
NGFN = National Genom Research Network
PAED-Net=Paediatric Network
POH = Paediatric Oncology and Haematology
QM = Quality management
SOP = Standard Operating Procedure
TMF = Telematic Platform for Medical Research Networks
VFA = Association of Research- based Pharmaceutical Manufacturers

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A national workshop was held in Frankfurt on 5 October 2004 to support the establishment of a European Clinical Research Infrastructures Network (ECRIN). The objective of the ECRIN is to formulate guidelines for an infrastructure which will serve as a basis for the harmonisation of the support, training and conduct of clinical trials on a European level. The aim is to provide international support for both publicly funded and industrially sponsored multicentre clinical trials. The ECRIN Consortium already comprises existing national study-centre networks and the European Forum for Good Clinical Practice (GCP). At present, there are 8 networks with more than 100 study centres in 6 European countries. The workshop served to document the status quo in the German national network of Coordination Centres for Clinical Trials (*Koordinierungszentren für Klinische Studien; KKS*¹), to characterise the role of the KKS network in national clinical research, and to assess framework conditions for the conduct of clinical trials in Germany. The workshop was attended by representatives of the KKS, other research networks, public sponsors, government agencies, the pharmaceutical industry, ethics committees and data protection. This report is based on the presentations given and the discussions at this workshop, and will serve as Germany's contribution to the establishment of the ECRIN. Since it was not possible to address all significant aspects at the workshop and because of recent developments with regard to the implementation of the 12th Amendment to the Federal Drug Act (*Arzneimittelgesetz; AMG*), some of the information presented was supplemented or updated. The report reflects the personal view of the authors and focuses on the role of the KKS in Germany.

1. Structure and objectives of the centres and the network

1.1 Centres

Two competitive calls for tender put out by the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung; BMBF*) made possible the setting up and establishment of 12 KKS in medical faculties in Germany (1999/2000 and 2002). KKS now exist in Berlin, Dresden, Düsseldorf, Freiburg, Halle, Heidelberg, Cologne, Leipzig, Mainz, Marburg, Münster und Tübingen. They are financed with basic funds from the local faculty, degressive sponsorship from the BMBF, and increasing income from public funding and the private sector (1). With one exception (gGmbH), all KKS are university centres and are therefore not independent legal persons. They generally have a board of directors with a scientific head and a business manager. KKS offer expertise and infrastructures for the planning, conduct and evaluation of clinical trials in Germany. These services are performed for the private sector and for academic trials. KKS also offer education and training in all aspects of clinical trials. Almost all KKS have expertise and resources for study planning and design, project management and study coordination, biometrics, monitoring, study assistance, electronic data processing and management, education and training, support with

¹ KKS is used as both the singular and plural in this paper.

methodology and quality management (QM). Activities for investigator-initiated trials consist mainly of study design, protocol development and biometrics, study coordination, data management and databank hosting; study assistance and monitoring are the dominant activities for industry-sponsored trials. Further services are also increasingly being offered, particularly for trials sponsored by small and medium-sized companies. In addition to this, individual sites offer specific expertise in other areas or have a special focus, e.g. information technology for clinical trials, clinical pharmacology, pharmacogenomics, pharmacovigilance, drug development, health economics, methodology research and study design. Some also focus on particular medical specialties or special types of study, such as paediatrics. On average, a KKS has a budget of € 1m per year, about 20 employees, and supports 27 trials running at one time, of which 45% are industry-sponsored.

1.2 Network

The KKS have been grouped in a working federation since 2000 (KKS-AG), with the heads of each KKS on the executive committee. In order to harmonise and standardise work and procedures in the KKS, the KKS-AG has formed three working groups: Quality Assurance, Data Management/Telematics, and Basic and Education/Training. At present, the organisation of the KKS-AG is being converted to a network consortium, to further intensify collaboration and put it on a permanent base. The first step was to open up a Business Office for the KKS-AG, whose principal task, amongst others, is the coordination of KKS-wide activities and public relations.

A paediatric network (PAED-Net) especially for paediatric trials has been set up with a coordinating centre in Mainz, with 6 PAED-Net modules linked with the KKS in Cologne, Freiburg, Heidelberg, Leipzig, Mainz and Münster (2). The PAED-Net offers a country-wide infrastructure for the conduct of multicentre paediatric trials in Germany.

1.3 Cooperation partners

The Medical Competence Networks sponsored by the BMBF are important partners of the KKS-AG (3). The networks, focused on specific disease entities, promote interdisciplinary cooperation between basic scientific research and clinical research, and one of their principle activities is to conduct clinical trials. KKS – although not countrywide – collaborate with these networks. The KKS-AG also collaborates very closely with the Telematic Platform for Medical Research Networks (TMF), also sponsored by the BMBF. The task of the TMF, to which medical research networks including the KKS belong, is to develop and expand high-performance IT infrastructures and set up networking structures to link up different groups across the country (4). The collaboration mainly takes the form of working groups, forums and concrete projects, dealing with common topics such as software evaluation and validation, expansion and operation of biomaterials banks and quality management for IT solutions.

Close collaboration is also planned with other organisations sponsored by the BMBF, such as the National Genome Research Network (*Nationales Genomforschungsnetz*; NGFN; 5), and the Study Centre for the German Surgical Association (*Deutsche Gesellschaft für Chirurgie*).

In addition to the partners from the public sector, the private sector is also an important partner for the KKS-AG. The KKS are increasingly supporting clinical trials sponsored by industry, and are therefore contributing to collaboration between universities and industry. Important partners here are the Association of Research-based Pharmaceutical Manufacturers (*Verband Forschender Arzneimittelhersteller*; VFA), the Federal Association of the Pharmaceutical Industry (*Bundesverband der Pharmazeutischen Industrie*; BPI), and the Federal Association of Medical Contract Research Organisations (*Bundesverband Medizinischer Auftragsinstitute*; BVMA).

Outside the KKS there are other efficient study infrastructures, for example in the area of oncology (lymphoma, leukaemia etc.). At present, however, there are very few with research beds.

2. Financing/Sponsoring

1,349 trials were processed by the Federal Institute for Pharmaceutical and Medicinal Products (*Bundesinstitut für Arzneimittel und Medizinprodukte*; BfArM) in 2002: 445 phase I trials, 336 phase II trials, 421 phase III trials and 57 phase IV trials (6). The R&D development expenditure of the member companies of the VfA amounted to € 3.8bn in 2003, of which 40% were invested in clinical research, 50% of which went to establishments involved in clinical research. It must be said that the number of clinical trials conducted in Germany is smaller than in other countries with similar population figures. According to an investigation conducted by Boston Consulting (7), for example, markedly fewer trials were conducted in Germany per 100,000 inhabitants than in other similar-sized industrialised countries. Industry-sponsored trials are also more frequently being performed in other countries, particularly Eastern Europe and Asia. A large proportion of industry-sponsored trials are put in the hands of contract research organizations (CROs). At present, there are about 270 CROs in the USA and 470 in the EU. About 20 CROs have 60% of the market. The entire European CRO market is estimated to be worth US\$ 10.43bn, with 58% of investments going into clinical research.

In addition to this, clinical research activities were and are directly and indirectly supported by numerous activities on the part of the BMBF. Indirect financing is given by the Health Research Programme via the support of the Interdisciplinary Centres for Clinical Research, the Medical Competence Networks and other research networks. Between 1999 and 2008, € 260m have been and are being invested into the Medical Competence Networks and research networks investigating different disorders. Direct financing of clinical trials has taken place by the establishment of KKS at 12 university sites. This measure has benefited both industry- and publicly-sponsored trials. € 31m

were provided for this as part of a degressive structural investment. The BMBF and German Research Foundation (*Deutsche Forschungsgemeinschaft; DFG*) established a sponsorship focus on 'clinical trials'. Initially for 4 years, this measure provided € 10m per year for scientific trials initiated by academia without restrictions to the questions investigated. The first call for projects in 2004 elicited 362 draft projects with a total volume of € 260m. In a two-stage process, 43 draft projects were first of all selected, of which between 10 and 20 will finally be selected to receive support. In addition to this, even though to a lesser extent, trials are supported by standard DFG grants and by the BMBF by specific grants. German Cancer Aid (*Deutsche Krebshilfe*), founded in 1974 as a registered charity, is the leading sponsor in the area of oncology. In 2003, it sponsored projects worth € 60.4m, including € 15.1m for clinical activities (including clinical research)(8). Foundations, associations and scientific societies also sponsor selected trials, but it is not possible to estimate how much money they provide.

There are large deficits in the sponsoring of trials into the provision of healthcare ("Versorgungsforschung"). A joint research programme sponsored by the BMBF and the leading associations of statutory health insurance funds is running, but only the very low sum of about € 1m per year has been provided for this. In this area, selected trials have also been sponsored (e.g. by the Federal Ministry for Health and Social Affairs (*Bundesministerium für Gesundheit und Soziales*) and health insurance companies). New programmes, for example an initiative launched by the Federal Chamber of Physicians (*Bundesärztekammer; BÄK*) to support health services research are under preparation.

Overall, it can be said that the sponsoring of scientific trials in Germany is inadequate, with the exception of the area of oncology. Considerably more financial support for the conduct and quality assurance of clinical trials is necessary to secure scientific progress, particularly to enable us to guarantee compliance with national and international legislation and the maintenance of quality standards.

3. Ethics

At present, Germany has 48 independent ethics committees, including 18 in State Chambers of Physicians Organisations or on an official state level, and 30 at universities. In addition to international guidelines and ethical standards (Declaration of Helsinki, GCP), the responsibilities of the ethics committee for clinical trials on a national level are determined on the one hand by the Physicians' Professional Code (*Berufsordnung für Ärzte*) and on the other by the AMG, Medicinal Products Act (*Medizinproduktegesetz; MPG*) and other specific legislation (9,10). According to the Professional Code, before conducting biomedical research in humans – with the exception of exclusively retrospective epidemiological investigations – physicians must consult with their competent ethics committee in accordance with state law (Chamber of Physicians or medical faculty) with regard to ethical and legal

aspects. In accordance with the 12th Amendment of the AMG, a drug may only undergo clinical testing in humans if the competent ethics committee has given its approval. The application for approval has to be made by the sponsor to the competent independent ethics committee responsible for the investigator, principal investigator or coordinating investigator of the clinical trial. The MPG also decrees that ethics committee approval must be sought for planned trials.

The consultation procedure for multicentre clinical trials is regulated in detail by the 12 Amendment of the AMG and the GCP guidelines (11). The so-called coordinating ethics committee responsible for the coordinating investigator of the clinical trial is responsible for the assessment, but the assessment must include the ethics committees responsible for other investigators and centres. In agreement with the other ethics committees involved, the coordinating ethics committee makes the assessment. All internal consultation must be complete within 30 days. The coordinating ethics committee then conducts a final meeting and issues its decision with reasons within a maximum of 60 days, which is then nationally valid. Special periods are valid for trials with gene transfer preparations, somatic cell therapeutics, genetically modified organisms and xenogenic cell therapeutics. In addition to this, the ethics committee has to approve amendments to study protocols and the addition of new study centres. Within defined periods, the ethics committee also has to be informed of any incidents that alter the risk-benefit assessment, premature discontinuation of the study at any study centres, premature discontinuation of the entire study, and suspected unexpected serious adverse events.

Although the procedure laid down in Germany fulfils the requirements of the EU Directive, it is specific to Germany (12). In the opinion of the pharmaceutical industry, the regulations in Germany are too complex to achieve a unanimous ethics committee decision, and in some cases those regulations involved do not have the necessary expertise (13). The 12th Amendment of the AMG has given the ethics committees a quasi-authority status. The increased responsibility emerging from this caused several Chambers of Physicians (because of problems of liability) to stop, at least temporarily, providing ethics committee services at very short notice. In general, the work of ethics committees must urgently be put on a much more professional footing in order to do justice to the increased requirements introduced by the 12th Amendment of the AMG (14). The establishment of a database for joint use by ethics committees to exchange information on decisions represents a first step towards the optimisation of the management of the procedure. At present, a uniform documentation form for applications for national use is under development, and is urgently necessary.

4. Legislation

The conduct of clinical trials is governed by national and international legislation, guidelines and standards. On a national level, the conduct of trials with pharmaceutical preparations has been governed, since 6 August 2004,

by the 12th Amendment of the AMG, and the Decree on the Use of GCP (GCP Decree, 12 August 2004) (9, 11). These laws embody the EU Directive 2001/20/EG in German law (12). The 12th Amendment of the AMG decrees that trials with pharmaceutical preparations may not start until they have been approved by the competent supreme federal authority. The application procedure for approval is described in the '3rd Announcement on the Clinical testing of Pharmaceutical Preparations in Humans', which is at present being revised (15). The new regulations are not restricted only to trials intended for regulatory submissions, but are valid for all trials with pharmaceutical preparations. Medicinal products are governed by the MPG of 7 August 2002 (10). This Act contains a section on clinical testing which is largely based on older versions of the AMG. Trials with radioactive substances or ionising radiation in humans are also governed by the Statute on Radiation Protection (*Strahlenschutzverordnung*) and the Statute on X-ray Protection (*Röntgenschutzverordnung*). The area of clinical trials is also affected by data protection legislation. Data protection in the medical field is largely governed by the Hippocratic Oath, general data protection legislation, and state legislation, where it exists. The principal provisions are that medical findings collected during clinical research may only be processed with the express agreement of the patient, only for the purpose of the research being conducted, in pseudo-anonymised form, with complete anonymisation as soon as this is possible.

Pursuant to the AMG and MPG, patients enrolled into clinical trials must be insured for at least € 500,000 in case they die or become permanently unable to work as a result of the research. Provisions for statutory compensation must also be made for trials with radioactive substances or ionising radiation. In accordance with the 'Atomgesetz'², university teaching hospitals may be exempt from this requirement. Insurance can be problematic for clinical trials not governed by the AMG or MPG, such as trials on surgical techniques or psychosomatic trials. It is sometimes not possible to obtain insurance for such trials in Germany, or the premiums cannot be paid as they are too high. Similar regulations to those in the AMG are not available. This situation represents a significant barrier to the conduct of scientifically based trials outside the jurisdiction of the AMG and MPG.

5. Pharmacovigilance

Pharmacovigilance procedures are governed by national (AMG, MPG) and European legislation. The national legal instruments for pharmaceutical preparations are the 12th Amendment of the AMG together with GCP regulations, and the 3rd Announcement on the Reporting of Adverse Reactions, Interactions with other Agents and Pharmaceutical Preparations (at present being revised). The terms 'adverse reaction', 'serious adverse reaction' and 'unexpected adverse reaction' are defined in §4 of the AMG.

² *Gesetz über die friedliche Verwendung der Kernenergie und den Schutz gegen ihre Gefahren* – Legislation governing the peaceful use of atomic energy and protection against its effects, including insurance for those exposed.

The reporting requirements for investigators and sponsors are set out in the GCP regulations. In accordance with these, serious unexpected adverse events must be reported to the sponsor without delay, excluding adverse events that are listed in the study protocol as not subject to immediate reporting. If a person suffering an adverse event dies, the investigator supplies the ethics committee responsible, and any other ethics committees involved, the supreme federal authority and the sponsor with all additional information required. Sponsors report cases of unexpected serious adverse events within 15 days to the ethics committee responsible, the supreme federal authority, if necessary, other EU member states, and the investigator involved in the study. If a suspected adverse event is fatal or life-threatening, the report must be made within 7 days. Further details of reporting requirements are laid down in the AMG and GCP regulations.

The German Physicians' Professional Code decrees that they must report adverse events for approved products to the Pharmaceuticals Commission for the Medical profession (*Arzneimittelkommission der deutschen Ärzteschaft; AkdÄ*). However, physicians also report them to the manufacturer of the pharmaceutical preparation, the hospital pharmacy, and commercial organisations, such as 'arznei-telegramm'. The 'arznei-telegramm', a publication financed by subscribers, operates a spontaneous reporting system for reports of suspected adverse events to pharmaceutical preparations which at present contains about 12,000 reports. The outcome of this situation is that reports are made to different places and not consistently to national or regional agencies, as in most European countries. The BfArM und the AkdÄ do, however, have a joint database for the documentation of spontaneously reported adverse events to pharmaceutical preparations. 2,067 spontaneous reports of adverse events to pharmaceutical preparations were made to the AkdÄ in 2001 (16). Approximately 13,000 different patients reports were registered in the joint database of the AkdÄ and BfArM in 2002. Searches can be made on the adverse event data in the joint BfArM and AkdÄ database using the Phoenix^R system. Analyses of the data are regularly published by the AkdÄ in the 'Deutsches Ärzteblatt' (wide-circulation physicians' journal issued by BÄK) or in the information publication "Arzneiverordnung in der Praxis" (*Prescription of Drugs in Medical Practice*)(17).

6. Data management

The European Guideline 2001/20/EG (12) and the internationally valid Guidelines ICH E6 Good Clinical Practice (18) and ICH E9 Statistical Principles for Clinical Trials (19) specify requirements for the management of data from clinical trials to different extents. Further requirements are given in documents issued by the Food and Drug Administration in the USA (Guidance for industry: computerized systems used in clinical trials, April 1999, and 21 CFR 11: Electronic records, electronic signatures, March 1997). In addition, different

national laws have to be observed (German Signature Act (*Deutsches Signaturgesetz*), data protection legislation). The Working Group on Quality Assurance of the KKS-AG has issued a position paper that describes the requirements for data management processes to comply with ICH and GCP. The basic principles are SOPs specifically for data management processes and the use of validated study software. Because of differences between the hardware, orgaware and software in use at the different KKS centres, site-specific rather than harmonised SOPs are used for data management. Data management procedures at KKS have been externally audited.

The unavailability of validated study software was a considerable problem in the early stages of setting up the KKS. In-house developments were mainly used, with the exception of standard commercial statistical analysis software (e.g. SAS, SPSS). The Working Group on Data Management at KKS tackled this problem and, in a painstaking procedure in 2001, evaluated study software with a focus on remote data entry (20). The evaluation was based on a survey of pharmaceutical companies and CROs in Germany, the production of user profiles by KKS, and the development of requirements for software products. With support from TMF, two commercial software products were purchased: MACRO[®] from InferMed and eResNet[®] from eResearchTechnology. MACRO[®] was installed in the KKS in Cologne, Freiburg, Heidelberg, Mainz, Marburg, and eResNet was installed in the KKS in Düsseldorf, Halle und Leipzig. So far, 7 KKS units have conducted 28 trials using MACRO[®] and eResNet[®], including 10 with external users. A user survey conducted in January 2004 showed a high degree of user acceptance for these software products, and they were also felt to be user friendly. In addition to these software products, the high-performance open-source software PhOSCo[®] – also available at reasonable cost to academia – is used, as well as other programmes for certain applications. A number of different questions are at present being investigated in collaboration with TMF: validation of study software, use of Clinical Data Interchange Standards Consortium (CDISC), incorporation of mobile computing in the study software and the production of standardised macros for analysis. Furthermore, the work with the Medical Dictionary for Regulatory Activities (MedDRA) is being supported with licences, tools and training events. The aim of the activities of the Working Group is to implement a professional IT infrastructure at all KKS sites and to integrate the different software products and modules. In addition to this, the intention is to offer a range of IT services (e.g. online randomisation) and to establish remote functionalities for the support or working processes (e.g. eMonitoring).

An IT infrastructure for use in clinical trials has also been put in place or is still being implemented in the different research networks sponsored by the BMBF (e.g. Medical Competence Networks, NGRN), which has resulted in some positive examples of collaboration with the KKS (e.g. the Heart Failure, Sepsis and Paediatric Oncology and Haematology (POH) Medical Competence Networks). No systematic coordination with regard to study software has yet taken place. Quality assurance of the IT infrastructure is conducted to different degrees, but it is worth stressing that the activities of the telematics

platform have been harmonised across organisations and sites. Generally, the pharmaceutical industry and larger CROs have validated software solutions, often with remote functionalities. A very wide range of products are in use.

Despite significant advances in the area of data management for clinical trials in Germany, there are still many problems in academia. Many centres do not have professional, validated study software. Financial means to purchase study software must be provided, although in some cases the very high prices for licences represent a considerable barrier for academic centres. Because of uncertainties in the software marketplace, the use of 2 or 3 different software products is certainly recommended, provided that suitable interfaces can be implemented. An important topic for the future is the integration of study software and hospital information systems.

Biometric planning and analysis at the KKS is performed in collaboration with independent biometrics departments or by the KKS' own experienced biometricians. Standard software (e.g. SAS) is used for this work.

7. Quality management/SOPs/Audits

The aim of quality management is to ensure that the laws, regulations and standards governing the conduct of clinical trials are fulfilled. Clinical trials on pharmaceutical preparations must be conducted in accordance with valid legislation and GCP (18). Until the passing of the 12th Amendment of the AMG, this principally applied only to trials that would be used to support market authorisation, and now it applies to all trials with pharmaceutical preparations. In addition to this, there are legal and regulatory requirements governing trials on medicinal products. To improve quality, these requirements – and in particular GCP – now have to be applied to trials conducted for scientific research purposes (investigator- initiated trials). The implementation of a QM system is principally intended to improve the quality and efficiency of multicentre clinical trials. The basis for a QM system are standard operating procedures (SOPs). The objective of the Quality Assurance Working Group of the KKS-AG is to develop QM SOPs for the KKS and support their implementation, in order to achieve harmonisation of procedures across all KKS sites. Each KKS should have a quality manager. This person is responsible for the implementation of the Working Group results, supervises the local SOPs, working procedures/instructions und technical procedures, conducts internal training events and generally manages all quality assurance measures taken within the KKS. 16 harmonised SOPs have now been developed by the Working Group responsible at the KKS-AG, of which 12 were in force in September 2004. All KKS units use the same wording from the harmonised SOPs, but may add KKS-specific local processes. At present, teams are working on the adaptation of the harmonised SOPs to the requirements of the 12th Amendment of the AMG, the development of alternative QM procedures for investigator-initiated trials, and the development of a procedure for internal and external system audits.

So-called external system audits were conducted in the KKS, commissioned by the BMBF, in which the organisation structures and the activities of the KKS were reviewed and evaluated. The basis for the evaluation was the fulfilment of the requirements for the conduct of clinical trials in accordance with GCP and valid legislation. The audits certified that the KKS conform with GCP in their work. In addition to system audits, successful study audits have also been conducted at some KKS.

Separate QM systems have been implemented and SOPs produced as part of the different research programmes of the BMBF (e.g. Telematic Platform, NGRN, Medical Competence Networks). In individual cases, for example for joint projects between KKS and Medical Competence Networks, the harmonised SOPs of the KKS have already been able to be used.

Pharmaceutical companies and CROs have also, of course, developed quality assurance and quality control systems. A good example is the system set up by the BVMA. Members of the BVMA certify that they will comply with jointly issued standards of quality assurance, membership is contingent upon successful completion of a system audit, and this has to be repeated every 3 years.

Despite impressive efforts on the part of the KKS to implement QM and harmonise procedures, the pharmaceutical industry is still of the opinion that the quality of the work done by the KKS has yet to be demonstrated. Greater efforts and, above all, more transparency are needed here. The different QM systems and SOPs can hamper collaboration between the pharmaceutical industry, CROs and KKS in individual cases. Because of different levels of financing and structures, academic trials are often run with considerably different degrees of QM. More should be invested here to ensure that academic clinical trials are conducted using standardised and harmonised SOPs.

8. Communication and partnership

Institutionalised collaboration between KKS and scientific associations is sensible to strengthen clinical research activities. At present, this only takes place in individual cases, not least because only few scientific associations (e.g. The Clinical Trials Commission of the German Diabetes Society (*Kommission Klinische Studien der Deutschen Diabetes Gesellschaft*), Oncological Study Institute of the German Cancer Society/German Cancer Aid (Studienhaus Onkologie der Deutschen Krebsgesellschaft/Deutschen Krebshilfe)) have appropriate structures that can act as central contact points for the KKS. However, when conducting individual trials, the KKS often collaborate with principal investigators and study groups, who often have close links with professional societies. For paediatric trials, for example, and by the German Surgical Association, study structures and centres have been established, partly funded by the BMBF, who will be working closely together with KKS. Experience will show which model (e.g. own study centre of the professional

association, cooperation of the professional society with external organisations, several KKS units, or the KKS-AG) and which conditions best serve the desired aim, and are most efficient and successful. In setting up these models, not least from the point of view of funding, collaboration with the pharmaceutical industry and medical devices industry should be included.

One of the primary objectives of the KKS-AG when it was formed in 2000 was to improve communication with sponsors, the public, and patient organisations. The aim was to achieve this by an agreed procedure with the naming of principal contacts and by setting up a special 'Public Relations' working group. This task will now be supported by the newly formed Business Office of the KKS-AG and will be taken over in future by the consortium being formed at present. Their aim is to inform 'customers' about an agreed range of services. Further activities are representation and lobbying, public relations and publications, collaboration with national and international scientific groups and support for the establishing of a register for clinical trials.

This has now fulfilled the requirement from the private sector for a central contact person. The KKS have also been shown to comply with quality standards in external audits, as has already been described. The KKS are in regular contact with the pharmaceutical industry and CROs, although so far actual collaboration on large study projects has only been established in a few cases. The acceptance by industry of the services offered by the KKS has to be improved. At different sites, different models for collaboration between pharmaceutical industry, CROs and KKS are being developed or tested. This collaboration has to be intensified in the future.

Communication with patient organisations (e.g. self-help groups) is in its early stages at present. Activities so far have been involvement in events for patients and the general public, and the production of information materials (e.g. patient brochures). Collaboration with patient organisation should be very much intensified, to increase patient awareness of clinical trials. This could improve the image of clinical trials and have a positive influence on recruitment.

9. Study register

The EU Guideline 2001/20/EG and therefore also the 12th Amendment of the AMG require that trials on pharmaceutical preparations are registered in the EudraCT Database (9,12). This database is, however, not publicly accessible. Germany has no laws regulating public access to study information. For individual disorders or medical specialist areas, registers of trials running have already been set up, including the register run by the German Cancer Society and the German Register for Somatic Gene Transfer Trials (*Deutsches Register für somatische Gentransfer-Studien*). Some KKS and universities have started registers at their local site in collaboration with local ethics committees. Some

study groups or particular research group structures also have smaller registers. Other researchers also use the metaregister of Current Controlled Trials to register randomised clinical trials.

The usefulness of and necessity for a study register in Germany with international links is not controversial (21). Numerous organisations have demanded the implementation of such a register for ethical reasons (e.g. the Health Research Advisory Council of the BMBF). In 2000, a round-table discussion attended by the parties concerned and sponsored by the DFG was held on this subject. A KKS-AG project group has developed concepts for the implementation of such a register, but these have so far not been able to be realised because of lack of support. In 2004, the KKS-AG, the German Cochrane Centre and the Working Group of Scientific and Medical Professional Associations (*Arbeitsgemeinschaft Wissenschaftlich Medizinischer Fachgesellschaften*; AWMF) launched a national initiative to speed up the process of study registration. A paper appealing for the implementation of a study register was written and will shortly be published. The national initiative is supported by numerous groups, amongst others by the Working Group on Medical Ethics Committees (*Arbeitskreis Medizinischer Ethikkommissionen*), the AWMF, the Medical Competence Centres, the Conference of Medical Faculties (*Medizinischer Fakultätentag*), the Health Research Advisory Council, the Central Commission for the Preservation of Ethical Principles in Medicine and Related Fields (*Zentrale Kommission zur Wahrung ethischer Grundsätze in der Medizin und ihren Grenzgebieten*), the Social Service Organisation VdK Germany (*Sozialverband VdK Deutschland e.V.*), the Federal Association of Consumers' Associations (*Verbraucherzentrale Bundesverband e.V.*) and the Institute for Humans, Ethics and Science gGmbH (*Institut Mensch, Ethik und Wissenschaft gGmbH*). The pharmaceutical industry also supports the setting up of a study register, but favours a solution based on EudraCT and a publication of study summaries in Europharm. A working group has been formed, to formulate the requirements for such a register, and to develop a concept for implementation. The BMBF has stated that it would be prepared to support the implementation of the register with the payment of a launch grant.

Any planned German register must be harmonised with international developments and incorporated into a common, internationally accepted study register. Entering data twice should be avoided. So far, the metaregister of Current Controlled Trials was the dominant international resource. The National Institutes of Health Register (www.ClinicalTrials.gov) in the USA is now open to non-US trials. The editors of renowned medical journals and the Cochrane Community (Ottawa Statement, 2004) are demanding a central study register with free, public access (22). In its Mexico Statement, the WHO said that registration was necessary and declared that it would be prepared to assist in setting up a network for an international study register with one entry portal and unique identification of trials (23). These are all points which must be discussed when setting up such a register. The investment required for such a register would be considerable. If it is to be useful, the German register

would have to be a valuable source of information for all partners involved in clinical research, including doctors, patients, healthcare researchers, industry and politicians. The register should therefore be bilingual and contain patient information.

10. Education and training

Pursuant to the 12th Amendment of the AMG, ethics committees, when assessing a planned study, have to consider the suitability of the investigator, the study team and the study facility. This is described in more detail in the GCP regulations. In accordance with this therefore, the ethics committee must be supplied with suitable proof of the qualifications of the investigator and information on the suitability of the study facility, in particular the suitability of the premises and equipment, and of the qualifications of the team that will be conducting the study, and also information on previous experience with conducting clinical trials. There are no further requirements. No further details of what constitutes suitable proof of qualifications are given. In practice, this is most likely to be fulfilled by submitting curricula vitae and training certificates.

There are generally no institutionalised further education programmes in the area of clinical trials. Different institutions offer those concerned a wide range of different courses and training events. The KKS-AG has therefore concentrated especially on the area of investigators and study nurses, and has developed and offers standard courses (1). The study nurse course consists of 120 hours of theory and two weeks of practical work in a study facility. The study nurse course is now offered at several different KKS sites, who all offer certificates. Between 1999 and 2003, 803 participants took part in 30 courses. The investigator course has 16 hours of theory and has been established at several KKS sites. Between 1999 and 2003, 782 investigators took part in 30 courses. The KKS offer further courses on study management, monitoring and study coordination.

Study nurse courses are also offered by other institutions, including the Working Group on Study Nurses (*Arbeitskreis Study Nurse*) of the Working Party for Applied Human Pharmacology (*Arbeitsgemeinschaft für Angewandte Humanpharmakologie e.V.*), SKM Clinical Research Europe, Pharma Academy GmbH und the Parexel Academy. Investigator courses are offered by the German Society for Pharmaceutical Medicine (*Deutsche Gesellschaft für Pharmazeutische Medizin e.V.*) Also available are a wide range of training courses, workshops, seminars, training events and courses offered by a range of different suppliers, such as the Colloquium Pharmaceuticum of the BPI. The University of Witten/Herdecke offers a 'Master of Science in Pharmaceutical Medicine' for physicians and scientists who wish to work in the pharmaceuticals sector. Heidelberg University offers a postgraduate course in medical biometrics, which is also to be upgraded to a masters degree. There are also plans to offer a similar masters degree in Bremen. In the area of medical documentation, in addition to the classic courses, such as medical

documentalist, new qualifications are emerging, such as 'specialist in media and information services, majoring in medical documentation'.

As far as the KKS-AG is concerned, the tasks for the future in this area are to make the course organisation more professional, to reach further agreement on courses to be offered, and to extend the KKS certificate to external courses. There are early deliberations about bringing all activities together to form a KKS-AG Study Academy. The pharmaceutical industry still sees considerable deficits in the possibilities for training clinical researchers and above all complains about the lack of institutionalised training programmes and inadequate freedom for physicians to become involved in clinical trials. At present, there are some – albeit few harmonised and institutionalised – courses for the training and further training of study staff (e.g. investigators and study nurses). The activities of the KKS-AG consisting of standard curricula and certification represent a first logical step, but must now be followed up by further efforts at harmonisation.

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