BMBF COMPETENCE NETWORKS

Midterm Report

and

Follow-up Proposal

of the Competence Network

Pediatric Oncology and Hematology

Contents

Section 1

Speaker's Midterm Report

Title Page

Network title	:	Competence Network Pediatric Oncology and Hematology
Period covered by this report	:	01.07.1999–31.03.2002

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Part A – Research Results

1 **Publications**

a) How many network-related English papers have been published in reviewed journals during the funding period or are momentarily in press?

8 6

b) How many of the publications listed in a) involved at least three network partners from different universities or non-university research institutions?

2 4

c) How many of the publications listed in b) have an international partner?

2 1

Attach full citation in the annex and mark those referring to questions b) and c).

2 **Patents**

a) Are patents planned or applied for within your network?

☐ no, not intended

☒ yes,

0 number of patents in preparation

3 number of patents applied for

0 number of accepted patents

b) How many of the patents listed in a) involved at least three network partners from different universities or non-university research institutions?

0

Attach a full list of all patents applied for or accepted in the annex.

3 **Describe the scientific highlights of the network so far**.

During the first funding period, the scientific highlights of this competence network were the following:

Organizational

- The inauguration of a comprehensive system for the networking of pre-existing and newly created research and health care structures.
- The introduction, training, and efficacy assessment of assistants for clinical research and quality control (Forschungs- und Studienassistenten) in the 27 largest Pediatric Oncology institutions throughout Germany (cf. project A)
- The first-time nation-wide employment of a common patient identification code („PID") available for trial participating institutions over a legally secure public internet system for data exchange in clinical trials (cf. B/2)
- The deployment of a common computer application for therapy and documentation (including the nation-wide harmonized coding of diagnoses and procedures according to international and national classifications, cf. B/1 and A)
- The development of a common tumor tissue bank (commencing with embryonal tumors, extending to other entities, cf. G)
- The commencement of the measurement of the health-related quality of life in two frequent malignancies (cf. I), including a newly built-up network of psychosocial and medical care providers
- The nation-wide registration of second malignancies and the start of associated epidemiological studies (cf. K)
- The establishment of prolific co-operations on MRD (studies on the minimal residual disease, cf. F) and the consolidation of Germany's leading position in this field
- The establishment of co-operations on apoptosis and drug resistance, including the development of novel methods (cf. D)
- The start of a internet presentation of the network and the scientific society (GPOH) with their respective personal and institutional members, aiming at public visibility and making internal co-working easier (cf. B/2 and A)
- The initiation of a registry of studies employing immuno- and gene therapy in Pediatric Oncology in Germany (cf. H)

Specific, single project related

- Newly identified molecular changes and prognostic factors (cf. project G): A characteristic gene expression profile in embryonal tumors (ref. G/26), A new, two entity genetic concept in medulloblastomas (refs. G/6, G/8), c-myc as a prognostic marker in medulloblastoma (ref. G/7), telomerase as an important prognostic marker in neuroblastoma (ref. G/13), Gam 1q as an important prognostic marker in Wilm's tumors (ref. G/28).
- The development of a new flow cytometry method for detection of mitochondrial cytochrome c release, a major apoptosis signaling molecule (patents applied for) and the revelation that chemotherapy in vivo predominantly induces apoptosis in an immature sub-population of leukemia cells identified by the progenitor marker CD34 (cf. D)

Part B – Network Organization and Management

4

a) Which instruments were implemented to assure the quality and efficiency of the collaboration within the network?

- ☒ assessment of the progress of projects
- ☒ joint measures for scientific/methodological quality assurance
- ☒ joint measures for quality assurance of medical care
- ☒ mechanisms for the management of conflicts between network members
- ☒ mechanisms for the controlling of finances
- ☒ questionings concerning satisfaction of network members and external clients with the network
- ☐ mechanisms for the acceptance of new projects within the network
- ☐ mechanisms for the dismissal of unsuccessful projects
- ☐ other instruments, please list ----------

b) List eventually newly accepted projects and/or dismissed projects

Accepted:

TOPP – Telemedizin in der onkologischen pädiatrischen Palliativmedizin, by Dr. B. Zernikow,University's Children Hospital, Münster (cf. section 4, project T)

Project G – Application „Collection of malignant germ cell tumor tissue samples, an extension to the tumor bank for neuroblastomas and rare tumors," by Prof. Göbel, Dr. Schneider, University Children's Hospital, Düsseldorf (cf. section 3, project G)

c) Describe each of the instruments and mechanisms used in your network so far, report the results achieved and problems with the handling of the instruments. Describe the proposed activities for the second funding period.

Assessment of the progress of projects

A structured form for the cumulative documentation of a project's progress and changes has been developed in early 2000 and since has been gradually adopted by the project leaders. The competence network has entirely been modeled with MS Project software in late 2000, including changes in the projects' status. However, these instruments have not yet been used at all times. During status meetings and using questionnaires, several projects have repeatedly assessed their status as reported in the corresponding sections of this midterm report.

The project leaders have reported the progress to the „Erweiterte Leitgruppe", and adjustments were discussed, if necessary, in order to achieve the projected aims or to focus on specific aspects that turned out to be particularly important. Decisions were made mostly unanimously or by the majority of votes within the „Erweiterte Leitgruppe" or within the group of project leaders.

Joint measures for scientific/methodological quality assurance

Various pre-existing measures for quality assurance were refined or newly defined related to the specific needs of the project:

The „basic data set" is the one common basis of all clinical trials and most research projects. It is used for storing and exchanging data related to patients, diseases, and treatments. Although its inauguration precedes this competence network, a major revision of the basic data set (version 2.0) has recently been achieved by network personnel and by the society's experts. Both constitute a so-called „Joint Standardization Group" which will continuously adapt the basic data set to future needs. Before the network's support, only minor revisions were done discontinuously and were not made publicly available.

Projects D (Drug resistance), F (MRD) and H (Gene- and immunotherapy) have each succeeded with regard to inter-group methodological quality assurance (e.g., quantitative PCR, flow cytometry, apoptosis assays), as reported in their corresponding sections of this midterm report.

The annual workshops of the scientific collaborators from various clinical trial offices were concerned with the standardization of electronic data bases, of procedures for survival analysis, of inter-trial harmonization, and with the adoption of the GCP guidelines, where applicable. It was decided that all newly planned clinical trials should be in agreement with GCP rules.

The newly founded tumor tissue bank constitutes a joint instrument for quality assurance, of both patient samples processing and of transparent usage for scientific research (ref. section 3 of project G). The latter is most important because the procedures agreed upon („Statutes", ref. annex) preclude that the precious patients' samples are exclusively exploited by individuals. Instead, the tumor bank's operators re-distribute samples to scientifically approved projects.

…

The quality assurance of medial procedures and of laboratory techniques has been promoted as the main topic during special workshops, which were conducted either by the network or collaboratively by the network and the scientific society (GPOH).

A special education program for the network's assistants in clinical research and quality control (Forschungs- und Studienassistenten, FSA) has been devised and successfully put into practice. This includes common training meetings, training on site, standardized site visits, and performance tests on and off site. A special program for the certification of the FSA is presently under development.

The network tried to rapidly and liberally communicate results and various pieces of information including own surveys, reviews of external information sources, protocols of our meetings, and own presentations and speeches. For this purpose, mainly our internet web pages and circular letters were used.

Joint measures for quality assurance of medical care

For the quality assurance of medical care, clinical trials are of utmost importance. 23 such trials are conducted in German Pediatric Oncology (ref. to annex for a complete list and details). In contrast to other countries, inclusion rates are extraordinarily high (estimate, 95%). In addition, the proportion of regular study subjects (as compared with surveillance subjects) among included patients is high (average, 92%) because of rather strict adherence to the prescribed diagnostics and treatment and because of the control and interventions exercised by trial office staff. By means of close contact between trial offices and participating trial centers, patients are followed closely and medical problems or errors can be detected and tackled. It can be incurred from external sources (ref. annex) that Pediatric Oncology trials reduce early mortality, morbidity, and overall costs and that they increase survival rates and health-related quality of life.

It is of note that no single clinical trial or trial office has been supported directly with network resources, based on reviewers' recommendation for the first funding period. The extent to which the clinical trials improve medical care in German Pediatric Oncology can hardly quantified because the trials already constitute a dispersed, but comprehensive quality assurance structure that has been developed over the past 30 years and ist working successfully.

However, the network is supporting trial offices by a central service group which is called the „study support" (ref. section 3, project A). The aims of this group include reducing redundant work load in trial offices, standardizing workflow, and harmonizing trial details.

Parallel to and in context and ccoperation with network activities, European education guidelines for physicians in Pediatric Oncology and Hematology were coauthored and have been put into practice in Germany since 2001. The recognition of this education program („Arzt/Ärztin für Kinder- und Jugendmedizin, Schwerpunkt Pädiatrische Onkologie und Hämatologie") by the German Medical Council („Bundesärztekammer") has been assented but will be formally completed not before 2003.

Medical guidelines are to be described according to a question below (part E).

…

Recommendations and guidelines for daily care

Specific recommendations for daily care have been set up and have been made available with the help of the network. These are intended to be used during routine daily care by physicians working in this field of medicine. Presently, they entail guidelines for the supportive care, for the emergency treatment of cytostatic drug paravasation, vaccination recommendations, and other topics which are continuously worked-up or completed.

Follow-up guidelines are largely the results of the network's project I (Late effects and quality of life). These are published as easily usable single-page sheets intended for both scheduling and documenting individual patient information.

Mechanisms for the management of conflicts between network members

Conflicts have been openly discussed with the project leaders and/or within the „Erweiterte Leitgruppe". In general, agreement could be achieved. If a broader basis was necessary to achieve specific goals, a task force was instituted (e.g., project B/1). In part, conflicting issues discussed between members of the „Erweiterte Leitgruppe" and external experts. So far, there was no need to install persistent mechanisms for conflict resolution.

Mechanisms for the controlling of finances

Financial responsibility rests with the various autonomous project leaders of this network, who in turn mostly rely on their respective institutions' administrative and financial controlling. In order to render resources and results more transparent among network members, some information on job costs and other costs were obtained as part of the project progress documentation (see above). Although such information was incomplete, almost all changes of projects' plans and resources were communicated to the coordination and management group.

As project A comprises about one half of the entire network's funding, its finances were controlled by about monthly reviewing balances. Vacant positions were actively sought to be occupied. Usage of travel resources was restricted by initially agreed upon network rules. Resources for new sub-projects (e.g., public relation activities, evaluation proceedings) were covered by resource re-allocation in accordance with DLR/PT. Project A's expenditures in 2000 were sampled, checked, and identified correct by a consulting agency (Ernst & Young) on behalf of the Charité Innenrevision (the voluminous report is available from Ms Schensick, Charité, phone +49 (0) 30 – 45 05 – 57 20 21 on request.)

Questionings concerning satisfaction of network members and external clients with the network

Comprehensive questionings were developed and carried out by the coordination and management group together with two commercial partners of project A, WIAD (Wissenschaftliches Institut der Ärzte Deutschland e.V., Scientific institute of the German physicians) and Prognos AG (a consulting agency). These partners and the external evaluation measures were newly introduced by the end of 2001, when funding according to a scientific grant application was obtained from the DLR/PT.

The questionings covered amongst other topics the satisfaction with changes and problems perceived, and the details of local, structural, and procedural characteris-

tics of the collaboration within German Pediatric Oncology. These questionings were carried out at base-line in December, 1999, and for comparison in an extended fashion in January, 2002. Independently from network member status, leaders of the 54 largest Pediatric Oncology institutions, 35 Pediatric Oncology trial offices or reference laboratories, and 65 assistants (FSA or documentation staff) were questioned with 4 to 6 page questionnaires.

In a nutshell, preliminary results of the latest questioning (2002) on the status of networking within Pediatric Oncology since the competence networks's start were

(a) 55% of central institutions experienced a substantial improvement of data and documentation quality; 89% noticed the largest effect on the completeness of data; 70% reported to be well informed about the competence network; 80% expect further improvements to be delivered;
(b) 70% of 32 participating hospitals feel comprehensively informed on network activities; 25% report improvements on information exchange and general communication with regard to clinical trials; but workload reduction by the assistants for clinical research and quality control (FSA) is only moderate;
(c) on the other hand, 90% of the FSA report to greatly unburden other staff members; 70% are more than weekly communicating with trial offices (also please refer to project A for more details.).

Mechanisms for the acceptance of new projects within the network

Putative new projects were identified by network members and asked to hand in a project draft, including motives for joining the network. During the first funding period, no new project was accepted, but two new projects were identified, one of which is proposed for funding during the second funding period (ref. section 4 of this midterm report).

Mechanisms for the dismissal of unsuccessful projects

Mechanisms for the dismissal of unsuccessful or non-compliant projects were agreed upon in the network's by-laws. The „Erweiterte Leitgruppe" (advisory board, project leaders, experts from the medical society) and the „Task force" (see above) decided on project B/1 to be endangered for discontinuation of funding if specified criteria were not to be met in 2002.

Proposed activities for the second funding period

In order to maintain and extend both quality and efficiency of the network, the following measures are proposed:

To strengthen the activities to extend the process of networking, i.e., improve exchange of data between hospitals, research laboratories, reference laboratories, registries and trial offices by using the tools and structures created during the first funding period:
the assistants in clinical research and quality control (FSA), „Study support" group, PID, DOSPO, internet information services, the revised „basic data set" etc.

All relevant information should be made available not only to already existing network partners, but also to medical laymen, private practitioners, parents and patients in suitable form (vertical networking).

Part B – Network Organization and Management

5 **a) Which organizational support and services for network partners are provided by the network[1]?**

- [x] organization of scientific and network meetings
- [x] providing information about the state of the projects for the network partners
- [x] brokerage of general information
- [x] providing information about the availability of devices and materials among the partner institutions
- [ ] arrangement of joint purchases of devices, licenses etc.
- [x] set up, maintenance of, and user support for material banks
- [x] set up, maintenance of, and user support for data banks
- [x] set up, maintenance of, and user support for information and knowledge services
- [x] providing advice on the requirements concerning:
  - [x] ethics
  - [x] biometry
  - [x] human genome and gene technology
  - [ ] clinical pharmacology
  - [ ] patents
  - [ ] funding and legal requirements
  - [ ] others
- [x] set up and maintenance of reference centers
- [ ] co-ordination of clinical studies

[1] **By any of the network partners**

Part B – Network Organization and Management

☒ providing advice for media presentation

☒ other services and support, please list: PID service, DRG support

b) Describe each of the services which have been installed and which expert advice and support is provided in your network so far, and describe the proposed activities for the second funding period.

Organization of scientific and network meetings

The following regular meetings are organized with resources of the network (content competence, preparation, support on site, travel expenses partly; protocols published on the internet sites):

- Semi-annual scientific meeting of network members (about sixty participants, main topics: discussion of interim results and further proceedings, inter-project transparency checks, inspection of project leaders' steering mechanisms and results)
- Annual status meeting of the GPOH (so-called „Strukturtagung", about seventy participants, main topics: agreements on long-term aims, perspectives and measures to take with regard to clinical trials, lectures on generally important issues such as legal requirements, ethics, funding, and trial reporting)
- Project meetings (multiple, five to 35 participants, at least annually; main topics: working group sessions, agreements on standardized procedures, involving external project partners, training on the project)
- Meetings of all medical documentarists in Pediatric Oncology and Hematology were initiated as a consequence of the interest in the very close guidance of the assistants in clinical research and quality control (FSA)
- Annual meetings of clinical trial offices' staff (about thirty participants, main topics: common data problems; exchange of solutions; promotion of GCP-adoption; harmonization of documentation; procedures, recalls)

Brokerage of general information,
Providing information about the state of the projects for the network partners

Information can be obtained by regular meetings (as described above), by conventional circular letters, by email distribution lists and by searching or browsing th internet sites (as described below, part B, question 6 b in section 1).

Set up, maintenance of, and user support for data banks

- An internet data bank for electronic slide exchange has been built up and fed since 2000 (project A). Until now, four clinical trials' offices have contributed more than 80 slides (MS PowerPoint format) with recent general and special information. These key reference slides shall be used for medical education such as lectures.

- A generic data bank for the administration of laboratory samples has been developed in the year 2000 (project A). Since, it is being continuously used in Hannover, Münster and Freiburg laboratories (projects E and F). The data bank is freely available to network members.
- A special data bank for the administration of laboratory samples has been set up for the use with the embryonal tumors' bank. It has been developed in cooperation with a commercial IT-firm (cf. project G). Accordingly, the data bank is freely available to network members (Oracle license required).

Set up, maintenance of, and user support for material banks

Setting up a new material bank was part of project G's strategic concept to foster research. The expected delivery of patients' samples was repeatedly compared with their actual numbers. In order to improve the input, the cooperation with hospitals and especially with pathologists was intensified on a broad basis.

A new material bank is being built up for leukemic cells in collaboration with trials on ALL, AML, relapsed ALL and project F.

A special data bank has been set up and is maintained to support the ALL immunophenotyping reference laboratory since the year 2000.

Providing information about the availability of devices and materials among the partner institutions

Information on the availability of materials, devices or drugswere communicated via the described services (question B.6).

Set up, maintenance of, and user support for information and knowledge services

Knowledge services are being built up. The design of content structure and layout has been completed for the incorporation into our new internet information portal on children's cancer (www.kinderkrebsinfo.de).

Providing advice on the requirements concerning biometry

Biometry counseling has been offered cautiously to planned and running clinical trials (project A).

Providing advice on the requirements concerning human genome and gene technology

Comprehensive information on general requirements, legal issues and administrative procedures for obtaining a production license in Germany has been compiled by project H as a result of its experience with the official bodies. Project H freely supplies this compilation and offers consulting services to researchers in this field.

Set up and maintenance of reference centers

A system of laboratory reference centers has been set up for investigating suspected myeolodysplastic syndromes (project E) and for investigating minimal residual disease (project F). Both laboratories receive several hundred samples per year. Most patients are examined repeatedly to assess the time course of changes. From the number of samples and of cooperating hospitals, these reference laboratories are well established and process literally every patient's samples. …

Maintenance of laboratory reference centers was realized by supporting them as part of research-related cooperations. Modest fiancial and personnel support should facilitate the establishment of networking structures. Support was given the immunophenotyping laboratory (project A), the cytogenetic laboratory and the molecular genetic laboratory (project F)

Co-ordination of clinical studies

To improve and to unburden clinical trial offices („clinical studies") are the two prime goals of a special working group of project A („Studienunterstützung"). However, the clinical trial offices are autonomous and liable to the respective funding organization only. Thus, the harmonization of clinical studies, that is, the propagation of the best legal, ethical, medical, and administrative practice of how to perform studies, is expected to change clinical studies in the long run only. Still, this central „Study support" group promotes the use of the basic data set (cf. annex), of the revised common toxicity criteria, of GCP adoption, usage of the „Masterprotokoll" (Deutsche Krebsgesellschaft) and of stringent data management practices in every clinical study.

The assistants in clinical research and quality control (FSA) coordinate clinical studies at their respective place of action/hospital. As stated in the initial agreement on the services the FSA have to perfom, they are „members of the hospital's multi disciplinary scientific team". The FSA's prime tasks are to prepare realizing, to locally coordinate and to practically carry out clinical trials in participating hospitals. (Approved clinical trials encompass exclusively the multi center cooperative GPOH trials, which have elsewhere been scientifically reviewed, funded and ethically approved.) FSA are bound to support the physician who is responsible for the respective trial („Prüfarzt") by scheduling examinations, by collecting and distributing patients' samples and by documenting the relevant data.

Providing advice for media presentation

Templates for media presentation have on a few occasions been prepared and have been used by project leaders e.g. for status lectures and posters. The press conference has been prepared by advising the participants on how to prepare the topics and speeches. A preceding audition was organized which turned out to be very helpful: redundant slides were omitted, speech duration was controlled and communicating with the journalists was anticipated.

Other services installed

With the help of the competence network, the following services were initiated and are working in practice:

- An electronic, unique patient identification service is accessible via the internet to provide a pseudonymous 8 digit number for the reliable identification of various patient data (e.g. blood and tumor samples, paper sheets, etc. „PID-Dienst", project B/2).
- An electronic certificate service provides file based certificates to individuals for use in their internet browsers with which access-limited information can then be obtained (project B/2). Likewise, certificates for secure email communication are obtainable („PGP", projects A and B/2). The use of these certificates is well accepted by the scientific community.

- A working group on the classification of diagnoses and procedures in Pediatric Oncology and Hematology has been founded together with the GPOH. This group published in 2001 a booklet with recommendations for the classification according to the ICD 10 and OPS301, which are very important to the forthcoming diagnosis related groups system of health care financing. In addition, this group stated current and anticipated problems of Pediatric Oncology to legal bodies such as the Deutsche Krebsgesellschaft and the Deutsche Krankenhausgesellschaft.

Activities for the second funding period: services, expert advice and support for network organization and management

The aims of the activities are to further strengthen the networking of experts, working groups, trial offices and hospitals and to manage the cooperation of the network members accordingly.

For this purpose, activities started during the first funding period will be continued. The contributions of the FSA to the performance of clinical trials have to be continued. For the second funding period, the education has to achieve a formal completion by certification and possibly a legal recognition (project A). The supported reference laboratories have to tailor investigations and to continue with standardizing the respective methods (projects E and F).

The internet knowledge services that have been prepared in concept are to be put into pratice (information portal on children's cancer). The use of the PID and certificate services has to be promoted to include all reference laboratories and clinical trial offices. Corresponding data security policies have to be implemented and put into practice.

Part B – Network Organization and Management

6 **a) Which IT-techniques are used for networking?**

- ☒ network web-site
- ☒ information server
- ☒ network mailing-address
- ☒ IT-support for clinical studies (remote data entry or other)
- ☐ electronic access to databanks
  - ☐ patient databanks
  - ☐ gene databanks
  - ☐ other databanks, please list_____
- ☒ other IT-techniques

b) Describe each of the strategies used for networking so far and problems with the handling of the techniques. Describe the proposed activities for the second funding period.

The strategies used for networking are intended to enhance communication between network members, personally meeting partners, creating corporate attitudes towards the promotion of general network aims, increasing the specialization and clustering of scientific competence as well as pushing for delegation of subtasks and partition of responsibilities with junior scientists.

These strategies are intended to bring about trusting, demand-oriented co-working and to reduce possible limitations. Technically, we use for networking

- conventional circular letters,
- email distribution lists for various network and GPOH groups. A discussion list for interested individuals (forum@gpoh.de) is moderated but not restricted to formal involvement with the network or society,
- several linked, searchable, and browsable internet sites.

Among the IT techniques, email correspondence has shown to be suitable to the aims mentioned and it has extensively been used by this network. On the basis of the network's recommendations and offerings on the use of PGP, it is also possible to use emails for trustful and personal communication.

Networking was also supported to a significant extent by employing internet web sites. The top most site (www.kompetenznetz-paed-onkologie.de) includes general descriptions of every project. Individual projects' internet sites can then be reached by following hyperlinks. Several cross-links exist from and to the GPOH internet site (www.gpoh.de).

However, these linked, but dispersed internet sites resulted in unexpected problems. Many users complained of difficulties navigating and finding information. Different authentication procedures were confusing. Most important, a number of requests received were directed to the GPOH clinical trials. Users requested to get an in-depth insight into these 23 trials, which should entail ways to review the trial protocol and recent results onlline. Only very few requests addressed patient information, which until now has not been covered by the network.

These problems may have arisen from the initiation of a comprehensive internet presentation only after the network has started. However, plans for IT networking support will be part of the proposed activities for the second funding period, including professionally producing and presenting scientist's and layman's information.

IT-support for clinical studies (remote data entry or other), patient databanks

The mainstay of this network's IT-support for clinical studies is DOSPO, the electronic documentation system for Pediatric Oncology. It is technically and financially supported comprehensively by project B/1, with logistic support by project A. Politically, it is recently supported by the DOSPO task force, and the „Erweiterte Leitgruppe". DOSPO is a multiple user data bank with forms corresponding to the usual documentation procedures in Pediatric Oncology. The program is vastly advantageous over paper documentation because it features comprehensive chemotherapy planning, diagnosis and procedures coding, toxicity documentation, statistical analysis and data exchange.

Thus, DOSPO constitutes IT-support for performing clinical studies in participating hospitals. However, compatibility problems and requirements for intranet data exchange are not yet met, but improvements are perceivable recently.

Electronic access to databanks

Eletronic access to data banks has not been requested by network members and thus is not provided by this network, partly because most members have access to restricted facilities through their respective university network, e.g. to the Cochrane library or special information retrieval services.

Other IT-techniques

Some of the network's research projects employ special IT-techniques for research. Neuronal networks (project G) and gene analysis (project H) were developed in conjunction with local experts in such data analysis.

The purpose of the unique patient identification service (PID, project B/2) is to support networking by labeling patients' samples and written or electronic data with a PID code that is suitable for matching records, but prohibits exposing any personal data. This technique supports both clinical trial offices, reference laboratories, and hospitals.

Proposed activities for the second funding period

The started activities will be persued during the second funding period and the developed techniques are to be used in continuation.

The network's internet sites will be completely revised. The GPOH internet site will be included into our restructuring of German internet information on Pediatric Oncology and Hematology. The internet information portal (www.kinderkrebsinfo.de) will present patient, nonprofessionals and expert information that is specially written by dedicated network scientists. This information shall complement the excellent „patient-to-patient" (or healthcare provider-independent) information published in the internet by the self-help organizations. Thus, the planned knowledge or information server will be realized. We also plan to achieve formal recognition of the quality of our internet contents and the coordination and management group will apply for the admission to the German afgis (Aktionsforum Gesundheitsinformationssystem of the BMBF).

The DOSPO system will be used in an increasing number of hospitals and compatibility problems will be tackled. With regard to telemedicine networking, a switch in focus towards a central medical image storage will be evaluated together with web based data capture methods for the purpose of supporting the exchange of image and clinical data within the clinical trials.

Part C – Added Value through Networking

7 **Cooperation within the network**

Design a matrix of the network projects indicating all research groups actively involved in each individual research project. Include associated projects, which are funded through other funding organizations (DFG, EU, BMG, foundations, industry) and mark the respective funding organization in footnotes.

For the matrix, please refer to this Midterm Report's Annex, page 20.

8 **Cooperation with other networks**

a) In which of the following network-overlapping joint activities is the network collaborating?

☒ Telematics Platform

☐ Brain-Net

☒ Public Relations Team

☒ other fields of cooperation
please point out the field and the cooperating network(s):

Cooperations were initiated with the competence networks „Acute and Chronic Leukemias" (an epidemiological investigation together with project A; project E, relapses post stem cell transplantation), and „Rare Diseases" (projects A, D, E)

Exchange with the competence network „Malignant Lymphomas" has been sought and taken up by collaborators of project A (research assistants for clinical trials; electronic chemotherapy systems).

b) Describe the contributions of your network to the joint measures so far, point out the initiatives of your network to the joint activities and the added value your network experienced from (which of) the joint activities, and describe the proposed activities for the second funding period.

Our contributions

The contributions of our network to joint measures and activities were:

- Three out of four existing working groups of the Telematics Platform and their projects were actively shaped by participants from our network (see below). Several meetings were hosted, including the first network-overlapping TMF workshop (03/2002).

Working group „Data protection and IT security“ (TMF): Concepts of project B/2 were offered, were then cooperatively extended and are now under realization, including chip card use and interfacing with a public key infrastructure.

Working group „IT Quality Management“ (TMF): Existing and evolving requirements for IT solutions were proposed and defined, resulting in a grant application (see below).

Working group „Urheber- und Verwertungsrecht” (TMF): Items and services suitable for commercialization were identified; examples out of this network served as model problems. In this context, project G developed a model contract for commisioning data bank development with mutual utilization. Moreover, the working group carried out model consultation talks about results transfer during a work shop of this network's project leaders.

- Working group „Public relations” (DLR/PT): Active-creative participation, delivery of presentation material for the use of others, representation of the network during public occasions.
- Active collaboration on the development of the „Midterm Report” as a tool for the structured reporting and the overlapping evaluation of medical competence networks.
- Relaying cases of disapproval of health care insurance payments for the treatment of children and young adults with cancer to the competence networks' speakers' speaker.

<u>Our initiatives</u>

- For the second funding period of the Telematics Plattform, three grant applications were intiated and submitted by our network, each in cooperation with at least three other networks:
  (1) “Data protection and IT security”,
  (2) “Public key infrastructure”,
  (3) “Telemedicine Infrastructure”.
- We conducted a workshop about the possibilities for „Long-term stabilization of networks” as part of the first symposium for competence networks (Darmstadt, 12/2001). In addition, our proposal (Prof. Friesdorf, co-investigator project A) was appreciated to transfer scientific and economic aims into a framework of a so-called „Eingetragene Genossenschaft” (cooperative society) and its subordinated firms, respectively.

<u>Experienced added value</u>

The competence networks have gained attention by the media through the coworking on public relations. In fact, the term „Kompetenznetze” seems to have turned into a hallmark that elicits interest into all competence networks.

The existence of the experts' Telematics Platform has enabled a productive cooperation of previously autonomous networks by funding overlapping projects which are already based on emerging demands and experiences from the first funding period of the respective network.

…

	Joint activities proposed for the second funding period The networking between the partnering competence networks will be continued and extended. The projects within the Telematics Platform will be energetically persued in order to evaluate their model solutions for our network. We will share tasks and responsibilities within the public relations team and take over the organization of coming events. Potential synergies have to be found out between the two networks' working groups on electronic systems for conducting clinical trials and tailoring chemotherapy (B/1 and „AG Telematik" of the competence network „Malignant Lymphomas").

Part C – Added Value through Networking

9

a) Are clinical multi-center studies performed in your network?

☐ No ☒ Yes

b) if yes, give the following numbers:

6	total number of multi-center studies
24	total number of network members involved
2	number of multi-center studies which have been newly initiated since the network exists
6	number of study groups which have started substantial cooperation through the network
3	number of new study groups which result from activities of the network

Give a list of all clinical multi-center studies performed in your network in the annex. Indicate:
– the number of network members involved in each study,
– the number of patients recruited in each study,
– percentage of recruited patients compared to the planned number.

Please, refer to this list in the annex, page 22.

c) Describe the activities and problems concerning clinical studies so far and describe the proposed activities for the second funding period.

Activities and problems concerning clinical studies and proposed activities for the second funding period

Virtually all multi-center clinical studies in Pediatric Oncology and Hematology are conducted under the auspices of the Society for Pediatric Oncology and Hematology (GPOH). The open 23 studies (cf. annex) cover not less than 90% of all the malignant diseases in childhood and young adulthood, including mistakenly termed „benign" brain tumors and Langerhans' cell histiocytosis. Indeed, more than 90% of patients receive diagnostic and therapeutic measures as proposed in these studies. Almost all current studies are based on preceding studies, the first of which were started in 1976.

…

These sequential studies have turned the clinical trials offices and the GPOH into one large virtual competence center. It is characterized by defined responsabilities, reporting and reviewing mechanisms, and intensive scientific exchange.

It is the most important obligation of this competence network to further increase cooperative networking and also to structurally stabilize this existing competence center. A prominent goal will thus be the creation of a continuous, sound financial support for the clinical studies, i.e. for diagnosis and treatment according to the state-of-the-art.

As shown, comprehensive multi-center studies („Therapieoptimierungsstudien") were not to be included in this competence network. However, the network's studies reported above [9 a), 9 b), annex] are accompanying add-on studies, which are accordingly multicentric („Begleitstudie"). Indeed, the studies listed are progressing from separate special funding to participating in regular clinical studies' funding such as granted by the Deutsche Krebshilfe, Deutsche Leukämieforschungshilfe or the Deutsche Krebsgesellschaft.

Moreover, succeeding multi-center studies will increasingly be international studies. The competence center still has to prepare for this situation. Trials and projects will have to take the internationalization process into account.

Part C – Added Value through Networking

10 **Are network projects performed together with international partners?**

☐ No ☒ Yes, number: 6

List those international network projects in the annex which involve at least three network partners from different universities or non-university research institutions, identify the international groups involved.

Please, refer to this list in the annex, page 23.

11 **Patient documentation**

Is the network using standardized patient documentation?

☐ No ☒ Yes

a) Has the network developed standardized procedures for patient documentation?

☐ No ☒ Yes: new development ☒ Yes: further development

b) Is the data processing IT-based?

☐ No, not intended ☒ Planned ☐ Yes, already in use

c) Are the data collected supra-regionally and centrally analyzed?

☐ No, not intended ☐ Planned ☒ Yes, already in use

d) Number of institutions documenting data

	actual number:	planned number:
university hospitals:	32	*
non-university hospitals:	40	*
private practices:	0	*

e) Total number of documented patients compared to overall-incidence and –prevalence (for specific diseases and regions):

nation-wide: 92–95% (Annual Report, German Childhood Cancer Registry)

f) Is it possible to describe changes in health care performance by the patient documentation system used in your network?

☒ no, not intended ☐ yes

Part C – Added Value through Networking

g) Describe the activities and problems concerning standardized patient documentation so far. Describe the proposed activities for the second funding period.

Most of patient documentation is performed by means of paper copies produced from respective clinical trial protocol sheets. The initial report of each newly diagnosed malignancy is performed by means of carbon copy forms provided by the German Childhood Cancer Registry. Thus, standardized patient documentation is used partly in the GPOH and the competence network. Studies accompanying clinical trials request separate patient documentation only if the information cannot be obtained from the trials' data banks.

Standardization of patient documentation is advanced through several approaches. Obligatory terms and definitions were being reconciled for base data and are under harmonization for disease-specific data. Paper forms of ongoing trials were repeatedly analysed and harmonizing changes were proposed. Paper flow sheets were newly developped with standardized contents and appearance („Check lists", cf. annex). Medical diagnosis and procedures coding was harmonization by explicit recommendations distributed to all GPOH members. DOSPO is a container application that can host similar documentation forms for use with various clinical studies. First standard operating procedures for practically performing the documentation were developed by clinical trial offices and are presently tested in the field by the assistants in clinical research and quality control (FSA).

As put forward in the initial grant application and in this continuation report, IT-based data documentation in hospitals participating in clinical trials shall substantially be improved. Presently, patient documentation is not IT-, but paper-based. This also holds true for the 23 clinical trial offices and the German Childhood cancer registry, which keep paper files of all 30000 patients. To accommodate long-term archiving, we evaluate to provide a service support for scanning and digitally archiving documents in conjunction with an appropriate retrieval application.

However, data collection is performed by the clinical trial offices, which are each responsible throughout Germany. Some clinical trial offices are also for responsible for Swiss, Austria, Spain, or some other European hospitals. These trial offices are the most central structure units. Analyses are not centralized any further.

The number of institutions documenting data varies largely with the clinical trials, that is, with the disease entity, and amount to maximally 130 institutions (e.g. osteosarcoma, Ewing's tumor). The actual numbers are estimated averages of the number of trial conducting hospitals.

* With regard to planned numbers of documenting institutions, there are no plans to further recruit institutions for participating in Pediatric Oncology clinical trials. (The questionnaire implies wanted increasing numbers.)

	Indeed, numbers of documenting institutions may decrease as a result of the planned introduction of a common quality control system into these institutions, including formal certification procedures and agreements with legal partners. Such a system is presently prepared and a special working group has been installed. It is not yet known how many private practices are to be summoned for documenting data during long-term follow-up (cf. project I). This largely depends on the acceptance in the medical community and on the pertinent advertisements of this project in relevant media. Pilot investigations are to be completed, which will help to estimate the necessary local infrastructure (cf. project A). The comparison of incidences and patients included in trials (11.E) is directed at the completeness of patient registration. Since the initiation of the German Childhood Cancer Registry (GCCR) in 1980, information relating to patients registered in trials is collected. This increasing registration with the GCCR was 66,7% (1980–1984), 74,6% (1985–1989), 90,5% (1990–1994) and is now 91,6% (1995–1999). However, the goal is to register 100% of patients – also those with a second malignant neoplasm – with the GCCR, for reasons of quality control (of diagnosis and treatment) and of honoring (analyzing) every patient's clinical course data.

Part C – Added Value through Networking

12 **Material banks**

Is your network setting up material banks?

☐ No ☒ Yes

Which materials are collected within your network?

Bone marrow aspirates, peripheral blood samples,
tumor samples (embryonal and germ cell tumors), blood smears.

Is the network using standardized documentation for materials?

☐ No ☒ Yes

a) Are the material data correlated with the medical patient records?

☐ No ☒ Yes: new development ☐ Yes: further development

b) Is the data processing IT-based?

☐ No, not intended ☐ Planned ☒ Yes, already in use

c) Are the data collected supra-regionally and centrally analyzed?

☐ No, not intended ☐ Planned ☒ Yes, already in use

d) Number of institutions sending materials and documenting data

	actual number:	planned number:
university hospitals:	32	*
non-university hospitals:	40	*
private practices:	0	*

e) Total number of documented materials: >4200

f) Total number of documented materials correlated with patient data: >4200

g) Are the materials and the material data used as diagnostic reference samples?

☐ No, not intended ☒ Yes

Part C – Added Value through Networking

h) Other use of the materials and/or the material data:

The patients samples („materials") are collected for the scheduled investigations, which are part of the various project's research question. In addition, materials can be requested from some of the material banks for use with hitherto unknown, new research questions. If such a request is to be fulfilled, the material banks provide patients samples, preliminary clinical data (full data to be obtained from clinical trial offices) and the formal legitimation for material use abroad. Fulfillment of researchers' requests is decided by designated independent scientific review panels.

i) Describe the activities and problems concerning material collection and documentation so far and describe the proposed activities for the second funding period.

Activities and problems concerning material collection

The activities of this network's projects were both to collect samples („materials") from newly diagnosed patients (e.g., projects D, E, F and G) as well as to additionally examine previously stored samples (projects E and F). Stored samples may serve as a reference with regard to molecular markers, portion of blasts, clone diversity or else. These projects incorporated results and (some) samples into their new banks for data and samples. Presently, material banks in German Pediatric Oncology and Hematology are established and working for all patients with a

- embryonal/rare tumor (project G),
- myelodysplastic syndrome, Fanconi anemia, severe aplastic anemia, and congenital neutreupenia (project E),
- solid tumor (Kindertumorregister Kiel, funded elsewhere),
- acute lymphoblastic leukemia (part of project F) or
- acute or chronic leukemia (immunophenotyping samples, part of project A).

There were differences in the portion of possibly suitable and finally collected materials, as reported in the respective projects' reports. No problems were observed by projects with immediate feedback and possible benefit for decisions on treatment options, such as reference examinations for suspected myelodysplastic syndrome and minimal residual disease. Less compliance was experienced with regard to submission of embryonal tumor samples, which is deemed to be due to competing research activities in non-delivering university hospitals and less cooperative pathologists in non-university hospitals. These problems have been addressed and compliance has increased recently.

* Thus, a comprehensive coverage of institutions caring for Pediatric Oncology and Hematology patients has already been reached. Therefore, there are no plans to further extend the number of institutions sending material. This situation is similar to the number of documenting institutions, as also explained in section C.11 g).

	Proposed activities for the second funding period The newly installed material banks will be continuing to collect samples. For the long-term sustainment of material banks, financing and organizational concepts have to be developed. So far, respective ideas are to operate material banks with a portion of the clinical trial funding on a per patient base. The information among scientists about the existence of the material banks will be distributed in order to elicit new research projects and to demonstrate that material banks facilitate judicious and time-conserving research performance. Scientific exchange with other networks (e.g., the BrainNet) on various topics related to material banks will be evaluated, for instance on legal implications, procedures for re-distribution, storage optimization, maintenance and sustainment mechanisms.

Part C – Added Value through Networking

13 **a) Which programs for the promotion of young scientists are realized by the network?**

☒ Promotion of scientific exchange

☒ Organization of continuing medical education („Fort- u. Weiterbildung")

☒ Career development paths for young clinical scientists

☐ Others

b) Describe the programs and activities realized in your network so far and describe the proposed activities for the second funding period.

Programs and activities

Young scientists were promoted by direct appointment and assignment of projects responsibilities (several network projects), by support with scholarships (completed in project H, planned in project F) and travel/meeting grants. Continuing medical education is delivered during scientific meetings as presented in B.5 b). For instance, the annual GPOH meetings 2001 were rewarded 11 and 9 CME points by the regionally responsible Lower Saxonia and Berlin Medical Councils, respectively.

Promising progress has been made towards establishing the formal education in Pediatric Oncology and Hematology: For the Federal Medical Council assembly, the proposal of a so-called „Schwerpunkt Pädiatrische Onkologie und Hämatologie" was accepted for decision in 2003. The proposal has been devised together with European coworkers (by U. Creutzig on behalf of the medical society).

Proposed activities for the second funding period

Special scholarships will be included in the second funding period. We propose to fund again scholarships for special research projects. These shall be granted with the approval of scientific applications by the „Erweiterte Leitgruppe".

Speaker's Annotation to Section 1, Part C – Added Value through Networking

Added value was obtained through networking in more places than listed above. With regard to clinical trials, these added values correspond to the following:

- data banks of clinical trials are more complete and more correct, resulting in a richer base for analyzing current and conceiving future clinical trials;
- network partners increasingly work together on a trusting, demand-oriented basis; resulting in overcoming abridging competition;
- separate projects on the quality control of diverse medical and laboratory procedures are getting coordinated; leading towards the wanted comprehensive quality control systems.

PART D – Visibility of the Network

14 **Has the network been presented comprehensively at scientific congresses?**

☐ No ☒ Yes

Attach a list in the annex including: name, date, site, organizer of the scientific congress, topic of the network presentation, approximate number of external participants during the network presentation, number of participating network members.

Please, refer to this list in the annex, page 24.

15 **a) Which public relation activities have been performed by the network for which addressees/multipliers?**

Give numbers of		Addressee:
press conferences	1	Invited special and regional journalists.
press reports	19	General and medical public.
TV presentations	2	General public.
radio presentations	2	General public.

Others, please list _____

Attach a list of all public relation activities in the annex.

Please, refer to this list in the annex, page 31.

b) Do you evaluate the echo of such presentations for instance via the collection of press reports (Pressespiegel)?

☐ No ☒ Yes

16 **Is your network cooperating with self help groups / other lay groups?**

☐ No ☒ Yes

17 **Is the network offering medical information for external groups?**

☐ No ☐ Yes, information for patients and family members ☒ Yes, information for doctors

18 **Describe the activities and problems concerning the visibility of your network so far and describe the proposed activities for the second funding period.**

Activities and problems

The public visibility of our network has recently increased. After the first scientific results were obtained and central structures were built up, we took several steps to arouse interest into Pediatric Oncology and Hematology. The first press release reported on the creation of this network and the funded research intentions, and the second press release was directed at some facts and outcome results of national health care in Pediatric Oncology. A corresponding press conference was jointly performed by members of the medical society (GPOH) and the competence network. The media reports on our network focused on the special requirements of the patient population and the comparatively good prognosis. Some media provided the communicated explanation that this is a result of the continuing networking.

The need for addressing the media evolved during the last two years. A comprehensive public relations concept was designed, and in 2001, was granted 40000 € by the DLR. Acitivites related to internet presentation the information brochure, media contacts and continuous press relations will be performed together with professional firms (project A). A first product is the information brochure on cancer in children and young adults. It features general facts on Pediatric Oncology, including important points such as the psychosocial implications, the importance of cooperative trials and the use of non-approved drugs. Network and GPOH contact information as well as space for further information sheets are provided. It will be available for network and GPOH members in May 2002 (preliminary version in the annex).

To increase the visibility among physicians and reseachers, there were several presentations on the network itself during scientific meetings (cf. annex). In addition, the network's status and changes are repeatedly presented during the scientific meetings. A forthcoming highlight is the „Second Scientific Bi-national Israel German Conference" (19.-20.11.2002), which is organized with the help of the network; project G will be one of the three main topics.

Proposed activities for the second funding period

Public relation activities will be continued and extended. Continuous attention shall be attracted to the successful health care and research in Pediatric Oncology. A successor information brochure has to be produced. About two more press conferences are planned (the measures are included in the professional partner's bid, annex page 86).

Providing expert medical information to all afflicted individuals and interested parties is part of our forthcoming information services (cf. B.6 b). Short texts will be produced and published by the coordination and management group (A) from mid-2002 on. Explicit and detailed patient information will be produced with the help of a separate project (grant application in preparation).

Part E – Transfer of Research Results into the Health Care System

19

a) Are meta-analyses or systematic reviews performed by the network?

☒ no, not intended

☐ in preparation number: ☐☐

☐ yes, published or in press number: ☐☐

Attach a list of all reviews in the annex

b) If yes, how many reviews are performed according to Cochrane criteria?

Number: ☐☐

Mark those reviews in the list attached in the annex

c) Is the network substantially involved in Cochrane Reviews?

☒ No

☐ Yes

If yes, give the number of network members involved as:

☐ formal member

☐ constant collaborator

☐ responsible for a chapter

Speaker's Annotation to Section 1, Part E, Question 19

All projects of our network are concerned with systematic data collection, analysis and reporting. These data enable clinical trial offices to perform systematic reviews with regard to scientific evidence for optimizations of the complex diagnostic and therapeutic strategies. However, we are presently not involved with the Cochrane Collaboration because of the complexity of Pediatric Oncology clinical trials as compared with regular Cochrane contents.

Part E – Transfer of Research Results into the Health Care System

20

a) Are network members substantially participating in the preparation and/or revision of national guidelines (local and regional guidelines are excluded) for diagnosis and therapy?

☐ no, not intended

☒ yes, please specify :

number: 21

topics: Pediatric Oncology and Hematology

b) Please describe for each guideline:

Kind of guideline:

☒ step 1 (expert group)

☐ step 2 (formal consensus process)

☐ step 3
(guidelines with all elements of systematic development: logical analysis, clinical algorithm, consensus, evidence based, decision analysis, outcome analysis)

number of persons within the network involved: 14

(planned) date of publication: _____

Please, refer to page 33 in the annex for a description of the guidelines.

Most of the guidelines are „step 1 + IDA" (i.e., with interdisciplinary agreement).

Speaker's annotation to the section 1, part E, question 20 b):

The „step" number is attached to a guideline by the working group of the scientific medical specialist societies in Germany (AWMF). From our point of view, requirements for classification according to step 3 are met by several of our oncology guidelines. Talks on re-classification are planned.

21	**Describe which new effective therapeutic or diagnostic methods have been developed by the network** The following methods were developed by the network Á MRD (minimal residual disease): The concept entails that changes of the individual's leukemic cell mass over time are traced. The smaller/slower the response to treatment, the higher is the risk of an adverse event. New molecular techniques permit quantification of the leukemic cell mass over about six decimal places, where previous techniques were limited to about two. MRD in acute lymphoblastic leukemia (ALL) has been introduced before the network's start. However, MRD in ALL relapses and MRD in acute myeloid leukemia is being developed and introduced as part of the network into the respective clinical trials and thus into clinical practice. The importance of this diagnostic method is the possibility to prospectively tailor and individualize the intensive chemotherapy. Although this procedure might not increase cure rates further, it could increase the patients' quality of life because less (toxic) chemotherapy would probably suffice for cure. (Extension to non-Hodgkin lymphomas is planned. Also please refer to project F.) Á QoL (quality of life): Comprehensive standardized diagnostics for the quality of life of children and young adults with ALL and with brain tumors (medulloblastoma) were delevoped and introduced into practice. These patient groups are diametrically opposed with regard to the possible impairment of QoL by the disease as well as by the treatment. In fact, to continue treatment in impaired patients always necessitates considering actual and future QoL. However, these standardized QoL assessments are not yet available in all participating hospitals due to the required resources of skilled staff. (Also please refer to project I.)

Part E – Transfer of Research Results into the Health Care System

22 **a) Which instruments are used to implement clinical guidelines and new effective therapeutic or diagnostic methods[2]?**

- ☒ Dissemination of guidelines (printed or computer based), continuing education
- ☒ Targeting opinion leaders
- ☒ Redesigning care pathways and documentation sheets
- ☒ Inventing checklists for clinicians
- ☒ Audit of performance and feedback to clinicians
- ☐ Others, please list _____

b) Number of network members involved 40

23 **Describe each of the efforts in your network and – if possible – their impact and the problems to transfer innovative research results into the health care system so far. Describe your collaboration with scientific societies in this respect. Describe the proposed activities for the second funding period.**

Efforts to transfer innovative research results into the health care system

The principle of response to treatment as a prognostic factor has been introduced in leukemia trials. Increasingly, molecular characteristics of leukemia and tumor cells are being used to select the appropriate treatment strategy. Unnecessarily toxic regimens may be avoided by this procedure. The tools to introduce these innovative research results into practical medicine are the nation-wide clinical trials.

Collaboration with scientific societies

The network originates from the Society of Pediatric Oncology and Hematology (GPOH) and has since kept close to the society's aims, members, and projects. Collaboration with the GPOH has been productive in as much as the competence network tried to shape and also to conduct projects on behalf of or in collaboration with the GPOH.

Beyond this, the competence network initiated unprecedented though important projects (such as telemedicine, research assistants and QoL implementation) for which funding on a broad basis could hardly be achieved otherwise.

[2] The question refers to guidelines and new methods in general, not only to those developed by the network

	Three delegates of the GPOH's board are permanent members of the network's „Erweiterte Leitgruppe". The most prominent common goal is to improve the clinical trials in Pediatric Oncology, both as a comprehensive system and each separately. Proposed activities for the second funding period Started activities will be continued using the potential of the improved networking structures developed during the first funding period.

Part F – Sustainability

24

a) Which measures have been installed or are planned to secure the network and its central facilities and services on the long run?

☒ formal alliance

∉ company constituted under German law („Gesellschaft bürgerlichen Rechts"), statutes installed („Satzung")?

☐ planned ☐ installed

∉ foundation of a registered association („eingetragener Verein")

☐ planned ☐ installed

∉ foundation of a limited liability company (Ltd., „GmbH")

☒ planned ☐ installed

☒ engagement of long term financiers
(for instance for the installment of the coordinating unit and the central services)

☒ acquisition of scientific grants, which were provided due to the existence of the network

☐ acquisition of donations to the benefit of the network („Spenden")

☒ further measures, please list: For a model description, please see below.

b) Describe the strategy to continue the network after the BMBF grant ended. Give the financiers, the amount, kind and period of all additional financial support obtained by the network so far.

Together with the GPOH, the network, has created structures such as the German Children's Cancer Registry, the Children's Tumor Registry, the Cooperative Pediatric Stem Cell Transplant Registry, reference laboratories for immunophenotyping, cytogenetics and molecular genetics, the central business office of the GPOH, as well as more than twenty trial offices. These institutions contribute substantially to state-of-the-art patient care and to ascertain a high degree of quality control in diagnostic as well as therapeutic measures.

This system has been established with the help of sponsoring and funding organizations and has thus never caused any costs to the responsible health insurance system. To ascertain quality control of patient care, however, is a legally required (financial) responsibility of the health insurance system. In order to sustain the created structures which are essential for the high quality patient care and responsible for the achieved high cure rates in Germany, it is planned

	to offer this highly effective system for quality control to the health insurance companies on a commercial basis. The expected income shall be used to finance and to maintain continuously the infrastructure. Additional income for this purpose may be achieved by patents, cooperations with pharmaceutical companies and selling of knowledge, e.g. on information technology or laboratory methods. <u>Financial support obtained by the network so far</u> So far, additional financial support to the network was limited to state subsidies. These amounted to 36 k€ (project A). In addition, some projects were financially supported by add-on grants obtained for own Telematics platform applications. Other grants are in preparation (e.g., patient information). <u>Strategies for the continuation of the network</u> Considerations for the continuation of the network are outlined above. The strategy is to develop a convincing concept during the second half of 2002 and to present it to representatives of health insurance companies and responsible politicians. This could set a precedent for other medical specialist societies and networks if accepted. Scientific aspects of clinical trials will be subject to funding as before. Basic science-oriented projects of the network have to be continued with funding by sponsoring institutions as usual.

Part G – Summary of the Status quo and Proposed Activities for the Second Funding Period

State whether the general objectives of the network, as set down in the project proposal, are still relevant and achievable. If not, explain why. Provide a short summary of the objectives in the first part of the funding project and those proposed for the second part.

General aims of the network were to start the process of networking between pre-existing structures (clinical trials, reference laboratories, registries and hospitals) of Pediatric Oncology and Hematology in Germany and to newly install tools and instruments for communication and transfer of data and material, thereby facilitating laboratory and clinical research with the final aim of improving prognosis and outcome in children and young adults with cancer.

The competence network consists of three parts: four projects addressing general coordinating and networking aspects (A, B/1, B/2 and C), four projects addressing basic science (D, E, F and G) and three projects addressing clinical research (H, I and K). The new project, telemedicine in palliative Pediatric Oncology, is related to both networking aspects and clinical support (see below).

(1) Projects addressing coordinating and networking aspects

Project A - Coordination and management group

Aims

- coordinating the single projects of the network
- improving documentation and material exchange
- providing structured support for clinical trial offices
- establishing public relations about Pediatric Oncology
- evaluating the network's progress

Results: FSA were introduced in the 27 largest hospitals and a training program was set up. A working group „Study support" has been established providing support in organizing clinical trials according to the needs defined by clinical trial offices. The design of an information system has been completed and the information server is being filled with information for professionals and laymen. Activities have taken place to present the network to the public at various occasions. Progress of networking in Pediatric Oncology has been documented by repeated evaluation.

…

During the second funding period, the started activities will be continued. It is aimed at completing the FSA training with a certification program. The information services will substantially be extended. Efforts are being made to establish a financial basis for the continuation of specific central structures of the network. The aim is to get the quality in Pediatric Oncology delivered by these structures financed by the health care system.

Project B/1 Computer-based application systems (DOSPO)

Aims

- developing a computer-based application system for Pediatric Oncology
- supporting clinicians, clinical trial offices and other research institutions
- developing a generic tool for study databases
- standardizing medical terminology for Pediatric Oncology

Results: The development, introduction and maintenance of DOSPO are in progress. A revised „Basic data set" will be published soon.

During the second funding period, all resources of B/1 will be concentrated on the introduction of DOSPO into hospitals. Thus far, this has been hampered by lack of compatibility with meanwhile installed competing patient information systems in the hospitals. Further aims are to be additionally funded by other sources.

Project B/2 – IT security and data protection, Knowledge server

Aims

- developing strategies and building up secure communications between network partners
- building up an information server framework

Results: In essence, both aims were achieved (parts are to be delivered by end of 2002).

During the second funding period, external data security services („Trust center") will be maintained with remaining funds from the first funding period.

Project C - Telemedicine in Pediatric Oncology

Aims

- promoting research and increasing the standards of care in Pediatric Oncology and Hematology
- enhancing communication standards and enabling ambitious network activities in research and patient care by implementation of telemedicine

…

Results: A demand profile for telemedicine in Pediatric Oncology has been gathered in two surveys. Several commercially available technical solutions were tested, but either not suitable to meet the requirements or too expensive. The attempt to start a broader use of telemedicine into clinical practice was hampered by the fact that a substantial part of external partners was a priori not willing to open their archives for access.

During the second funding period, the previous experience will be used to switch the project's focus on establishing a central server for telemedicine, for storage and exchanging of medical images between involved cooperation partners. Already existing cooperations between Münster, Homburg, Berlin and Würzburg will be continued and intensified (a suitable candidate for the position in Halle could be found only sixth months ago).

As soon as a usable, safe and working system and configuration is achieved, participation will be offered further to interested institutions. For the nephroblastoma trial, the exchange of medical images and clinical data as a telemedicine application will be realized using a remote data entry system.

(2) Basic science projects

Project D – Molecular parameters of drug resistance

Aims

- developing an acquisition system for collection of patient material for cellular, protein, RNA and DNA analysis
- developing methods for measurement of apoptosis signaling in primary leukemia cells
- analyzing leukemia cell apoptosis in drug response assays
- indentifying apoptosis gene mutations inferring drug resistance
- analyzing apoptosis gene expression profiles for prediction of drug resistance
- indentifying of apoptosis signaling in peripheral leukemia cells activated by in vivo chemotherapy

Results: Working cooperations on apoptosis and drug resistance were established, including comprehensive material exchange and newly developed methods for flow cytometry. It was then found out that only fresh material, but not frozen samples were suitable for analysis. Methodological expertise was transferred to project partners. A patent has been applied for (in two countries).

During the second funding period, the planned investigations will be continued, partly with modified approaches. In addition to patients' samples, which are to be tested in a larger set, mouse model leukemia cells will be established within in a new cooperation and also assessed for apoptosis and drug resistance.

…

Project E – Preleukemic bone marrow diseases

Aims

- characterizing preleukemic bone marrow disorders by various molecular biology studies
- screening for genetic changes in the NBS1 gene
- performing angiogenesis studies
- providing reference morphology and oncogenetic studies

Results Together with international partners, a novel classification of myelodysplastic syndromes has been elaborated which should also help to interpret molecular biology results. These were obtained in a very large number of samples. In addition, methodological advances were made. Some of the initial questions could already be answered.

During the second funding period, the analyses will be continued and completed, and the associations between laboratory results and clinical course will be elucidated in detail.

Project F – Minimal residual disease

Aims

- standardizing method for MRD analysis in relevant diseases
- building up and optimizing logistics for complete coverage of patient samples
- discovering the most suitable time points for sampling for MRD analysis
- investigating the time course of response in patients
- evaluating MRD monitoring as a prognostic factor

Results: The cooperation on MRD studies has been established, including the standardisation for MRD in AML. A large number of samples has been examined, according to schedule. New infrastructures at involved laboratories were established. First results to the stated aims are detailed in the report.

Germany has a leading position in assessing the prognostic value of MRD monitoring in childhood malignancies. The technique is already being used in the current protocol for frontline ALL and will be introduced in the trial for relapsed ALL on short notice. Therefore, the group of project leaders unanimously felt that this project would need definitely more scientific support.

During the second funding period, the work will be continued. The technical support by the network is planned to be tailored to the evolving needs. Detailed scientific analyses of the vast body of accumulated data, introduction of new methods (in particular in AML), advances in standardization and establishment of quality control and of reference laboratories have to be accomplished. As soon as MRD projects are separately funded as regular parts of clinical trials, the technical support by the network may be reduced.

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Project G – Clinical importance of molecular changes in embryonal tumors

Aims

- establishing tissue banks for embryonal and rare tumors
- collecting all relevant and suitable tumor tissue
- investigating the respective tumor entities for pertinent molecular changes
- reconsidering pathogenetic models
- identifying potential immune and/or gene therapy targets

Results: A comprehensive tumor tissue bank system has been built up. An independent panel of reviewers has been instituted to decide upon new applications for the redistribution of the precious patient samples to research groups. In addition, project G's research results comprise new prognostic markers and also hints to a new understanding of some of the embryonal and rare tumors. A patent for the tissue collection system has been applied for.

During the second funding period, the planned activities will be continued. Beyond this, further scientific support is proposed in order to optimize tissue preparation and delivery to the tumor bank system. These issues are a major problem and not sufficiently covered within the project. A scientific coworker is needed for persistent activities such as coordination, cooperation negotiation and hospital/pathologists information. Also, further technical assistance is necessary to conduct and prepare the planned gene screening investigations.

(3) Projects addressing clinical research

Project H – Immune- and gene therapy

Aims

- establishing a registry of trials employing immune- and gene therapy in Pediatric Oncology in Germany
- supporting the treatment centers concerning regulatory and legal issues
- improving communication between the treatment centers on an international and national basis, improving documentation
- creating synergies between research groups

Results - A survey of current trials has been performed. As part of a successful licensing process, experiences in legal issues were compiled. As stated in the Midterm Report (section 3), substantial parts of funds were reallocated to purchase DNA microarrays and reagents for gene chip preparation and processing. Results of these investigations are not detailed in the report.

During the second funding period, the stated aim is to achieve „a shift [*] from establishing network structures to using these efficiently for the advancement of pediatric immune and gene therapy". Furthermore, it is stated that „project H has been officially commissioned by the GPOH/KPOH to establish a quality coordination center for

gene chip analysis of pediatric tumors". Substantial funds are requested for materials and a position for a technical assistant. Details of the planned experiments are not specified.

Among the network's project leaders, the proposal was controversially discussed. The conceptual basis for immune-/genetherapeutic approaches is still unclear. The idea of identifying target structures for such approaches is probably correct and the method of gene expression analysis is adequate. There are, however, special projects funded by the BMBF in which also pediatric oncologists are involved. Thus, there is a definite interest in participating in this kind of research from various groups.

Therefore, the majority of the project leaders did not agree with the proposed aims of project H. They felt that at present, there is no publication-based expertise to decide upon a commission to establish a center for gene chip analysis of pediatric tumors. Furthermore, materials for laboratory investigations should be separately funded, e.g. within the German Human Genome Project. Instead, the activities of project H during the second funding period should be focused on coordinating the various efforts in gene expression in pediatric malignancies. This should result in creating a sound scientific basis for considerations on immune and gene therapy.

Project I – Late effects, quality of life and vertical networking

Aims

- developing, standardizing and promoting a set of instruments to assess the quality of life
- applying these instruments to two patient groups to prospectively assess HRQL
- designing structured guidelines for follow-up
- developing a vertical network for follow-up integrating various levels of health care providers

Results – A multicentric evaluation of late effects and quality of life in patients with brain tumors and ALL is underway. Cooperations between psychosocial and medical caregivers were set up.

During the second funding period the multicentric evaluation will be continued. Additional scientific support is needed for a comprehensive analysis of the data accumulated during the first funding period. Standardized flow sheets to assess QoL in ongoing clinical trials in Pediatric Oncology will be developed as amendments to the protocols. Information on pediatric cancer treatment and follow-up will be prepared for the internet presentation, for practical vertical networking among health care providers and for patients and families.

Project K – Second malignant neoplasms after childhood cancer

Aims

- establishing a nation-wide add-on registry to the GCCR (German Childhood Cancer Registry) for second malignancies

- establishing a consultant board of clinical trials' principal investigators
- preparing the intended epidemiological case-control study
- identifying risk factors responsible for the etiology of secondary malignancies
- improving long-term follow-up beyond childhood

Results: Second malignancies in survivors of childhood cancer were completely assessed. Procedures for the prospective validation of suspected new cases were settled. The planned epidemiological case-control study has been completed in design.

During the second funding period, the planned work will be continued. Emphasis will be given to systematically look for risk factors for SMN. The case-control study will be performed. Publication of the results is in progress.

Project T – Telemedicine in palliative Pediatric Oncology

With the aim of vertical networking and as an add-on project related both telemedicine and medical care, palliative care of bedridden patients together with their private practitioners shall be started as a regional pilot project (TOPP).

The group of project leaders felt that this is a valuable and practical application of telemedicine which might help to involve private practitioners more in the care of critically ill patients.

Summary

Many of the initially described aims could already be achieved. In some projects, it appeared to be necessary to make amendments or to focus more closely to certain aspects because of relevant, unforeseen experiences made during the first funding period.

With the proposed changes, the project leaders feel that the general aims as set down in the initial network proposal are still relevant and achievable.

Part H – Financing of Central Activities for the Second Funding Period

List in tabular form the expenditures of the following funding period. Separate the costs for the network and for single research projects.

Competence Network Pediatric Oncology and Hematology[3]

		First Funding Period				Second Funding Period		
#	**Project Title**	**Grant**	**Per-sonal**	**Other Costs[2]**	**Rest[4]**	**Re-quested**	**Per-sonal**	**Other Costs[5]**
A	Coordination and management[6]	**2751,3**	2557,9	193,4	0,0	**2770,1**	2431,0	339,2
B/1	Computer-based application systems	**650,1**	582,2	67,9	78,7	**415,6**	366,4	49,2
B/2	Data Protection, IT-security and knowledgeserver	**225,9**	165,7	60,2	20,2	**0,0**	0,0	0,0
C	Telemedicine in Pediatric Oncology	**743,5**	538,7	213,1	119,6	**396,0**	385,0	13,0
D	Apoptosis and drug resistance	**459,6**				**370,0**	308,0	52,0
E	Preleukemic diseases of the bone marrow	**485,8**			90,3	**238,3**	198,3	40,0
F	Prognostic relevance of minimal residual disease	**577,6**			0,0	**691,5**	613,1	78,4
G	Clinical relevance of molecular changes in embryonal tumors	**583,2**			0,0	**470,0**	392,0	78,0
H	Immune- and gene therapy	**221,4**	63,8	49,4		**386,8**	166,7	200,0
I	Quality of life and vertical network	**284,3**	133,3	132,8	4,2	**266,7**	261,7	25,0
K	Second malignant neoplasms	**238,9**	232,7	6,1	0,0	**198,2**	194,0	4,2
T	Telemedicine in palliative Pediatric Oncology (new)	**–**	–	–	–	**211,2**	138,0	73,2
	Sum total network	**7221,6**				**6414,4**	**5454,2**	**950,2**

[3] Figures are given in thousand Euros (k€). Differences may arise due to rounding.

[4] „Rests": Estimated remaining funds until the end of the first funding period. Calculation: grants minus (real expenditures plus projected expenditures). Please note that expenditures were not available for all projects due to local administration issues. The listed rests shall become part of the overall finances of the competence network. Date of calculation: 31.03.2002.
Zero rests indicate that the DLR granted an extension of the first funding period in order to synchronize the ends of the first funding period among the network projects. Such rests are consumed for the period extensions, at equal costs of the first funding period.

[5] „Other costs": commissions, consumables, investments, travel costs and various other costs.

[6] Network's executive, coordinator and secretaries; 17 assistants in clinical research and quality control (FSA); „Study support" group; commissioned public relations and evaluation activities; travel resources for all network meetings etc.

Section 2

Cover Page to list the Research Projects

Title Page

Network title : Competenc Network Pediatric Oncology and Hematology

Period covered by this report : 01.07.1999–31.03.2002

List of projects covered by this report:

No.	Grant No.	Project Title	Scientist-in-charge	Institution	Page
A	01 GI 99 58/5	Coordination and management group	Univ.-Prof. Dr. Günter Henze	Charité Children's University Hospital, Berlin	48
B/1	01 GI 99 59	Computer-based application system for Pediatric Oncology and Hematology	Dr. Ulrike Kutscha	Medical Informatics, Heidelberg	59
B/2	01 GI 99 67/3	Data protection, IT security and knowledge server	Univ.-Prof. Dr. Klaus Pommerening	IMBEI, Mainz	76
C	01 GI 99 60	Telemedicine in Pediatric Oncology	Univ.-Prof. Dr. Norbert Graf and Dr. Michael Paulussen	Children's University Hospital, Münster	83
D	01 GI 99 61	Molecular parameters of drug resistance	Dr. Karsten Stahnke and Univ.-Prof. Dr. Klaus-M. Debatin	Children's University Hospital, Ulm	97
E	01 GI 99 62	Preleukemic diseases of the bone marrow	Univ.-Prof. Dr. Charlotte Niemeyer	Children's University Hospital, Freiburg	110
F	01 GI 99 63/2	Prognostic relevance of minimal residual disease	Univ.-Prof. Dr. Jochen Harbott	Children's University Hospital, Giessen	123
G	01 GI 99 64/5	Clinical relevance of molecular changes in embryonal tumors	Univ.-Prof. Dr. Frank Berthold	Children's University Hospital, Köln	138
H	01 GI 99 65	Immune- and gene therapy of pediatric neoplasias	Univ.-Prof. Dr. Stephan Burdach	Children's University Hospital, Halle (Saale)	151
I	01 GI 99 66	Late effects, quality of life and a vertical network	Dr. Gabriele Calaminus	Children's University Hospital, Düsseldorf	167
K	01 GI 99 67/3	Second malignant neoplasms after childhood cancer	Dr. Peter Kaatsch	IMBEI, Mainz	176
T	N/A	TOPP (Telemedicine in palliative Pediatric Oncology)	Dr. Boris Zernikow	Children's University Hospital, Münster	187

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Coordination and management (Project A)
Grant No.	:	01 GI 99 58/5

Name of scientist-in-charge	:	Prof. Dr. med. Dr. h.c. Günter Henze
Institution	:	Klinik für Pädiatrie mit Schwerpunkt Onkologie und Hämatologie Charité Campus Virchow-Klinikum Medizinische Fakultät der Humboldt-Universität zu Berlin
Address	:	Augustenburger Platz 1 13353 Berlin
Phone	:	+49 (0) 30 – 45 05 – 66 03 2
Fax	:	+49 (0) 30 – 45 05 – 66 90 6
E-mail	:	guenter.henze@charite.de

Project home page (if different from Network homepage)	:	http://www.knm-poh.charite.de/

Part A - General Statements about the Project

A.1. **Subject**

Coordination and management group (CMG, project A) of
the competence network Pediatric Oncology and Hematology

A.2. **Co-Investigators**

- Prof. Dr. med. Ursula Creutzig, University Children's Hospital, Münster; Network executive
- Prof. Dr. med. Wolfgang Friesdorf; head, Lehrstuhl für Arbeitswissenschaften und Produktergonomie, Technische Universität Berlin;
  Chief executive officer, Clinical Systems Management e.G., Berlin
- Prof. Dr. Klaus Pommerening, Institut für Medizinische Biometrie, Epidemiologie und Informatik (IMBEI), Johannes-Gutenberg-Universität Mainz;
  IT coordinator competence network Pediatric Oncology and Hematology
- Dr. rer. hort. Martin Zimmermann, University Children's Hospital, Hannover, biostatistical consultant ALL-BFM, NHL-BFM and AML-BFM clinical trials; project leader „Study support"
- Dr. med. Ralf Herold, Charité, Berlin; Network coordinator

A.3 **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects	☐ yes	☒ no
(b) clinical trials	☒ yes	☐ no
(c) animal models	☐ yes	☒ no
(d) gene therapy	☐ yes	☒ no

A.4 **Requested Funds for the Second Funding Period***

Please note that the second funding period of project A starts on 01.10.2002 (to 30.09.2004), in contrast to that of the other projects (01.01.2003 – 31.12.2002).

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1]**	**Amount[1] Requested**
2002	296,3	5,3	8,4	12,5	11,6	334,10
2003	1209,6	16	0	50,0	77,9	1353,50
2004	925,1	11,3	0	37,5	108,7	1082,60

[1](amounts in thousand Euro), * should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The coordination and management group (CMG) is responsible for own projects and working as a coordinating and service unit for all partners involved in research in Pediatric Oncology and Hematology.

Major tasks have been to coordinate and manage the various projects and the cooperation within the network, to organize meetings, to employ coworkers, to organize an evaluation program and to organize public presentations of the network including press conferences and to prepare interim reports and the Midterm Report.

Among the CMG's own projects, the concept of implementing the new profession of the assistant in clinical research and quality control (FSA) in the largest treatment institutions has been put into practice and has shown first promising results (cf. section 1, B.4 c). A working group „Study support“ was instituted to support clinical trials in data management and documentation.

Tools for information exchange and PR have been developed and are working.

B.2 **Original aims of the project**

Aims

- coordinating and managing the structures and instruments of the competence network Pediatric Oncology and Hematology
- supporting the conduct of clinical trials as instruments of both quality control and clinical research by establishing and improving the systematic exchange of data and material (tissue, blood, bone marrow) between treating institutions, trial offices and the German Childhood Cancer Registry (GCCR), to be achieved by employing additional personnel (FSA)
- establishing a comprehensive training and certification program for the FSA
- supporting clinical trials in respect to data management, data base design, harmonization of information techniques, reduction of data queries
- building up a knowledge and information base using internet technology
- supporting reference laboratories with respect to cell banking and networking
- supporting a registry for pediatric stem cell transplantations
- organizing the external evaluation of the network
- organizing PR activities to present the network to the public
- building up a collaboration between professionals from treating institutions, private practitioners, patients and families for vertical networking
- searching for options to sustain the network beyond funding.

B.3	**Scientific results** The major purpose of the project is coordination and management. Therefore, scientific results in a strict sense are limited. However, most of the described aims have been achieved or are in progress. Highlights are: Á FSA have become meaningful skilled staff members in Pediatric Oncology. According to the results of the evaluation, their work is successful and highly appreciated by the physicians and trial offices. Á The network has been presented to the public at various occasions and has been well recognized by the audience and in the media. Á The internet presentation is of interest and recognized. The new media for information – internet presentation and newsletter – are well appreciated, recognized and used. Á Well attended and scientifically successful meetings have been organized between network members and/or GPOH members. Á Out of several potential options to reach sustainability of the network, concrete and promising ideas have been developed together with co-opted experts from the „Institute for Clinical Health Care Systems“ e.G., Berlin. Further important results of the CMG are listed all parts of section 1 of this Midterm Report.
B.4	**Publications and patents** Creutzig U, Calaminus G. Vertikale Vernetzung in der Pädiatrischen Onkologie. Onkologe 6: 814-188, 2000 Herold R, Schreiber B, Paulussen M, Längler A, Berthold F, Kodierempfehlungen für Diagnosen und Prozeduren in der Pädiatrischen Onkologie und Hämatologie, November 2001, published by the GPOH and the competence network, 60 pages Langer T, Henze G, Beck J.D. Basic methods and the developing structure of a late effects surveillance system (LESS) in the long-term follow-up of pediatric cancer patients in Germany. Med Pediatric Oncology 34: 348-351, 2000 Löning L, Zimmermann M, Reiter A, Kaatsch P, Henze G, Riehm H, Schrappe M. Secondary neoplasms subsequent to Berlin-Frankfurt-Münster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 95: 2770-2775, 2000 Herold R, Henze G, Creutzig U. Kompetenznetz Pädiatrische Onkologie und Hämatologie. humboldt spektrum 4: 4-9, 1999 Creutzig U, Jürgens H, Henze G. Kompetenznetzwerk Pädiatrische Onkologie und Hämatologie (Editorial). Klin Pädiatrie 211: 187-188, 1999 Herold R, Creutzig U, Henze G. Kompetenznetz Pädiatrische Onkologie und Hämatologie. InFoOnkologie 5: 292-295, 1999

	Henze G: Das Kompetenznetz Pädiatrische Onkologie und Hämatologie. BVM Medical, 2002, in press Herold R, Henze G, Creutzig U. Kompetenznetz Pädiatrische Onkologie und Hämatologie. In: Lebendige Wissenschaft – Medizin, alpha Verlag Lampertheim 2001 <u>Patents</u> None planned.
B.5	**Networking** All the activities of the CMG are directed at either implementing or improving networking between the structures of the network, the GPOH, external partners and interested professional and non-professional groups.

Part C – Follow-Up Proposal

C. 1	**Aims** The started activities will be continued according to the aims listed in B.2. During the second funding period, emphasis will be put on the following issues: Á developing a concrete concept to finance and to sustain the created network structures that are essential for high quality patient care Á developing and cataloguing qualification criteria for certification of treatment institutions Á developing a recognized certification program for the FSA Á supporting efforts to harmonize the design and conduct of clinical trials Á transporting the aims and ideas of Pediatric Oncology to the public Á providing professional and non-professionals with a comprehensive medical information service portal on the internet Á realizing and intensifying vertical networking Á evaluating the network internally in respect to the initially proposed aims as well as externally in respect to the network's lasting effects on patient care within the public health system
C. 2	**Methodological approach** Methods, instruments and tools will be the same as before (for details, please refer to parts B – F in section 1 of the Midterm Report).
C. 3	**Work plan** The general aims as stated in the initial project proposal are still relevant and achievable. The coordination and management group (CMG) will continuously provide the services established and, in particular, continue to coordinate and manage the various projects and the cooperation within the network. Milestones of the CMG activities are detailed in the annex (page 43).
C. 4	**Networking** All the activities of the CMG are directed at either implementing or improving networking between the structures of the network, the GPOH, external partners and interested professional and non-professional groups. The activities of the CMG during the second funding period will contribute to the general goals of the competence network and of the GPOH. The structures of the network facilitate the cooperation between the various research groups. Redundancy will be avoided. Exchange of data and material will be supported on various levels. Especially, putting the concept of sustainability into practice will result in added value to the network members, the GPOH and patients and families. These three groups are in the same way interested in achieving a permanent recognition and financing of those diagnostic and therapeutic measures which establish the quality of care.

Part D- Requested Funding for the Project

D.1 **Salaries**

Positions needed

#	Position	Justification	Description of main tasks
1	Network executive	Required for running the network's business and for persuing the realization of the medical, organizational and scientific network aims	Leading the coordination and management group routinely, directing running and new CMG subprojects Managing the cooperation between network projects Providing expert knowledge on Pediatric Oncology Communicating and equalizing with the GPOH
2	Network coordinator	Required for performing the coordination of network projects and for conducting CMG subprojects	Organizing and leading the FSA mission and employment and coordinating network projects Devising and realizing concepts and contents for FSA training, certification and profession establishment Establishing internet-based information services Devising a concept from the ideas for sustainability of the network and the quality system, starting to realize it
3	Biomedical documentarists (2,5 posts; 0,5 added as compared with first funding period; planned shift from a 1,0 post of a coworker in „basic data set" implementation from project B/1)	Required for the „Study support" as centrally established for GPOH clinical trials	Retrieving overlapping problems of clinical trials; devising solutions with regard to data management for trial offices and reference laboratories Providing advice on requirements relevant to trials such as biometry and GCP; evaluating and piloting the use of standard operating procedures Organizing and managing trial office staff meetings Starting to elaborate „trial specific data (terminology)

	4	FSA monitor	Required for the practical FSA action control	Monitoring the FSA action by performing site visits and reviewing local fulfillment of action requirements Registering on site workflows, identifying and reporting problems during the practical conduct of the clinical trials Organizing FSA training meetings, caring for FSA staff
	5	Assistants in clinical research and quality control (FSA) (9 full time posts, 16 half time posts*)	Required to improve practically performing clinical trials in participating treatment institutions and to markedly intensify the networking between pre-existing structures (i.e., clinical trials, reference laboratories, registries and hospitals)	The tasks have been laid down in the „Tätigkeitsprofil" which is part of the contracts between the CMG and participating hospitals on the local FSA grant (cf. annex) The tasks encompass registering patients, organizing investigations according to the trial protocols, gathering and reporting clinical data, exchanging patient samples, delivering material to the tumor banks, using electronic means such as DOSPO, informing involved coworkers about details of clinical trials and amendments, participate in trainings and improving local trial infrastructures.
	6	Secretaries (2 x 0,75; added 0,75 taken from FSA posts)	Required for running the network executive's office and for administrating the FSA and coworkers of the CMG	Running the network executive's office Coordinating and administratively managing CMG staff (about 39 individuals), including applications, resource control and meeting organisation
	7	Scientific coworker to the Speaker (0,5 post; new)	Required to enable the Speaker to be present and take respective responsiblities at various occasions for the network.	Taking over routine obligations in clinical care and medical education from the Speaker. The heavy workload was not anticipated for the first funding period.

8	Scientific editor (0,5 post; post was part of project B/2 during the first funding period)	Experienced medical coworker required for the information services (internet knowledge server)	Managing the contents and the presentation of the internet information services; generating contents and composing internet format articles Researching topics of Pediatric Oncology and Hematology and and equalizing also with the GPOH, network projects and self-help organizations
9	Documentarist/ Technical Assistant	Required for the continued support to the ALL immunophenotyping reference laboratory	continue managing data, materials, the data base, performing exchange of lab data with trials offices
10	Student coworkers (6 x 40 hrs/month[+])	Required for logistics and support of the CMG coworkers	According to the assignment[+]

*The assignment of FSA posts to treating institutions is based on the respective numbers of patients registered with the GCCR from 01.01.1996 to 31.12.2000. Half and full posts were assigned if more than 25 and 50 patients were registered, respectively. This procedure was again confirmed and agreed upon by the project leaders. Reductions in post assignments to three institutions from the first to the second funding period are due to fewer patients registered. To compensate for the administrative workload experienced during the first funding period (39 actual/former FSA), a 0,75 secretarial post is proposed for funding from the reduction of posts as stated above.

[+] The assignment of student coworkers is as follows: network executive's office (1), coordinator's office (1) and immunophenotyping reference laboratory (2 x 40 hrs/month). These assignments correspond to the well-established employment of student coworkers during the first funding period. Additionally, one student coworker is proposed as a (so far lacking) support of the ALL-BFM cell bank, which is necessary to guaranty material exchange with several competence network projects.

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Funds needed (given in €)

#	Position	Posts	2002	2003	2004
1*	BAT Ia	1	23008,13	94657,48	72385,13
2	BAT Ib	1	14826,00	60492,00	46278,00
3	BAT Iva	2,5	30180,00	123120,00	94207,50
4*	BAT Vb	1	10188,00	41340,96	31470,57
5	BAT Vb	17	173196,00	706656,00	540549,00
6	BAT Ivb BAT Vb	0,75 0,75	8349,75 7641,00	34065,00 31176,00	26061,75 23847,74
7	BAT Ib	0,5	7413,00	30246,00	23139,00
8	BAT Ib	0,5	7413,00	30246,00	23139,00
9	BAT Vb (Ost)	0,5	4228,50	17250,00	13198,50
10	Student coworkers	6	9875,89	40358,17	30862,13

* The funds are to be commissioned („Forschung und Entwicklung" contracts).

D.2 **Consumables (given in €)**

Title	Justification	2002	2003	2004
Position 0838, „Consum-ables"	Materials for circular letters, costs for own printed matters, refill material, costs for rented appliances, e.g. for meetings	1000	4000	3000
Position 0839, „Geschäfts-bedarf"	Network executive's office costs including telephone, online, postage and service costs.	2000	6000	4000
Position 0840, „Literature"	Costs of special literature not to obtained from the local library	1000	1000	500
Position 0841, PR team costs	Costs of overlapping PR activi-ties as proposed by the DLR/PT and the PR team of the medical competence networks (reference: protocol of the PR team meeting 15.12.2001).	1250	5000	3750

Please note that the costs of these consumables requested for funding correspond to expenditures during the first funding period.

D.3 **Investments**

Six computers are required to fulfill current requirements for data exchange, programming and information services applications associated with positions 1, 2, 3 (three individuals) and 8. Estimated costs (6 x 1400 €) total: 8400 €.

D. 4

Other Costs (given in €)

Travel costs

The costs of the travels of network's personnel and of own scientific meetings (such as detailed in section 1, B5, page 10) are administered and covered by travel funds which are associated with project A. These funds closely covered the needs. For the second funding period, an annual amount of **50000 €** for travel and meeting expenditures is again requested on behalf of the network.

Commissions

During the first period, both commissions listed below were funded by reallocating funds of project A according to an official arrangement with the DLR/PT. This was based on an approved grant application („Extern-wissenschaftliche Evaluation und Prozeßbegleitung des Kompetenznetzes") that extended until 2004. Accordingly, the following commissions are proposed for continuation of funding. The commercial bids of the partners are partly included in the annex.

Title/Contents (Partner)	2002	2003	2004
Network public relations, information brochure release, press conferences, media contact services and marketing; including concept refinement according to the first funding period. (drescher konzept grafik design, Berlin)	11600	46400	34800
Network evaluation and process management. (Wissenschaftliches Institut der Ärzte Deutschlands gem. e.V., Bonn, and Prognos AG, Köln)	0	31496	73882

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Computer-based application system for Pediatric and Oncology Hematology (Project B/1)
Grant No.	:	01 GI 99 59

Name of scientist-in-charge	:	Dr. sc. hum. Ulrike Kutscha
Institution	:	University of Heidelberg Institute for Medical Biometry und Informatics Department of Medical Informatics
Address	:	Im Neuenheimer Feld 400 D-69120 Heidelberg, Germany
Phone	:	+49 (0) 62 21 – 56 – 54 81
Fax	:	+49 (0) 62 21 – 56 – 49 97
E-mail	:	ulrike_kutscha@med.uni-heidelberg.de

Project home page (if different from Network homepage)	:	http://dospo.uni-hd.de/

Part A - General Statements about the Project	
A.1.	**Subject** The aim of this project is to provide a computer-based application system for Pediatric Oncology research networks that supports clinicians, trial centers and other research institutions in their routine work. The following developments are currently in progress: Á Aim1: Development, introduction and maintenance of the Pediatric Oncology documentation and therapy planning system (DOSPO). Á Aim2: Development of a terminology server for Pediatric Oncology. Á Aim3: Development of a generic tool for trial databases and trial specific data entry modules for DOSPO.
A.2.	**Co-Investigators** Á DOSPO Task Force, Chair: Prof. Dr. N. Graf, University Hospital, Department of Pediatrics, Homburg/Saar Á Medical Informatics in Pediatric Oncology Work Group, Chair: Dr. O. Basu, University Hospital, Department of Pediatrics, Essen; Co-Chair: Dr. U. Kutscha, University of Heidelberg, Institute for Medical Biometry and Informatics, Department of Medical Informatics Á Terminology Server, Prof. Dr. K. Welte, University Hospital, Department of Pediatrics, Hannover Á Data Protection, Knowledge Server, Prof. Dr. K. Pommerening, University of Mainz, Institute for Medical Biometry, Epidemiology and Informatics Á Telemedicine, Prof. Dr. H. Jürgens, University Hospital, Department of Pediatrics, Münster Á Standards committee, Chair: Dr. P. Kaatsch, German Childhood Cancer Registry, Mainz Á Several hospitals and trial centers are cooperating in tool applications, data exchange, and standardization of terminology

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects ☐ yes ☒ no

(b) clinical trials ☐ yes ☒ no

(c) animal models ☐ yes ☒ no

(d) gene therapy ☐ yes ☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	181,6	10,6	3,0	12,6	0	207,8
2004	184,8	10,5	0	12,6	0	207,8

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The B1 subproject is divided into three closely connected subprojects. During the course of the first subproject, a documentation system for Pediatric Oncology, DOSPO, was to be developed further and introduced in the hospitals. A considerable share of DOSPO's further development is taken in by the realization of a diagnosis and procedure documentation system, which is well-adapted to meet the needs of its competence network. Countless other improvements were also realized, or are currently underway. DOSPO has also been introduced to additional hospitals. Organizational prerequisites were established and systematically introduced to meet the requirements of the individual hospitals. They were harmonized to the goals of the whole competence network.

The terminology server needed to standardize terminology within Pediatric Oncology has been realized, and an application system developed to maintain it. Currently, the terminology server is being filled with content. A standardization committee has been established to oversee this process. The first task of the committee was to create of a new version of the basic data set used in Pediatric Oncology. This data set has been embedded into the terminology server. Meanwhile, a first study is being standardized and entered into the terminology server. Certain improvements to the terminology server are still necessary.

A first milestone has been reached in the development of the module generator, which generates study-specific modules for DOSPO. Study-specific databases can be generated based on the standardized terminology of the terminology server. To date, a second work phase is in progress in which study-specific forms (electronic and conventional) are being created.

The subproject was recognized with an international award for DOSPO's excellent architectural concept.

B.2 **Original aims of the project**

Aim1: Development, introduction and maintenance of the documentation and therapy planning system for Pediatric Oncology (DOSPO).

The documentation and therapy planning system for Pediatric Oncology will be developed further in close adherence to the needs of the participating hospitals. Beside further development, providing, or intensifying, support to the individual hospitals is also necessary.

Aim2: Development of a terminology server for Pediatric Oncology.

To ensure the comparability of the data collected in the clinical trials, and to simplify documentation within the hospitals, the documentation language for therapy optimization trials of the GPOH is to be standardized. A terminology server will be developed and realized to simplify administration of the documentation language.

Aim3: Development of a generic tool for trial databases and trial specific data entry modules for DOSPO.

	Specific data entry modules and interfaces to the databases of the trial centers must be implemented to collect trial specific data. To reduce manual effort, and to increase the accuracy of developing and updating trial-specific modules for DOSPO, we are implementing a generic software tool to automatically generate the modules. This generic tool uses the terminology server for Pediatric Oncology.
B.3	**Scientific results** The results of the project have been organized for presentation according to the project aims. <u>B.3.1 DOSPO Core System</u> Developmental standing of DOSPO (December 2001) During the past two years, the following most important further developments have been realized. Functions for clinical support Á - During the course of the project, the health policy reform 2000 was passed. Hereby, a DRG-oriented billing system will come into effect in 2003. It is of immense importance to the competence network that the necessary documentation is standardized and oriented towards specific specialty and medical aspects. Good documentation will become existential for hospitals. In cooperation with the hospitals in Homburg and Berlin Charité, a module was realized for systematic, centralized collection of diagnoses and procedures, and integrated into DOSPO. DOSPO was, therefore, expanded to include a documentation component that was not initially planned for the project. However, since its benefit to the competence network is rated extremely high, the development of the diagnosis and procedure documentation module was added and treated as a major project activity. Á The modules responsible for defining the protocol and for calculating therapy plans were expanded to include the possibility of randomization. Therapy branches were added, as well as presentation of the underlying calculations within the therapy schedules. Á Defining study protocols requires a high initial effort in terms of introducing therapy-planning components. To reduce these efforts, essential studies (currently 8) were inputted by the DOSPO team. Currently, the entered protocols have been distributed to interested hospitals. The necessary hospital-specific modifications are being supported. Á Discharge letter writing / report generation was revised in cooperation with the hospitals in Essen and Köln to ensure user-friendly presentation. Concurrently, the system was adjusted to support Microsoft Word 2000. Á -In cooperation with the hospitals in Stuttgart and Essen, DOSPO was modified to include a module for scheduling appointments. In addition, DOSPO was fitted with a patient-centered note pad function. Functions to support networking within the competence network Á The newly developed GPOH-PID (person identifier), stemming from the B/2 subproject, has been integrated into DOSPO. The PID can be entered and its

validity tested.

- Specific functions for evaluating the frequencies of diagnoses, procedures, chemotherapies, toxicities, participation in trials, other more general characteristics, as well as length of stay were included in DOSPO.
- The fundamental technical requirements for exporting data to the childhood cancer registry have been met. Currently, the interface needed to accept messages by the childhood cancer registry is currently under development. In addition, organizational tasks must be supported more extensively to actually bring the interface to operation.

Realization of technical requirements

- The installation program has been expanded to secure data during distribution of updates.
- The help function has been revised completely and expanded.
- In order to use DOSPO within a network environment, the data base management system was switched to a client/server-capable data base management system, Interbase.
- Data protection mechanisms for the DOSPO databases were improved in cooperation with the hospital Berlin Charité.

Realization of organizational requirements

Due to the immense efforts placed in bringing DOSPO to widespread routine use in the hospitals, several new requirements have arisen during the course of the project regarding functionality and user friendliness. The very different prerequisites brought by the various hospitals make clear how diverse the priorities and requirements of each are, some of which stand in competition to one another. An essential task arose from this aspect. The various requirements and priorities of the hospitals are being collected, structured, and their realization initiated in projects. Strategic planning of the further development should not be the sole responsibility of the subproject. Therefore, in September 2000, a steering committee (DOSPO Task Force) was formed. The steering committee members are important decision makers of the competence network (speakers, executives), as well as specialists of various areas (hospitals, trial centers, childhood cancer registry).
(Current task force members are Prof. Dr. U. Creutzig, S. Garde (System development DOSPO), Prof. Dr. N. Graf (chair of the task force), Prof. Dr. Henze, Dr. Herold, Dr. Kaatsch, Prof. Dr. Niemeyer, Dr. Kutscha (Project leader DOSPO), Dr. Schilling, Dr. Zimmermann.)

Standing of the introduction (December 2001)

DOSPO is running routinely in 6 hospitals. However, therapy planning functionality (4 hospitals, some with individual cycles only), physician discharge letter functionality (3 hospitals), diagnoses and service documentation (2 hospitals), scheduling of appointments (1 hospital) and note pad functionality (1 hospital) are not in use in all hospitals. Test installations were set up in 24 hospitals. The diagnoses and procedures documentation is receiving very positive acceptance due to its strong focus on the needs of Pediatric Oncology and its user friendliness. A pilot phase to introduce a HL7 interface is underway for three hospitals.

B.3.2 Development and establishment of a terminology server

Development of a computer-based application system for the terminology server

A semantic data model has been designed to represent the terminology. The item definitions are concept-oriented, while each concept can possess several synonymous terms. Relationships between concepts can be represented. In addition, standardized and non-standardized, items can be differentiated. Also, it is possible to define trial forms logically using the general items. It is possible to specify which trial item should appear in which context on which form. The semantic data model was realized as a relational database structure. This concept was kept very general to ensure portability to other specialty areas. An application system has been developed that allows building the terminology based on the semantic data model.

Standardizing the terminology

The basic data set of the GPOH was completely revised (final decision by 01/2001). The coding tables were modified to meet the latest international standards to ensure international comparability of the collected data. Ambiguities were removed from the GPOH classification. The basic data set was extended to include a glossary of definitions of the most important concepts contained. The basic data set is available to all hospitals and trial centers at http://www.dospo.uni-hd.de/mv/bds_dt.htm. „Standardizing terminology in Pediatric Oncology – the base date set“ was presented for publication in the specialty journal „Klinische Pädiatrie“ during mid-01/2002.

Entry of the terminology used in Pediatric Oncology

The old and new basic data sets have been maintained in the terminology server. Currently, the items of a first clinical trial (therapy trial SIOP 01-09 for Nephroblastoma, Wilms-Tumor) are being entered, taking standardization into account across all trials. The targeted standardization of all items, across all trials, is work intensive, and will require further resources throughout 2003 and 2004.

B.3.3 Module generator

Requirements analysis

Within the scope of requirements analyses, object-oriented business process analyses were conducted in two GPOH trial centers. The trial center of the Cooperative Soft Tissue Sarcoma Trial at the Olga Hospital, Stuttgart, Germany, was chosen as an example trial for solid tumors. The identified business processes were represented using UML use cases and specified in structured descriptions. Next, the trial center of the ALL-Relapse Trial of the Charité, Berlin, Germany, was examined. The modeling results of the trial center examinations were compared systematically. The requirements analysis resulted in important knowledge about the organizational sequences and setup of the trial centers.

Design and development of a program to generate study databases based on the terminology server

	An algorithm was designed and successfully realized to automatically generate trial databases based on the terminology server. The business processes identified in the requirements analysis were used. With the help of this algorithm, a database can be generated automatically for any trial defined in the terminology server. In combination with respective on-screen forms, the database is to become the primary part of the respective trial-specific DOSPO module. Currently investigations are underway to determine to what extent the generated database can also be used in trial centers. This may ease data exchange between the Pediatric Oncology centers and the trial centers considerably. Due to the automatic generation, terminological changes within the terminology server can be integrated into the respective database quickly and consistently. This is an important step toward integrating the standardized terminology into the documentation of the competence network. B.3.4 Consequence of the feedback of the external advisory board The feedback of the external advisory board in september 2001 triggered an intensive restructuring of the current project plan in cooperation with the task force. Derived from the recommendations of the advisory board, the task force initiated precise projects focussed on essential aims of DOSPO. The first main activity is the implementation of a HL7-Interface to automatically receive patient data from the hospital patient management systems. DOSPO was modified to represent the necessary HL7 case structure. The HL7 interface has been developped. Piloting of the HL7 interface's functionality in 3 cooperating pilot institutions is currently underway. Meanwhile, the Charité has successfully tested the interface in a routine environment. Secondly, comprehensive improvements of the modules protocol definition and therapy planning are initiated. A product requirement specification is created in close collaboration with selected users with DOSPO experience. A prototype has been developped which illustrates the improved user interface and functionality. Additionally, the prototype demonstrates new guidelines for the future design of DOSPO user interfaces. Currently the task force is revising the product requirement specification, which will be the base for the reimplementation of the therapy planning module.
B.4	**Publications and patents** Knaup P, Harkener S, Ellsässer K.-H, Haux R, Wiedemann T. On the necessity of systematically planning clinical tumor documentation. Meth Inform Med 2001;40, 90-98 Knaup P, Wiedemann T, Wolff A, Creutzig U, Haux R, Schilling FH (1999). Computer-assisted documentation and therapy planning in paediatric oncology--introduction of a nationwide solution. Klinische Pädatrie 211(4), 189-91. Merzweiler A, Knaup P, Creutzig U, Ehlerding H, Haux R, Mludek V, Schilling FH, Weber R, Wiedemann T. (2000). Requirements and Design Aspects of a Data Model for a Data Dictionary in Paediatric Oncology. In: Hasman, A, Blobel, B, Dudeck, J. et al. (Hrsg.). Medical Infobahn for Europe, 696-700. Amsterdam: IOS Press. Knaup P, Mludek V, Wiedemann T, Bauer J, Haux R, Kim L, Schilling FH, Selle B. (2000). Integrating Specialized Application Systems into Hospital Information

Systems -Obstacles and Factors for Success. In:Hasman, A, Blobel, B, Dudeck, J. et al. (Hrsg.). Medical Infobahn for Europe, 890-894. Amsterdam: IOS Press.

Merzweiler A, Knaup P, Weber R, Ehlerding H, Haux R, Wiedemann, T. (2001). Recording clinical data - from a general set of record items to case report forms (CRF) for clinics. In: Patel, V, Rogers, R, Haux, R. (Hrsg.). MEDINFO 2001. Proceedings of the 10th World Congress on Medical Informatics, 653-657. Amsterdam: IOS.

Weber R, Knaup P, Knietig R, Haux R, Merzweiler A, Mludek V, Schilling FH, Wiedemann T. (2001). Object-oriented business process analysis of the Cooperative Soft Tissue Sarcoma Trial of the German Society for Paediatric Oncology and Haematology (GPOH). In: Patel, V, Rogers, R, Haux, R. (Hrsg.). MEDINFO 2001. Proceedings of the 10th World Congress on Medical Informatics, 58-62. Amsterdam: IOS.

Knaup P, Merzweiler A, Mludek V, Weber R, Wiedemann T. (2000). Pädiatrische Onkologie. Rechnerunterstützte Dokumentation und Therapieplanung. Praxis Computer - Magazin für moderne Technologien und Management in der Arztpraxis (Beilage zum Deutschen Ärzteblatt), 16,6/2000,34-36.

Knaup P, Merzweiler A, Mludek V, Weber R, Wiedemann T. (2000). Pädiatrische Onkologie. Rechnerunterstützte Dokumentation und Therapieplanung. Deutsches Ärzteblatt, 97,45,B2564-B2566.

Knaup P, Wiedemann T, Bachert A, Creutzig U, Haux R, Schilling F. (2002). Efficiency and Safety of Chemotherapy Plans for Children. CATIPO – a nationwide approach. Artificial Intelligence in Medicine, 24,229-242.

B.5 **Networking**

The terminology server supports the standardization of the terminology. A new basic data set has been created and fit to meet current international standards. The development of a diagnoses and procedures documentation module supports a uniform presentation of the competence network to the outside. In the therapy planning area, the relevant study protocols, which have been created for DOSPO, are being made available to other hospitals. Hereby, a synergetic step and a contribution to quality assurance have been made.

Part C – Follow-Up Proposal

C.1 **Aims**

The computer-based documentation system for Pediatric Oncology (DOSPO) will help support clinicians in their daily work and documentation needs. A widespread use of DOSPO in hospitals will have a standardizing and quality assurance effect that goes beyond the individual hospitals. The data collected in the planning and documentation system will be made available to the hospitals, trial centers, and the childhood cancer registry. The central target of the B1 subproject is to fulfill this requirement within the present and upcoming funding period. The following aims arise from this target:

Aim 1: Expansion of routine DOSPO operation within the hospitals.

In February 2002, the extended leadership met to intensively discuss the DOSPO project and its further development. The extended leadership fully stands behind a continuation of the project. However, they point out that the development and evaluation of a user-friendly system for hospitals, capable of integration in standing hospital information systems, requires sufficient resources. Therefore, the extended leadership resolved to concentrate with highest priority on DOSPO's clinical introduction within the upcoming funding period. Furthermore, the module generator development subproject will be postponed to prevent endangering the achievement of this aim. More importance will apparently be attached to hospital needs (therapy planning, clinical documentation, …) in comparison with the first founding period.

The necessary measures to realize the expansion of routine DOSPO operation are discussed in the methodological approach (C.2).

Aim 2: Provide the trial centers with the support needed to achieve comprehensive terminological standardization of the trials.

Next to using computer supported data exchange to network the clinics and trial centers, a central task of this subproject continues to be networking the trial centers by supporting the standardization of terminology.

Aim 3: Secure DOSPO's operation and provide sufficient support to the user hospitals and trial centers beyond the funding period.

Software must continually be fitted to meet new requirements, for example, changes in legal requirements or technical innovations. Supporting the hospitals in the introduction and operation of DOSPO, or new DOSPO functionality, will require a continuous effort. In the long run, these activities will need to be secured independent of temporary funding. Therefore, Aim 3 was included as a further aim of this subproject. Building long term structures to support the competence network during the introduction and maintenance of the computer-supported application system requires efforts that must be covered by the upcoming funding period.

C.2	**Methodological approach** Steps to achieve Aim 1: Expansion of routine DOSPO operation within hospitals The intended measures to reach widespread routine use of DOSPO are described in the following. Provision of project management support to hospitals regarding the introduction of DOSPO In addition to the quality of a software product, the way the product is introduced also has a major impact on the success of the introduction. Software introduction must be recognized as a project. Therefore, it should be conducted using the methods common to project management. These methods include producing requirements specifications, as well as a project plan. The latter shows the timely sequence and necessary project resources. The specified requirements describe the basic requirements of the user clinic that are important to system introduction (e.g. standing patient management and communication systems). Also, it should specify how DOSPO will be used in the hospitals (work stations, study protocol). The user clinic and the project leader, in cooperation with the established DOSPO Task Force, dismiss the specifications and the project plan. These documents are the foundation upon which the following project phases of the system introduction build, such as system installation and customization to the individual clinic environments. Examples of necessary adjustments are setting interface parameters, performing integration tests (in which the application system is tested within a test scenario set by the clinic), user training, and beginning routine operation. The requirements specifications and the project plan can help supervise the progress and success of the project. The individual introduction projects are part of an overall project to comprehensively introduce DOSPO in the user hospitals. Close connection between the project phases development, piloting, comprehensive introduction, and routine operation The path certain modules take from development to comprehensive routine use in the user institutions is decided in specific interwoven project phases (development, piloting, comprehensive introduction, routine operation). For this reason, primary user contacts must be designated during the development phase. These individuals closely accompany the development phase. A pilot phase in 2 or 3 user hospitals directly follows the development phase in accordance to the project plan. Following the pilot phase, a comprehensive introduction of the module is planned and realized. Herein, the introduction of the module stands in the foreground, not its further development. Therefore, suggestions for improvements are gathered and projected for specific update cycles. However, the introduction is largely independent of the recommendations. Beside the introduction, preliminary tasks for later system operation are underway, for example, user support, acquisition of new user hospitals, planning and conducting introductions in new hospitals. Operational tasks include the systematic and continual collection of requirements placed upon DOSPO. Significant requirements are presented to the task force with an estimate of the efforts involved. The task force discusses the generality and priority of the individual aspects and dismisses procedures for their realization, while taking the proposed efforts into account. To a certain extent, the realization of these requirements can take place parallel to the main development activities (see below).

Steps to achieve Aim 2: Provide the trial centers with the support needed to achieve comprehensive terminological standardization of the trials.

To achieve Aim 2, a continuation of the subproject responsible for the development and establishment of the terminology server is essential.

The semantic data model of the terminology server was expanded to include reference integration components and version management for the items, as well as adjustments to the database schema. These expansions are also to be made to the functionality of the application system.

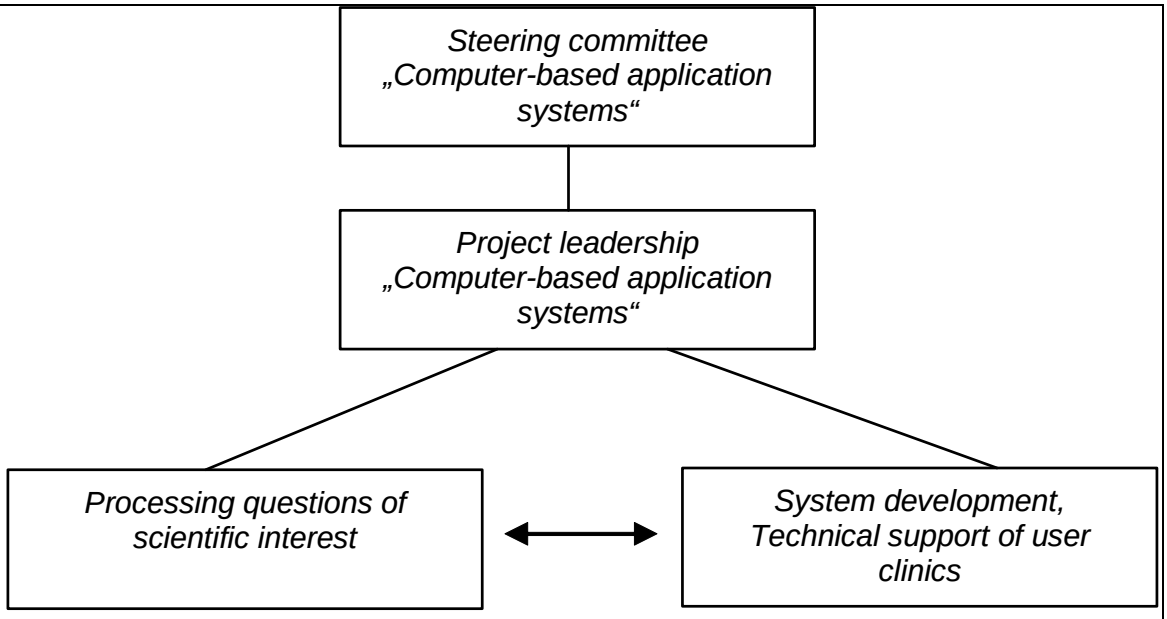
A pilot study will determine the necessary changes to improve the practicality of the functionality of the application system. The functionality will need to be adjusted accordingly. Simultaneously, the pilot study will evaluate how far standardization of the items used in the study forms can be increased by use of the terminology server.

In addition, in cooperation with the standardization committee, further items (by topic area) must be standardized and further trials taken up by the terminology server. This process has proven more work intense than initially planned. Therefore, a continuation of this subproject will be required beyond 2002. Medical informatic support will continue to be necessary throughout the second funding period.

Steps to achieve Aim 3: Secure DOSPO's operation and provide sufficient support to the user hospitals and trial centers beyond the funding period.

To ensure the utilization of DOSPO, as well as the long-term continuity of maintenance and technical support to the user hospitals, a concept must be designed and realized that reflects the increasing routine use of the system. In this case, hand over to a cooperation partner, e.g. a transfer or industrial partner, is reasonable and should be established within the upcoming funding period. The following aspects must be considered in this regard. The activities must be coordinated according to the terms of the competence network. The project leader position must be upheld within the competence network. Beside the project management tasks, the project leader is responsible for conceptional activities, quality assurance of the software, consulting, and training of the user hospitals. In case highly innovative scientific questions (e.g., an overall system evaluation) arise, cooperation should be maintained with research centers (see figure below). The lobby of the competence network should be strengthened by a higher-ranking steering committee. As shown, the functions of the project leader bridge an important gap.

…



Summary

The upcoming funding period is dedicated to ensuring that DOSPO finds wide use in the hospitals. Realization of system improvements and provision of intense introductory support to the hospitals are necessary parts of this dedication. The previous work invested in standardizing the terminology must be continued. By the end of the funding period, maintenance and technical support of DOSPO is to be handed over to a cooperation partner. By building up the cooperation during the funding period, the transfer of know-how is to be ensured.

C.3 **Work plan**

Work plan for the further development and introduction of DOSPO in hospitals

The DOSPO development and introduction work plan is divided into the various project modules. It can be found in the appendix section (DOSPO Work Plan). The plan contains the activities required for further development and introduction of the current DOSPO core system. A detailed list of the necessary activities and their dependencies are contained in the work plan. It presents the time schedule planned from 2002 to 2004 to make the relationships among remaining tasks more transparent. Blue activities mark software development projects and pilot phases. Blue-green activities represent widespread introduction projects in hospitals. Green activities stand for operative tasks of the components. For example, until mid-2003 the development and piloting of the HL7-Interface is finished and their introduction in further hospitals combined with the introduction of the documentation of diagnoses and procedures is underway. Furthermore, the reimplementation of the modules protocol definition and therapy planning is finished and they are introduced in selected pilot hospitals.

The time schedule is based on the resources requested below. With the proposed personnel, the subproject will be able to complete the development and introduction of DOSPO in hospitals within the second funding period. A transition to ongoing routine operation can be achieved.

	Work plan to achieve widespread terminological standardization of the studies. The work plan for widespread standardization of the terminology can be found in the appendix section. (Terminology Server Work Plan). Work Plan to ensure the routine use of DOSPO beyond the funded time period. In 2003, different cooperation schemes will be developed. Possibly, a call for tenders will be conducted. In cooperation with the steering committee, selection of the cooperation scheme best suited for the competence network will be selected. In 2004, the hand over of the maintenance of the application system and its users will be prepared.
C.4	**Networking** The terminology server provides the prerequisite for comprehensive evaluations across the clinical trials. Integration of the trials into the terminology server, while simultaneously providing standardization, enables finding answers to medically relevant questions beyond the bounds of a single trial. In this area, medical informatics research directly provides important methods for medical research. Since other competence networks also see the need for a terminology server, the following project phase also examines the usability of the terminology server for other competence networks. Furthermore, cooperation with other competence networks in the area of therapy planning is targeted. A first contact has been achieved with the competence network „Malignant Lymphoma“, which is developing similar functionalities (e.g. therapy planning) within the scope of a development of an 'onco-work station' for adult oncology. Next to exchanging experience among work groups, an examination of whether certain developments and activities can be brought together is planned to achieve a synergy effect.

Part D- Requested Funding for the Project

D.1 **Salaries**

Project leadership

The project must remain under the leadership of a project leader (BAT Ib). The project leader is responsible for the keeping the budget and the overall project plan. A good calculation of the resources is very important for the various project areas and subprojects. The project is a combination of system development and system introduction. The hospitals and trial centers involved must be networked. The project leader fosters contacts to the hospitals and trial centers, and supports system introduction through project management measures.

Another important task of the project leader is to continue establishment of a model for cooperation between the competence network, system development, system support, as well as research. This is important to ensure the stability of the model beyond the funding phase. Also, to ensure that scientific results are transferred to practical everyday routine use in both hospitals and trial centers.

Resources and time planning: ½ Bat Ib 1/2003 – 12/2004

System development, System introduction and routine operation

Conception and realization of the necessary modules, and their improvements, belong to the area of system development. Both occur in tight cooperation with the user. Thereupon, a pilot phase within the user hospitals must take place. As presented in C.2, it will be necessary to support the users intensely during the introduction phase of DOSPO. Each introduction, in each clinic, is seen as a subproject. Therefore, it must be accompanied by project management measures. On location customizing of the system to meet the needs of the specific clinical environment (especially, setting interface parameters and adjusting study protocols to the hospitals), as well as user training remain part of the system introduction phase. Following a resource intensive introduction, a certain amount of effort remains for supporting everyday clinical routine operation.

Outstanding developments, as well as system introduction, will require the support of 2 scientific employees by the end of 2004, in order to provide full functionality to all of the hospitals involved.

Resources and time planning: 2 Bat IIa 1/2003 – 12/2004

System development and introduction

During system development and introduction, a certain amount of well-bounded subtasks arise, for example, buildup of a gateway for an interface in one of the user hospitals, or the realization of a note pad function for DOSPO. To effectively support the areas of system development and introduction, the employment of 2 assistants is sensible.

Resources and time planning: 2 scientific assistants 1/2003 – 12/2004

Standardization of Terminology

Maintenance functionality for the terminology server and the application system must be expanded. Evaluation of the terminology server must be continued, as it will help make the terminology server utilizable for other competence networks.

Resources and time planning: ¼ Bat IIa 1/2003 – 12/2004

Overall personnel requirements (in €)

	Estimated Personnel costs 2003 (per Month)	2003	Estimated Personnel costs 2004 (per Month)	2004
1/2 Project leader	5041,00	30246,00	5142,00	30852,00
2 Scientists (System development, system introduction)	4734,00	113616,00	4828,00	115872,00
¼ Scientist (Support uniformity of terminology)	4734,00	14202,00	4828,00	14484,00
2 Scientific assistants	11779,14	23558,28	11779,14	23558,28
Annual sum		181622,28		184766,28
Overall sum				366388,56

D.2 **Consumables**

To professionally further the development of the system, an update of the development environment (Delphi and special tools) will be necessary for several workstations. The update is to take place during the year 2003. An exact listing can be found in the table below. In addition, 500 € per year will be necessary for smaller hard and software components. The handover of software operation to a cooperation partner in the year 2004 requires a calculation of 10,000 €.

Consumables (in €)	2003	2004
2x Delphi 6.0 Enterprise	7669	–
2x InfoPower 3000 Professional	823	–
2x Orpheus 4	818	–
1x Upgrade Delphi 6.0 Professional	357	–
2x IBExpert	392	–
Smaller SW and HW components	500	500
Handover to cooperation partner	–	10000
Annual sum	10559	10500
Overall sum		21059

D.3 **Investments**

The roll out of DOSPO results in a lot of location support of the hospitals. In this way, the mobility requirement increases. The developers need a laptop for efficient support. In 2003 we want to replace one project PC, which no longer meets the increasing hardware requirements for software developing, by a laptop. The prices listed below are taken from the current recommendations posted by the Center for Information Management, Heidelberg.

List of Annual hard and software investments exceeding 400 € (in €):

	2003	2004
Laptop	approx. 3000	–
Annual sum	3000	–
Overall sum		3000

D.4 **Other Costs**

Due to the relevance of the project throughout the entire competence network, many business trips are necessary. The present intensity of the support required by the participating hospitals shows how important presence is for a successful introduction of DOSPO. However, this requires 2 employees to be on the road for 2 days every 2 weeks. The costs of other necessary regular meetings are presented in the following. The frequent business trips make the purchase of a Bahncard (140 €) sensible. The average expenses amount to 80 € for travel, 14 € pocket money for one day (18 € for two days), and 60 € for one night. The following annual calculation can be shown:

	Nr / Year	Number of Employees	Overnight	Costs (in €)
Layovers	Costs / Year			
Bahncard	1	4	–	560
DOSPO task force meeting	6	4	–	2256
Meeting of extended leadership	3	1	1	474
Meeting Informatics work group	2	4	–	752
Meeting with cooperating partners	4	2	1	1264
Meeting with other work groups of competence network	2	3	1	948
Introduction into clinic	20	2	1	6320
Annual sum				12574
Overall sum				25148

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Data Protection, IT Security and Knowledge Server – Computer-based Application Systems (Project B/2)
Grant No.	:	01 GI 99 67/3

Name of scientist-in-charge	:	Univ.-Prof. Dr. Klaus Pommerening
Institution	:	Institut für Medizinische Biometrie, Epidemiologie und Informatik (IMBEI) Johannes-Gutenberg-Universität Mainz
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E-mail	:	pommerening@imsd.uni-mainz.de

Project home page (if different from Network homepage)	:	http://www.kompetenznetz-paed-onkologie.de/prjb/net_B.xml

Part A - General Statements about the Project

A.1. **Subject**

Part 1: Data Protection and IT Security

Part 2: Knowledge Server

A.2. **Co-Investigators**

- Coordination and Management Group, Prof. Dr. G. Henze, Berlin
- Telemedicine, Prof. Dr. H. Jürgens, Münster
- TMF Coordination Center Fraunhofer ISST, Dr. W. Glitscher, Berlin
- German Childhood Cancer Registry, Dr. P. Kaatsch, Mainz

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects	☐ yes	☒ no
(b) clinical trials	☐ yes	☒ no
(c) animal models	☐ yes	☒ no
(d) gene therapy	☐ yes	☒ no

A.4 **Requested Funds for the Second Funding Period***

None.

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	0	0	0	0	0	0
2004	0	0	0	0	0	0

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The Project B/2 consists of two parts. Part one is „Data Protection and IT Security“, part two is „Knowledge Server“. Due to a delayed start the project is 4½ months behind its schedule. The delay affects part one only, whereas part two is in time.

In part one we established secure communication by PGP and secure client-server interaction by SSL and X.509 certificates. We worked out concepts for data protection and IT security, in particular with regard to access control on servers, access to and use of mailing lists, confidentiality of communication and integrity of information. We carried out a market analysis for a smart card based public key infrastructure and decided to delay its introduction until - at the end of 2001 - a consensus was reached in the telematics platform TMF. As an additional working package for part one, a pseudonymisation service turned out to be of fundamental importance for the network. We developed and installed this service which is in production since the beginning of 2002.

In part two we established a working web server that offers a considerable body of information as well as many mailing lists. As it turned out the workflow can be improved by transferring the knowledge server to the coordination center. This transfer will be accomplished in steps beginning with april 2002.

The results on IT security as well as the software for pseudonymisation will be of use for the other networks of the TMF as well.

B.2 **Original aims of the project**

Part 1: The Competence Network for Pediatric Oncology and Hematology develops a comprehensive communication infrastructure. The requirements of data protection in medicine necessitate a carefully developed concept for IT security and its implementation; in particular for

- confidentiality of patient data and other person-related data,
- authenticity and integrity of data and information contents,
- access protection and access control for network services.

The communication channels to be protected use e-mail and client-server interaction.

Part 2: The Competence Network for Pediatric Oncology and Hematology needs a knowledge server that

- provides medical information such as study and treatment protocols as well as recommendations for hospitals, practitioners and patients,
- offers information for education and training,
- hosts mailing lists and discussion groups,
- contains results by the projects of the network.

B.3	**Scientific results** The projects focus is on essential elements of the infrastructure for the competence network. The scientific innovation consists in part only in showing how to exactly specify and realize well-known general and theoretical demands. The most pretentious part of the project was the development of the pseudonymisation service. Some recommendations and specification documents are accessible via the project URL. B.3.1. Concepts We developed policies, defined roles and formulated access rights for information access and interactive web services, including telemedicine services. The essential roles in the network are „member of the network", „physician", „study nurse (FSA)". Access is restricted to members for some documents on the knowledge server, the server of the coordination center, and some study centers. There are special access restrictions for file upload, the pseudonymisation service, the management of mailing lists, the maintenance of the user database, and some special functions. B.3.2. E-mail communication We established secure e-mail communication by PGP, including means for centrally signing and distributing public keys. In particular PGP is used for data transfer to the childhood cancer registry, and provides confidentiality, integrity, and authenticity of e-mail messages in a really simple and cheap way. B.3.3. Secure client-server interaction We developed recommendations for the setup of secure web servers, including the „hardening" of servers that is making them secure against attacks from the internet. As a first step we used SSL-enabled servers to Á establish cryptographically secure connections and Á password protected access to confidential documents; due to the SSL connection the passwords are not exposed on the internet. As a second step we introduced soft user certificates (X.509) to enable strong authentication for web services. Up to now (march 2002) this is used for the pseudonymisation service. A uniform infrastructure that allows single logon to all services in the competence network is in preparation. We offer a web interface for users to sign on to the access restricted services and get a certificate. Furthermore we set up a central user directory that supports the management of roles and rights for web services and the dynamic generation of mailing lists. A data base (postgreSQL) feeds the directory. A java frontend gives access to the data base; access is restricted to a few individuals and controlled by certificates. A distributed object approach presents the data base as a CORBA service and allows authorized access through firewalls. B.3.4. Smart card based public key infrastructure The implementation of a smart card based public key infrastructure (PKI) is delayed. An initial market analysis early in 2000 showed that the available PKI solu-

tions were either proprietary or had no provisions to integrate them into the existing or planned applications. There's not even a simple way to integrate the smart card PKI into existing web browsers. To get to a usable, portable, standardized open solution, we sought the close cooperation and consensus within the TMF platform. In the meantime the market situation is unchanged but, after many efforts, a global (TMF wide) solution is in sight and will be implemented in the competence network in the remaining months of 2002.

Because of the delay there remain some unused funds for external trust center services that should be spent in the second funding period to extend the PKI as far as originally planned.

B.3.5. Pseudonymisation (PID service)

As an additional working package a pseudonymisation service turned out to be of fundamental importance for the network. This was realized as a web based service that gives a unique patient identifier (PID) to be used as a pseudonym. The software is highly configurable, allows several steps of pseudonymisation, and provides flexible database and record-matching schemes. The matching strategy also

- covers cases where the input data are marked as unsure and tries to give a best match,
- tries to avoid homonym errors that are unacceptable in a treatment context,
- minimizes synonym errors.

The matching algorithm and the PID generating algorithm are innovative. The PIDs are constructed by a new cryptographic algorithm and contain redundant information for optimal error detection and correction.

The PIDs are useful as pseudonymous identifiers for multicenter studies as well as epidemiological studies and for the childhood cancer registry. This service is in production since the beginning of 2002.

B.3.6. Web service

The web server was set up with a content management on XML basis together with a search engine. The server contains a large but still incomplete quantity of information. The acceptance is quite good; we count several hundreds visits per day. A part of the information is static documents, another part, such as news or the collection of useful links, are dynamically generated from the data base.

To enhance the workflow and the content management the service is being transferred to the network coordination center in the second half of 2002.

B.3.7. Mailing lists and discussion groups

We established several mailing lists and discussion groups, some of them with archives, that are maintained in the user directory and dynamically generated from there.

B.4	**Publications and patents** Pommerening K. Sicherheit für ein medizinisches Kompetenznetz. In: Victor N et al (Ed.), Medical Informatics, Biostatistics and Epidemiology for Efficient Health Care and Medical Research, Urban & Vogel MMV, München: 272-275, 1999. Pommerening K. IT-Sicherheit in medizinischen Netzen -- aktuelle Probleme und Lösungsansätze. Zentralbl Gynakol 122: 658-662, 2000. Pommerening K. Medizinische Netzwerke: Sicherheit - eine dauerhafte Aufgabe. Dtsch Arztebl 98: A 2085-2087, 2001. Pommerening K, Wagner M. Ein Pseudonymisierungsdienst für medizinische Forschungsnetze. Informatik, Biometrie und Epidemiologie in Medizin und Biologie 32: 251, 2001. <u>Patents</u> None planned.
B.5	**Networking** Both parts of the project constitute fundamental infrastructure components for the competence network. Part one is of basic importance for communication and interaction with respect to data security requirements in medicine and medical research. The public key infrastructure enables the confidential transfer of patient data for multicentric studies and to the childhood cancer registry. The pseudonymisation service reduces the transfer and storage of person-related data and gives an unique - pseudonymous - patient identifier across the competence network, including the childhood cancer registry. Part two, the knowledge server, is an essential tool for horizontal and vertical networking, for cooperation and communication inside the network, and for the visibility of the network to the general public. Part one of the project has pilot character for the other networks under the roof of the TMF; the results are being transferred to other networks.

Part C – Follow-Up Proposal	
C.1	**Aims** Part 1: Data Protection and IT Security. This part is essentially finished with the first funding period. Due to the delayed decision with respect to smart card technology, there are some unused funds for external services (ca EUR 18000) that should be transferred to the coordination center in the second funding period. Part 2: Knowledge Server. This part should be transferred to the coordination center for the second funding period.
C.2	**Methodological approach** N/A.
C.3	**Work plan** N/A.
C.4	**Networking** N/A.

Part D- Requested Funding for the Project	
D.1	**Salaries** None.
D.2	**Consumables** None.
D.3	**Investments** None.
D.4	**Other Costs** None.

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Telemedicine in Pediatric Oncology (Project C)
Grant No.	:	01 GI 99 60

Name of scientist-in-charge	:	Dr. med. Michael Paulussen (responsible)
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Institution	:	Universität des Saarlandes, Universitäts-klinik für Kinder- und Jugendmedizin, Pädiatrische Hämatologie/Onkologie
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Project home page (if different from Network homepage)	:	http://medweb.uni-muenster.de/telemed/

Part A - General Statements about the Project

A.1. **Subject**

Telemedicine in Pediatric Oncology

A.2. **Co-Investigators**

- Prof. Dr. G. Henze, Humboldt-University Berlin, Charité
- Prof. Dr. J. Dunst, University of Halle
- PD Dr. J. Kühl, University of Würzburg

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects	☐ yes	☒ no
(b) clinical trials	☒ yes	☐ no
(c) animal models	☐ yes	☒ no
(d) gene therapy	☐ yes	☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	Personnel[1]	Consumables[1]	Investments[1]	Travel[1]	Other[1] *	Amount[1] Requested
2003	192,5	2,5	2,5	1,5	0	198
2004	192,5	2,5	2,5	1,5	0	198

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The telemedicine project of the Competence Network Pediatric Oncology was instituted with the aim to evaluate the needs for and possibilities of the use of telemedicine applications in Pediatric Oncology.

The project has analyzed the needs of the network Pediatric Oncology institutions for electronic exchange of medical information, focusing on teleradiology and telemicroscopy. Suitable information technology (IT) systems were identified in a market survey. System installations were undertaken in the participating institutions, and a test phase of the use of teleradiology systems in Pediatric Oncology was started. The results of these tests will lead to the identification of suitable systems for the needs of Pediatric Oncology, which may then be further analyzed during routine use in participating institutions.

As a first result of the projects it was noted that the IT and network facilities in the majority of Pediatric Oncology and radiology institutions participating/co-operating in the Competence Network Pediatric Oncology are sufficient, but there is a lack of qualified personnel to implement and maintain telemedicine applications in every day use. Moreover, acquisition of such personnel seems difficult at present.

A second major result relates to prerequisites for electronic exchange of radiological data. Electronic picture archiving and communication systems (PACS) are in internal use in the majority of radiology departments involved in German Pediatric Oncology. Certain aspects of data exchange with other institutions, however, are regarded problematic: While most institutions are willing to accept electronic images as DICOM data from external sources, they refuse to give external clients access to the own electronic data archive. In contrast, active transmission of DICOM data to trusted partners is generally regarded as non-problematic, provided data security and consistence and the fulfillment of legal requirements are ensured.

Hence, as conclusion from the first phase of the telemedicine project, it is suggested that the evaluation of options for the establishment of a central electronic image clearing institution for German Pediatric Oncology should be a major new task for the second funding period of the telemedicine project of the KPOH. To this end, certain modifications to the original work program are required, as outlined in part C below.

B.2 **Original aims of the project**

The telemedicine project of the Competence Network Pediatric Oncology was instituted with the aim to evaluate expectations, requirements and possibilities regarding a potential use of telemedicine applications in Pediatric Oncology.

The primary focus was to analyze, if the use of electronic information technologies (IT) in radiographic image based communication between Pediatric Oncology hospitals and clinical phase III trial centers of the Society of Pediatric Oncology and Hematology (Gesellschaft für Pädiatrische Onkologie und Hämatologie, GPOH) might be useful in terms of increasing data quality, data transfer speed,

	and data reproducibility, thus potentially improving the quality of treatment decisions and ultimately of patient care. In case these analyses should indicate potential benefits from the use of IT technologies in Pediatric Oncology, it was planned to define scenarios for such structures, to analyze the available IT market for solutions eventually available, and to plan example implementations.
B.3	**Scientific results** The project strategy included the gathering of a demand profile for telemedicine services within the Pediatric Oncology community and the evaluation of currently available telemedicine systems, focusing on teleradiology, with the ultimate goal of designing a set of recommendations for their actual implementation. In order to objectify the demand for telemedicine services, two surveys were conducted within the Pediatric Oncology and radiology communities in Germany. The first questionnaire was mailed to 54 Pediatric Oncology units participating in GPOH trials, with a return rate of 45 (83%). The response was generally positive expecting beneficial uses of teleradiology (98% for CT/MR images, 73% for planar images, 61% for ultrasound) as well as telemicroscopy (82% for hematology and 59% for histology specimens). The majority of participating institutions reported existence of an internal data network (84%) and internet access (95%, 43% with high bandwidth). Six participants were involved in other telemedicine projects during the survey period. 70% of participants expressed interest in implementing a telemedicine infrastructure within the next two years. The main precautions expressed concerning future implementations of telemedicine regarded data security, standardization of protocols and applications as well as the non-ambiguous identification of images used in telemedicine sessions. 43% of participants expressed a willingness to make investments of at least €10.000 in local telemedicine infrastructure. A separate survey was conducted as a combined paper/online questionnaire mailed (via their corresponding Pediatric Oncology units) to 110 radiology departments providing diagnostic services for Pediatric Oncology units. With the survey still being in progress, at present (after six months) only 26 questionnaires (24%) have been returned or entered into the online database. Main requirements expressed towards teleradiology systems concern data security, image quality and usability. A preliminary analysis of the results shows that 61% of the participants are operating digital imaging infrastructure with picture archiving and communication systems (PACS), using the Digital Imaging and Communication (DICOM) Standard of ACR (American College of Radiology) and NEMA (National Electrical Manufacturers Association). 66% of the participants intend to introduce teleradiology services within the next 5 years. Only 19% (5) of the participants are willing to open their image archives to external participants. With 57% of participants a far larger number of institutions are prepared to actively exchange images with external participants. Workflow analysis in three major GPOH multi-centre solid tumor trials (EURO-E.W.I.N.G. 99, COSS 96, SIOP 93-01/GPOH) showed that handling of radiology films accounted for a relevant share of the daily workload. For an average Pediatric Oncology study, an inflow of 2-3 new patients was registered per week. An average of 60 therapy documentation forms per week were typically received and filed. Handling of radiology films varied between 20 to 120 per week. The time

allocated to receiving, handling, searching for and mailing out of films was given as 4-15 hours per week. In a typical hematological study centre (AML-BFM 98), about 30 bone marrow samples were handled per week.

Prior to installation and evaluation of teleradiology systems, a set of basic requirements was conceived by the project participants. The requirements were mailed to providers of teleradiology systems located by means of a web search. The responders' systems were compared in a side-by-side matrix regarding the required criteria. Two systems (CHILI, KAMEDIN) were found to match the relevant criteria and were thus chosen for evaluation. At a later stage, the „eFilm“ and „Siemens MagicWeb“ systems became available and were added to the evaluation panel.

The systems cover a wide range of radiology image software functionality from simple DICOM file viewers over image workstations with advanced conferencing and image manipulation features to full PACS applications with integrated image storage and routing features. The DICOM image file standard is supported by all products, but not all packages offer network connectivity using DICOM. An HL7 interface for exchange of administrative, order, or report data is not available in any of the systems evaluated. Usability is comparable between products, but the DICOM interface configuration methods varies between graphics user-interface-(GUI)-based (e.g. eFilm) and file-based (e.g. CHILI) applications. Software set-up and DICOM configuration necessary to achieve connectivity to locally existing PACS installations as well as to external data sources and/or recipients proved to be a non-trivial task requiring intimate knowledge of the local radiology network as well as a firm grasp of DICOM terminology.

In conclusion, both providers and recipients of radiology images seem to be interested in the introduction of telemedicine services within the Pediatric Oncology community. Analyses of ongoing clinical trials have shown that the handling of image hard-copies, reports and samples constitute a relevant share of the daily workload. Especially in solid tumor studies relying heavily on radiological imaging, the introduction of teleradiology services could optimize workflow and resource usage. With local area networks, internet connections and PACS available at many partner hospitals, the necessary infrastructure is largely in place. Teleradiology systems are commercially available at varying degrees of functionality, facilitating their integration into existing imaging networks. Vendor-independent interoperability is, however, currently limited to exchange of DICOM data, as there is no standardized conferencing and collaboration protocol. Data security, data confidentiality, and image quality are main focuses of concern in electronic data exchange.

Hence, as first major result, core assumptions of the initial project proposal were confirmed during the first project period:

- A survey among Pediatric Oncology study hospitals showed a high demand and positive attitude towards telemedicine applications, based on the expectation that such services would increase patient treatment quality while reducing costs.
- Building largely on existing network infrastructure more than two thirds of the participants stated plans to introduce telemedicine applications within a two-year period.

…

- These results were corroborated by workflow analyses of Pediatric Oncology studies that showed a high volume of radiology images being mailed between participants, the handling of which constituted a major time burden on study personnel.
- A survey among radiology partner institutes showed that 60% of participants were already using digital imaging and archiving systems as well as in-house online image distribution.
- An evaluation of teleradiology systems showed that systems commercially available cover a broad range of functionality allowing a selection according to the individual needs of participating hospitals.
- As a second major result of the initial evaluation period, some relevant implementation barriers could be identified:
- While more than 50% of surveyed radiology institutes were willing to actively send images to and retrieve them from external partners, only 19% were willing to open their own archives for external access.
- Configuration and integration of teleradiology systems into imaging infrastructures proved to be a nontrivial task requiring intimate knowledge of the DICOM standard as well as detailed insight into local imaging data infrastructures and proprietary imaging modalities.
- Recruitment of skilled personnel meeting these requirements emerged as a relevant problem at several partner locations.
- Point-to-point communication strategies necessitate the establishment of several individually configured connections between several imaging systems at multiple locations and from various vendors. Apart from these technical difficulties, the problem of trust between partners that have to provide mutual access to their archives increases disproportionately with the number of partners involved.

To evaluate the benefit of telemedicine services within a prospective trial of the Pediatric Oncology community (SIOP 93-01/GPOH and SIOP 2001/GPOH) forms were developed, asking for time aspects, for the quality of transferred imaging studies and logistics regarding problems in transferring and viewing of imaging studies, problems in making a correct diagnosis and reporting this diagnosis to the local center. These forms are filled out for electronically transferred imaging studies as well as for hardcopies. By comparing these results , it is possible to measure the benefit of telemdicine services within a prospective trial of the Pediatric Oncology community. This analysis started in 2000 and is still going on.

Up to now, only few centers (Berlin, Göttingen, Krefeld, Münster, Mannheim, Oldenburg, Zürich) and one radiologist outside a center (Deggendorf) did send imaging studies electronically to the study center in Homburg. In all these cases an electronic exchange of these imaging studies was done between Homburg (study center for the nephroblastoma trial) and Heidelberg (radiological reference center of the nephroblastoma trial, Prof. Tröger, Heidelberg) and the imaging studies were discussed regarding quality of the images and the logistics of the electronical exchange using the developed forms.

As a preliminary result the following three aspects can be concluded:

- The electronic transfer of imaging studies is much more difficult than expected before. Main problems are: firewalls, the absence of a PACS system at the local radiological institution and the refusal of local radiologists to send imaging

	studies outside of their hospital. Á Only the transfer of the whole imaging set as DICOM files is sufficient to perform a reference radiologist diagnosis. Incomplete imaging studies or imaging studies send as JPEG-files or in an other NON-DICOM format are not sufficient regarding quality for making a correct radiological diagnosis. Á Without the knowledge of the clinical data, it is impossible to make a right diagnosis by reference radiologists. In contrast to the transfer of hard copies - usually done by clinicians and send together with clinical data - the DICOM files are transferred by radiologists or informatics in the radiological department without any clinical data. The request for clinical data is time consuming and delays the radiological diagnosis by the reference center. Hence, options for the establishment of a central electronic image clearing institution for German Pediatric Oncology should be evaluated during the second funding period of the telemedicine project of the KPOH.
B.4	**Publications and patents** Graf N, Paulussen M, Huf T, Ganslandt T, Stahl J, Jürgens H. Telemedizin in der Pädiatrischen Onkologie. Ergebnisse einer Fragebogenaktion des Kompetenznetzes Pädiatrische Onkologie. Klin. Pädiatr. 214:8-19, 2002 Ganslandt T, Paulussen M, Graf N, Huf T, Prokosch HU, Jürgens H: Etablierung eines Telemedizinnetzwerkes in der pädiatrischen Hämatologie/Onkologie. In: Achim Jäckel (Hrsg): Telemedizinführer Deutschland, Ausgabe 2002, Medizin Forum AG, Ober-Mörlen, S. 95 Ganslandt T, Korsching E, Prokosch HU, Herbst H, Böcker W, Senninger N, Spiegel HU. Telepathologie: Unausgeschöpfte Potentiale. In: Achim Jäckel (Hrsg): Telemedizinführer Deutschland, Ausgabe 2002, Medizin Forum AG, Ober-Mörlen, S. 170
B.5	**Networking** The telemedicine project primarily involves six participating institutions, all being members of the KPOH and the GPOH. These institutions have set up IT facilities to communicate electronic data and images among them. A test phase for practical use is under way. These example installations will lead to further detail results of both advantages and barriers of electronic image exchange within the competence network and form the rationale for future implementation strategies. As an early result achieved during the implementation phase of these test installations, the potential benefits of a central electronic image clearing institution and potentially resulting networking activities extending over the existing KPOH network have become apparent. The discussion about the implementation of such a structural concept is under way; more detailed descriptions can be found in part C.4 below.

Part C – Follow-Up Proposal

C.1 **Aims**

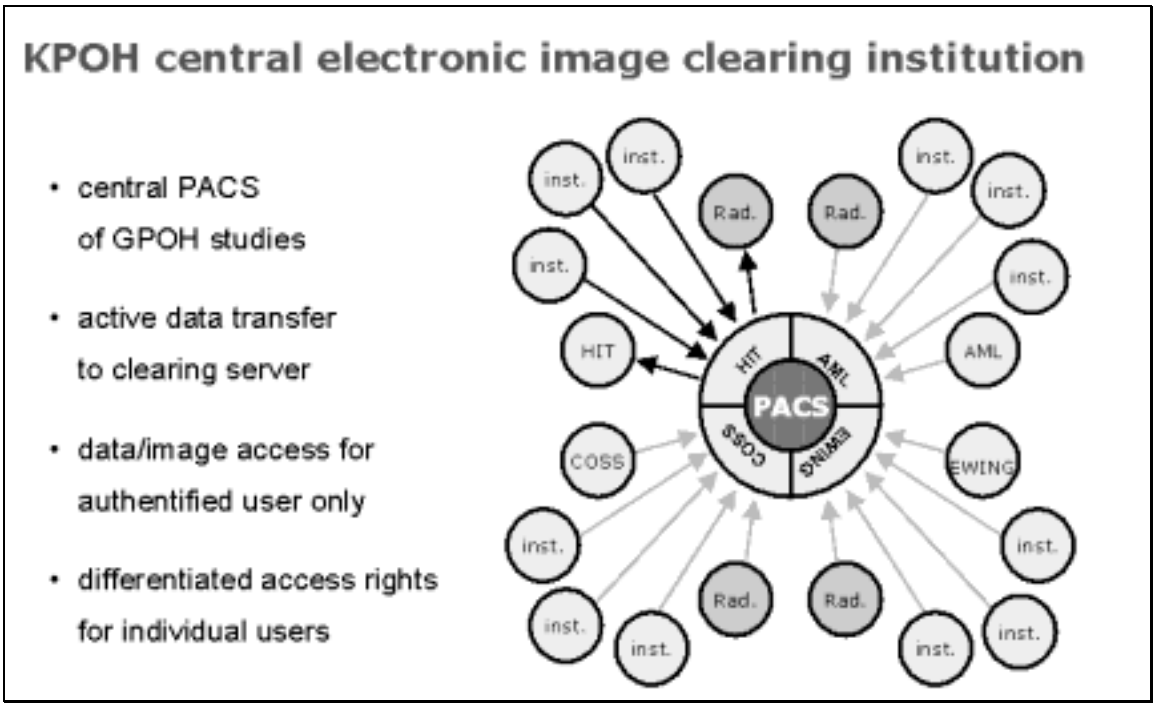
The results outlined above (see B.3) lead to the following conclusions:

- There is a high demand for and acceptance of telemedicine services; workflow analyses suggest a relevant potential for optimization.
- Network infrastructure required for the implementation of telemedicine services is in place or presently being introduced at many GPOH and KPOH institutions, including in-house radiology image distribution; installed systems vary to a high degree between institutions, however.
- Thus the approach of establishing a standardized recommendation for telemedicine system installations applied throughout the complete GPOH study community might in many cases lead to the construction of parallel infrastructures. Aspects of costs as well as demands for qualified personnel might present problems in a GPOH-wide adoption of this strategy.
- Furthermore, point-to-point communication strategies necessitate the establishment of several individually configured connections between several imaging systems at multiple locations and from various vendors. Apart from these technical difficulties, the problem of trust between partners who have to provide mutual access to their archives increases disproportionately with the number of partners involved.

To overcome such implementation barriers, the project aims need to be modified to look into the evaluation of a centralized imaging/telemedicine infrastructure. Such a central electronic image clearing institution will function as a central radiology image repository that is accessed by the participating hospitals and radiology institutions but itself has no reciprocal access to the participants' image archives.

This multipoint-to-point paradigm provides several advantages:

- Decrease of interface complexity: Connections need only be established between each participant and one central server, not directly between all participants (see figure below). Point-to-point teleconferences could be made possible by means of a web-based teleradiology server that can be used without local installation of specialized software.
- Integration of existing local infrastructures avoiding the need for separate image-viewing applications: In-house distribution of images is facilitated by image communication systems largely already in place. Hospitals that have not yet introduced such systems can make use of the recommendations established within the project when procuring a system.
- Reduction of trust barriers: Participating radiologists could actively send images to the central archive, and only authorized study participants would actively download images from the archive. Both activities can be achieved without compromising the participants' own archives.
- Resource optimization: A single team can be leveraged to maintain the central server and support participants without the need for specially trained personnel in every participating institution. Advances in interconnectivity will automatically benefit all participants.

	Á Added value: A central anonymised image repository would provide an enormous image database which could be used for advanced applications like reference image collections, computer-based training systems, teaching purposes, and quality management, among others. Such projects could be realized either within the telemedicine project, or in co-operation with other network members, with partners from other networks, other members of the scientific community, or even commercial health care providers. An established centralized electronic infrastructure could moreover facilitate the implementation of other network-based applications like remote data entry (RDE) systems and could hence act as a focus for secure electronic data collection and transmission, thus representing an example of both vertical and horizontal networking communication. Figure: Outline of potential KPOH central electronic image clearing institution: 
C.2	**Methodological approach** In continuation of the original work plan, point-to-point teleradiology systems will be installed at more partner locations, and network connections will be established between locations. Usage patterns, stability and usability of systems will be evaluated. Experience gathered on interoperability and configuration of DICOM connections between PACS and teleradiology systems of different vendors will be collected in a central knowledge base and made available for future use, enabling point-to-point image communication for institutions interested in such solutions. These activities will, however be less extensive than planned in the initial project proposal. Instead, in accordance with the results of the telemedicine evaluation achieved so far (and outlined in section B.3 above), there will be a switch in the project focus (see also section C.1 above): Á The implementation of a central electronic image clearing institution concept will be evaluated. This will include analyses of acceptance as well as structural, technical and functional prerequisites as outlined under C.3 below.

	Á Aspects of secure network connections crucial for the implementation of such a structural concept will be evaluated, including a survey of security infrastructure (e.g. firewalls) already in place at participating hospitals and of secure connectivity products (e.g. virtual private network software) available. Á A remote data entry (RDE) tool will be implemented and evaluated within the nephroblastoma SIOP 2001/GPOH study. This will easily provide the connection of clinical data with imaging studies. The implementation of a DICOM viewer in such a system facilitates the work of the reference radiologists by the possibility to get information from and to give information into only one single system. By implementation of a report function, that automatically generates and sends reports, it is easy to inform the local institution that did send the imaging studies without time delay. Facilitating the electronical exchange of imaging studies together with clinical data on a secure basis will help to increase the cooperation with local radiologists and the Pediatric Radiologic Society in the telemedicine project, which is mandatory for the whole project. Á RDE evaluation will be carried out in close cooperation with the competence network subprojects B/1 (computer-based application systems) and B/2 (data protection and data security) as well as with Telematics platform of the medical competence networks of the BMBF (TMF). Regarding the subproject B/1 and DOSPO the database of the RDE is based on the developed „basic database“, which makes it easy to exchange data between DOSPO and the RDE system. The integration of data exchange between DOSPO and the RDE system will be a mandatory issue of the RDE. By restricting the database of the RDE to the „basic database“ this RDE can be transferred to other study centers.
C.3	**Work plan** The work plan outlined below contains work packages of the further test of individual teleradiology systems for point-to point connections, as originally proposed in the first application for funding. These efforts will, however, be reduced in extensiveness as compared to the former proposal. Instead, for reasons outlined in B.3 and C.1-C.2 above, a new major project focus will be implemented regarding the evaluation of possibilities for the implementation of a KPOH central electronic image clearing institution. For time schedule of deliverables, and for responsible partners, see the table in the annex. See part D.1 further below for individual allocation of tasks to deliverables and personnel positions.
C.4	**Networking** The discussion about the implementation of a central electronic image clearing institution is under way, delivering the potential to participate by means of electronic remote data entry and image communication systems in nation-wide or even international internet based electronic image (and data) exchange services. This will open the opportunity to all network participants and eventually to other interested institutions to enter electronic images and to discuss difficult cases with participating colleagues. Eventually, an expert panel for specialist consultation could be set up, e.g. involving the reference specialists of the established GPOH trial centers. Moreover, an anonymised image archive could serve teaching or scientific needs. Finally, the technology could be used for other purposes, e.g. remote data entry for documentation and monitoring of clinical trials in Pediatric Oncology, or even similar purposes in other medical disciplines. A close cooperation regarding these aspects within the competence network projects A (co-

ordination) and B/1 and B/2 (documentation system for Pediatric Oncology, DOSPO; data confidentiality and security) is mandatory. Networking contacts to other networks and other partners in medical care are warranted.

Such tools could hence be used in the implementation of several other projects of the competence network, and would readily increase networking activities among the competence network partners and ultimately all KPOH and GPOH institutions. This would foster performance and efficacy of several existing and potential future projects, and add to rational use of resources.

Part D- Requested Funding for the Project

D.1 **Salaries**

	Münster	Homburg/ Saar	Halle	Berlin / Charité	Würzburg	Total
2003	55000	55000	27500	27500	27500	192500
2004	55000	55000	27500	27500	27500	192500

Individual tasks of project personnel:

Münster (1 scientist, medical informatics, 55000 € per annum)

General:

- General project co-ordination and structural conception (permanent)
- General project reports (annual reports, final report)

Point-to-point telemedicine applications:

- Installation of local test systems (co-operation with Homburg, Berlin, Würzburg, Halle; before 12/2002)
- Technical tests (co-operation with Homburg, Berlin, Würzburg, Halle; before 03/2003)
- Practical tests in clinic routine (co-operation with Homburg, Berlin, Würzburg, Halle; before 09/2003)
- Feasibility report, suggestions for implementation (co-operation with Homburg, Berlin, Würzburg, Halle; before 12/2003)

Central electronic image clearing institution concept:

Evaluation of acceptance, organizational co-ordination:

- Definition of expectations, tasks and structures for a central electronic image clearing institution architecture (in co-operation with Homburg, Berlin; before 06/2003)
- Acceptance report, suggestions for implementation (in co-operation with Homburg, Berlin; before 03/2004)

Analysis of technical requirements for set-up and maintenance:

- Survey of security infrastructure (e.g. firewalls) at participating hospitals; co-ordination with project B2 data security (Co-operation with Berlin, Homburg; before 06/2003)

	Á Survey of secure connectivity products (e.g. virtual private network software) available (in co-operation with Berlin, Homburg; before 06/2003) Á Analysis of staff and financial requirements for central electronic image clearing institution architecture (in co-operation with Berlin, Homburg; before 06/2003) Á Technical feasibility report (in co-operation with Berlin, Homburg; before 09/2003) Test installation of central electronic image clearing institution functionality Á Set-up sketch for eventual central electronic image clearing institution architecture (in co-operation with Berlin, Homburg; before 06/2003) Á Test installation of central electronic image clearing server (in co-operation with Berlin, Homburg; before 06/2003) Á Function tests (Co-operation with Homburg, Berlin, Würzburg, Halle; before 09/2004) Á Feasibility report on central electronic image clearing institution concept (Co-operation with Homburg, Berlin; before 12/2004) <u>Homburg (1 scientist, medical informatics, 55000 € per annum)</u> Point-to-point telemedicine applications: Á Installation of local test systems (co-operation with Münster, Berlin, Würzburg, Halle; before 12/2002) Á Technical tests (co-operation with Münster, Berlin, Würzburg, Halle; before 03/2003) Á Practical tests in clinic routine (co-operation with Homburg, Berlin, Würzburg, Halle; before 09/2003) Central electronic image clearing institution concept: Evaluation of acceptance, organizational co-ordination: Á Co-ordination with project B/1 DOSPO (co-operation with Berlin, Münster; 01/2003- 03/2004) Test installation of central electronic image clearing institution functionality Á Function tests (Co-operation with Münster, Berlin, Würzburg, Halle; before 09/2004) Remote Data Entry (RDE) for GPOH Trials Á Analysis of available RDE systems (co-operation with Berlin, Münster; before 12/2003) Á Test implementation of an RDE system for the SIOP 2001 / GPOH trial (co-operation with Berlin, Münster; before 03/2003) Á Establishment of DOSPO (project B) compatibility (co-operation with Berlin, Münster; before 06/2003) Á Evaluation of the established RDE for the SIOP 2001/ GPOH (co-operation with Berlin, Münster; before 09/2003) Á Evaluation of RDE for other GPOH trials (co-operation with Berlin, Münster; before 09/2004) Á RDE feasibility report, suggestions for implementation (co-operation with Berlin, Münster; before 12/2004)

	Berlin (1/2 scientist, medical informatics, 55000 € per annum) Point-to-point telemedicine applications: Á Installation of local test systems (co-operation with Münster, Homburg, Würzburg, Halle; before 12/2003) Á Technical tests (co-operation with Münster, Homburg, Würzburg, Halle; before 03/2003) Á Practical tests in clinic routine (co-operation with Münster, Homburg, Würzburg, Halle; before 09/2003) Central electronic image clearing institution concept: Evaluation of acceptance, organizational co-ordination: Á Co-ordination with telematic-platform, and project A (co-operation with Münster, Homburg; 1/2003-3/2004) Á Co-ordination with project B/2 „Data Security, Knowledge Server“ (co-operation with Münster, Homburg; before 3/2004) Test installation of central electronic image clearing institution functionality Á Function tests (co-operation with Münster, Homburg, Würzburg, Halle; before 09/2004) Halle (1/2 scientist, medical informatics, 27500 € per annum) Point-to-point telemedicine applications: Á Installation of local test systems (co-operation with Münster, Homburg, Berlin, Würzburg; before 12/2002) Á Technical tests (co-operation with Münster, Homburg, Berlin, Würzburg; before 03/2003) Á Practical tests in clinic routine (co-operation with Münster, Homburg, Berlin, Würzburg; before 09/2003) Central electronic image clearing institution concept: Test installation of central electronic image clearing institution functionality Á Function tests (co-operation with Münster, Homburg, Berlin, Würzburg; before 09/2004) Würzburg (1/2 scientist, medical informatics, 27500 € per annum) Point-to-point telemedicine applications: Á Installation of local test systems (co-operation with Münster, Homburg, Berlin, Halle; before 12/2002) Á Technical tests (co-operation with Münster, Homburg, Berlin, Halle; before 03/2003) Á Practical tests in clinic routine (co-operation with Münster, Homburg, Berlin, Halle; before 09/2003) Á Central electronic image clearing institution concept: Á Function tests (co-operation with Münster, Homburg, Berlin, Halle; before 09/2004).

D.2	**Consumables** To guarantee permanent availability of central electronic image clearing institution functionality: Á Maintenance: hardware, software: 3000 € Á Backup media (streamer tapes): 1000 € Á Permanent storage media (DVD, CD-ROM) and other consumables: 1000 € Total: 5000 €
D.3	**Investments** Á Hardware: webserver (available from first funding period): 0 € Á Software: webserver, RDE: 5000 € Total: 5000 €
D.4	**Other Costs** To help in setting-up of hardware and software, to present results on network and non-network meetings, to establish co-operation between partners within the project, with other network projects, with the telematic platform, and with other networks. Total: 3000 €

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Molecular Parameters of Drug Resistance (Project D)
Grant No.	:	01 GI 99 61

Name of scientist-in-charge	:	Dr. med. Karsten Stahnke (responsible) Univ.-Prof. Dr. Klaus-Michael Debatin
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Project home page (if different from Network homepage)	:	----------

Part A - General Statements about the Project

A.1. **Subject**

Molecular parameters of drug resistance

A.2. **Co-Investigators**

- Prof. Dr. W. D. Ludwig und Dr. L. Karawajew, Robert-Rössle-Klinik, Charité, Berlin
- Prof. Dr. G. Janka-Schaub, Universitätskinderklinik Hamburg

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects	☒ yes	☐ no
(b) clinical trials	☒ yes	☐ no
(c) animal models	☒ yes	☐ no
(d) gene therapy	☐ yes	☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	79	23	75	3	0	180
2004	79	23	75	3	0	180

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

Progress in the treatment of acute leukemia has been achieved by development of empirically designed chemotherapy protocols applying different cytostatic drugs in an optimized time course. Still, primary chemo- resistance or reemergence of a drug resistant leukemic clone is a major problem in the treatment of acute leukemia. It has been shown that cytotoxic drugs used in anti-cancer chemotherapy induce the physiologic program of apoptosis by activation of apoptosis signaling molecules. Functional defects in apoptosis molecules or inhibition of activation of apoptosis signaling pathways may therefore be responsible for resistance and treatment failure of malignant diseases. This project aims at the identification of molecular parameters for prediction of treatment failure by analysis of function and expression of apoptosis molecules.

In a corporation of three different laboratories in Ulm, Berlin and Hamburg, 6 scientists are working on a) standardization of material acquisition for analysis of apoptosis signaling molecules b) the establishment of a functional assays for the assessment of drug sensitivity and resistance in primary leukemia cells c) the development of new methods for the detection of activated apoptosis signaling and d) the detection of apoptosis signaling during in vivo chemotherapy. Methods have been established for standardized acquisition and storage of patient material for future analysis in expression and function assays. We have developed a drug independent assay, which tests the functional ability for activation of apoptosis pathways in primary leukemia cells. A major focus of the project was the development of methods for measurement of activated apoptosis signaling pathways in primary cells. A new method for flow cytometric detection of mitochondrial cytochrome c release (patent pending) has been developed and evaluated for detection of deficient mitochondrial signaling in resistant cells. Application in primary leukemia cells demonstrated a heterogeneous pattern of mitochondrial apoptosis signaling in different leukemia samples.

Further analysis will be performed on the basis of a larger set of samples. Investigation of apoptosis induction by chemotherapy in vivo revealed that apoptosis is predominantly induced in immature CD34 positive leukemia cells, indicating differential sensitivity among leukemia subpopulations. In the second funding period, these assays capable of detecting deficient mitochondrial or caspase apoptosis signaling on a single cell level will be performed on a large number of patient samples. In addition, mutation and expression analysis of apoptosis genes will be performed by sequencing and with a c-DNA array system respectively.

B.2 **Original aims of the project**

General aim:

Identification of molecular parameters for prediction of the individual risk for treatment failure by analysis of function and expression of apoptosis molecules.

Specific aims:

1. Development of an acquisition system for collection of patient

	material for cellular-, protein-, RNA- and DNA-analysis. 2. Development of methods for measurement of apoptosis signaling in primary leukemia cells. 3. Analysis of leukemia cell apoptosis in drug response assays. 4. Identification of apoptosis gene mutations inferring drug resistance. 5. Analysis of apoptosis gene expression profiles for the prediction of drug resistance. 6. Identification of apoptosis signaling in peripheral leukemia cells activated by in vivo chemotherapy.
B.3	**Scientific results** B.3.1. In a cooperative work, procedures for acquisition of patient material were tested and general strategy for isolation, handling, storage and shipment of patient samples established. It turned out that the average amount of patient cells is not sufficient for a separate storage of cells, RNA and DNA. Therefore, all cells obtained in the study laboratory are stored as viable cells in DMSO permitting further expression analysis on cellular level as well as RNA and DNA expression. In addition, it was decided to perform the analysis in sequence i.e. the material obtained is primarily used for cellular drug response assays until a sufficient number of samples has been obtained, in a second step expression analysis of apoptosis genes will be performed. B.3.2. Major focus of the project was the development of a method for the detection of apoptosis signaling in primary leukemia cells. Bulk methods using lysates of cells turned out to be of insufficient sensitivity for the detection of apoptosis in primary cells. In addition, we found that apoptosis is predominantly induced in a subset of leukemia cells (see 6). We therefore developed flow cytometric methods for the analysis of apoptosis permitting analysis on a single cell basis. In this project, we first analyzed a method for the simultaneous detection of caspase activation and mitochondrial membrane potential developed in our group. We found that mitochondrial membrane permeability transition is not a common feature of apoptosis in leukemia cells, thereby limiting the applicability of MMP measurement for detection of apoptosis. Caspase activation could reliably be detected in cell lines by fluorogenic caspase substrates developed in our group. However, in primary leukemia cell no such activity could be detected upon induction of apoptosis. In summary, this method is a reliable research tool for detection of caspase and mitochondrial activation in cell culture systems but not for analysis of primary leukemia cells (manuscript in preparation). Since deficient activation of mitochondrial apoptosis signaling may be responsible for drug resistance, we developed another method specifically aiming at detection of mitochondrial cytochrome c release. The release of cytochrome c from mitochondria to the cytosol represents an early and specific step of apoptosis signaling, activating further downstream events like caspase cleavage. We developed a method for the detection of cytochrome release in intact cells by flow cytometry. Jurkat T cell leukemia cells, mitochondrial cytochrome c release could be detected in CD95 receptor, and cytotoxic drug induced apoptosis.

A good correlation was found to results obtained in conventional immunoblotting and fluorescence microscopy. Differential requirement for mitochondrial signaling in CD95 induced apoptosis in SKW (type I) and Jurkat (type II) was detected by the method. By simultaneous measurement of cytochrome c release and active caspase-3 in multicolor flow cytometry, we identified deficient mitochondrial apoptosis signaling in the presence of caspase-3 activation in Jurkat cells overexpressing Bcl-2. In addition, we found the method to be applicable for analysis of primary leukemia cells identifying heterogeneous patterns of mitochondrial signaling and caspase activation. This method will now be applied for analysis of a larger number of primary leukemia cells in combination with the functional apoptosis response assay (see 3). The method is currently being patented.

B.3.3.

Another focus of the project was the analysis of leukemia cell apoptosis in drug response assays. This part of the project aimed at the identification of apoptosis signaling pathways specifically induced by different cytostatic drugs. Since a large number of leukemia cells are stored as frozen samples in Berlin and Hamburg, we first analyzed whether functional drug response assays could be performed with frozen material. Since the clinical course of the patients over the last 4 to 5 years is known, experimental data could have been directly correlated to a clinical outcome. We found that in B precursor ALL samples, apoptosis was generally high, and specific drug-induced apoptosis after 12 to 16 hours incubation with cytostatic drugs could not be detected. Results also varied with time of storage. In summary, we found frozen samples generally not applicable for apoptosis sensitivity assays. In the second funding period, it is therefore necessary to perform these assays with fresh material. In order to collect sufficient number of samples, the assays will be performed in all three participating laboratories in parallel (see C.2).

We therefore investigated fresh material obtained either at the Children's Hospital in Hamburg and Ulm or material sent to Berlin over night. Again in about 30 to 50% of B precursor ALL samples drug specific apoptosis could not be detected after 16 hours incubation probably due to high spontaneous apoptosis. In another subproject, we analyzed kinetics of drug-induced apoptosis in precursor B and T leukemia derived p53 proficient cell lines. We found different kinetics in different drugs, for example early induction of apoptosis by etoposide and cyclophosphomide and late induction more than 24-48 hours for vincristin. These data are complemented by analysis of a cell cycle dependency of drug-induced apoptosis demonstrating that in some cells, apoptosis induction depends on cell cycle entry. Taken together, these data suggest that treatment of primary leukemia cells in vitro requires a 24 to 48 hours incubation, which conflicts with the high spontaneous apoptosis of B precursor leukemia cells. In order to overcome this problem, we further divided the project into 2 parts. First, we developed an apoptosis sensitivity assay aiming at detection of apoptosis signaling in primary leukemia cells upon unspecific stress induction, for example staurosporine. With this approach, we overcome the problem of high spontaneous apoptosis upon prolonged in vitro cultivation. The method permits measurement of general apoptosis sensitivity and induction of caspase activation and mitochondrial apoptosis signaling. The method has been established in the study laboratory in Berlin.

The first results show a heterogeneous pattern of apoptosis induction in 6 primary ALL samples analyzed until now. The method will be further applied in a large-

scale analysis of primary samples in Berlin and Hamburg after modification and optimization of the assay.

In order to address the question of differential sensitivity towards different cytostatic drugs, we are currently working on the optimization of culture conditions by supplementation with cytokines or co-incubation with feeder cells. In addition, we will investigate whether the analysis of remaining leukemia cells after 48 hours in culture by gated acquisition permits prediction of drug sensitivity or resistance.

B.3.4.

Within a project for analysis of apoptosis gene mutations in our group, methods for bax gene mutations have been established on RT-PCR level. Methods were evaluated by analysis of bax mutations in established cell lines. Additional funding is required for analysis of large number of patient samples. Funding will be applied for at the Deutsche Krebshilfe.

B.3.5.

Analysis of apoptosis gene expression profiles for prediction of drug resistance. The development of a cDNA chip for analysis of apoptosis gene expression has made further progress. In cooperation with a local company (Interactiva Ulm), we have developed an apoptosis gene chip consisting of 96 positions with 10 controls and 86 apoptosis genes. The 96 cDNAs have now been completely synthesized. The PCR products will now be amplified for the production of the first set of arrays. The chip has been successfully evaluated with cell lines using controls and a limited set of a major apoptosis regulators like caspase-3.

B.3.6.

Identification of apoptosis signaling peripheral leukemia cells activated by in vivo chemotherapy. In this part project we analyzed depletion and induction of apoptosis during the acute phase of leukemia cell reduction in patients with AML and ALL undergoing first cycle chemotherapy. Since it has recently been shown that leukemia arises from immature leukemia stem cells positive for CD34, we analyzed apoptosis induction in the subset of CD34 positive peripheral blood leukemia cells. We found expression of CD34 on leukemic blasts in 20 of 23 cases and the proportion of leukemia cells expressing CD34 varied from 0% to 85.7% and 1.5% to 74.5% in AML and ALL patients respectively. During chemotherapy, CD34+ leukemia cells were more rapidly depleted than CD34- cells. Furthermore, a significant increase in leukemia cell apoptosis ex vivo in this immature subpopulation was detected during treatment, while no such increase was observed in the CD34- subpopulation. In vitro treatment of ALL and AML leukemia cells with cytostatic drugs did not constantly result in predominant induction of apoptosis in CD34 positive leukemia cells, indicating different conditions for apoptosis induction in vivo and in vitro. CD95 expression and sensitivity on both CD34 positive and negative subpopulations remained low during in vivo chemotherapy and upon in vitro drug treatment, suggesting induction of apoptosis in peripheral leukemia cells independent of the CD95 system. These data indicate that in vivo chemotherapy for remission induction eliminates leukemia cells by induction of apoptosis especially in an immature subpopulation of CD34+ cells. These results underline the necessity for analysis of apoptosis induction on a single cell level (manuscript in preparation).

B.4	**Publications and patents**

Strauß G, Osen W, Debatin K-M. Clin. Exp. Induction of apoptosis and modulation of activation and effector function in T cells by immunosuppressive drugs. Immun. 200, In Press

Wuchter C, Ruppert V, Schrappe M, Dorken B, Ludwig WD, Karawajew L. In vitro susceptibility to dexamethasone- and doxorubicin-induced apoptotic cell death in context of maturation stage, responsiveness to IL-7 and early cytoreduction in vivo in childhood T-ALL. Blood 2002, In Press

Stahnke K, Fulda S, Friesen C, Strauss G, Debatin KM Activation of apoptosis pathways in peripheral blood lymphocytes by in vivo chemotherapy Blood 2001,98:3066-7330

Herr I, Debatin K-M . Cellular stress response and apoptosis in cancer therapy. Blood 2001,98: 2603-2614

Wuchter C, Krappmann D, Cai Z, Rup-pert V, Scheidereit C, Dorken B, Ludwig WD, Karawajew L. In vitro susceptibility to TRAIL-induced apoptosis of acute leukemia cells in the context of TRAIL receptor gene ex-pression and constitutive NF-kappa B activity. Leukemia 2001,15:921-8

Cai Z, Lin M, Wuchter C, Ruppert V, Dorken B, Ludwig WD, Karawajew L. Apoptotic response to homoharring-tonine in human wt p53 leukemic cells is independent of reactive oxygen spe-cies generation and implicates Bax translocation, mitochondrial cytochrome c release and caspase activation. Leukemia 2001;15:567-74

Wuchter C, Karawajew L, Ruppert V, Schrappe M, Harbott J, Ratei R, Dorken B, Ludwig WD. Constitutive expression levels of CD95 and Bcl-2 as well as CD95 function and spontaneous apoptosis in vitro do not predict the response to induction che-motherapy and relapse rate in child-hood acute lymphoblastic leukaemia. Br J Haematol 2000;110:154-60

Karawajew L, Ruppert V, Wuchter C, Kosser A, Schrappe M, Dorken B, Ludwig WD. Inhibition of in vitro spontaneous apop-tosis by IL-7 correlates with bcl-2 upregulation, cortical/mature immunophe-notype, and better early cytoreduction of childhood T-cell acute lymphoblastic leukemia. Blood 2000;96:297-306

Fulda S, Meyer E, Debatin KM. Metabolic inhibitors sensitize for CD95 (APO-1/Fas)-induced apoptosis by down-regulating Fas-associated death domain-like interleukin 1-converting enzyme inhibitory protein expression. Cancer Res 2000;60:3947-56

Beltinger C, Fulda S, Kammertoens T, Uckert W, Debatin KM. Mitochondrial amplification of death signals determines thymidine kinase/ganciclovir-triggered activation of apoptosis. Cancer Res 2000;60:3212-7

Patent applications

„Method of detecting release of substances from cell organells by means of flow cytometry“ (USA: US-09-987,206; Germany: 10155518.0; as of 13.11.2001).

B.5	**Networking** In the first funding period, a close collaboration between the study laboratories was established. New methods were developed in basic research (Ulm) and applied for patent. These methods could immediately be established in the clinical reference laboratories in Berlin and Hamburg for evaluation with primary material (transfer of know-how). Thereby, a new structure for translational research was established, which would not have been possible without the network.

Part C – Follow-Up Proposal

C.1 **Aims**

General aim:

Identification of molecular parameters for prediction of the individual risk for treatment failure by analysis of function and expression of apoptosis molecules. Perspective: Individual risk adapted therapy and identification of molecular target structures for future development of leukemia therapy. The general aim and perspective is still relevant and achievable. The specific aims were modified according to the results of the first funding period.

Hypotheses and Objectives:

1. Hypothesis: The leukemia cells' constitutive capability of efficiently activating apoptosis signaling pathways is a major prognostic factor for treatment outcome.
   Objective: Analysis of caspase activation and mitochondrial signaling by in vitro culture and conditions of factor deprivation, chemical stress and caspase inhibition.
2. Hypothesis: Deficient activation of apoptosis signaling pathways in the primary leukemia cells upon in vitro treatment with different drugs predicts drug resistance in vivo and identifies resistance towards a specific drug.
   Objective: Analysis of caspase activation in mitochondrial apoptosis signaling upon in vitro drug treatment in T-ALL ad AML. Development of an in vitro drug sensitivity assay based on measurement of activated apoptosis signaling pathways for B precursor ALL.
3. Hypothesis: Drug resistance in leukemia is caused by loss of function mutations in mitochondrial apoptosis signaling molecules.
   Objective: Analysis of Bax mutations in drug resistant leukemia.
4. Hypothesis: Apoptosis gene expression is a predictive parameter for drug resistance and sensitivity.
   Objective: Analysis of apoptosis gene expression in correlation to clinical outcome and functional apoptosis assays.
5. Hypothesis: Analysis of apoptosis related functional changes in leukemia cells during in vivo chemotherapy permits monitoring of drug efficacy.
   Objective: Detection of molecular changes during in vivo chemotherapy and development of assays for the detection of early proapoptotic changes in leukemia cells.
6. Hypothesis: The risk of relapse can be assessed by analysis of drug-induced changes in the stem cell compartment of leukemia cells.
   Objective: Analysis of SCID repopulating activity of primary leukemia samples treated with different cytostatic drugs.
7. Structural aim: Establishment of a central database for the study laboratories compatible with databases of the clinical studies.

C.2	**Methodological approach** Due to the results from the first funding period, the methodological approach is modified as follows. We will establish an apoptosis sensitivity assay based on rapid induction of apoptosis by staurosporine. With this approach, it will be possible to overcome the problem of high spontaneous apoptosis in primary B precursor ALL samples. Upon incubation with staurosporine, induction of apoptosis signaling pathways via caspase activation and mitochondrial cytochrome c release will be measured. The assay is currently standardized and will be applied in large scale in the second funding period. With this approach, it will be possible to characterize constitutive apoptosis resistance/sensitivity in primary leukemia cells, irrespective of drug sensitivity. The aspect of drug specific sensitivity or resistance will be further pursued by development of a long-term assay which permits analysis of drug effects in primary leukemia cells (see section B3 and C3). In order to prolong viability of leukemia samples, different culture conditions will be tested such as composition of culture media, addition of feeder cells and addition of cytokines. Since frozen samples are not suitable for analysis in functional assays (see B.3.3), all assays have to be performed in the participating laboratories in parallel with fresh material. This requires additional logistical effort concerning transfer of know how and data management. In order to meet these requirements, we plan to establish a central database for experimental data, which is accessible via internet and is compatible with databases of clinical studies (see C.1.7). Expression analysis will be done by RNA expression array as described in B3. In addition to the indicated modifications of our methodological approach, we will establish a human leukemia mouse model using the NOD/SCID system, which will be established in corporation with Dr. Iduna Fichtner, Max Dellbrück Center (MDC) Berlin-Buch. With this method, we will address questions of chemosensitivity and resistance in the leukemia stem cell compartment.
C.3	**Work plan** 1. Objective: Analysis of caspase activation and mitochondrial signaling by in vitro culture and conditions of factor deprivation, chemical stress and caspase inhibition. Primary leukemia cells sent to the study laboratories are isolated and cultured for different incubation times under conditions of a factor of deprivation (medium alone), induction of a chemical stress (e.g. staurosporine) and caspase inhibition (zVad-fmk). Apoptosis is assessed by PI-annexin staining after defined time points, mitochondrial cytochrome c release and caspase-3 activation is measured in subsets of leukemia cells by flow cytometry. Data are analyzed in conventional dot blots and by algorithms on list mode data. First, chemical stress and caspase inhibition assay is standardized in the study laboratory in Berlin, in corporation with Hamburg and Ulm. A database for experimental data is established. In a second step, the assay is applied in all study laboratories on freshly sent samples from the pediatric ALL and AML studies. Clinical and data from the CoALL and BFM studies are implemented in the database and analyzed together with the experimental data for prognostic significance. Tools for data analysis will be developed. 2. Objective: Analysis of apoptosis signaling upon in vitro treatment with cytostatic drugs. Based on the results of the first funding period, we are now able to perform an in vitro drug sensitivity assay with different cytostatic drugs with the endpoint

of caspase and mitochondrial activation analysis. Samples sent to the study laboratories will be cultured with a defined panel of cytostatic drugs for a defined time period. The method is established and is currently standardized. Analysis will be performed for T-ALL and AML samples since these leukemias show low background apoptosis facilitating detection of drug specific apoptosis. Since the frequency of these leukemias is low in childhood, assays will be performed during the whole second funding period. Due to the high background apoptosis of B-precursor leukemias, which represent the majority of childhood acute leukemias, this assay is not generally applicable for this disease (see B3). Therefore, a long term assay will be developed in order to preserve viability of B-precursor ALL cells for a time sufficient to analyze drug effects (see C2). After successful establishment, this assay will also be standardized and applied in the study laboratories.

3. Objective: Analysis of Bax mutations in drug resistant leukemia.
   Drug resistant leukemias as defined by the clinical non-response or identified by functional assays in subproject 1 or 2 will be analyzed for Bax mutations and related mitochondrial apoptosis signaling molecules. This work will be performed within a broader project for analysis of apoptosis gene mutations in our group. The currently established method of Bax mutation analysis by RT-PCR will be substituted by sequencing of genomic DNA, once the genomic sequence of the Bax gene is available.

4. Objective: Analysis of apoptosis gene expression in correlation to clinical outcome and functional apoptosis assays.
   In this part-project, we will apply the apoptosis gene chip developed in our group. The chip is currently produced. It will be validated in the first six months of the second funding period. Spotting and hybridization procedures will be optimized for primary samples. RNA preparation will be optimized for array analysis. Acquisition of RNA samples will be performed in the study laboratory according to the standardized RNA preparation protocol. Expression analysis will be done in the chip facility in Ulm. Tools for data analysis are currently developed and have to be modified for implementation of clinical data.

5. Objective: Analysis of apoptosis during in vivo chemotherapy.
   We will analyze p53 induction in leukemia cells by a flow cytometric method currently developed in our group: by this method it will be possible to detect p53 localization to the nucleus in combination with surface marker analysis. The method will be standardized in the second funding period and consecutively applied in the study laboratories. In addition, we will develop methods for detection of functional changes in leukemia cells applying fluorogenic substrates indicative for protease activation, radical oxygen production and ph-changes.

6. Objective: Analysis of drug-induced changes in the leukemia stem cell compartment.
   In corporation with MDC Berlin Buch, we will analyze SCID repopulating activity of leukemia cells after drug treatment in vitro. Representative human transplantable leukemia cell lines will be established. Retransplantation characteristics upon drug treatment will be characterized.

7. Objective: Establishment of a central data base for experimental data.
   Since a main part of research work is performed on fresh primary samples in three different laboratories in parallel, exchange of data between the study laboratories will be important. The requirements for an IT solution are best

	met by a central database accessible via internet. All reports will be anonymous and will identify patients by unique patient number UPN. Data will be reported to the central database by browser based data entry. We plan to use the browser base ProMISe Project Manager Internet Server system as the data management system of the subproject. Users are able to enter experimental data directly over a secure internet connection. All users have access to the same copy of the entire project, but users can download their own data for analysis. The Promise is used by other ongoing European projects. In particular, the European group for blood and bone marrow transplantation (EBMT) has implemented promise as a data management system in 1999. Within the GPOH, the Pediatric Stem Cell Registry (Th. Klingebiel, Frankfurt) is currently establishing a Promise based database, which is localized at the University of Essen. In cooperation with this project (O. Basu, Essen) and the department of medical statistics section advanced data management at the Leiden University Medical Center (Ronald Brand) a solution could be set up within 9 months. The use of promise has been discussed with the Telematic platform for the planned network „acquired disorders of hematopoesis in children and adults, Aplastic anemia and related disorders" in the BMBF program „rare diseases" (H. Schrezenmeier, Berlin). The design of the database is easy to perform and does not require additional personell for this project. The costs for database set up and work in the Department of Medical Statistics Leiden or Universität Essen can be roughly estimated at approximately 10000 €¤ per year (FuE contract). Results from this developmental work could be used by other laboratories in the network. For the table of Tasks and Milestones, please refer to the appendix.
C.4	**Networking** Within this project, a close collaboration has been established between study associated reference laboratories (Berlin and Hamburg) and basic research group (Ulm). New methods developed in basic research are immediately transfered to the clinical laboratories and evaluated with primary patient material (transfer of know-how). Since it turned out that shipment of frozen material is not a suitable approach for this research project, an even closer collaboration is necessary in the second funding period. The establishment of a common database for the study laboratories compatible to databases of clinical studies is another important contribution to a long-term constitution of stable structures for future research projects. Through this close collaboration, we will contribute to the networks aim of establishment of new research structures connecting clinical and basic research. In addition, experimental data obtained from this project will be analyzed together with clinical data obtained from clinical studies in the network. The scientific progress obtained by this corporation represents an added value that would not have been achieved without the network.

Part D- Requested Funding for the Project	
D.1	**Salaries** Scientist BAT IIa: The scientist is responsible for the establishment and standardization of the functional apoptosis assay as stated in (C.3.1 and C.3.2). In addition, the scientist will be responsible for the further development of assays for detection of early functional changes associated with apoptosis as stated in C.3.5 and will be involved in analysis of apoptosis gene expression (C.3.4): 2003 – 56000 €, 2004 – 57000 €¤ Technician BAT Vb1/2 for the work on the large amount of clinical samples: 2003 – 22000 €, 2004 – 22000 €¤ Change compared to the first funding period: + 1/2 BAT Vb.
D.2	**Consumables** Consumables are required for cell culture media, monoclonal antibodies, fluorogenic substrates for flow cytometry and cytostatic drugs. Requested amount: 2003 – 23000 €, 2004 – 23000 € No change compared to first funding period.
D.3	**Investments** Investment is needed for financing the employees working in Berlin and Hamburg (FuE Vertrag): University Hospital Charité Berlin – 1 Bat Vc (Czervony, Grit) University Hospital Hamburg Eppendorf – 1 BAT IV b (Biermann, Birgit) Requested amount: 2003 – 75000 €, 2004 – 75000 €
D.4	**Other Costs** Travel expenses: 2003 – 3000 €, 2004 – 3000 €.

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Characterisation of Pre-Leukemic Bone Marrow Disorders (Project E)
Grant No.	:	01 GI 99 62

Name of scientist-in-charge	:	Univ.-Prof. Dr. med. Charlotte Niemeyer
Institution	:	Klinik IV: Pädiatrische Onkologie und Hämatologie Zentrum für Kinderheilkunde und Jugendmedizin Universität Freiburg
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Project home page (if different from Network homepage)	:	.....

Part A - General Statements about the Project

A.1. **Subject**

Characterisation of pre-leukemic bone marrow disorders

A.2. **Co-Investigators**

- Prof. Dr. med. Karl Welte, MHH Kinderklinik, Hannover
- Prof. Dr. med. Christine Bender-Götze, Dr. med. Monika Führer, Kinderpoliklinik der Universität München
- Dr. med. W. Ebell, Charité Campus Virchow-Klinikum, Klinik für Allgemeine Pädiatrie und Knochenmarktransplantation, Berlin
- Prof. Dr. rer. nat. Jochen Harbott, Zentrum für Kinderheilkunde, Universität Giessen
- Prof. Dr. med. R. Schneppenheim, Dr. J. Rischewski, Universitäts-Krankenhaus Eppendorf, Kinderklinik, Hamburg
- Dr. med. I. Baumann, Dr. rer. nat. A. Jung, Pathologisches Institut der Universität Erlangen
- Prof. Dr. med. A. Schmitt-Gräff, Pathologisches Institut der Universität Freiburg

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects ☒ yes ☐ no

(b) clinical trials ☒ yes ☐ no

(c) animal models ☐ yes ☒ no

(d) gene therapy ☐ yes ☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	Personnel[1]	Consumables[1]	Investments[1]	Travel[1]	Other[1]	Amount[1] Requested
2003	98,9	20,0	0	0	0	118,9
2004	99,4	20,0	0	0	0	119,4

[1](amounts in thousand Euro), * should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The molecular genesis of hematopoietic neoplasm is complex. Different genetic abnormalities like defects of cell surface receptors, signal transduction pathways, transcriptions factors or regulators of cell cycle are known to play an important role. Congenital and acquired bone marrow failure disorders can serve as model systems for the study of leukemic transformation in a previously non-malignant hematopoietic system. Because bone marrow failure disorders are rare, our knowledge of the leukemogenesis in these diseases is patchy. Within this network, we attempt to characterize pre-leukemic disorders with a systematic and comparative approach. In cooperation with international investigators, we have developed a new classification of myelodysplasia. We performed extensive and consecutive oncogenetic studies and screened for heterozygous mutations of the Fanconi anemia genes. We analyzed the role of G-CSF receptor and RAS mutations. In addition, we started to investigate clonality and apoptosis. Overall, these studies have contributed to our understanding of the mechanisms of leukemic transformation.

B.2 **Original aims of the project**

For all patients/subsets of patients with pre-leukemic disorders:

- To evaluate bone marrow aspirates/biopsies by reference pathologists
- To perform oncogenetic studies (FISH/banding cytogenetics) on all bone marrow samples
- To study clonality based on polymorphisms of the gene of the androgen receptor (HUMARA)
- To study the frequency of heterozygous states of Fanconi anemia among patients with pre-leukemic disorders
- To study G-CSF receptor mutations
- To study the frequency and importance of activating RAS mutations
- To demonstrate apoptosis by TUNEL assay and perform cell cycle analysis
- To study the expression of genes involved in apoptosis

B.3 **Scientific results**

Pre-leukemic bone marrow disorders are rare diseases in childhood. Official guidelines for diagnosis and classification of myelodysplastic syndromes (MDS) have been missing. During the last 2 years, international consensus has been achieved on the classification of pediatric MDS (Submitted: Proposal for the classification of myelodysplastic diseases in children. Henrik Hasle, Charlotte Niemeyer, Irith Baumann, John M Bennett, Judith Chessells, Gitte Kerndrup, David Head). The current proposal for classification reflects our present knowledge and concepts. It is based in part on the experience we gained by the reference evaluation of all morphological specimens of all patients with suspected pre-leukemic bone marrow disorder within this project.

During the first 24 months of funding about 1700 samples of bone marrow aspirates/biopsies of patients with suspected or rule-out pre-leukemic bone marrow

disorders have been evaluated by the MDS or SAA study centers and the reference pathologists in Erlangen and Freiburg. Because myelodysplasia is not an uncommon finding in sick children, a variety of non-malignant disorders like infectious diseases, nutritional or metabolic disorders or diseases with mitochondrial deletions have to be excluded by repeat studies and clinical observation. Eventually, about 1 in 13 patients studied was diagnosed of a pre-leukemic bone marrow disorder. Of the 114 patients known to be diagnosed of MDS during the study period (data form the Kinderkrebsregister in Mainz) 112 (98%) had at least 1 bone marrow aspirate or biopsy evaluated by the reference pathologists. During the same period we are aware of 69 patients with congenital bone marrow failure disorders (severe congenital neutropenia, Shwachman syndrome, Fanconi anemia) who had their annual bone marrow evaluations to rule out MDS. Reference morphology could be performed in 45 of these children (65%).

The demonstration of chromosomal abnormalities can be an important mean to diagnose MDS in pre-leukemic bone marrow disorders. Monosomy 7 followed by trisomy 8 are the most common cytogenetic abnormalities. Fluorescence *in situ* hybridization (FISH) can be a rapid and effective method to screen bone marrow samples for these numerical changes. Until December 2001 bone marrow mononuclear cells from 116 children with MDS were analyzed using centromer-specific probes for chromosomes 7 and 8. Monosomy 7 was detected in 37% and 58% of patients with primary and secondary MDS, respectively, while trisomy 8 was noted in 9% of patients with primary MDS. For most cases follow-up samples (2-19 samples) were available to study clone size. Big clones (70-100%) generally remained stable in size. Interestingly, small clones (6-30%) could disappear spontaneously or evolve into big and stable clones. FISH results could be compared to standard cytogenetic investigations. Discrepant results were noted in about 10% of cases mostly involving small clones detected by FISH but not by cytogenetics. Current investigations include the use of probes for the long arm of chromosome 7 and FISH on aspirate smears. We believe that we have systematically studied the biggest cohort of pediatric patients with pre-leukemic bone marrow disorders. Combined with clinical data these results will provide new insights in the prognostic values of chromosomal changes.

Hypoplastic MDS may be difficult to discriminate from aplastic anemia. Clonal hematopoiesis is strongly suggestive of MDS. Therefore, evidence of clonality could be an important mean to demonstrate a pre-leukemic state. Clonality studies depend on a clonal marker that differs between the normal and tumor cell population. The HUMARA (human androgen receptor) locus resembles such a marker but unfortunately the highly heterozygous CG rich STR is prone for the generation of hairpin loop superstructures and is thus difficult to amplify in PCRs. To overcome this problem we have modified the HUMARA method (Jung et al., 2002). Consequently, the analyses worked well in about 92 % of leukemias from adult women. However, the modified method failed in most DNA-samples of girls with MDS. The standard HUMARA assay depends on the presence of at least 60 % tumor cells because the PCR is biased for the amplification of DNA containing the shorter STR. To overcome this problem a new technique based on MSP-PCR (methyl specific PCR) was established. We investigated the methylation pattern of the HUMARA locus (position 46-358: accession # M27423) in healthy women by bisulfite sequencing and found a CGCG repeat (position 201-203) that is constantly either methylated or unmethylated on each of the two X-chromosomes. Based on this knowledge new primer sets were designed which take advantage of the fact that treatment of DNA by sodium bisulfite leads to deamination of deoxy-cytidine residues which are converted into deoxy-uracils.

But in case of methylation of the deoxy-cytidin the base remains unaltered. As in mammals only deoxy-cytidins which are followed by a deoxy-guanosine are methylated the above mentioned CGCG sequence will be changed into UGUG on the one and kept as CGCG on the other X-chromosome. Based on amplification rates of primer sets ending on CGC (methylated allele) or TGT (unmethylated allele) the distribution of methylation of the template can be analyzed. This new method is currently being evaluated using cases kindly provided by Rosemary Gale, Ph.D. (UC London) for this project. Overall, this project is technically difficult. It is not known whether small clones can reliably be detected. In addition, our studies, like all clonality studies, are hampered by the question of the most appropriate controls For these reasons, we decided to exclude this project from our follow-up proposal.

Fanconi anemia is a pre-leukemic bone marrow disorder with a risk of greater than 50% to develop a clonal hematopoietic neoplasm. The risk for heterozygous individuals is not clear, epidemiological data are inconsistent. We screened a total population of 187 pediatric patients suffering from 1° or 2° MDS and AML for mutations in the Fanconi anemia genes (FANC) to clarify the role of heterozygosity as possible risk factor. At least eight different complementation groups (FANCA, B, C, D1, D2, E, F, G) have been described, representing different genes. Screening FANCA, C, F and FANCG on a molecular base will allow to identify approximately 75-80% of the causative mutations. 72 PCR products have to be amplified and screened for each individual. The FANCA gene is very large and highly polymorphic, which hampers screening efforts. To allow for the planned screening program, a reliable high throughput screening procedure was needed. A Denaturing High Pressure Liquid Chromatography (DHPLC) based PCR product screening was established, using a semiautomatized setup. PCR is performed in a newly developed temperature gradient cycler setup, allowing simultaneous amplification of all 72 PCR products from one individual. This setup allowed the identification of several potential pathogenic heterozygous sequence variations in the screened genes. One clearly pathogenic FANCC gene mutation, previously not described, was identified in a family with siblings suffering leukemia. A second pathogenic mutation was discovered in a neuroblastoma patient, being a sibling of a Fanconi anemia patient. A further previously described mutation was identified in the FANCA gene in an AML patient. Several other, previously undescribed, sequence variations have been identified. They are currently under evaluation of their pathogenic role using site directed mutagenesis and retroviral transfection. As a carrier rate of only 1/300 is to be expected, the results need further evaluation, a pathogenic role especially of FANCC gene mutations is possible. The results are partially published, and have been presented on national and international scientific meetings, in collaboration with the patient organizations (the international „Fanconi Anemia Research Foundation" and the national „Deutsche Fanconi Anämie Hilfe"). It is planned to continue and expand the studies presented above in the follow-up period.

Mutations in the *G-CSFR* gene have recently been reported in patients with congenital neutropenia progressing to leukemia suggesting a contribution of these mutations to the pathogenesis of leukemia arising from CN. These mutations occurred in a region in the cytoplasmic domain of the *G-CSFR* spanning nucleotides 2340-2530. All these mutations were nonsense mutations that introduce a premature stop codon leading to the truncation of the distal carboxy-terminal domain of the G-CSFR that is critical for maturation and growth arrest signaling. In the cases studied, *G-CSFR* mutations are acquired during the course of disease and are not responsible for the pathogenesis of CN. Within this project patients

	with cyclic (n=9), idiopathic (n=21) and congenital neutropenia (n=101) were tested for mutations in the *G-CSFR*. The *G-CSFR* mutation were present in 30 % of the CN patients, but absent in patients with cyclic or idiopathic neutropenia and patients with severe aplastic anemia (n=56) or primary leukemia (AML, CMML or ALL) (n=13). Therefore, somatic *G-CSFR* mutations do not seem to play a role in the development of primary leukemia or MDS/AML other than in congenital neutropenia. The fact that *G-CSFR* mutations were absent in the majority of CN patients indicates that these mutations are not causally involved in the pathophysiology of severe congenital neutropenia. As 87 % of the patients with CN/MDS/leukemia were shown to harbor a *G-CSFR* mutation, these results strongly indicate that these mutations are highly associated with the leukemogenesis in CN. In our follow-up proposal studies on the pathophysiology of congenital neutropenia will be excluded because these studies will be part of new network (see B.5 networking). Mutations resulting in a deregulated Ras pathway are among the most common abnormalities associated with hematologic malignancy. Activating *RAS* mutations have been demonstrated in up to 30% of patients with MDS and AML. To estimate the frequency of *RAS* mutations in children with pre-leukemic and leukemic bone marrow disorders we studied DNA from granulocytes of 20 children with MDS or AML for mutational changes in *N-RAS* codon 12 and *K-RAS* codon 12 und 13. While none of the patients with refractory anemia (RA) or RA with excess of blasts was shown to have a *RAS* mutation at the time of diagnosis, 1 of 5 children with juvenile myelomonocytic leukemia (JMML) had a *K-RAS* (codon 12 GGT⇓ GTT) and 1 of 3 patients with myelodysplasia-related AML an *N-RAS* mutation (codon 12 GGT ⇓ GAT). Both patient had rapidly progressing disease and relapsed post SCT. We will have to expand these studies in the follow-up period and study all patients diagnosed of MDS for *RAS* mutations to correlate this later event in leukemogenesis with clinical presentation, chromosomal abnormalities and patient outcome. In leukemogenesis defects in apoptosis have been postulated. As a model system we studied apoptosis in JMML, a disorder in which reduced apoptosis might be expected. Granulocytes from children with JMML were isolated and spontaneous as well as Fas-mediated apoptosis was examined. While there was no difference in Fas-mediated apoptosis between granulocytes from patients with JMML compared to granulocytes from healthy donors, granulocytes from patients with JMML showed a delay in spontaneous apoptosis. However, due to the rapid spontaneous apoptosis, these experiments were only feasible with granulocytes from freshly obtained blood specimens and not from shipped patient samples. Since any study of changes in apoptotic pathways on a molecular level in preleukemic bone marrow failure disorders would require a large sample size for statistical evaluation and since a sufficient sample size cannot be obtained at any institution as a single center, these studies are currently not further pursued.
B.4	**Publications and patents** Tschan CA, Pilz C, Zeidler C, Welte K, Germeshausen M. Time course of increasing numbers of mutations in the granulocyte colony-stimulating factor receptor gene in a patient with congenital neutropenia who developed leukemia. Blood 97: 1882-84, 2001. Germeshausen M, Ballmaier M, Schulze H, Welte K, Flohr T, Beiske K, Storm-Mathisen I, Abrahamsen TG. Granulocyte colony-stimulating factor receptor mu-

tations in a patient with acute lymphoblastic leukemia secondary to severe congenital neutropenia. Blood 97: 829-830, 2001.

Germeshausen M, Ballmaier M, Welte K. Implications of mutations in hematopoietic growth factor receptor genes in congenital cytopenias. Ann NY Acad Sci 938: 305-21, 2001.

Jung A, Ruckert S, Frank P, Brabletz T, Kirchner T. 7-deaza-2`-deoxyguanosine allows PCR and sequencing from CpG islands. Mol Path 55, 55-57, 2001.

Rischewski J, Schneppenheim R. Screening strategies for a highly polymorphic gene: DHPLC analysis of the Fanconi anemia group A gene. J Biochem Biophys Methods 30;47:53-64, 2001.

Rischewski J, Clausen H, Leber V, Niemeyer C, Ritter J, Schindler D, Schneppenheim R: A heterozygous frameshift mutation in the Fanconi anemia C gene in familial T-ALL and secondary malignancy. Klin Padiatr 212:174-6, 2000.

Rischewski J, Schindler D, Ziegler K, Janka-Schaub G, Schneppenheim R: Discrepancy of diagnostic hallmarks of Fanconi anemia in a patient with myelodysplastic syndrome. Klin Padiatr. 2002, in press.

Rischewski J, Wierzbinski J., Schneppenheim R: Detektion von Sequenzvariationen im Fanconi Anämie A Gen unter Verwendung der DHPLC. Medizinische Genetik 2002, Sonderband zum Fanconi Anämie Symposium in Würzburg 2002, in press.

Hasle H, Niemeyer CM. Myelodysplastic syndrome and juvenile myelomonocytic leukemia in children. In: Trends in Molecular Medicine (formerly: Molecular Medicine Today) 2002, 2: 468-457, 2002, in press

Patents

None planned.

B.5	**Networking** Within the competence network close scientific contact is established to project F „Minimal Residual Disease". Because ~20% of all cases of MDS occur after therapy for malignant disease or aplastic anemia there is also an intensive exchange of data with project K „Second Malignancy". All cases of secondary MDS registered at the Children's Cancer Registry in Mainz in project K are verified and studied in detail by investigators of this project E. For asservation of patient material (blood cells, marrow cells, DNA, RNA, slides) collected within this project data bases had to be constructed. Guidelines for handling of patient material had to be formulated. To achieve these aims there was intensive contact with the coordination and management group in Berlin/Hannover (Mantelantrag, project A) and project G „Clinical Relevance of Molecular Changes in Embryonal Tumors". Co-operations within and out-site of this network led to the participation of several investigators in the proposed new BMBF networks on rare diseases. One of these proposed networks is on congenital bone marrow failure disorders and will be coordinated by K. Welte. K. Welte and W. Ebell will transfer their research projects (severe congenital neutropenia, clinical study on Fanconi anemia) to this newly proposed network. They will not apply for further funding in a follow-up period within this network of pre-leukemic bone marrow disorders. Chr. Bender-Götze/M. Führer will participate in a network on acquired aplastic anemia (coordination by H. Schrezenmeier) and transfer their research previously funded within this network to the proposed network on aplastic anemia. Although there is an intense exchange of ideas and concepts between this project E on pre-leukemic bone marrow disorders and the proposed new networks on rare diseases, there will be no overlap in funding of individual projects. The aims of each network are distinct and unique. This project has an excellent international network. The principal investigators of the different forms of per-leukemic bone marrow disorders like congenital neutropenia, Shwachman-Diamond syndrome, Fanconi anemia, acquired aplastic anemia etc. are actively participating in international research groups. Consequently, there is synergy on a number of national and international levels.

Part C – Follow-Up Proposal

C.1 **Aims**

Reference morphology: Evaluation of the new childhood classification of MDS in childhood (I. Baumann, Erlangen; C. Niemeyer, Freiburg)

Recently, we and others developed a new classification for childhood MDS and bone marrow failure disorders. The proposed classification will be evaluated prospectively. In addition, standard procedures and measurements of quality control will have to be developed for the reference evaluation of morphological and clinical data. These standards will have to be evaluated and communicated with the participating local centers. To transfer knowledge of the morphological evaluation of blood and marrow specimens and to educate pediatric hematologists on current classification schema a morphology course will be offered at the University of Freiburg (splitted in 2 work-shops à 2.5 days for 25 participants each, the 1. work-shop on 25.-27.09.2002)

Oncogenetic studies (J. Harbott, Gießen)

- Studies on the relevance of small FISH clones for monosomy 7 or trisomy 8
- Evaluation of a guided step-wise approach to oncogenetics in children with (suspected) MDS

Fluorescent in situ hybridization (FISH) offers a rapid method to screen for monosomy 7 and trisomy 8. It also allows detecting small clones not recognizable with standard banding cytogenetics. These small clones with up to 30% of cells demonstrating monosomy 7 or trisomy 8 on FISH analysis tend to be quite unstable in size. They can increase in number or disappear during consecutive evaluations. In these follow-up studies we want to determine which cells are clonal (FICTION = immunophenotyping and FISH analysis) and whether short term culture prior to FISH analysis will change clone size by initiating apoptosis or proliferation of defined cell lineages.

Oncogenetic studies are an important tool to establish the diagnosis of MDS. They provide prognostic information and greatly influence therapy. Therefore, complete oncogenetic information with timely reporting of results is a prerequisite for good quality patient care. Annually, the oncogenetic reference laboratory in Gießen receives more than 500 samples of (suspected) MDS cases for evaluation. In this follow-up proposal we want to investigate a rational approach to oncogenetic studies in this patient population by applying a step-wise investigational procedure. All incoming MDS samples will be handled and stored in a standardized manner that will allow all necessary future studies. Further oncogenetic analyses (banding cytogenetics, FISH studies for monosomy 7 or trisomy 8, PCR to detect the typical translocations in AML) will await and depend on the results of the morphological reference review. By tailoring the investigations to the specific clinical diagnosis – and thereby eliminating all unnecessary investigations – relevant oncogenetic information should be available for most patients within 21 days. Although theoretically simple, this approach will require intensive and structured communication between the reference centers and consent from the participating local physicians.

…

Molecular studies: Influence of RAS, p53 and FLT3 gene mutations for disease progression and relapse post stem cell transplantation (C. Niemeyer, Freiburg and A. Jung, Erlangen)

A number of molecular abnormalities have been associated with poor response of hematopoietic neoplasm to chemotherapy in most, although not all clinical studies. We want to study some of these molecular abnormalities in patients with pre-leukemic bone marrow disorders to evaluate whether they are also predictive for relapse after SCT. Next to the ongoing studies on RAS mutations we want to evaluate p53 and FLT3 gene mutations. The importance of the Ras pathway is substantiated by the fact that RAS mutations often occur in the absence of chromosomal abnormalities, suggesting the involvement of a limited number of genetic defects in pathogenesis. In contrast to RAS, most cases of MDS with p53 mutations have complex cytogenetic abnormalities. It is unknown whether the complex karyotype is secondary to the p53 mutation, because p53 inactivation can lead to chromosomal instability. The precise role of p53 mutations in leukemogenesis remains unknown. Internal tandem duplication within the exons 11 and 12 of the FLT3 gene, a subclass III tyrosine kinase receptor, has been reported in approximately 10% of MDS cases, and is associated with a high risk of progression to AML. The latter studies will be performed in collaboration with S. Schnittger, München (Competence Network „Acute and Chronic Leukemias").

Genetic predisposition to MDS: Studies on the Fanconi anemia and Nibrin gene (R. Schneppenheim and J. Rischewski, Hamburg)

The previously not described sequence variations of the FANCC and FANCA genes have to be evaluated for their pathogenic role. With an expected carrier rate of 1/300 the current results on heterozygosity for FANC mutations need further evaluation to include or exclude a pathogenic role especially for FANCC gene mutations. The likely functional „end-point" of the Fanconi anemia protein cascade, FANCD2, seems to be closely connected to the Nibrin gene product (NBS1). Defects in Nibrin cause the Nijmegen breakage syndrome, whose patients suffer an increased risk for the development of lymphatic neoplasms. The screening setup therefore was adapted to the NBS1 gene product. Heterozygosity as a risk factor for the development of lymphomas could be excluded, studies to exclude a possible risk of heterozygous for the development of lymphatic leukemias are under way. Here we propose to expand the NBS1 gene analyses to patients with pre-leukemic bone marrow disorders. Depending on upcoming results the method of Denaturing High Pressure Liquid Chromatography (DHPLC) based PCR product screening can be adapted to identify sequence variations in different genes suspected of predisposing to MDS.

Angiogenesis in pre-leukemic marrow disorders (C. Niemeyer and J. Rößler, Freiburg, I. Baumann Erlangen)

The importance of angiogenesis, the formation of new blood vessels from existing ones, is well established in regard to growth and progression of solid tumors. Recent studies indicate that angiogenesis is also an important feature in the pathogenesis of leukemias. For example, vessel counts in bone marrow from children with acute lymphatic leukemia are higher than in bone marrow from control patients (Perez-Atayde et al, 1997). Increased angiogenesis has also been reported in the bone marrow of patients with acute myeloid leukemia. Here, normalization of bone marrow microvessel density could be demonstrated when patients achieved a complete remission after induction chemotherapy. Furthermore, leukemic blasts were found to over-express angiogenesis mediators such as

	VEGF (vascular endothelial growth factor) (Padro et al, 2000). Therefore, leukemia might be angiogenesis dependent and angiogenesis could offer a new target for therapy. We plan to determine vessel densities in bone marrow biopsies of pre-leukemic disorders. Moreover, the expression of angiogenic mediators such as VEGF and bFGF (basic fibroblast growth factor) will be examined. The major aim is to demonstrate the role of angiogenesis in the different pre-leukemic bone marrow disease compared to bone marrow of control patients. We will study angiogenesis in all patients diagnosed of pre-leukemic disorders and correlate the results with other characteristics such as chromosomal abnormalities and clinical data. Finally, the possible role of blood vessel formation in the pathogenesis from pre-leukemic disease to leukemia could be clarified.
C.2	**Methodological approach** 1. Reference morphology: The reference evaluation will be continued as established. 2. Oncogenetic studies: The techniques for FISH analysis and standard banding cytogenetics are established. New molecular probes for gene loci on the long arm of chromosome 7 will be introduced. 3. Molecular studies: The methods of mutational analysis (ASRA SSCP, sequencing) are established. Cell lysates of mononuclear cells and granulocytes of blood and marrow of patients with pre-leukemic bone marrow are stored for DNA/RNA extraction. 4. Genetic predisposition to MDS: To examine the role of heterozygosity as a risk factor for malignancies, DHPLC was introduced. DHPLC analysis can reproducible recognize known sequence aberrations and screen for unknown mutations of highly polymorphic genes. The method is established. 5. Angiogenetic studies: Bone marrow biopsies sent for reference pathology are available for the study on angiogenesis. According to the International Consensus on the Methodology and Criteria of Evaluation of Angiogenesis (Vermeulen et al 1996), we will perform immunohistochemical staining of endothelial cells in the bone marrow with a CD 31 antibody. Vessels will be counted and an individual vessel index for each bone marrow will be determined. The mediators of angiogenesis in the bone marrow will be identified by immunohistochemistry with a VDGF and a bFGF antibody (see: J. Wilting, M. Papoutsi, B. Christ, K. Nicolides, C.S. von Kaisenberg, J. Borger, G.B. Stark, K. Alitalo, S.I. Tomarev, C. Niemeyer, J. Rössler: The transcription factor PROC 1 is a marker of lymphatic endothelial cells in normal and diseased tissues. Submitted). Statistical test will evaluate correlation with other disease and patient characteristics.
C.3	**Work plan** Projects 1 and 2 will be performed continuously during the study period. In project 3, DNA will have to be extracted from frozen cell lysates (2 months), for the mutational analyses of RAS, p53 and FLT-3 we estimated a time frame of 3, 4 and 4 months, respectively. In project 4, the previously unknown sequence variations were identified. They are currently under evaluation of their pathogenic role using site directed mutagenesis and retroviral transfection (18 months). Screening for mutational changes in the NBS1 gene product is estimated with a time frame of 12 months. …

	For project 5 it is estimated that CD31 staining will require 2 months, vessel counts 1 month and statistical evaluation 1 month. The immunohistochemical studies for expression of VEGF and bFGF in the bone marrow are estimated with 4 months.
C.4	**Networking** The current networking (see B.5) will be continued.

Part D- Requested Funding for the Project	
D.1	**Salaries** The following positions are required to conduct this project: Freiburg: 0,5 BAT IIa. The scientist will be responsible for molecular studies on RAS, p53 and FLT3 mutations. He/she will also perform the studies on angiogenesis. Costs in 2003: 28266 €, in 2004: 28692 € Hamburg: 0,5 BAT IIa. The scientist will perform DHPLC based PCR product screening of the NBS1 gene product and continue the current expression studies of the FANC genes. Costs in 2003: 28266 €, in 2004: 28.692 € Gießen: 1 MTA Va/b. The MTA will perform all required cytogenetic studies. The funding of only a 50% position till midterm of this project was insufficient. It resulted in a backload of incomplete studies and a significant delay in reporting oncogenetic results to the local physicians. Costs in 2003: 41364 €, in 2004: 41988 €.
D.2	**Consumables** Freiburg: The cost of primers, sequence kits and antibodies for immunohistochemistry is estimated 7500 € per year. Hamburg: Estimated costs for DHPLC analysis is 5000 € per year. Gießen: Consumables are estimated at 5000 € per year. Erlangen: Annual cost of consumables is estimated at 2500 €.
D.3	**Investments** There will be no investments.
D.4	**Other Costs** There will be no additional costs.

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Prognostic relevance of minimal residual disease in childhood acute leukemia and malignant lymphoma tested by quantitative polymerase chain reaction (RQ-PCR) and multiparameter immunophenotyping (Project F)
Grant No.	:	01 GI 99 63/2

Name of scientist-in-charge	:	Univ.-Prof. Dr. Jochen Harbott
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Project home page (if different from Network homepage)	:	.....

Part A - General Statements about the Project

A.1. **Subject**

Prognostic relevance of minimal residual disease in childhood acute leukemia and malignant lymphoma tested by quantitative polymerase chain reaction (RQ-PCR) and multiparameter immunophenotyping.

A.2. **Co-Investigators**

- Prof. Dr. Hartmut Kabisch, Children's Univ. Hospital, Hamburg (ALL, CoALL, Ig/TCR gene rearrangements)
- Dr. Dirk Reinhardt, Children's Univ. Hospital, Münster (AML, Immunophenotyping)
- Dr. Dr. Karl Seeger, Charité - Virchow Klinikum, Berlin (ALL relapses, Ig/TCR gene rearrangements, Fusion genes)
- Prof. Dr. Alfred Reiter, Dept. Ped. Oncology/Hematology, Gießen (Lymphoma, Fusion genes)
- Prof. Dr. Martin Schrappe, Dept. Ped. Oncology/Hematology, Hannover (ALL, ALL-BFM, Cell bank and preparations)
- Prof. Dr. Claus R. Bartram, Department of Human Genetics, Heidelberg (ALL, ALL-BFM, Ig/TCR gene rearrangements)
- PD Dr. Frank Griesinger, Internal Medicine, Göttingen (AML, Immunophenotyping)

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects	☐ yes	☒ no
(b) clinical trials	☒ yes	☐ no
(c) animal models	☐ yes	☒ no
(d) gene therapy	☐ yes	☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1]**	**Amount[1] Requested**
2003	338,1	35	0	4,2	0	377,3
2004	275,0	35	0	4,2	0	314,2

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

During the last years it could be shown by two large studies (Cavé et al (1998) N.Engl.J.Med. 339,591; van Dongen et al (1998) Lancet 352,1731) that MRD is an important independent prognostic factor and can be used for therapy stratification in childhood ALL. Therefore, in Germany a MRD based multicenter therapy trial was started together with the Austrian BFM and the Italian AIEOP group. Up to now, this is the only study using MRD for stratification. For other types of malignant diseases, however, the clinical relevance of MRD is not yet clear.

Beside the MRD markers used in the mentioned studies (Ig/TCR-gene rearrangements) other markers like fusion genes or immunophenotype are known to be useful for MRD detection in other malignant diseases.

The aim of this cooperative study is the evaluation of the most suitable marker for minimal residual disease in childhood acute leukemia and Non-Hodgkin's lymphoma (NHL) and to clarify its meaning for therapy stratification and monitoring of the response to therapy.

<u>The following markers are tested:</u>

Leukemia specific fusion genes:

- ALL-relapses – Seeger, Berlin
- AML – Harbott, Gießen
- NHL – Reiter, Gießen

Ig/TCR gene rearrangements:

- ALL-relapses – Seeger, Berlin
- ALL (BFM) – Schrappe, Hannover, and Bartram, Heidelberg
- ALL (CoALL) – Kabisch, Hamburg

Immmunophenotyping:

- AML – Reinhardt, Münster, and Griesinger, Göttingen

All results will be compared with clinical data provided by the therapy studies ALL-BFM (Schrappe, Hannover), AML-BFM (Creutzig/Ritter, Münster), ALL-REZ (Henze, Berlin), CoALL (Janka-Schaub, Hamburg), and ALL-NHL (Reiter, Gießen).

During the past 30 months the detection methods were established by the different groups and more than 20.000 blood and bone marrow samples were analyzed. After some difficulties with recruiting of follow up samples the compliance has increased in all subprojects. The cooperation between the subprojects works well and technical knowledge or missing samples are exchanged between the labs. Also the comparison of clinical data and laboratory results is regularly performed. First preliminary results were given in several oral and poster presentations at national and international conferences.

B.2	**Original aims of the project** Á Evaluation of a uniform system of data management and transfer between hospitals, therapy study, and laboratories Á Standardization of MRD techniques Á Optimizing of material recruitment at diagnosis and during follow-up Á Evaluation of prognostic meaning of MRD in different malignancies Á Evaluation of therapy influence to decrease and increase of the leukemic cell number Á Evaluation of the best time points for MRD analysis and individual follow-up controls Á Comparison MRD results of peripheral blood and bone marrow Á Comparison of MRD techniques
B.3	**Scientific results** <u>Fusion genes as MRD marker in AML</u> The aims of this project are the comparison of results gained by different methods to find the most suitable technique for each type of malignancy. Furthermore the best time points for therapy control should be evaluated. Leukemia specific fusion genes in AML were analyzed with RT-PCR and real time quantitative (RQ-) RT-PCR. During the first phase of this project RT-PCR was used to identify the rearrangements and to use them as MRD marker. In the period from 1999 to 2001, 284 samples of children with newly diagnosed AML were successfully screened by RT-PCR for one of the fusion genes AML1/ETO, CBFß/MYH11, MLL/AF9, and PML/RARa and 52 of them were found to be positive for one of these rearrangements (19 %). Evaluation of follow-up samples showed different results for each of these rearrangements (PML/RARa excluded because of low numbers). AML1/ETO was detectable in nearly all samples at the early time points (TPs) 1 and 2 (before HAM). During the course of treatment at the TPs 3 – 5 (before and after consolidation and after HD/VP) about 60 % of the children remained positive and also after HD/VP and during maintenance therapy about 37 % showed the rearrangement. For CBFß/MYH11 the number of follow-up samples was much smaller. But also here a decrease of positive samples was visible from TP1 and 2 (75 and 80 %) to TP5 and later, where only 1/7 was positive for the rearrangement (14%). The treatment response for MLL/AF9 positive patients was even better: The number of positive samples decreased from TP1 (50%) to TP3 (10%) and after HD/VP only 2/22 samples (8 %) remained positive. The second phase of the project, the analysis by RQ-RT-PCR started in 2000 and was performed at 49 samples of 12 AML1/ETO positive patients. The results show a different response to treatment, with a decrease of copy numbers of 3 – 4 log at TP3 and remain positive at this low level. One patient, however, showed a decrease of only 2 log, later on copy numbers increased to 440 before HD/VP and a relapse appeared after 2 months. …

Leukemia associated immunophenotypes in AML (LAIP)

The AML-BFM 98 MRD study started in 1/2000 in order to evaluate, standardize and establish immunophenotyping in AML in children. In a first phase, the participating laboratories in Muenster, Göttingen, Vienna and Prague agreed on identical antibody-panels and standardized procedures of sample processing, analysis and data management. The consensus panel was evaluated and adapted to 3- and 4-color flowcytometry. The complete panel was applied to each follow-up samples in order to minimize the risk of false negative results due to the loss or shift of antigens during treatment, a known phenomenon in myeloid blasts. Between 1/2000 and 10/2001 in total bone marrow samples of 355 children have been analyzed. In detail a leukemia-associated immunophenotype could be defined in 168 of 198 (88%) protocol patients of the AML-BFM 98 study. In addition 89 observation patients of the AML-BFM study and 23 children with a relapse of AML were included. Samples of 65 children with ALL, CML, JMML, MDS, or solid tumors were measured to evaluate sensitivity and specificity of the consensus panel. In 149 of 185 protocol patients (78%) more than two follow-up samples were available.

Three kinds of immunophenotypes could be defined. (1) Asynchronous expression of stem cell and myeloid antigens i.e. CD34/CD117 combined with CD13/CD15 had a low specificity because precursors in regenerating or normal bone marrow expressed this pattern in 0.47% (0.1 to 1.5%). (2) The aberrant co-expression of stem cell antigens and lymphatic antigens such as CD7 or CD2 showed a median level of specificity (0.07% (0.05 to 0.19%). (3) Aberrant expression of stem cell antigens combined with B-lymphatic (CD19, CD10) or NK-cell antigen (CD56) showed the best specificity. The maximal level in normal bone marrow was 0.05%. Sensitivity of different immunophenotypes was evaluated by diluting known leukemic blasts in regenerating bone marrow. Minimal level of sensitivity was found to be at 0.05%.

According to these data highly specific immunophenotypes could be detected in 33%, median specificity was seen in 71% and low specificity was seen in 88% of the protocol patients.

Two laboratories (Göttingen/Münster) analyzed simultaneously 17 samples of children with AML from diagnosis and during therapy. A high correlation of blast quantification could be demonstrated (correlation R^2=0.98). In addition, two independent explorers quantified the raw data of 16 samples. All results correlated well (R^2=0.97).

Based on these data cut-off levels of each antigen combination for MRD diagnostics could be defined, calculated from median+2 standard deviations. By an online form MRD levels were centrally registered in a central data base, combining the results of immunophenotyping, molecular MRD diagnostics, morphology and outcome.

The prospective study phase, started 1/2002, aims to test the impact of MRD diagnostics as an independent prognostic factor in AML in children. This might facilitate future treatment stratification and consequently optimize outcome.

…

MRD in ALL relapse

During the project phase (1999-2001), 1900 bone marrow and blood samples were sent to the reference laboratory of the relapse trials ALL-REZ BFM in Berlin. Two hundred fifty one samples were drawn at relapse diagnosis and 885 follow-up samples were taken during treatment and were used for minimal residual disease (MRD) assessment in children with first ALL relapse. MRD was quantified using T-cell receptor and immunoglobulin gene rearrangements (TCR-ν,-ι, IgH, Igμ) and fusion transcripts (TEL-AML1, BCR-ABL, MLL-rearrangements).

In 72 patients treated according to ALL-REZ BFM (strategic group S2), MRD was quantified during initial phases of therapy using TCR and Ig gene rearrangements as clonal MRD markers. In patients with MRD $<10^{-3}$ (n=43) at day 36 (after second therapy course), probability of event-free survival (pEFS) was 0.89; by contrast, patients with MRD Ó10^{-3} (n=29) had a pEFS of 0.46 (p=0.001). Using the gene expression of the TEL-AML1 fusion for quantification of MRD, patients with MRD $<10^{-3}$ (n=20) at day 36 had a pEFS of 0.75, where as those with MRD Ó10^{-3} (n=7) had a pEFS of 0.00 (p=0.034). d

The data suggest that in children with ALL relapse the extent of early response can be used to predict long-term outcome. There is evidence that rapid molecular responders are likely to have an excellent prognosis with chemotherapy. Thus, transplant procedures carrying a high risk for morbidity and mortality may not be necessary in these children. In the BFM Study-Group it has been agreed that results of MRD monitoring will be used for patient stratification in the new relapse trial ALL-REZ BFM 2002. Recently, the pilot phase of the protocol has started.

MRD in ALL (BFM)

The analysis of minimal residual disease (MRD) has significant prognostic value for the evaluation of early treatment response and contributes to the individualization of chemotherapy protocols. The International BFM Study Group used clone-specific immunoglobulin (Ig) and T-cell receptor (TCR) gene rearrangements as MRD-PCR targets with a sensitivity of Ò10^{-4} on two follow-up time points to define three risk groups: a low-risk group (LR) of 43% of patients with MRD negativity at the end of induction therapy (day 33) and before consolidation treatment (week 12) and a 5-year relapse-free survival (RFS) of 98%; a high-risk group (HR) of 15% of patients with MRD levels Ó10^{-3} at time point 2 and 5-year RFS of 16%; an intermediate-risk group (IR) containing the 43% remaining patients with a 5-year RFS of 76%.

Relying on previous experience the BFM study group introduced MRD-adapted treatment stratification in the current trial ALL-BFM 2000. Based on quantitative real-time PCR (RQ-PCR) analysis, junctional regions of Ig and TCR gene rearrangements have effectively been used for the quantification of MRD in childhood ALL. LightCycler-assisted RQ-PCR in combination with SYBR Green detection proved to be an accurate, highly flexible and sensitive method for routine monitoring of ALL patients and until 12/2001 the remission status of more than 600 children has been analyzed.

581 eligible patients were enrolled from Aug 99 to May 2001. Risk group assignment on the basis of MRD detection was possible in the case of 453 (78%) patients, with 45% stratified into the LR group, 46% into IR and 9% into the HR group. Taking into consideration additional risk group parameters (prednisone

response, translocations 9;22 and 4;11) patients were eventually classified as LR (34%), IR (49%) and HR (17%), respectively.

On-time MRD-based stratification in large prospective trials is feasible using rapid cycle real-time PCR protocols in combination with very reliable logistics and high laboratory standards.

Cell bank of the ALL-BFM study

The basis for prospective and retrospective studies is a well organized cell bank. The cell bank of the ALL-BFM study was originally founded to process and store samples for the analysis of Ig and T-cell receptor gene rearrangements in the molecular genetic laboratory in Heidelberg. In addition, material was provided for other projects from within and outside the network.

60 to 80 bone marrow and/or blood samples per week are mailed to this laboratory by all Pediatric centers cooperating in the ALL-BFM-trials. All samples have to be processed immediately during 6 days a week. All of them will be used for a morphological analysis and once or twice a week the collected material will be send to the molecular laboratory in Heidelberg for marker analysis.

Within this group a new project was started in 2001 dealing with MRD in high risk patients. In the meantime, more than 20 of these children were analyzed at several time points during first CR before transplantation. Among them five were BCR/ABL positive at diagnosis and the follow up data will be compared to the RT- and RQ-RT-PCR data gained in the molecular reference laboratory for fusion gene analysis in Gießen.

Furthermore the collaboration with the molecular laboratory of the German ALL relapse study (ALL-REZ) was intensified: The Ig and T-cell receptor gene rearrangements identified at diagnosis and relapse will be compared and an evaluation of clinical data and follow up data is planned.

MRD in ALL (CoALL)

One fourth (~120 pts/year) of the German children with acute lymphoblastic leukemia (ALL) is treated according to the CoALL protocol. In parallel to the BFM study group specimens for MRD analysis were collected since 1992 at comparable time points.

Standardization of MRD techniques:

- Identification of clone-specific (i.e. patient-specific) sequences by PCR and sequencing; subsequent selection of allel-specific oligonucleotides for each patient and MRD analysis.
- Establishment of at least two individual clone specific markers utilizing the T-cell-receptor-ν-chain as well as the immunoglobulin heavy chain (IgH) and the kappa-deleting element (ρ-de).
- Evaluation of the WAVE technology for identification of clonal TCR rearrangements.

Clonality of PCR amplified Vι2-Dι3 products were examined on a high resolution micropellicular DNASep matrix (WAVE, transgenomic). 310 B-cell precursor ALL (221 C-ALL; 76 Pre-B-ALL; 13 Pro-B-ALL) were subjected to DHPLC analysis

and subsequently classified into clonal, biclonal or negative samples. The overall incidence of clonality discovered by WAVE technology was 48.4% with no differences between the two subgroups c-ALL and pre-B-ALL, but with only 1 out of 13 clonal pro-B-ALL samples. In 66 of 150 positive cases bi- or oligoclonality was detected (44%). From these results we suggest that DHPLC analysis is a rapid and reliable tool for identification of MRD targets in large series of newly diagnosed leukemias under standardized conditions.

Optimized material recruitment at diagnosis and during follow up:

A mean recruitment of 2×10^7 cells per specimen was achieved at the time point of diagnosis, whereas 1×10^7 cells were sufficient for follow up samples.

Evaluation of therapy influence on MRD leading to the best time points for MRD analysis and individual follow up:

Surprisingly, at the end of induction therapy (after 5 weeks of therapy) of the CoALL study higher MRD values were observed in comparison to the ALL-BFM and other European studies. The slower clearance of leukemic cells in the initial phase might be due the lower cytotoxic potency of the three-drug induction regimen used by the CoALL study compared to the four drug regimen employed in BFM protocol. Both protocols, however, have the identical long-term survival. It will be very interesting to identify the therapeutic element(s) with such an antileukemic potency in the context of the CoALL study.

As the MRD detection after CoALL induction therapy has low prognostic potential because high and low risk patients cannot be discriminated at the end of induction therapy, we introduced an additional time point at day 43. This time point is supposed to give more prognostic information regarding MRD because it follows a therapy block with three further drugs.

This new time point for MRD analysis was introduced in July 2000. Until January 2002, 130 bone marrow samples were collected and about 1×10^7 cells (range 1×10^6 to 1×10^8 cells) were stored and DNA was isolated.

MRD investigations of CoALL patients with late response or after relapse who underwent an allogeneic blood stem cell transplantation demonstrated clearly that a high MRD level before and after transplantation rises the risk of subsequent relapse significantly.

In this transplantation related MRD study, information and specimens were exchanged frequently between the involved laboratories and may lead to more effective therapy protocols.

<u>MRD in NHL</u>

The t(8;14)(q24;q32), involving MYC gene (8q24) and the immunoglobulin heavy chain (IgH) locus (14q32), represents about 75% of all translocations in childhood Burkitt's lymphomas (BL) and B-cell ALL. Due to the great variability of the breakpoint region, a standard polymerase chain reaction (PCR) assay is not sufficient for the detection of this chromosomal translocation. The recently improved long-distance (LD) PCR for the detection of t(8;14)(q24;q32) allows to identify the specific breakpoint region within the MYC gene and the IgH locus. The combination in different reactions of one primer specific for MYC exon II and four primers for the IgH locus, localized within the joining region (JH) and the constant regions

	(Cμ, Cν and Cζ), reveals the specific breakpoint region. Our investigations of Burkitt´s lymphoma cell lines and several childhood BL or B-ALL, positive for t(8;14)(q24;q32), showed a product ranging in size from 1 to 10 kb. The LD-PCR, however reached a sensitivity of 10^{-2} only, which is not sufficient for detection of minimal residual disease. Therefore, we established a more sensitive nested PCR with a specific primer combination for each patient based on sequence analysis of the variant breakpoint regions. Thereby, two primers were specific for the MYC-gene close to the MYC/IgH breakpoint and one primer is located in the IgH locus, whereas another one overlapped the breakpoint of each specific breakpoint region. To establish the specification, we investigated the Burkitt lymphoma cell line CA-46 and several pediatric BL or B-ALL using their specific primer combination for the nested PCR in comparison with lymphoma cell lines and pediatric leukemia which are negative for t(8;14)(q24;q32). Using this breakpoint specific nested PCR, we could detect the translocation in 1 out of 104 hematopoietic cells lacking this translocation. In conclusion, we represent a combination of LD- and nested PCR method as a specific and sensitive tool for the evaluation of minimal residual disease in patients affected by t(8;14)(q24;q32) positive lymphomas.
B.4	**Publications and patents** Eckert C, Landt O, Taube T, Seeger K, Beyermann B, Proba J, Henze G. Potential of LightCycler technology for quantification of minimal residual disease in childhood acute lymphoblastic leukemia. Leukemia 2000;14:316-323 Eckert C, Biondi A, Seeger K, Cazzaniga G, Hartmann R, Beyermann B, Pogodda M, Proba J, Henze G. Prognostic value of minimal residual disease in relapsed childhood acute lymphoblastic leukaemia. Lancet 2001;358:1239-1241 Nakao M, Janssen JW, Bartram CR. Duplex PCR facilitates the identification of immunoglobulin kappa (IGK) gene rearrangements in acute lymphoblastic leukemia. Leukemia 2000;14:218-219 Nakao M, Janssen JW, Flohr T, Bartram CR. Rapid and reliable quantification of minimal residual disease in acute lymphoblastic leukemia using rearranged immunoglobulin and T-cell receptor loci by LightCycler technology. Cancer Res 2000;60:3281-3289 Schrappe M. Workshop on minimal residual disease. Leukemia 2001;15:272 Seeger K, Buchwald D, Peter A, Taube T, von Stackelberg A, Schmitt G, Henze G. TEL-AML1 fusion in relapsed childhood acute lymphoblastic leukemia. Blood 1999;94:374-376 Seeger K, Buchwald D, Taube T, Peter A, von Stackelberg A, Schmitt G, Kochling J, Henze G. TEL-AML1 positivity in relapsed B cell precursor acute lymphoblastic leukemia in childhood. Berlin-Frankfurt-Munster Study Group. Leukemia 1999;13:1469-1470 Seeger K, Kreuzer KA, Lass U, Taube T, Buchwald D, Eckert C, Korner G, Schmidt CA, Henze G. Molecular quantification of response to therapy and remission status in TEL-AML1-positive childhood ALL by real-time reverse transcription polymerase chain reaction. Cancer Res 2001;61:2517-2522

	Seeger K, Taube T, Eckert C, Hanel C, Pogodda M, Henze G. Unusual T-cell receptor-delta gene rearrangement patterns revealed by screening of a large series of childhood acute lymphoblastic leukaemia by multiplex polymerase chain reaction. Br J Haematol 2001;113:318-322 Seeger K, Viehmann S, Buchwald D, Harbott J, Schrappe M, Stary J, Henze G, Trka J. Treatment response and residual-disease monitoring in initial and relapsed TEL-AML1 positive childhood ALL. Leukemia 2001;15:280-282 zur Stadt U, Harms DO, Schluter S, Schrappe M, Goebel U, Spaar H, Janka G, Kabisch H. MRD at the end of induction therapy in childhood acute lymphoblastic leukemia: outcome prediction strongly depends on the therapeutic regimen. Leukemia 2001;15:283-285 zur Stadt U, Rischewski J, Schneppenheim R, Kabisch H. Denaturing HPLC for identification of clonal T-cell receptor gamma rearrangements in newly diagnosed acute lymphoblastic leukemia. Clin Chem 2001;47:2003-2011 <u>Patents</u> None planned.
B.5	**Networking** The seven laboratories and the cell bank have started the cooperation with an exchange of methods leading to a standardization of the techniques. E.g. fusion gene MRD is performed in the laboratories in Gießen (1, 5) (AML and lymphomas) and Berlin (4) (ALL-Relapse), in the laboratories of Heidelberg (6b) (ALL-BFM), Hamburg (2) (ALL-CoALL), and Berlin (4) (ALL relapse) Ig/TCR-gene rearrangements are analyzed and the immunophenotyping of AML material is done in Göttingen (7) und Münster (3). Common protocols were developed and adapted to the laboratories. Logistic problems had to be solved by the cell bank in Hannover (6a) where DNA is extracted and the samples are shipped to the laboratory in Heidelberg (6b) to be proceeded. Furthermore, a transfer of data and material has started between the cooperation partners. At diagnosis of the disease and during follow-up, they all receive bone marrow and/or peripheral blood from all pediatric oncologic departments in Germany, which all together are the center of this network. Also with the hospitals a data exchange– clinical data vs. results – takes place. All laboratories as well as the oncologic departments are in a close connection with the coordinating centers of the therapy studies involved in this project (ALL-BFM, Hannover, CoALL, Hamburg, AML-BFM, Münster, ALL-REZ, Berlin, and NHL-BFM, Gießen). In addition to the exchange within the competence network several national and international co-operations were started or joined mainly to standardize techniques to make all results comparable: The Group in Gießen (1) is a member of the European Project for standardization of RQ-PCR (Taqman) funded by Europe against Cancer. The flow cytometry labs in Göttingen (7) and Münster (3) have joined the European Group for MRD in ALL by phenotyping (Berlin, Vienna, Prague). The cell bank (6a) and the lab in Heidelberg (6b) are members of the European MRD task force project, which initiated a standardization of Ig/TCR gene rearrangement detection some years ago.

Part C – Follow-Up Proposal

C.1 **Aims**

During the first funding period, the structure of a network for sample collection and standardization was built up. The methods to use were discussed between the laboratories of this project or with other national and international partners. All clinical centers were informed how to send bone marrow and blood for the MRD analyses. Although the compliance of the centers has improved since the start, there is still a large number of missing samples at different time points which finally will hamper the evaluation of the data.

The second funding period will be used to build up a scientific network. The first aim is to receive more follow up sample and to perform the analyses and submit the results in an adequate time to the hospital as well as the coordinating study center. In addition, more efforts are needed for an inter-laboratorial evaluation. To find the best time points for BMT during therapy a comparison of the results of different studies has to be performed (ALL-BFM vs. CoALL). The markers identified at diagnosis and at relapse can give important hints for leukemogenesis. A comparison of the Ig/TCR marker found at diagnosis in Hamburg and Heidelberg will be compared to those detected at relapse in Berlin. Similar studies will be performed for the AML laboratories: Comparison of positivity detected with LAIP and PCR, sensitivity of both methods, exchange of missing samples etc.

Other evaluations will need by far more time. To determine whether a continuing marker positivity at a low level for a long period has a clinical meaning or the identification of the best time points for BMT will need a longer follow-up period and more samples of a larger number of patients.

In addition to the original projects, the immunophenotyping analysis of patients with ALL relapse is planned and in Hannover an intensive evaluation of high risk patients has started.

C.2 **Methodological approach**

All methods which were initially described are established in the laboratories of the project and standardized as described before (B.5.).

During the past two years it became obvious that the workload caused by the huge number of samples shipped to each of the cooperating laboratories is too much for one half time technician. The technicians have to prepare the samples for analyses, perform the analyses and enter patient's data and results into a computer. Furthermore, they are responsible for the transfer of material from one lab to the other. Therefore, a full time technician is needed in each of the laboratories.

For the organization of the scientific network within the MRD project a scientist is needed. In addition to the tasks of the coordination between labs and hospitals as well as coordinating study centers the preparation of publications including data collection and statistical analyses will be performed.

It is planned to have two half post doctoral positions responsible for the ALL part of the network (BFM-ALL, Hannover; ALL-REZ Berlin) and another one for the AML laboratories (BFM-AML, Münster). All three scientists should be experienced with all the problems of coordination of different groups, hospitals and

	therapy studies as well as evaluation of scientific, clinical and statistical data. Except these three groups all others will have a full technician during the first funding period (2003). Because in 2004 no new patients will enter the studies and only follow up samples will be analyzed, all groups will apply for only a half technician position with the exception of the project management where an additional half position is needed as assistance for the documentations used for the final report.
C.3	**Work plan** The initially described work plan has not changed. All preparatory work as standardization, mailing logistics etc. were finished during the first months. Data collection is still running and will proceed until the end of 2003. In 2002 a further midterm evaluation will be performed to control preliminary results, compare different methods and markers and discuss again the problems of compliance. During the year 2004 no further patients will be added to the project, but only follow-up studies will be performed. A final evaluation, however, concerning the prognostic meaning of all MRD markers (especially for the rare ones) can not be performed in this period, but will last for some other years.
C.4	**Networking** The network structures built up so far by this project are described in B.5. In addition, further co-operations are planned, e.g. the ALL relapse laboratory in Berlin is going to start immunophenotyping as well and a co-operation with the marker laboratory in Berlin (Prof. Dr. W.-D. Ludwig) is planned. The lymphoma group in Gießen will join in an international MRD study initiated by groups in Toulouse, France and Padua, Italy. In addition, a co-operation has started between this project and Project H of the competence network. In general, the scientists included in the network of the MRD project will help to fulfill the aims of the whole competence network by creating closer, faster, more effective and long lasting connections between reference laboratories and the pediatric centers as well as the coordinating centers of the therapy studies.

Part D- Requested Funding for the Project

D.1 **Salaries (given in €)**

Project	Position	2003	2004	Total
AML-fusion genes	1/1 TA +1/1 TA	44785	45456	
ALL (CoALL)	1/1 TA + ½ TA	44785	22728	
AML (Immunol. /Mü)	½ TA + ½ TA	22392	22728	
	½ WA	30594	31052	
ALL relapses	½ TA + ½ TA	22392	22728	
	½ WA	30594	31052	
Lymphoma	1/1 TA + ½ TA	44785	22728	
ALL (BFM)/ cell bank	½ TA + ½ TA	22392	22728	
	½ WA	30594	31052	
AML (Immunol. /Gö)	1/1 TA + ½ TA	44785	22728	
Total		338098	274980	613078

D.2 **Consumables**

Project	Consumables	2003	2004	Total
AML-fusion genes	Reagents and lab ware	5000	5000	
ALL (CoALL)		5000	5000	
AML (Immunol. /Mü)		5000	5000	
ALL relapses		5000	5000	
Lymphoma		5000	5000	
ALL (BFM)/ cell bank		5000	5000	
AML (Immunol. /Gö)		5000	5000	
Total		35000	35000	70000

As already stated in the initial grant application the amounts for consumables are not sufficient to perform all analyses. The cooperating partners, however, take the chance of the project to build up a long lasting network. The above mentioned amount of money will be needed mainly to build up the network and keep it running.

D.3 **Investments**

None.

D.4 **Other Costs**

Project	Position	2003	2004	Total
AML-fusion genes	Travel costs	600	600	
ALL (CoALL)		600	600	
AML (Immunol. /Mü)		600	600	
ALL relapses		600	600	
Lymphoma		600	600	
ALL (BFM) / cell bank		600	600	
AML (Immunol. /Gö)		600	600	
Total		4200	4200	8400

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Clinical Relevance of Molecular Changes in Embryonal Tumors (Project G)
Grant No.	:	01 GI 99 64/5

Name of scientist-in-charge	:	Univ.-Prof. Dr. med. Frank Berthold
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Project home page (if different from Network homepage)	:	.....

Part A - General Statements about the Project

A.1. **Subject**

Clinical relevance of molecular changes in embryonal tumors

A.2. **Co-Investigators**

- T. Pietsch, Institute of Neuropathology, University of Bonn
- W. Scheurlen, Children's Hospital, University of Heidelberg/Mannheim
- M. Gessler, Biocenter, University of Würzburg
- H. Christiansen, Children's Hospital, University of Marburg:

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects ☒ yes ☐ no

(b) clinical trials ☒ yes ☐ no

(c) animal models ☐ yes ☒ no

(d) gene therapy ☐ yes ☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	196	30	0	9	0	235
2004	196	30	0	9	0	235

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The project G was successful in establishing three tumor banks (neuroblastoma/rare tumors; hepatoblastoma/medulloblastoma; nephroblastoma) which have been attractive to the group „germ cell tumors" and „soft tissue sarcomas" (application for joining). The tumor tissue set, the tumor box for mailing (patent application) and software programs proved to be useful. An independent board of directors provides tumor tissue for scientific use (4 applications). Although number and quality of the collected tissue samples increased significantly with time, they are far from covering all trial patients. Further improvements are clearly necessary.

The proposed parameters per tumor entity have been studied in many instances and new molecular characteristics were developed for medulloblastoma, nephroblastoma and neuroblastoma. Some markers and many trial patients were not investigated due to the lack of tumor tissue. Early data of neuroblastoma gene profiling (differential expression, SAGE analysis, selective expression) indicate new areas of research and give hope for specific gene and immunotherapeutic targets.

B.2 **Original aims of the project**

Molecular abnormalities have pathogenetic, diagnostic and prognostic implications in each of the embryonal tumors. A main task at the beginning consisted of the utilization of experience of each group to synergize the efforts and pathways to be followed. Two major achievements were made:

- Establishment of 3 separate tumor banks working with the same tumor tissue set, tumor box and logistics.
- Beginning of a closer cooperation between labs and clinical trial office (data exchange) and of prospective molecular studies intending to cover all trial patients.

For common and specific aims see section B.3.

B.3 **Scientific results**

Aim 1: Collection of tumor tissue

Refer to section B.5 – Networking.

Aim 2: Definition of new molecular entities and
Aim 3: Description of pathogenetic hierarchies

As the referees initially pointed out, the aims 2 and 3 may be achieved only late „since a wealth and mature body of data in necessary". However, the molecular distinction of medulloblastoma subtypes demonstrates first results (papers G/6, G/7 and G/8):

- classical: LOH 17p, HIC-1 inactivation, c-myc-amplification, trkA p75 expression negative from
- desmoblastic: LOH 9q22, PTOH inactivation, trkA p75 expression positive.

Aim 4: Identification of potential targets for gene and immunotherapy

MAGE-1, MAGE-3 and NY-ESO-1 were found to be selectively expressed in neuroblastoma (paper 10) and are currently used as targets in a phase 1 vaccination trail (peptides, peptide-pulsed dendritic cells). The results of serial analysis of gene expression (SAGE) in neuroblastoma are pending.

Aim 5: Infrastructure for quick evaluation of future molecular and cell biological parameters

The availability of tumor and reference tissue through the three tumor banks represents a major step to that aim. However, the number of samples, the quality and the size of the provided samples need to be improved dramatically. Small series (n=30) utilizing already prepared RNA and histological sections e.g. to check the use of recently reported markers ALK tyrosine kinase and Her2neu neuroblastoma were successfully performed (demonstrating no use).

Aim 6: hepatoblastoma markers LOH 11p15.5, wingless signaling pathway, ß-catenin mutations

In 56 patients, no prognostic information could be derived from LOH 11p15.5, LOH 1p, LOH 1q and ß-catenin mutations (paper 5), LOH 11p and 1q were more frequently, but not exclusively found in the embryonal subtype. The number of ß-catenin mutations was surprisingly high (54 %) and the accumulation of ß-catenin products even more (87%) suggesting a major role in hepatoblastoma tumorigenesis.

Aim 7: medulloblastoma/ PNET markers c-myc, LOH 17p13.1, LOH 17p 13.3, 16q, 9q31; PTCH mutations

c-myc amplifications were found in 10 % (5/52) of classical medulloblastomas and proved to be a very powerful poor prognosis indicator. All c-mcy+ patients experienced early and treatment resistant progression. c-myc amplifications were always associated with 17q isochromosomes. A good discrimination was obtained by trkC expression studies (better prognosis with expression, p=0.034, n=33). New is the diagnostic use of LOH INI1/h SNFS for patients with malignant cerebral rhabdoid tumor a rare entity in children. LOH 17p, 16q, 9q could not yet be analyzed systematically due to the lack of sufficient tumor tissue.

Aim 8: nephroblastoma markers LOH 1p, 11p13, 11p15 11q, 16q, 22q and imprinting analysis 11q15

The LOH screening has been standardized on a European level recently, but data are not yet available. Mutation screening including SNF5/ SWI5, e-cadherin, cadherin-11 showed no tumorspecific mutations in genomic or cDNA and are finished (paper 3). 1q gain by CGH appears to be a poor prognostic factor (collaboration with Dr. Pritchard-Jones) and will be included in further analysis. Currently 70 blastemateous nephroblastomas are investigated for allelic loss, p53 and ß-catenin mutations on the basis of archival paraffin embedded tissue (due to the lack of fresh tumor tissue).

Aim 9: neuroblastoma markers MYCN, LOH1p36.2, DNA ploidy, CD44, MRP, trkA, telomerase

	The MYCN determination is essential for the treatment of neuroblastoma, since amplification qualities for high therapy. The competence network helps to provide that service. Comparisons between two labs demonstrated discordances in 9/125 paired investigations. Detailed reanalysis could solve the discrepancies in all 9 cases. This resulted in the request for double testing of stratifying parameters (two labs, two methods). In addition to deletion, the 1p imbalance was found to represent a poor prognostic factor as 1p deletion occurring in 9 % of patients (n=196). TrkA and CD44 were investigated in 320 patients, the data are currently been analyzed. A major progress was made assessing differential gene expression of 6567 genes in 88 small, round and blue cell tumors. Utilizing artificial neuronal networks typical profiles could be described for neuroblastoma, Ewing's, rhabdosarcoma and Burkitt's lymphoma. 15 genes were selectively expressed in neuroblastoma including 12 unknown expressed sequence tags (EST) (paper 26).
B.4	**Publications and patents** Otano-Joos M, Mechtersheimer G, Ohi 2, Wilgenbus KK, Scheurlen W, Lehnert T, Willeke F, Otto HF, Lichter P, Joos S. Detection of chromosomal imbalances in leiomyosarcoma by comparative genomic hybridization and interphase cytogenetics. Cytogenet Cell Genet 2000; 90:86-92 Granzow M, Popp S, Weber S, Hager HD, Boschert J, Scheurlen W, Jauch A. Multiplex-FISH classifies chromosome rearrangements in a child with intracranial ependymoma. Cancer Genet. Cytogenet (in press) Schulz S, Becker KF, Braungart E, Reichmuth C, Klamt B, Atkinson M, Gessler M, Hofler H. Molecular analysis of E-cadherin-11 in Wilm’s tumours. J Pathol 2000; 191:162-169 Hartmann W, Waha A, Koch A, Albrecht S, von Schweinitz D, Pietsch T. p57-KIP2 is not mutated in hepatoblastoma but shows increased transcriptional activity - a comparative analysis of three imprinted genes p57-KIP2, IGF2 and H19. Am J Pathol 2000; 157:1393-403 Weber RG, Pietsch T, von Schweinitz D, Lichter P. Characterization of chromosomal imbalances in hepatoblastomas: a role for gains on 8q and 20 as predictors of outcome. Am J Pathol 2000; 157:571-578 Bühren J, Christoph AHA, Buslei R, Albrecht S, Wiestler OD, Pietsch T. Expression of the neurotrophin receptor p75-NTR in medulloblastomas is correlated to distinct histological and clinical features: Evidence for a medulloblastoma subtype derived from the external granule cell layer. J Neuropathol Exp Neurol 2000; 59:229-40 Herms J, Neidt I, Lüscher B, Sommer A, Schürmann P, Schröder T, Bergmann M, Wilken B, Probst-Cousin S, Hernaiz-Driever P, Behnke J, Hanefeld F, Pietsch T, Kretzschmar HA. c-myc expression in medulloblastoma and its prognostic value. Int J Cancer 2000; 89:395-402. Koch A, Waha A, Tonn JC, Sörensen N, Berthold F, Hartmann W, Friedl W, Reifenberger G, Wiestler OD, Pietsch T. Mutations of components of the wingless/WNT signaling pathway in sporadic primitive neuroectodermal tumors. Int J

Cancer 2000; 93:445-9.

Kraus JA, de Millas W, Sörensen N, Herbold C, Schichor C, Tonn JC, Wiestler OD, von Deimling A, Pietsch T. Evidence for a tumor suppressor gene at 22q11-q12 involved in the pathogenesis of human ependymomas and distinct form hSNF5/INI1. Acta Neuropathol 2001; 102:69-74.

Söling A, Schurr P, Berthold F. Expression and clinical relevance on NY-ESO1, MAGE-1 and MAGE-3 in neuroblstoma. Anticancer Res 1999; 19:2205-09.

Müller S, van den Boom D, Zirkel D, Köster H, Berthold F, Schwab M, Westphal M, Zumkeller W. Retention of imprinting of the human apoptosis-related gene TSSC2 in human brain tumors. Hum Mol Gen 2000; 9:757-763.

Poremba CH, Hero B, Heine B, Scheel CH, Schaefer KL, Christiansen H, Berthold F, Kneif S, Stein H, Juergens H, Boecker W, Dockhorn-Dworniczak B. Telomerase is a strong indicator for assessing the proneness to progression in neuroblastomas. Med Pediat Oncol 2000; 35:651-655.

Poremba C, Scheel C, Hero B, Christiansen H, Schaefer K, Nakayama J, Berthold F, Juergens H, Boecker W, Dockhorn-Dworniczak B. Telomerase activity and telomerase subunits gene expression patterns in neuroblastoma: A molecular an immunhistochemical study establishing prognostic tools for fresh-frozen and paraffin-embedded tissue. J Clin Oncol 2000; 18:2582-2592.

Ladenstein R, Ambros IM, Poetschger U, Amann G, Urban C, Fink FM, Schmitt K, Jones R, Slociak M, Schilling F, Ritter J, Berthold F, Gadner H Ambros PF. Prognostic significanes of DNA Di-tetraploidy in neuroblastoma. Med Pediat Oncol 2001; 36:83-92.

Theobald M, Christiansen H, Schmidt A, Malekian B, Wolkewitz N, Christiansen N, Brinkschmidt C, Berthold F, Lampert F. Sublocalization of putative tumor suppressor gene loci on chromosome arm 14q in neuroblastoma. Genes, Chromosomes & Cancer 1999; 26:40-46.

Bown N, Cotterill S, Lastowska M, O´Neill S, Pearson ADJ, Plantaz D, Meddeb M, Danglot G, Brinkschmidt C, Christiansen H, Laureys G, Spelemann F. Gain of chromosome arm 17q and adverse outcome in patients with neuroblastoma. N Eng J Med 1999; 340:1951-1962.

Poremba C, Willenbring H, Hero B, Christiansen H, Schäfer KL, Brinkschmidt C, Jürgens H, Böcker W, Dockhorn-Dworniczak B. Telomerase activity distinguishes between neuroblastomas with good and poor prognostic. Ann Oncol 1999;10:1-7.

Dötsch J, Harmjanz A, Christiansen H, Hänze J, Lampert F, Rascher W. Gene expression of neuronal nitric oxide synthase and adrenomedullin in human neuroblastoma using real-time PCR. Int J Cancer 2000; 88:172-175.

Brinkschmidt C, Christiansen H, Terpe HJ, Simon R, Lampert F, Böcker W, Dockhorn-Dworniczak B. Distal chromosome 17 gains in neuroblastomas detected by comparative genomic hybridisation (CGH) are associated with a poor clinical outcome. Med Pediat Oncol 2001; 36:11-13.

Vandesompele J, Speleman F, van Roy N, Laureys G, Brinkschmidt C, Christiansen H, Lampert F, Lastowska M, Bown N, Pearson A, Nicholson JC,

Ross F, Combaret V, Delattre O, Feuerstin BG, Plantaz D. Multicentre analysis of patterns of DNA gains and losses in 204 neuroblastoma tumors: How many genetic subgroups are there. Med Pediat Oncol 2001; 36:5-10.

Bergmann E, Wanzel M, Weber A, Shin I, Christiansen H, Eilers M. Expression of p27Kip1 is prognostic and independent of MYCN amplification in human neuroblastoma. Int J Cancer 2001; 95:176-183.

Dötsch J, Repp R, Rascher W, Christiansen H. Diagnostic and scientific applications of TaqMan real-time PCR in neuroblastomas. Expert Rev Mol Diagn 2001; 1:233-238.

O´Neill S, Estrom L, Lastoska M, Robets P, Brodeur GM, Kees UR, Schwab M, Bown N. MYCN Amplification and 17q in neuroblastoma: Evidence for structural association. Genes, Chromosomes & Cancer 2001, 30:87.

Boon K, Caron HN, van Asperen R, Velantijn L, Hermus MC, van Sluis P, Roobeek I, Weis I, Voute PA, Schwab M, Versteeg R. N-myc enhance the expression of a large set of genes functioning in ribosome biogenesis and protein synthesis. EMBO Journal 2001; 20:1-11.

Savelyeva L, Schwab M. Amplification of oncogenes revisited: From expression profiling to clinical application. Cancer Letters 2001; 167:115-123.

Khan J, Wei JS, Ringner M, Saal LH, Ladanyi M, Westermann F, Berthold F, Schwab M, Antonescu CR, Peterson C, Meltzer PS. Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks. Nature Medicine 2001; 7:673-679.

Bauer A, Savelyeva L, Claas A, Praml C, Berthold F, Schwab M. Smallest region of overlapping deletion in 1p36 human neuroblastoma: A 1-Mbp cosmid and PAC contig. . Genes, Chromosomes & Cancer 2001; 31:228-239.

Hing S, Lu YJ, Summersgill B, King-Underwood L, Nicholoson J, Grundy P, Grundy R, Gessler M, Shipley J, Pritchard-Jones K. Gain of 1q is associated with adverse outcome in favourable histology Wilm's tumors. Am J Pathol 2001; 158:393-8.

Przkora R, Meyer-Puttlitz B, Schmitt O, Berthold F, Nöthen M, Krauss J, Tonn JC, von Deimling A, Wiestler OD, Pietsch T. Analysis of the TSC2 gene in human medulloblastoma. Acta Neuropathol 2001; 102:380-4.

Dahmen RP, Koch A, Denkhaus D, Tonn JC, Sörensen N, Berthold F, Behrens J, Birchmeier W, Wiestler OD, Pietsch T. Deletions of AXIN1, a component of the WNT/ wingless pathway, in sporadic medulloblastomas. Cancer Res 2001; 61:7039-43.

Patent application

Application for the newly developed tumor box (application number A2 101 31828.6, dated 25.06.2001). With the tumor box frozen and non-frozen tissue samples may safely be mailed together within one box to a central address (tumor bank). The tumor bank distributes the samples further to the cooperating labs.

B.5	**Networking** Four aspects contribute to added value and synergy: <u>1. Establishing three tumor banks</u> Tumor tissue and blood/other tissue for comparison are collected systematically from Á neuroblastoma, germ cell tumors, rare tumors (in Cologne, F. Berthold) Á medulloblastoma/PNET and other brain tumors, hepatoblastoma (in Bonn, T. Pietsch) Á nephroblastoma (in Würzburg, M. Gessler) Two applications for collecting germ cell tumors and soft tissue sarcomas were received (one approved, one still to be discussed). The Langerhans cell histiocytosis trial is considering to use the tumor box system and to establish an own tumorbank. <u>2. Software development</u> The data of sampled tumor and reference tissue (e.g. date of collection, site, viability) and of the investigated parameters (e.g. MYCN, 1p, 11q, 17q status) are collected in an Oracle data base (Cologne) and compared to the clinicial trial data. The tumor banks of Bonn and Würzburg use an access data base and observe a yearly exchange of data with the clinical nephro-, hepato- and medulloblastoma trial. <u>3. Informed consent paper</u> To obtain the approval of the parents for research investigations in the tumor tissue of their child an informed consent proposal was made, approved by the Ethical commission of the University of Cologne and provided to all network participants via the clinical trial offices. <u>4. Independent board of directors</u> The board of directors independent from the people sending tissue and running the tumor banks decides which investigators outside the network may be provided with samples for serial analyses. 4 formal applications have been received so far (and were approved).

Part C – Follow-Up Proposal

C.1 **Aims**

The objectives of the initial project are still relevant and achievable. As discussed in section 3, B3 several aims can be achieved not earlier than at the end of second period:

Two points need a change of the initial proposal:

1. The number of collected tumor tissue is too low. Physicians of the cooperating hospitals – according to recent experience in particular the large and very busy Pediatric Oncology units – need to be scientifically sound informed to give the project the adequate high priority in their units. Similarly the research nurses need education about the importance and the skillful handling of tumor and non-tumor tissue. Furthermore the coordinated running of the tumor banks and the presentation of their model character require scientific experience. For significant improvement of that performance a BAT IIa/Ib position is needed as suggested by the referees.
2. The new development of an artificial neural network detecting characteristic neuroblastoma gene expression profiles requires further studies and gene screening in the tumor tissue of all patients. For the preparation of adequate cDNA microchips and the gene screening a ½ BAT Vb position is requested for the Heidelberg group, which is already a competence network member. Those data will be supplemented by SAGE results derived from progressing and regressing neuroblastomas (Cologne).

C.2 **Methodological approach**

No change except DNA chip technology established in Prof. Schwab's laboratory (Heidelberg, NCI) and SAGE technique established in Cologne.

C.3 **Work plan**

<u>Aim 1: Collection of tumor tissue</u>

a) Improvement of number and amount of tissue collection (tumor and non-tumor material)

- Á Continuous information on the high scientific priority in clinical routine 2002 – 2004
- Á Continuous education of FSA 2002 – 2004
- Á Mailing campaigns to pathologists, urologists, pediatric surgeons. 2002 and 2003. Presentation of current results at their meetings.
- Á Publication of results (public media) 2003 and 2004
- Á Improvement of feedback to applicants for the tumor bank material (2002 – 2004)

b) Integration of system applicants (soft tissue tumors, Langerhans cell histiocytosis) to the tumor bank system (use of tumor box, separate tumor bank) 2002

	Aims 2 and 3: Definition of new molecular entities. Description of pathogenetic hierarchies. These goals are achievable after collection of many and mature data, thus at the end of the project 2004 (end of period) and should be continued even afterwards. Aim 4: Identification of potential targets for gene and immune therapy This goal depends very much on the earlier findings. Tumor selective markers need to be investigated for the use as potential target. Close cooperation with project H (synergy). Á First evaluation: 2003 Á Final evaluation: 2004 (end of project) Aim 5 Infrastructure for quick evaluation of future molecular and cell biological parameters The infrastructure is set up and can be used. The only shortening is the availability of the material (see: Aim 1) Á 2002 Á 2003 Á 2004 Aim 6 Hepatoblastoma markers Investigation of 50 tumors with all proposed markers 2004 (end of project) Aim 7 Medulloblastoma markers Investigation of 150 – 200 tumors with all proposed markers Á 2004 (end of project) Aim 8 Nephroblastoma markers Investigation of 120 – 140 tumors with all proposed markers Á 2004 (end of project) Aim 9 Neuroblastoma markers Investigation of 250 – 280 tumors with all proposed markers Á 2004 (end of project).
C.4	**Networking** 1. Project H (Immune- and gene therapy) a) supported by tumor tissue for the gene core facility (application for second period) b) comparison of gene expression data (neuronal network (Heidelberg), SAGE (Cologne) and chip (Halle) data) …

	2. Structured joining of molecular data with clinical parameter and survival analyses to define subgroups of different biological behavior. Suggestion of adapted treatment strategies. Medulloblastoma 2003 Neuroblastoma 2003 Nephroblastoma 2004 Hepatoblastoma 2004 3. International cooperation continued Wilm's tumor: European Wilm's tumor trial, ICR (UK) Neuroblastoma NCI (USA) Hepatoblastoma Karolinska institute (Sweden) Medulloblastoma Queensland (Australia).

Part D- Requested Funding for the Project

D.1 **Salaries (given in €)**

	Tumor-box Center Köln	Co-Investigators							
		Köln	Bonn	Mann-heim	Würz-burg	Mar-burg	Heid el-berg		
	Scientists			**Technicians**					
Year	½	1	1	½	½	½	½	Sum	Total
2003	28	42	42	21	21	21	21	196	
2004	28	42	42	21	21	21	21	196	**392**

Justification:

Position:

- Technicians Köln, Bonn, Mannheim, Marburg
  No change compared to application and granting for the first period and as suggested by the referees
- Change:
  reduction of the technician Würzburg (from 1 to ½ position) as suggested by the referees.
- New: ½ position of a scientist (BAT IIa/Ib) as suggested by the referees
  Duties:
  - Information and education of the partners in the cooperating hospitals (pediatric oncologist, neurosurgical, pediatric surgical, urological units) on the necessity to collect tumor and non tumor tissue from all patients
  - Coordination of the tumor banks (running of, processing, applications for tissue requests, updating information material)
  - Presentation of results to the public
- New: ½ position of a technician (BAT Vb) for Heidelberg
  (Prof. Dr. M. Schwab, Heidelberg) (position from Würzburg)
  Duties:
  - preparation of cDNA microchips for neuroblastoma according to the artificial neuronal network data and screening of neuroblastoma patients

D.2 **Consumables (given in €)**

Tumorbox: Costs for tumor tissue sets (approx. 500 per year à 11 tubes, 20 slides, information sheet, wrapping, shipping) and replacement of damaged styropore parts.

Other: No change compared to application/granting for first period.

Year	Tumorbox Center Köln	Co-Investigators						Sum	Total
		Köln	Bonn	Mann-heim	Würz-burg	Mar-burg	Heid el-berg		
2003	6	5	5	3	5	3	3	30	
2004	6	5	5	3	5	3	3	30	**60**

D.3 **Investments**

None.

D.4 **Other Costs (given in €)**

Travel: no change compared to application and granting for 1. period.

Year	Tumorbox Center Köln	Co-Investigators						Sum	Total
		Köln	Bonn	Mann-heim	Würz-burg	Mar-burg	Heid el-berg		
2003	3	1	1	1	1	1	1	9	
2004	3	1	1	1	1	1	1	9	**18**

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Immune and Gene Therapy of Pediatric Neoplasias (Project H)
Grant No.	:	01 GI 99 65

Name of scientist-in-charge	:	Univ.-Prof. Dr. med. St. Burdach
Institution	:	Universitätsklinik und Poliklinik für Kinder- und Jugendmedizin, Martin-Luther-Universität Halle-Wittenberg
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Project home page (if different from Network homepage)	:	.....

Part A - General Statements about the Project

A.1. **Subject**

Immune and Gene Therapy of Pediatric Neoplasias

A.2. **Co-Investigators**

- G. Henze, J. Köchling, A. Borgmann, Charité, University Children's Hospital, Berlin
- D. Dilloo, U. Dirksen, H. Hanenberg, C. Hirschmann, C. Kramm, H.-J. Laws, T. Niehues, C. Kratz, D. Schneider, University Children's Hospital, Düsseldorf
- R. Esser, T. Klingebiel, U. Koehl, D. Schwabe, Frankfurt
- K. Hanewinkel, G. Hansen, U. Hattenhorst, R. Hühn, C. Hutter, M. Messerle, F. Meyer-Wentrup, M. Staege, A. Wawer, Halle
- O. J. C. Hellwinkel, H. Kabisch, Hamburg
- F. Berthold, B. Hero, M. Jensen, M. Wölfl, Köln
- C. Rössig, J. Vormoor, Münster
- D. Beck, P. Lang, Tübingen
- M. Eyrich, S. Rutkowski, P.-G. Schlegel, Würzburg

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects ☒ yes ☐ no

(b) clinical trials ☒ yes ☐ no

(c) animal models ☒ yes ☐ no

(d) gene therapy ☒ yes ☐ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	83,4	90	5	5	0	183,4
2004	83,4	90	5	5	0	183,4

[1](amounts in thousand Euro), * should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The aim of Project H - Immune and Gene Therapy - is to improve the overall prognosis of pediatric neoplasias through immune and gene therapeutic strategies and to decrease the unwanted effects of mutagenic therapy in malignant diseases of childhood. The project is designed to create a network of experimental, pharmaceutical and clinical immune and gene therapeutic research projects. Its primary purpose is to generate synergies between researchers in the development of novel treatment modalities and to help clinicians incorporate new immune and gene therapeutic insights into their treatment protocols promptly.

To this end the partners co-operating in Project H have initiated a therapy and research registry that is freely accessible on the internet. It includes 43 research projects conducted in 10 institutions and 8 clinical trials. In the controversial field of pediatric gene and immune therapy the registry has increased transparency. It serves as a reliable source of information for anyone afflicted by malignant disease or interested in evolving therapies.

To document the current treatment practice a survey has been completed. It shows the heterogeneity of immune and gene therapeutic treatment practice in Germany.

All immune and gene therapeutic treatment concepts face strict regulatory demands. The project has helped individual treatment centers to meet these demands. In the network created by Project H treatment centers could profit from each other's experiences.

Project H has made significant advances towards the goal of analyzing the gene expression profile of every malignant disease in childhood and of making the data available for the pediatric community.

Research scholarships granted to members of the institutions participating in Project H have led to the implementation of new laboratory techniques and to a further extension of the competence network of pediatric immune and gene therapy.

B.2 **Original aims of the project**

The project aims at improving the overall prognosis of malignant diseases in childhood through immune and gene therapeutic strategies.

To achieve this ambitious aim the original proposal comprises the establishment of a project and study registry to document current treatment practice and to promote the implementation of general treatment standards. Furthermore, it includes the initiation of monitoring programs to validate the effects of immune and gene therapeutic treatment strategies. The project wants to offer support for treatment centers in regulatory and legal issues which will help to standardize immune and gene therapy procedures and will increase safety and efficacy of these new therapeutic strategies.

To support the identification of new tumor-specific targets for immune and gene therapy the project wants to build an efficient infrastructure for the transfer of tumor samples to network partner's equipped with the technology necessary for

	gene expression analysis. In addition, the project aims at improving the communication between treatment centers on a national and international basis to make scientific progress in the field of immune and gene therapeutic research more readily available for the benefit of all afflicted patients. Research scholarships are granted to support the implementation of new techniques in the laboratories of the partners co-operating in the network. The synergy of basic research and clinical application of immune and gene therapy guarantees the continuous development of new treatment strategies and techniques meeting the pharmaceutical and medical demand.
B.3	**Scientific results** <u>Establishment of the Pediatric Immune and Gene Therapy Registry (PIaGen)</u> A registry of German and Austrian immune and gene therapy research projects and clinical studies has been established. Currently 43 research projects and 8 clinical studies are registered. A total of 158 patients have been treated. 150 patients have been treated with antibodies. 8 patients have received cellular therapies with wild type or gene modified cells. The registry has increased the flow of information between the treatment centers. It has begun to generate synergy effects between research projects and has already decreased the number of redundant activities. It enables the participating centers to focus their activities and to co-operate wherever possible. The project registry can be accessed online on the homepage of the competence network. It serves as a source of information for affected patients, their families, primary care pediatricians and the public interested in gene and immune therapy. In addition to supplying information about clinical studies and research activities the project registry encompasses a collection of treatment protocols that are freely accessible to all partners in the network. <u>Transfer of Tumor Samples</u> To facilitate a standardized transfer of tumor samples to centers equipped with the technology for gene expression analysis Project H has written a memorandum to the GPOH explaining the technique and rationale of gene expression analysis of pediatric tumors and asking for support for the gene expression analysis approach. <u>Documentation of Treatment Practices</u> Treatment practices of the participating centers have been documented. Heterogeneity and discrepancies with regard to study design and regulatory issues have been identified. The results reflect the different historical back-ground of the treatment centers. While one institution holds a production license for the engineering of cellular and gene therapeutic agents, many others rely on the license of their blood bank or other institutions. There are four models for leukapheresis and processing and storage of cell products. In 38 % of all pediatric centers leukapheresis is performed in the Departments of Transfusion Medicine. 21 % cooperate with the Departments of Internal Medicine and 8 % have outsourced the process of leukapheresis. 33 % of the Children's Hospitals perform leukapheresis in their own facility. For processing and storage of cell products the situation

	is similar. 33 % of the Pediatric Centers co-operate with the Departments of Transfusion Medicine and 21 % with the Departments of Internal Medicine. 13 % have outsourced the processing and storage to biotech companies, while 8 % have outsourced to other Departments of Pediatrics. 25 % of the Children's Hospitals have their own facilities for processing and storage of cell products. Some centers have not obtained a production license. All research and clinical studies have been approved by the local ethics committees. One study of the University Children's Hospital of Halle concerning the use of IL-2 transgenic Ewing Tumor cell lines for the treatment of advanced Ewing Tumors has been approved by the Commission for Somatic Gene Therapy of the BÄK (Federal Medical Board). Regulatory Procedures and Decision Making The project has helped individual institutions to meet the regulatory demands for research or clinical projects. It has improved communication between the clinical centers to establish treatment algorithms and standards for immune and gene therapy. Overall co-operation and communication has improved. Research Scholarships So far, two research scholarships have been granted to collaborators of the clinical institutions co-operating in Project H. The scholarships have allowed them to learn new techniques and to establish them in their laboratories. Furthermore, the scholarships have led to an increased knowledge transfer and to the initiation of new co-operations with partners outside of the pediatric competence network. € 40000 originally allowed for traveling expenses have been dedicated to the purchase of DNA-Micro-Arrays and reagents for gene chip-preparation and -processing. Advancement of the International State of the Art The international state of the art in immune and gene therapy of pediatric malignant disease includes therapeutic trials conducted primarily in the US, i.e. at the laboratory of Malcolm Brenner at the University of Houston. In the US efforts are made for gene expression analysis of pediatric tumor samples using high density arrays. However, so far there is no American equivalent to Project H. Network structures are a major prerequisite for the successful planning and conduction of gene and immune therapeutic trials. For example, the register of immune and gene therapeutic research projects and clinical trials (PIaGen) established by Project H has increased the transparency of immune and gene therapeutic research and has helped to decrease the incidence of redundant research projects. The register, which can be accessed online, also provides reliable information to patients, their families and the public. The collaborators of Project H believe that meeting the public need for reliable information in particular on the prospects of immune and gene therapy will pave the way for a broader acceptance of these innovative approaches. In addition, the network structures support the advance of tumor gene expression analysis by improving the transfer of tumor samples to treatment centers equipped with the necessary technology and know-how. By establishing unique network structures Project H has already advanced the international state of art in gene and immune therapy of pediatric malignant disease and wants to continue doing so.

B.4 **Publications and patents**

Bader P, Stoll K, Huber S, Geiselhart A, Handgretinger R, Niemeyer C, Einsele H, Schlegel PG, Niethammer D, Beck J, Klingebiel T: Characterization of lineage-specific chimaerism in patients with acute leukaemia and myelodysplastic syndrome after allogeneic stem cell transplantation before and after relapse. Br J Haematol 108:761, 2000

Borgmann A, Baldy C, von Stackelberg A, Beyermann B, Fichtner I, Nurnberg P, Henze G: Childhood all blasts retain phenotypic and genotypic characteristics upon long-term serial passage in NOD/SCID mice. Pediatr Hematol Oncol 17:635, 2000

Bornhauser M, Theuser C, Soucek S, Holig K, Klingebiel T, Blau W, Fauser A, Runde V, Schwinger W, Rutt C, Ehninger G: Allogeneic transplantation of G-CSF mobilized peripheral blood stem cells from unrelated donors: a retrospective analysis. Haematologica 85:839, 2000

Burdach S, van Kaick B, Laws HJ, Ahrens S, Haase R, Korholz D, Pape H, Dunst J, Kahn T, Willers R, Engel B, Dirksen U, Kramm C, Nurnberger W, Heyll A, Ladenstein R, Gadner H, Jurgens H, Goebel U: Allogeneic and autologous stem-cell transplantation in advanced Ewing tumors. An update after long-term follow-up from two centers of the European Intergroup study EICESS. Stem-Cell Transplant Programs at Dusseldorf University Medical Center, Germany and St. Anna Kinderspital, Vienna, Austria. Ann Oncol 11:1451, 2000

Burdach S, Baersch G, Hansen G: Immunogenetherapy with IL-2 or IL-7 transfected Ewing tumor cells in NOD/SCID mice. Med Ped Onc 37(3):178 2001

Deeg HJ, Amylon ID, Harris RE, Collins R, Beatty PG, Feig S, Ramsay N, Territo M, Khan SP, Pamphilon D, Leis JF, Burdach S, Anasetti C, Hackman R, Storer B, Mueller B: Marrow transplants from unrelated donors for patients with aplastic anemia: minimum effective dose of total body irradiation. Biol Blood Marrow Transplant 7:208, 2001

Felzmann T, Buchberger M, Jechlinger M, Kircheis R, Wagner E, Gadner H: Xenogenization by tetanus toxoid loading into lymphoblastoid cell lines and primary human tumor cells mediated by polycations and liposomes. Cancer Lett 161:241, 2000

Felzmann T, Buchberger M, Lehner M, Printz D, Kircheis R, Wagner E, Gadner H, Holter W: Functional maturation of dendritic cells by exposure to CD40L transgenic tumor cells, fibroblasts or keratinocytes. Cancer Lett 168:145, 2001

Fisch P, Moris A, Rammensee HG, Handgretinger R: Inhibitory MHC class I receptors on gammadelta T cells in tumour immunity and autoimmunity. Immunol Today 21:187, 2000

Hattenhorst U, Glynne R, Murray R, Burdach S: Differential gene expression analysis in pediatric c-ALL versus normal pre-B-cells and bone marrow DNA-microarrays. Blood 96(11):107a, 2000

Heinsohn S, Scholz RB, Weber B, Wittenstein B, Werner M, Delling G, Kempf-Bielack B, Setlak P, Bielack S, Kabisch H: SV40 sequences in human osteosar-

coma of German origin. Anticancer Res 20:4539, 2000

Khan J, Wei JS, Ringner M, Saal LH, Ladanyi M, Westermann F, Berthold F, Schwab M, Antonescu CR, Peterson C, Meltzer PS: Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks. Nat Med 7:673, 2001

Kroger N, Zabelina T, Kruger W, Renges H, Stute N, Durken M, Graf von Finkenstein F, Erttmann R, Kabisch H, Schafhausen P, Jaburg N, Loliger C, Zander AR: Anti-thymocyte-globulin as part of the preparative regimen prevents graft failure and severe graft versus host disease (GvHD) in allogeneic stem cell transplantation from unrelated donors. Ann Hematol 80:209, 2001

Kurre P, Burdach S: A potential role for leukemia inhibitory factor in the increased clonogenicity of human fetal progenitor cells. Blood 96:1199, 2000

Packer RJ, Raffel C, Villablanca JG, Tonn JC, Burdach SE, Burger K, LaFond D, McComb JG, Cogen PH, Vezina G, Kapcala LP: Treatment of progressive or recurrent pediatric malignant supratentorial brain tumors with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration. J Neurosurg 92:249, 2000

Ottinger HD, Muller C, Schmitz N, Kubanek B, Arnold R, Ebell W, Eberhard HP, Ehninger G, Fronz U, Goldmann S, Grosse-Wilde H, Havers W, Klingebiel T, Kolb HJ, Seeber S, Schaefer UW, Baldomero H, Gratwohl A: Transplant activities in Germany in 1998--a survey facilitated by the National Registry for Hemopoietic Stem Cell Transplantation. Ann Hematol 79:437, 2000Schilbach KE, Geiselhart A, Wessels JT, Niethammer D, Handgretinger R: Human gammadelta T lymphocytes exert natural and IL-2-induced cytotoxicity to neuroblastoma cells. J Immunother 23:536, 2000

Packer RJ, Raffel C, Villablanca JG, Tonn JC, Burdach SE, Burger K, LaFond D, McComb JG, Cogen PH, Vezina G, Kapcala LP: Treatment of progressive or recurrent pediatric malignant supratentorial brain tumors with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration. J Neurosurg 92:249, 2000Schilbach K, Geiselhart A, Handgretinger R: Induction of proliferation and augmented cytotoxicity of gammadelta T lymphocytes by bisphosphonate clodronate. Blood 97:2917, 2001

Peters C, Minkov M, Gadner H, Klingebiel T, Vossen J, Locatelli F, Cornish J, Ortega J, Bekasi A, Souillet G, Stary J, Niethammer D: Statement of current majority practices in graft-versus-host disease prophylaxis and treatment in children. Bone Marrow Transplant 26:405, 2000Schlegel PG, Eyrich M, Bader P, Handgretinger R, Lang P, Niethammer D, Klingebiel T: OKT-3-based reconditioning regimen for early graft failure in HLA-non-identical stem cell transplants. Br J Haematol 111:668, 2000

Rischewski J, Bismarck P, Kabisch H, Janka-Schaub G, Obser T, Schneppenheim R: The common deletion 657del5 in the Nibrin gene is not a major risk factor for B or T cell non-Hodgkin lymphoma in a pediatric population. Leukemia 14:1528, 2000Schwinger W, Urban C, Lackner H, Kerbl R, Benesch M, Dornbusch HJ, Sovinz P, Schauenstein K, Schumm M, Handgretinger R: Unrelated peripheral blood stem cell transplantation with 'megadoses' of purified CD34+ cells in three children with refractory severe aplastic anemia. Bone Marrow

	Transplant 25:513, 2000 Ruck P, Wichert G, Handgretinger R, Kaiserling E: Ep-CAM in malignant liver tumours. J Pathol 191:102, 2000 Schafer H, Bader P, Kaiserling E, Klingebiel T, Handgretinger R, Kanz L, Einsele H: Extramedullary relapses at uncommon sites after allogeneic stem cell transplantation. Bone Marrow Transplant 26:1133, 2000 Schilbach KE, Geiselhart A, Wessels JT, Niethammer D, Handgretinger R: Human gammadelta T lymphocytes exert natural and IL-2-induced cytotoxicity to neuroblastoma cells. J Immunother 23:536, 2000 Schilbach K, Geiselhart A, Handgretinger R: Induction of proliferation and augmented cytotoxicity of gammadelta T lymphocytes by bisphosphonate clodronate. Blood 97:2917, 2001 Schlegel PG, Eyrich M, Bader P, Handgretinger R, Lang P, Niethammer D, Klingebiel T: OKT-3-based reconditioning regimen for early graft failure in HLA-non-identical stem cell transplants. Br J Haematol 111:668, 2000 Schwinger W, Urban C, Lackner H, Kerbl R, Benesch M, Dornbusch HJ, Sovinz P, Schauenstein K, Schumm M, Handgretinger R: Unrelated peripheral blood stem cell transplantation with 'megadoses' of purified CD34+ cells in three children with refractory severe aplastic anemia. Bone Marrow Transplant 25:513, 2000 Schwinger W, Urban C, Lackner H, Kerbl R, Benesch M, Dornbusch HJ, Sovinz P, Schumm M, Handgretinger R: Unrelated partially matched peripheral blood stem cell transplantation with highly purified CD34+ cells in a child with Wiskott-Aldrich syndrome. Bone Marrow Transplant 26:235, 2000 <u>Other publications</u> Burdach S, Braun T: Translational research in stem cell biology and cell based therapy. ESPHI 2001 – XVIII Congress of the European Society for Paediatric Haematology and Immunology. Lucerne, 2001 Burdach S: Patentrecht: eine neue Dimension der medizinischen Ethik? Mitteilungen der deutschen Patentanwälte Januar:9,2001. <u>Patents</u> None planned.
B.5	**Networking** The project has successfully increased horizontal knowledge transfer by intense networking between treatment centers on a national and international level. Common concepts for the clinical application of immune and gene therapy have evolved from discussions among the partners working on the project. This has led to increased transparency of treatment protocols and to the establishment of treatment standards, one of the aims of Project H. Project H has also emphasized the vertical knowledge transfer to patients, their families, primary care pediatricians and the interested public by placing the regis-

	try of research projects and clinical studies on the project's webpage. The co-operating partners of the project consider the provision of reliable information concerning immune and gene therapy of malignant disease a major added value of Project H. On the basic research level networking with the BioinformaticsCenter of the Martin-Luther-University Halle-Wittenberg and the IPK Gatersleben has been a major step towards the creation of a gene expression data base of pediatric malignancies. Project H has also begun to co-operate closely with Project G (embryonic tumors) and D (resistance to chemotherapy). It goes without saying that Project H is well integrated into the network of the GPOH. In particular cooperative efforts have been made with the LESS-Project of the GPOH to identify a genomic risk profile for the development of secondary malignomas. On behalf of Project H the University Children's Hospital of Halle has submitted a research proposal for a BMBF-PaedNet-Module to promote the pharmacological evaluation of immune and gene therapy of pediatric malignancies. The networking activities with the BMBF-project will foster further progress in the development of gene and immune therapeutic treatment strategies. Two research scholarships granted to collaborators of Project H have led to the initiation of new co-operations with national and international partners. Finally, Project H has co-operated closely with the BMBF-Research Center Immunology Sachsen-Anhalt. In summary the added value of the project's networking activities include the increased transparency of immune and gene therapeutic treatment options, the establishment of general therapy standards, the preparation of a gene expression database, horizontal and vertical knowledge transfer and an improved dialogue with institutions in- and outside the pediatric community. As a result of the work of the first funding period Project H has been officially commissioned by the GPOH/KPOH to function as a coordinating quality assurance facility for gene expression analysis of pediatric tumors in the second funding period of the competence network.

Part C – Follow-Up Proposal

C.1 **Aims**

The aims set down in the initial proposal have been achieved. The goals of Project H, in particular with respect to functional genomics, public relations, provision of information concerning regulatory and legal issues and project registry (PIaGen) are still relevant. Project H wants to shift its focus from establishing network structures to using them efficiently for the advancement of pediatric immune and gene therapy. Project H has been officially commissioned by the GPOH/KPOH to establish a quality coordination center for gene chip analyses of pediatric tumors.

<u>Functional Genomics</u>

Analysis of gene expression profiles of tumor cells using gene chip technology has the advantage of generating in shortest time a huge quantity of data which is then available for further studies. In addition to the direct identification of target structures for new therapeutic (e.g. immunological) strategies it provides the possibility to use gene expression profiles for the identification of risk groups and to utilize these data for prognosis. Both, the identification of new target structures and the molecular definition of risk groups are still at the beginning. It is indispensable for the mentioned tasks to examine a preferably high number of tumor samples. This should be organized and coordinated concomitantly to studies of the GPOH.

Today the non-standardized preparation and processing of samples still constitutes a major problem of gene chip analysis since it complicates the comparability of data from different laboratories and the interpretation of partly contradictory results is difficult.

A major aim of Project H is the coordination of gene expression analysis of all pediatric malignancies reported in Germany and Austria. In the initial phase of the project great effort has been made to standardize the processing of tumor samples and to create the necessary network structures.

The focus of the follow-up proposal is on using the established structures for efficient tumor gene expression analysis and identification of target structures for immune and gene therapy. Data obtained with the tools of functional genomics will be made available to all participating centers. The data can then be used for the design of individual immune and gene therapies (vaccines, antibodies). A data base containing the genetic expression profiles of all screened pediatric malignancies is planned in co-operation with the BioinformaticsCenter of the Martin-Luther-University Halle-Wittenberg and the IPK Gatersleben.

Significant synergy will be created by establishing reference centers and by sharing the resulting data. In addition, the standardized processing and analysis of tumor samples will improve quality of tumor gene expression analysis leading to more precise and targeted therapeutic strategies.

…

	Public Relations The participating centers wish to continuously increase the acceptance of immune and gene therapeutic treatment strategies in the general public as well as in the medical and legal community with educational campaigns, a national meeting and various public relation activities. Provision of Information concerning Regulatory and Legal Issues There is still a significant information deficit concerning the regulatory and legal issues of gene therapy and immunotherapy. The project will continue to provide the necessary information to the treatment centers. The heterogeneity documented in the treatment practices of the participating centers calls for standardized approaches to study and research planning, approval and conduction. Project Registry (PIaGen) Project H wants to maintain the registry of immune and gene therapeutic research projects and clinical trials (PIaGen) which has been initiated in the first funding period. Recently, a collection of immune and gene therapeutic treatment protocols has been started. A major aim of the second funding period is the documentation of the clinical effects of immune or gene therapy on all patients individually in Germany and Austria to increase the comparability of different trial designs. Research Scholarships The two research scholarships granted to collaborators of Project H in the first funding period have led to a significant knowledge transfer on a national and international basis. The fast progress in the field of immune and gene therapy of malignant disease necessitates continuous exchange and networking of all scientists involved. The development not only of immune and gene therapeutic treatment strategies but also of monitoring techniques for their effects requires cooperation between treatment centers on a national and international level. Hence, Project H wants to continue its successful strategy of granting research scholarships to support collaborating researchers in their efforts towards establishing new techniques and concepts in their laboratories in the second funding period. The traveling expenses include research scholarships and have been cut significantly in comparison with the first funding period on request of the network coordinating center in favor of the Micro-Arrays and reagents for chip-preparation and -processing.
C.2	**Methodological approach** Functional Genomics - Implementation of a coordination center for gene chip analysis For analysis of gene expression profiles of pediatric tumor samples, we (i) will use commercially available chips and (ii) will develop new chips with optimized design for the analysis of these samples (“PedOncoChips”). Our experience with the analysis of more than 400 tumor samples during the last years demonstrated that reproducibility and inter-sample-comparability is highest when sample-processing and chip-processing of all samples are performed under the same defined conditions. …

For this reason the aim of this project is to create the basis for standardized and validated investigation and storage of expression profiles of tumor material from the area of the GPOH and the KPOH. For this end, reference centers for gene chip analysis have to be established and supported in the establishing period which can carry out study-accompanying gene expression profiling of tumor samples. At the same time, establishing standards for sample preparation is supposed to ensure that gene expression profiles, which result from the examination of different tumor entities, can be used for comparative investigations. In the course of the setup period, the reference centers which have to be established should have the opportunity to achieve proper certificates by fulfillment of quality standards that have to be established first by the cooperating institutes. These certificates should qualify these centers as „gene chip reference centers" for the accompaniment of clinical studies. With regard to comparative analysis of data material the introduction of these standards is absolutely essential. In addition, the conditions for gene chip experiments in the participating centers have to be optimized by the foundation of a „Chip Consortium" that uses an appropriate quantity of chips for optimized purchase conditions.

In the laboratories of the Children's Cancer Research Center Halle and other centers of the KPOH the complete equipment for processing of high-density and/or spotted arrays is well established. For the development of "PedOncoChips", samples from tumor banks of the KPOH will be send to these centers and will be analyzed on high density chips with complete genome information first. The data will be processed and stored on a server with access for all interested members of the competence network and the GPOH. In parallel, we will use data from the literature, from our previous experiments, and from the data obtained in this study using commercial chips for the development of a "PedOncoChip". With increasing knowledge about gene expression in tumors the design of the "PedOncoChip" will be improved continuously.

The obtained information on gene expression in pediatric tumors can be used for example for molecular classification of tumors or for the identification of new targets for immune and gene therapeutic interventions. The surplus value of such data for the pediatric oncology is evident.

<u>Provision of Information concerning Regulatory and Legal Issues</u>

Project H wants to continue the successful concept of making information concerning regulatory and legal issues of immune and gene therapy gathered through networking activities available for all partners co-operating in the network. Among others the project's experience includes writing of standard operating procedures (SOPs), setting up GMP-suitable laboratories and treatment facilities and study design. All network partners will hence profit from the experiences made by others.

<u>Project Registry (PIaGen)</u>

Project H invites all German and Austrian treatment centers to register their research projects and clinical studies. The registry will continue to be available online on the homepage of the project. The project registry will be expanded to include a collection of treatment protocols and a database containing the data on the clinical course and outcome of all pediatric patients having received immune or gene therapy.

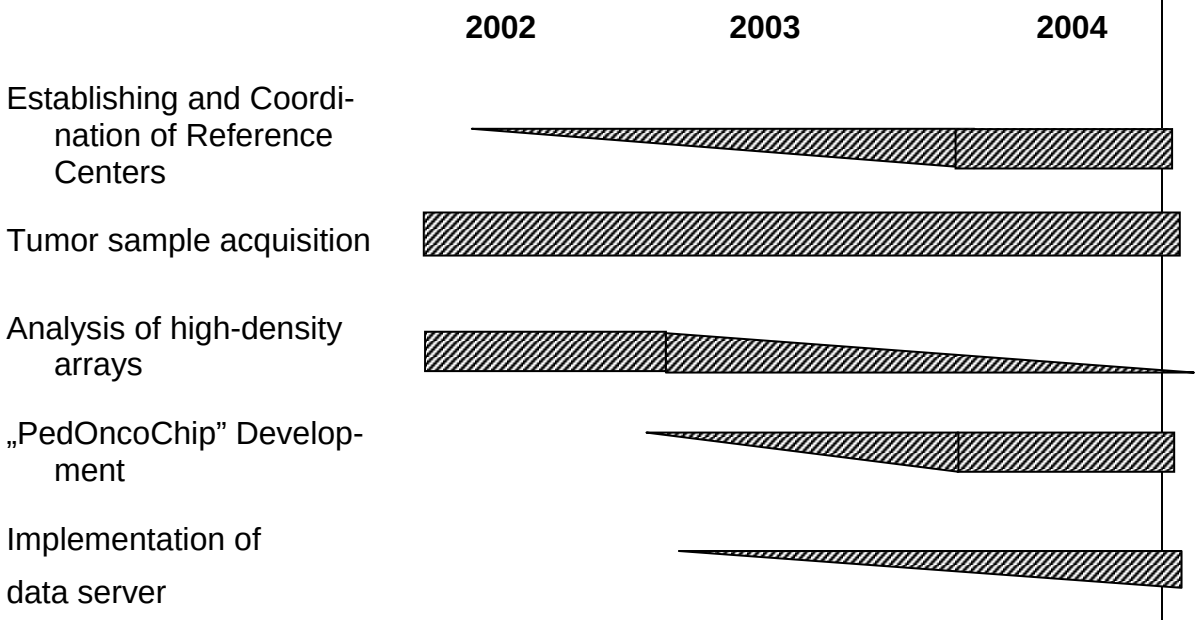
…

	Public Relations The centers co-operating in Project H want to satisfy the public need for reliable information on the options of immune and gene therapy for the treatment of pediatric malignant disease. The project's home page displays the state of the art of immune and gene therapeutic research in Germany and Austria. The registry of clinical studies shows the scope of clinical application of different treatment concepts. Project H will participate in the creation of booklets and brochures of the competence network. The dynamic field of immune and gene therapy can easily evoke unrealistic hopes and expectations in patients and their families. Project H wants to provide realistic and reliable information on the options and chances of immune and gene therapy. To this end national meetings are planned. Research Scholarships Research scholarships will be granted to co-operating partners with the aim of establishing new techniques necessary for the development of immune and gene therapeutic treatment strategies in their laboratories. All proposals must meet standard requirements. If necessary, the proposals will be reviewed by external experts.
C.3	**Work plan** Functional genomics In order to establish a coordination center for gene chip analysis, we will determine the current gene chip activities in the field of the KPOH. This investigation is supposed to register: 1. which institutions are interested in carrying out own chip analysis, 2. which institutions are already using this technology, 3. which institutions have the necessary technical equipment at their disposal resp. which devices may be used, 4. which technology is being used currently, 5. what was the whole amount of analyzed samples during the last 12 months, 6. which tumors have been worked on and 7. which institutions for bio-informatics support the project with how many scientists. One major aim of this part of the investigation will be the identification of laboratories working on the same tumor entities. This will help to avoid the accidental redundant analysis of the same tumor samples at different centers and will lead to optimal utilization of limited resources. Furthermore, in order to establish an appropriate standard of quality, it is necessary to document the protocols that have been used for the processing of the samples and to let them circulate between the participating institutions. These protocols shall give the basis of the standard that has to be agreed upon. Moreover, during the period of establishment of the reference centers, representative samples, either from the hybridisation dilutions which have already been used in the particular institutions or (if possible) fresh tumor material, shall be

sent to the coordination centers in Halle and other locations to be determined in order to analyze the corresponding samples again. The results of these data analysis have to be exchanged between the corresponding centers. Thus, it ought to be achieved that potentially occurring problems can be recognized and solved at an early point of time.

Gene expression data generated in participating centers will be used for the development of a chip with optimized design for pediatric oncology ("PedOncoChips"). Chips will be designed that contain all known oncogenes and tumor markers relevant for pediatric tumors. In addition to the detection of full-lengths wild-type RNA-species, these chips will allow detection of mutated genes (i.e. point mutations and translocation-related fusion transcripts).

Data from the literature and the results from the high density chips will be used for continuous improvement of the design of the "PedOncoChip". A cooperative data storage and maintenance system will be established that includes a searchable data base with gene expression profiles of all tumor samples that have been processed. This data base will be available for further studies.



In addition, Project H will provide reliable information on immune and gene therapy of pediatric malignancies throughout the entire second funding period. It will participate in the creation of information brochures and booklets for patients, their families and primary care pediatricians.

The collaborators of Project H see a persisting need for the provision of expertise to meet regulatory and legal demands on the practical application of immune and gene therapeutic treatment strategies. The centers will therefore increase the cooperative efforts in the second funding period.

The project registry (PIaGen) and the collection of treatment protocols will be continued.

A database containing information on the clinical course and outcome of all pediatric immune and gene therapy patients will complement the registry and will in-

	crease treatment transparency. Finally, research scholarships will be granted throughout the entire second funding period.
C.4	**Networking** Networking in Project H will continue contributing to the overall goals of the competence network. All centers involved will join in the ambitious functional genomics project aiming at the implementation of quality standards for gene expression analysis of all pediatric malignancies in Germany and Austria. This can only be achieved in a joint effort of all centers involved in gene expression analysis. Co-operation with the GPOH-LESS study will be intensified to use the gene chip technology for identification of patients at risk of developing secondary malignancies. The added value will consist of an increased amount of tumor samples to be analyzed because all centers can send in their tumor material and gene expression analysis under standardized conditions. The implementation of quality standards and of requirements to be met by centers performing gene expression analysis of pediatric tumors will increase the overall quality and validity of the resulting data. The data will be stored in a gene expression data base to which all participating centers will have free access. The data base will be generated in close co-operation with the BioinformaticCenter of the Martin-Luther-University Halle-Wittenberg and the IPK Gatersleben. Treatment centers and functional genomics facilities will work hand in hand. The increased amount of tumor samples available for analysis and the improved quality of gene expression analysis are major added values of Project H. Efficient gene expression analysis will fasten the discovery of relevant tumor antigens as targets for immune and gene therapy, ultimately leading to new therapeutic options for afflicted patients. The register of immune and gene therapeutic research projects and clinical trials (PIaGen) which is available online also contributes to the goals of the competence network by increasing horizontal and vertical knowledge transfer. The project registry creates significant synergy by reducing redundant research and increasing communication between the participating centers. The extension of the registry to document the clinical course of every pediatric patient treated with immune and gene therapy is another networking effort of Project H. It will increase the comparability of different treatment trials, which is of particular importance because the numbers of patients treated in the individual protocols is usually small. This should lead to the initiation of co-operative immune and gene therapy trials to allow for a thorough statistical evaluation. The registry is a central element of quality control of treatment regimens. Project H will continue improving horizontal and vertical knowledge transfer concerning evolving concepts of immune and gene therapy by networking between treatment centers, patients, their families and primary care pediatricians. Project H has become a platform providing reliable information on the state of the art of immune and gene therapeutic research and clinical trials in Germany and Austria. It will keep up its efforts in this regard. Research scholarships for investigators of the participating centers have led to a transfer of new techniques and scientific approaches into their laboratories and to increased networking between centers on national and international basis in the first funding period. Therefore, Project H wants to continue granting research scholarships in the second funding period.

Part D- Requested Funding for the Project	
D.1	**Salaries** 1 Scientist; BAT-O IIa: 48246 € p.a.: The scientist will support the register of immune and gene therapeutic research projects and clinical studies (PIaGen). He will also co-ordinate the implementation of the gene chip analysis quality assurance project and the development of a „PedOncoChip". 1 Technician; BAT Vc: 35106 € p.a.: This technician will be responsible for isolation and processing of RNA from tumor samples in course of the gene chip analysis quality assurance project.
D.2	**Consumables** Micro-Arrays and reagents for chip-preparation and -processing required for the gene chip analysis quality assurance project: 78500 € p.a. Reagents for the development of the „PedOncoChip": 11500 € p.a. Included are costs for commercially available chips and for the development of new chips with an optimized design for the analysis of pediatric tumor samples („PedOncoChip").
D.3	**Investments** Two high-performance PCs for data analysis and -storage: 10000 €. One PC will be necessary for comparative data analysis in Halle. This PC will be used for analysis of data sets in course of standardization and quality assurance of gene chip analysis. A second PC will be necessary for the implementation of an on-line data base of gene-chip data with restricted access for members of the GPOH network.
D.4	**Other Costs** Traveling expenses: 5000 € p.a. The traveling expenses include research scholarships and have been cut significantly in comparison with the first funding period on request of the network coordinating center in favor of the Micro-Arrays and reagents for chip-preparation and -processing. The implementation of efficient quality assurance structures requires sufficient financial support for the organizing of meetings and the provision of local on-site support.

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Late Effects and Quality of Life [1] A Vertical Network for Pediatric Oncology [2] (Project I)
Grant No.	:	01 GI 99 66

Name of scientist-in-charge	:	Dr. Gabriele Calaminus
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Project home page (if different from Network homepage)	:	http://www.med.uni-duesseldorf.de/kmnpoh-Lq/

Part A - General Statements about the Project

A.1. **Subject**

Evaluation of Late effects and QoL in patients with ALL and brain tumors [1]

Establishment of a vertical network between medical caregivers and creation and implementation of disease specific standardized operating procedures for (long) term follow-up [2]

A.2. **Co-Investigators**

- J. Beck, University Children's Hospital, Erlangen [1]
- U. Ravens-Sieberer, Robert Koch Institute, Berlin [1]
- J. Kühl, H. Ottensmeier, Würzburg [1]
- U. Creutzig, Coordination and Management Group, Competence Network Pediatric Oncology and Hematology, Hannover [2]

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects	☒ yes	☐ no
(b) clinical trials	☒ yes	☐ no
(c) animal models	☐ yes	☒ no
(d) gene therapy	☐ yes	☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	130,9	12,5	0	0	0	142,40
2004	130,9	12,5	0	0	0	142,40

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

This project which is unique in in Europe comprises two parts : [1] Late effects and Quality of Life and [2] A Vertical Network for Pediatric Oncology

[1] Within the first funding period an effective cooperation between 18 institutions was established to estimate somatic, psychological and QoL data in newly diagnosed ALL and brain tumors. Compliance to the testset and to the participation in the project is satisfactory. Regarding Concerning the results it becomes clear that patients with a brain tumor suffer more from impairements and negative influence of the disease and treatment than patients with leukemia . Specifically visuomotoric and concentration is a problem, whereas global intelligence is not significantly different. It becomes visible that patients groups of high risk for psychosozial, neuropsychological and QoL abnormalities can be defined, who therefore need more extensive support than the others. The used instrument set was useful in most of its parts. Since a reduction of tests was planned after the first period, extensive analyses were prepared and led to a first suggestion. A problem appaers in collecting and completion of somatic data, as this cannot be done by the psychologists who are the main cooperators in the project. As these data are of importance for correlation with psychosozial and QoL issues this must be improved.

[2] Contacts between involved expert groups and professionals were established as well as the development of standardized recommendation for relapse diagnostic and follow-up for most GPOH trials. Preparations in cooperation with the coordination centre of the whole network and especially the LESS office (Prof. Beck) are ongoing to prepare presentations concerning disease, treatment, toxicity and long term after care for medical caregivers as well as for laymen for presentation in the network.

For both parts, it became visible that administrative work within the projects needs more manpower because this very important part of the project is steadily increasing. Therefore financial support for an AIP Arzt im Praktikum) will be needed and applied for.

B.2 **Original aims of the project**

[1] Children with cancer suffer from disease, treatment and the consequences for their life, which can sometimes be impaired lifelong. A prospective evaluation of health status, psychological aspects and well-being has never been investigated so far, although a systematic evaluation of these areas in P.O. is lacking. Therefore, a core set of instruments should be identified for broad use within P.O. to measure these areas and adapt patients and familiy support to the results, which are collected at 4 different time points during treatment and within the follow-up. This is only possible in a multicentre setting, which is established within the project. Target groups are patients with ALL as the most common disease and patients with brain tumors, who have the highest burden of disease and treatment.

	The question shall be cleared, what differences in health status, psychological issues and QoL between these groups are detecable and what specific problems can be defined (A). Within the first part of the project it was also aimed to validate the instruments and suggest a first reduction after two years, if possible (B) [2] The vertical network aims to build up structures for the exchange of information between caregivers and to patients and laymen. The task is also to develop standardization for relapse diagnostic and follow-up recommendations. (C, D)
B.3	**Scientific results** 1 A: Neuropsychology: (see Annex 1) Intellectual abilities (K-.ABC, K-Tim) are not significantly different between leukemia and brain tumor patients. There is a difference but for both group at time point 1 and 2 Global IQ is within the normal range. For visuomotoric integration (VMI) there is also a difference but not a significant one. Speed components and concentration (D2, DL-KG and DL-KE). Brain tumor patients show impairment in these components from the beginning (tumor related?). QoL: (Annex 2) Children with cancer at diagnosis (E1) express negative QoL ratings specifically in the domains: physical functioning (K), cognition (C) emotion (E) and autonomy (AUT). Brain tumor patients express specifically autonomy and social functioning (Fam) within the family negative. At E 2 these negative ratings are again obvious although they are little improving in most domains. Comparisons of patients' and parents' ratings reveal a significantly more negative rating of the parents viewing their children QoL. Comparison of psychosocial and QoL data. (Annex 3): Patients with abnormalities in their psychosocial history are at risk to develop (neuro-) psychological and QoL impairment. This has to be evaluated further when different time points of evaluation can be compared. In conclusion. The project generates important and unique, never reported information on health status and QoL. Late effect data will be available within the follow-up at time point 4. 1B: On major task underlined by the reviewers of the project is the survey of the used instruments in terms of concurrent validity (Annex 4), practicability and relation of expense and utility. Therefore, all available data sets of leukemia and brain tumors were compared for correlation of tests, to find out if redundant measures are used. This is not the case. Through checking of practicability, tapping as the measure of testing motor speed and reaction time appears to be problematic: Only old computers can be used, the software is often problematic and the test itself is reported to be not very attractive, as also no direct correlation can be drawn from the test between the measured values and the impairment, this instrument will not longer be recommended. It is free for the institutions to use it. Patients who were already tested with tapping should proceed with this to compare the different time points. In Würzburg all patients will continue to be tapped as there the optimal setting (expertise) is provided. Within the project as compensation additional parts of the VMI will be used and circulated to the cooperating institution. The FBT is a test with a high percentage of children at time point 2 who still remember the first evaluation, this influences the result. Therefore the FBT should be used at time

	point 1 and 3 and not at every time point. K-TIM: The experimental version, which is used in the project, bears several problems: It is not user friendly. Children with a brain tumor are often frustrated and do not want to go further. The K-TIM is not able to differentiate global IQ within lower ranges. Therefore as also stated in the literature for brain tumor patients, the Wechsler scale will be suggested for use in the second part of the project for all patients with brain tumors, already at 6 years of age. The use of the Wechsler scales will also implement a part for concentration and speed which is redundant to D2/DL-KE/DL-KG, so these can be exchanged if the Wechsler scales are used. QOL instruments (Annex 5): The first investigation with the MAP analysis revealed that the sensitivity and the concurrent validity between the used instruments is good and that the PEDQOL is a sensitive and reliable QoL measure for patients with cancer. Therefore, no changes will be done for the QoL set. As it appears that the CHQ as the parent measure is more pointing out on behavior than on well-being, the parents' form of the PEDQOL will be used in addition and circulated to the participating institution. 2C. The preparations for presentation of information for caregivers and laymen about disease and treatment as well as follow-up are still under process. An information portal is already created and the contents will be added in second part of the funding period. 2D. Within the vertical network so far the following guidelines in form of flow sheets are prepared or nearly finished so far: AML/ALL, germ cell tumors, Neuroblastoma, Wilm's-Tumor, Hepatoblastoma, NHL, sarcoma, still pending are Hodgkin and brain tumors (Annex 7).
B.4	**Publications and patents** Langer T, Martus P, Ottensmeier H, Hertzberg H, Beck JD, Meier W. CNS late-effects after ALL-therapy in childhood Part III: Neuropsychological performance in long-term survivors of childhood ALL. Impairments of distractibility, attention and memory and its interferences to CNS morphology. Med Pediatr Oncol. In Press 2002 Marx M, Beck JD, Grabenbauer GG, Dörr HG. Spontaneous nocturnal growth hormone secretion in children after medulloblastoma therapy. Med Pediatr Oncol 36:494-496,2001. Langer T, Henze G, Beck JD. Basic methods and the developing structure of a late effects surveillance system (LESS) in the long-term follow-up of pediatric cancer patients in Germany. For the German Late Effects Study Group in the German Society Pediatric Oncology and Hematology (GPOH). Med Pediatr Oncol 34:348-51,2000. Müller HL, Bueb K, Bartels U, Roth C, Harz K, Graf N, Korinthenberg R, Bettendorf M, Kühl J, Gutjahr P, Sörensen N, Calaminus G. Obesity after childhood craniopharyngioma–German multicenter study on pre-operative risk factors and quality of life. Klin Pädiatr. 213:244-9,2001 Calaminus G, Weinspach S, Teske C, Göbel U. Quality of life in children and adolescents with cancer. First results of an evaluation of 49 patients with the PEDQOL questionnaire. Klin Pädiatr. 212:211-5,2000.

	<u>Patents</u> None planned.
B.5	**Networking** The character of the project itself is a total network project as it can only be established and successfully promoted with a network of partners. 1. Late effects and QoL Here the cooperating institutions build up a network to require information on health status and well-being, added through the collaboration of the 3 study centers (CoALL, ALL-BFM and HIT 2000). The partners are networking through the project center in Düsseldorf and the cooperation partner in Erlangen. Within the project as a result for the network a core set for evaluation of late effects and QoL will be defined for broad use in P.O. 2. Vertical Network Here different groups are networked for designing standard operational procedures (SOP) for relapse diagnosis and follow-up of children with cancer. Together with the coordination center of the whole network an information structure via internet will be established for distribution of information according disease, treatment and follow-up. To generate the information needed, again networks of partners have to be established (clinicians, general practitioners, health care system, LESS, QoL, study coordinators, experts, cancer registers). As a surplus for the health care system, SOPs for most disease groups in Pediatric Oncology will be available as well as an information system for all target groups of the vertical network (see point 2).

Part C – Follow-Up Proposal

C.1 **Aims**

The objectives of the initial project are still relevant and achievable. Several aims can be achieved at the end of the second period:

Three points need a change according to the initial proposal

1. The collection of the somatic data in the institutions is an immanent problem. These data are absolutely necessary to correlate somatic and psychosocial and QoL data. Also late effects cannot be valued which is an important part of the project. Therefore, medical students on an hourly base will be applied for to support the cooperating institutions. This system is working very efficiently in Berlin and Münster, which are paying students for such a support from own expenses already.
2. The administrative work within the project part [1] and part [2] has increased and is still further increasing. In Düsseldorf for both parts of the project only one BAT Ib/2 position is available for the whole work load. Therefore it is planned to apply for an AIP (Arzt im Praktikum) position in addition, which would be able to do part of the administration, contact the cooperating institutions, has the responsibility for the students and for the data collection through students for the medical data.
3. Change in the set of instruments as recommended test set will be the use of the FBT at time point 1 and 3, the extension of VMI, no more recommendation to use the tapping , a use of the Wechsler scales in patients with brain tumors and then, the abdication of D2, DL-KG, DL-KE, if the Wechsler scales are used. Therefore, all institutions will be asked to implement the HAWIK/HAWIE in their test set. The K-TIM will be continuously used in the ALL population.

C.2 **Methodological approach**

See point 3 above.

C.3 **Work plan**

Part [1]

- Further recruitment of patients until the end of 2002,
  further collection of somatic, psychosocial and QoL data
- Improvement of feedback of medical data
- Interim analyses of data at the end of 2002, presented at scientific meetings.
- Publication of results (public media and scientific media) 2003 and 2004
- Further work on the definition of a core set.
  Planned definitely for the end of 2004.

Part [2]

- Creation and establishment of SOPs for all diseases, in term of relapse diagnosis, follow-up and risk of second-malignancies (2003 and 2004)

…

	Á Establishment of the internet presentation of an information structure for medical caregivers and laymen according to disease, treatment, aftercare (2003 and 2004) Á First publication of results in public and scientific media (2003 and 2004).
C.4	**Networking** 1. With the coordination and management group (project A) of the competence network for part [2] of the project I. Establishment of the net presentation of information structure for medical caregivers and laymen according to disease, treatment, aftercare (2003 and 2004) 2. With Project K for follow-up SOPs concerning second malignancies, with APRO, LESS, GPOH and associated groups for the relapse and after care guidelines. Creation and establishment of SOPs for all diseases, in term of relapse diagnosis, follow-up and risk of second-malignancies (2003 and 2004).

Part D- Requested Funding for the Project

D.1 **Salaries (given in €)**

Position	Post	Location	2003	2004
Scientific personnel	AiP	Düsseldorf	20452	20452
	0,5 BAT Ib	Düsseldorf	31000	31000
	0,5 BAT IIa	Erlangen	29000	29000
Data Manager	0,25 BAT IVb	Düsseldorf	7000	7000
Student coworkers		Düsseldorf	36500	36500
		Erlangen	4600	4600
		Würzburg	2300	2300
Sum			**130852**	**130852**

<u>Scientific personnel</u>

Düsseldorf: administration of the project, development of SOPs for vertical network, scientific preparations: ½ BAT Ib

Coordination and collection of medical data supervising of partner institution and medical students in respect to complete and quick data transfer: supporting the administrative work, data entry, data checks in the data bank, transfer of data to Erlangen: 1 AiP (Arzt im Praktikum)

databank, scientific presentations, evaluation of neuropsychological data, data transfer to Düsseldorf

Non-scientific personnel

Düsseldorf: Data entry of QoL data, scientific evaluations ¼ data manager For all cooperating institutions support for medical data collection: 4 x 19,5 hours of a medical student/week

Erlangen: Data entry from paper forms: medical student 10 hours a week

Würzburg: Support of the psychologist in charge of the study in Würzburg, data entry and evaluation of tapping data: medical student 2,5 hours a week

D.2 **Consumables (given in €)**

Position	**Location**	**2003**	**2004**
Administrative costs	Düsseldorf	2000	2000
Bonus system costs	Düsseldorf	1500	1500
Instruments	Erlangen	6000	6000
MAP analys	Berlin	3000	3000
Sum		**12500**	**12500**

Düsseldorf

Administrative costs (copies, stamps, prints of QoL measures) 2000 €/year

Costs to pay the bonus system: For improving compliance of patients to have all 4 evaluation time points a bonus system was implemented: For each evaluation time point they can receive a little present or they can save their points until the whole evaluations are done (2 years) After these system was integrated compliance improved and number of patients who refused to be tested again decreased to nearly zero. Therefore in the next two years 1500 €/year has to be applied for to pay this system which would cover the costs for about 50 new patients.

Erlangen

Costs for neuropsychological measures (added part of VMI): 6000 €/year

Berlin Robert Koch Institute

Sensitivity tests at the end of 2002 and at the end of the project for final definition of core set of QoL evaluation 3000 €/year for MAP analysis.

D.3 **Investments**

None.

D.4 **Other Costs**

None.

Section 3

Midterm Report of Running Projects and Application for Continued Funding

Title Page

Network title	:	Second Malignant Neoplasms after Childhood Cancer (Project K)
Grant No.	:	01 GI 99 67/3

Name of scientist-in-charge	:	Dr. Peter Kaatsch, PhD
Institution	:	German Childhood Cancer Registry (GCCR, Deutsches Kinderkrebsregister)
Address	:	Institute for Medical Biostatistics, Epidemiology and Informatics (Institut für Medizinische Biometrie, Epidemiologie und Informatik, IMBEI) 55101 Mainz
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Project home page (if different from Network homepage)	:	----------

Part A - General Statements about the Project

A.1. **Subject**

Second Malignant Neoplasms after Childhood Cancer

A.2. **Co-Investigators**

Name of scientists: None.
Institutions: None.

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects ☐ yes ☒ no

(b) clinical trials ☐ yes ☒ no

(c) animal models ☐ yes ☒ no

(d) gene therapy ☐ yes ☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	95	0,6	0	1,5	0	97,1
2004	99	0,6	0	1,5	0	101,1

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part B – Results from the First Funding Period

B.1 **Summary**

The goal of the project is estimating incidence rates and risk ratios for secondary malignant neoplasms (SMN) after childhood malignancies and determining which risk factors might cause SMN.

In cooperation with the GPOH, its therapy optimization trials (clinical trials), and the treating hospitals, the German Childhood Cancer Registry (GCCR) has established an integrated information flow. This allows systematic documentation of SMN after childhood cancer and makes various clinical parameters (e.g. therapy, previous diseases) available. It is the basis for analyzing potential risk factors for developing SMN.

With the help of the principal investigators of the clinical trials we have validated all already known cases with SMN; furthermore we developed a uniform procedure to prospectively validate new SMN cases. We are progressively optimizing our long-term follow-up for 25000 individuals with cancer in childhood documented as living at the GCCR, supported by a computerized managing system. Nearly full coverage of SMN cases is thus ensured.

Based on the currently 373 SMN cases fulfilling our inclusion criteria we calculated a preliminary 15-fold risk for developing SMN until age 30 compared to the general population.

We are preparing a case-control study assessing potential risk factors.

B.2 **Original aims of the project**

The original aims were,

- quantifying incidence rates and risk ratios of developing a secondary malignancy for children with a malignancy,
- investigating to what extent elements of the primary therapy and/or genetic factors influence the risk for developing a secondary malignancy,
- giving input for conceptualizing programs for post-treatment care and suggestions for modifying primary therapy.

B.3 **Scientific results**

<u>During the first funding period the following results have been achieved so far:</u>

(a) The infrastructure and uniform procedures for documenting and validating all SMN cases after childhood cancer and for performing an optimized long-term follow-up were established:

Registration and processing of newly reported SMN cases were integrated into the routines of the GCCR.

To ensure high data quality, we had all SMN cases known to us until 12/1999 validated in close cooperation with the principal investigators of the relevant therapy optimization trials. All cases reported since 2000 are immediately validated

prospectively together with the relevant clinical trials.

To ensure completeness we are basically organizing a life-long long-term follow-up. It is intended to ensure full coverage of SMN, including adult SMN. We developed computerized managing routines for requesting information from hospitals, clinical trials, and families, as well as an automated reminder system. The basis for this is complete information (such as the address) at the primary registration. With the help of the managing system the following routines were implemented so far:

- The hospitals are reminded of missing information 3 times a year shortly after the primary report.
- The further follow-up is included in the managing system. A status report of the patients is requested annually – in the first years after diagnosis from the clinical trials and later from the hospitals. In 2000 about 4500 children were included when addressing the hospitals. We were able to obtain follow-up information more completely than before (e.g. follow-up of osteosarcoma cases has improved: in 2000 20% more patients have follow-up data than in 1999).
- We personally contact patients, who have reached or exceeded their 16th birthday asking them to renew the consent to document their data, which had previously been given by their parents. We plan to repeat this annually for individuals who reach their 16th birthday, because adult patients without informed consent have to make anonymous. In January 2002 we addressed about 3500 families. 900 had moved with unknown address, which means that - in an additional step – the project group will have to research their addresses with the help of the municipal offices for the registration of residents. More than 55% of those who were reached by mail (about 1400 patients) sent their consent without a reminder. Only 44 families have so far explicitly refused their consent to further documentation. The remaining families are being reminded.

Additionally we already made agreements with a number of general German cancer registries to match their data on cancer in adulthood with our data to ensure complete registration of SMN.

(b) Incidence rates and risk ratios for developing an SMN until age 30 were calculated in Germany for the first time :

In order to estimate risk rates for developing SMN until age 30, the base risk in the general population was determined using data of the GCCR (until age 15) and - from age 15 - of the Saarland cancer registry and the cancer registry of the former GDR. Currently this is the only data available in Germany with full coverage of the respective region. Based on currently 373 SMN cases fulfilling our inclusion criteria (SMN diagnosed since 1980, residence in Germany, primary malignancy diagnosed at age less than 15 years) a 15-fold risk for developing SMN until age 30 compared to the general population was calculated.

The cumulative risk of SMN after a childhood malignancy in a defined period (e.g. 10 years) is usually estimated using the Kaplan-Meier-estimator. We recommend using the Aalen-Johanson estimator instead, because this method considers death as a competing risk instead of a censoring event. The cumulative risk of developing SMN within 10 years after the primary neoplasm is 1.8%.

(c) Establishing procedures for the documentation of therapy data and other clini-

cal data of SMN cases; preparing a case-control study of potential risk factors:

In accordance with the application we started preparing a case-control study of SMN risk factors. A comprehensive (still preliminary) protocol was set up for this study. The controls will be sampled from the registry. The study required revising the questionnaires for obtaining the specific data needed in the study; this step is finished. Next we needed an infrastructure, by which the clinical trials can pass their data (mainly therapy data of the first malignancy) on to us. A survey among the clinical trials found that electronic documentation was not generally possible. Many clinical trials have stored only some of the data in electronic form. Especially for patients treated long ago and for patients treated outside of protocol data are not available in electronic form. Because of this, we still send paper forms to the clinical trials, where they are filled in by hand. Some clinical trials may require researching data locally by GCCR personnel. Data entry masks for the documentation forms are being prepared. The managing system is set up to accommodate the special needs of the case-control study.

(d) An increasing number of requests regarding disease specific frequencies of SMN were answered promptly:

The importance of our database is also emphasized by frequent requests from hospitals and clinical trials regarding specific combinations of SMN, relative frequency of SMN or requests for risk estimates for specific constellations. Since the beginning of the funding period we were able to address about 20 such requests quickly and competently. This has an added value for the Pediatric Oncology as a whole.

<u>International state-of-the-art compared to our project</u>

We are certain that data quality, completeness, and total number of SMN cases available in our database are up to, or possibly above the current international standard (see e.g. Neglia et al. J Nat Cancer Inst 2001, 93: 618-629). We consider this to be due to the well-established intense cooperation of the GCCR with the GPOH and its clinical trials.

The risk estimates will become increasingly more reliable as the number of cases and the follow-up increase with time. So far the time period covered by the GCCR (which started in 1980) is not long enough to calculate realistic risk rates for cancers occurring as a second malignancy after a long latency period. Therefore, the risks calculated at present are underestimated. Scandinavian cancer registries presumably have better calculations regarding this type of SMN.

Population-based studies on risk factors for SMN have been published rarely. (Hawkins et al., Br J Cancer 1987, 56:339-347; Sankila et al., J Clin Oncol 1996, 14:1442-1446; Garwicz et al. Int J Cancer 2000, 88:672-678; Neglia et al., J Nat Cancer Inst 2001, 93: 618-629). We expect to make a major contribution to this issue internationally when we publish the results of our case-control study.

<u>Milestones as defined in the initial proposal</u>

The results obtained so far correspond to the work plan of the initial proposal. The milestones were accomplished, with one exception: the case-control study will start with a delay, as the discussion on the main hypotheses needed more time than expected; the delay is about 9 months.

B.4	**Publications and patents** Löning L., Zimmermann M., Reiter A., Kaatsch P., Henze G., Riehm H., Schrappe M. Secondary neoplasms subsequent to Berlin-Frankfurt-Münster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 95: 2770-2775, 2000. Kaatsch P, Rickert CH, Kühl J, Schüz J, Michaelis J. Population-based epidemiological data on brain tumors in German children. Cancer 92: 3155-3164, 2001. Wibbing R, Kaatsch P, Kaletsch U, Michaelis J. Epidemiologische Untersuchungen von Sekundärmalignomen nach Krebserkrankungen im Kindesalter. Monatsschr Kinderheilkunde 147: 982, 1999. Kaatsch P, Spix C, Michaelis J. Second malignancies after childhood cancer. 20 Years German Childhood Cancer Registry – Annual Report (www.kinderkrebsregister.de) 64-5, 1999. <u>Patents</u> None planned.
B.5	**Networking** We are contributing considerably to the improvement and consolidation of the integrated information flow between hospitals, clinical trials and GCCR with our project. We were able to observe a general attentiveness to documenting each case with SMN, and notifications are made timelier than before. Information on newly diagnosed SMN cases is being exchanged between the contributing institutions more rapidly than before. The increasing number of requests regarding frequencies of SMN, which we were able to respond to promptly, also demonstrates the added value of the project for the paediatric oncology as a whole. By optimizing the long-term follow-up we are not only improving the completeness of registered SMN cases, but also the data quality of other follow-up information (such as long-term survival probabilities or late effects). This will benefit the network as a whole. The direct personal contact of the GCCR with the patients helps to obtain further valuable data. The oldest individuals registered at the GCCR are meanwhile 35 years old. This opens perspectives for further investigations, e.g. regarding fertility or descendants of former patients. This leads to an especially strong synergy with the project „Late Effects, Quality of Life and Vertical Network“ of the Network (project I). Furthermore the SMN project provides important information for optimizing post-treatment care: such as frequency of SMN, latency periods, or risk estimates for specific entities. We established a cooperation with the Pädiatrischen Register für Stammzelltransplantation (Pediatric stem-cell transplantation registry, PRST) during the funding period. It is important for obtaining therapy data for children, who received stem-cell transplantation (SCT) and developed a SMN later. The GCCR in turn provides the PRST with the information, which children developed a SMN. If the PRST does not have the therapy data itself, it addresses the treating clinic. The PRST is not part of the competence network, but this cooperation does nevertheless improve the networking within Pediatric Oncology.

	The increase in data quality may generally lead to better quality in research. This may lead to improvements in diagnostics and therapy, a decrease in late effects, and a better quality of life for the patients.

Part C – Follow-Up Proposal

C.1 **Aims**

The research objectives of the second funding period are in principle the same as in the first phase. It is the consequent continuation of the work plan, which from the beginning covered a first and second funding period.

The emphasis of the second period lies on the investigation of potential risk factors for SMN and on the continuation of the documentation of SMN cases, the therapy data of the primary malignancy, genetically caused prior diseases and previous malignancies or genetic dispositions of the parents and sibling.

This requires further extension of the long-term follow-up. The workload this creates increases continuously as the number of cases and survivors increases with time (currently there are 25,000 living cases in the registry). The cooperation with the German general cancer registries (usually one per German state) in order to match their patients and the patients at the GCCR will have to be consolidated.

To investigate to what extent elements of the primary therapy and genetic factors influence the risk for developing a secondary malignancy, we are now carrying out the case-control study on risk factors for SMN. The start of the study will be later than originally intended, as the discussion, which hypotheses are the most suitable ones and the general preparation for conducting the study took longer.

One of the aims defined at the beginning of the first funding period was deriving recommendations for the post-treatment care of former patients. The results of the case-control study and the risk estimates are intended to contribute to this. Meanwhile we have realized that the translation of scientific results into specific rulings for patients and physicians requires more medical expertise and time than we have available. The channeling of such results into the practical work is possible only in close cooperation with the GPOH and the clinical trials. We expect finishing this will not be possible within the funding period. Nevertheless, our results will certainly initiate such changes.

Scientific publications and the final report will also be important parts of the further project.

C.2 **Methodological approach**

At the beginning of the project, we had not decided what kind of study we would perform to investigate potential risk factors for SMN. After internal discussions and consulting external experts, we decided to use a matched case-control study as the most appropriate type of study for our purpose.

Meanwhile we have found that assessing therapeutic as well as genetic risk factors exceeds the framework of our time, personnel, and also the case-control study as a method. We were recommended to focus on fewer specific questions. We therefore will focus on therapeutic risk factors. However, potential genetic risk factors remain a relevant aspect of the project.

We are still looking for a cooperation partner regarding the genetic aspects. We had first consultations with the newly established genetic institute of the university clinic in Mainz, as well as with an interested group at the National Cancer Institute in the USA. It may be necessary to interview the families in question directly. In case this were recommended by the experts, it would go beyond the

	original scope of the study. We document the therapy data and some aspects of the genetic predisposition of the patient and his relatives in close cooperation with the clinical trials and the hospitals. The GPOH named a board of consultants (principal investigators of a number of clinical trials) who helped generating specific working-hypotheses and provided advice regarding the practical aspects of obtaining data. Through this we understood that we might need to travel to research data locally (at the clinical trial or clinic) by ourselves, as some of them do not have the personnel required for this. The application and possibly further extension of biometric methods for risk assessment will continue to be relevant in the second funding period.
C.3	**Work plan** The attached table shows the work plan and the intended time periods for the items for the period spring 2002 up until the end of the funding period in December 2004. (The year 2002 is part of the first funding period.) Milestones are: Á The case-control study starts in spring 2002 after extensive preparations Á Consultations regarding genetic aspects in spring 2002 Á End of the field phase of the case-control study in fall/winter 2003 Á Establishing a regular data matching with the state cancer registries until fall/winter 2003 Á Evaluation of the case-control study in spring 2004 Á Publication of results in summer 2004.
C.4	**Networking** The networking presented under B.5 is relevant also for the second funding period, as it consists of a continuous exchange of information. Synergy is achieved by providing important data, such as the frequency of SMN, latency periods, and disease combinations. In order to obtain complete data for the case-control study we need a close cooperation with the clinical trials and the hospitals. The results of the case-control study and the continuing efforts for high quality data will benefit the patient and patient care in the long run; specifically therapy optimization, reduction of late effects, and the quality of life of the patients. In the long run the patient is meant to profit.

Part D- Requested Funding for the Project

D.1 **Salaries**

There are no changes compared to the previous application. The sums are adapted to the actual employees.

One scientific employee:

- conceptualizing and coordinating of the case-control study
- calculation of risk estimates
- contact with clinical trials and consultants
- preparation of meetings
- writing the final report
- publishing results in international scientific publications

½ medical documentarist:

- assisting in the practical working of the case-control study (produces serial letters, codes data, enters data, etc.)
- study documentation
- assists the statistical evaluation
- technical assistance for the final report and publications.

	Costs (in €)
2003	
Scientific employee	69000
Medical documentarist	26000
2004	
Scientific employee	72000
Medical documentarist	27000

D.2	**Consumables** Á Literature: buying recent publications on SMN or statistical methods Á For the case-control study: mailing costs, letters, envelopes, telephone costs, printer Á For evaluating the case-control study and the risk estimates: updates of PC-programs, such as statistical software. Costs (in €) 2003 Literature 200 Mailing costs etc. 150 Software 200 2004 Literature 200 Mailing costs etc. 150 Software 200
D.3	**Investments** No change compared to the original application. Per year we estimate about 1,500 € of travel costs. Travel to scientific conventions, travel to cooperation partners (e.g. regarding the genetic aspects), travel to clinical trials to obtain data, travel of consultants and the expert group named by the GPOH.
D.4	**Other Costs** None.

Section 4

New Projects
Application for the Second Funding Period

Title Page

Network title	:	TOPP (Telemedicine in palliative Pediatric Oncology) (Project T)
Grant No.	:	N/A

Name of scientist-in-charge	:	Dr. med. Boris Zernikow
Institution	:	Universität Münster, Universitätsklinikum, Klinik und Poliklinik für Kinderheilkunde, Pädiatrische Hämatologie/Onkologie
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From 01.10.2002 on:

Institution	:	Vestische Kinderklinik Datteln Witten/Herdecke University
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Project home page (if different from Network homepage)	:	

Part A - General Statements about the Project

A.1. **Subject**

TOPP – Telemedicine in palliative Pediatric Oncology

A.2. **Co-Investigators**

- Dr. med. Stefan Friedrichsdorf, Vestische Kinderklinik Datteln, Witten/Herdecke University

A.3. **Research with Human Subjects/Animals/Gene Therapy**

This project includes:

(a) examination of human subjects	☐ yes	☒ no
(b) clinical trials	☐ yes	☒ no
(c) animal models	☐ yes	☒ no
(d) gene therapy	☐ yes	☒ no

A.4 **Requested Funds for the Second Funding Period***

Fiscal year	**Personnel[1]**	**Consumables[1]**	**Investments[1]**	**Travel[1]**	**Other[1] ***	**Amount[1] Requested**
2003	60	20	18,2	5	7,5	110,7
2004	78	10	0	5	7,5	100,5

[1](amounts in thousand Euro),

* should correlate to funds specified in Part D

Part C- Proposal for a New project

C.1 **Summary**

In Germany each year about 540 children and adolescents die of malignant disease. Although several German oncology departments developed their individual model of care for dying children, during their palliative period most children with cancer have no access to home care. The local pediatrician or the general practitioner, who usually has not been involved during therapy at the pediatric cancer ward, suddenly might become the primary care giver once a child is in palliative care in the home care setting. TOPP is aiming to introduce a close relationship between the local pediatrician (general practitioner) and the pediatric oncologist by means of telemedicine in order to improve palliative care for children with cancer.

C.2 **State-of-the-Art and Own Previous Work**

Introduction

In Germany coordination of medical, nursing and psychosocial care for the pediatric cancer patient during his or her end-of-life period is organized on an individual „from case to case" basis. Apart from the physician of the oncology ward or the outpatient clinic the general pediatric practitioner has a major role in coordinating care for a palliative child. He is not only responsible for medical treatment but for all aspects of palliative care (nursing and psychosocial care as well as support of parents, siblings and other family members).

The Network of Care

Professionals from various medical or psychosocial disciplines as well as individuals from school, nursery, kindergarten, religious and spiritual groups or self-help groups are involved in the care for the dying child. Each care team is individually composed for an individual family. Preferably the care team should be of moderate size. Typically the team might consist of:

- General practitioner, local pediatricians or pediatric hematologist/oncologist
- Nurses or pediatric nurses based in a hospital or outpatient clinic, from home care centers or from hospices
- Pediatric psychiatrist, pediatric psychologist
- Physiotherapist, ergo therapist, music therapist or nutritional specialist/dietician
- Pharmacist
- Social worker
- School teacher or clinic-based teacher
- Pastor
- Voluntary staff, neighbors

The local pediatrician (general practitioner)

When a pediatric malignancy is diagnosed, the child will usually be referred by the local practitioner or pediatric clinician to a pediatric cancer centre. During the

sophisticated therapy at the cancer centre the local pediatrician (or general practitioner) is hardly involved in the child's treatment. If the disease turns out to be incurable and if it is the wish of the child and his or her family to return home, quite suddenly – from the local pediatricians' point of view it may be too sudden - the practitioner becomes the main coordinator of treatment and the family's main counterpart. His task comprises both medical care and – functioning as the main coordinator – multi-professional palliative care. However, in a practitioners' daily routine the care for a dying child is rather exceptional. Thus most practitioners will be glad to tightly cooperate with a pediatric oncologist/hematologist experienced in palliative medicine. It could be demonstrated that there was a significant improvement in palliative care if practitioner and pediatric oncologist are involved simultaneously (Wolfe et al. 2000).

Present infrastructure of German palliative care

An investigation performed by the German Cancer Society (Deutsche Krebsgesellschaft) in the year 1998 stated that „today's German palliative medicine is wretched, miserable, and extremely bad. The doctors' level of specific knowledge is moderate at best. The general public is totally ignorant with respect to those issues – there is nobody to teach them. There is not only the lack of those more organizational prerequisites. What is more alarming is that even the idea of palliative care is but faintly present in academic life" (Röglin 1998).

Throughout Germany there is not a single institutional network providing pediatric palliative care. Prospective investigations are missing. There is no nationwide database installed covering therapy or adverse effects during the end-of-life period. There are no curricula on pediatric palliative medicine for medical professionals. The literature on symptom control, on adverse effects or psychosocial care of dying children is very limited. Practically all books or journals covering palliative care are written in English, but even an English textbook on pediatric palliative care is missing. Guidelines covering pediatric palliative care in oncology/hematology are missing, too.

Although several German oncology departments developed their local model of care for dying children, during their palliative period still most children with cancer lack access to home care.

Key References

Cook DJ, Dolittle GC, Whitten PS. Administrator and provider perceptions of the factors relating to programme effectiveness in implementing telemedicine to provide end-of-life care. J Telemed Telecare 2001;7 Suppl 2:17-9

Currell R, Urquhart C, Wainwright P, Lewis R. Telemedicine versus face to face patient care: effects on professional practice and health care outcomes (Cochrane Review). In: The Cochrane Library, 1, 2002.

Graf N, Paulussen M, Huf T, Ganslandt T, Stahl J, Jürgens H. Telemedizin in der Pädiatrischen Onkologie - Ergebnisse einer Fragebogenaktion des Kompetenznetzes Pädiatrische Onkologie. Klin Pädiatr 2002;214:8-19

Leggett P, Graham L, Steele K, et al. Telerheumatology – diagnostic accuracy and acceptability to patient, specialist and general practitioner. BJGP 2001: 51;749-52

Röglin H-C. Menschenwürdiger Umgang mit dem Sterben aus Sicht praktizierender Onkologen. Forum DKG 1998;13:244-52

Wolfe J, Grier HE, Klar N et al. Symptoms and suffering at the end of life in children with cancer. N Engl J Med 2000;342:326-33

Own previous work: The PATE project

On June 1, 2001, a project of the German Pediatric Oncology and Hematology Society (GPOH – Gesellschaft für Pädiatrische Onkologie und Hämatologie) called „PATE“ (in English: „godfather”) (Palliative Care, Therapy and its Evaluation; in German: Palliativmedizin und -therapie sowie ihre Evaluation in der Pädiatrischen Hämatologie/Onkologie) supported by the German Childhood Cancer Foundation (Deutsche Kinderkrebsstiftung) was initiated.

The aims of PATE are

1. to analyze the structure and the content in Germany of today's pediatric palliative care in oncology
2. to disseminate recommendations with respect to symptom control and psychosocial care, and to provide those information on a teaching basis
3. to work on proposals with respect to organization and financing of local palliative care
4. to collect data reflecting the need in pediatric palliative care in oncology and hematology, in order to deliver arguments to support care givers in the discussion with health insurance companies and politicians on how and where to establish programs for palliative home care
5. to provide an infrastructure for the investigation of quality of life in the end-of-life period

PATE is financially supported by the German Pediatric Cancer Society (Deutsche Kinderkrebsstiftung, covering 1/2 a doctor's post and 1 pediatric nurse's post.

Ad 1: On Dec 12, 2001 the first invitational conference was held in Recklinghausen, Germany, on pediatric palliative care. More than 100 pediatricians, pediatric nurses and psychosocial professionals from 30 German Pediatric Oncology departments attended the meeting. The meeting's aim was to document the status-quo of care of children with cancer during their end-of-life period. The distinctive departments presented details on their individual practice of pediatric palliative care. Based on these data an investigation of the infrastructure of palliative care of German Pediatric Oncology wards is currently under way.

Ad 2: As a first step to provide German-speaking information the World Health Organisation (WHO)-guidelines „Cancer Relief and Palliative Care in Children“ were translated (in German: „Schmerztherapie und palliative Versorgung krebskranker Kinder”). Printing of the brochure was financially supported by the German ministry of health (Bundesministerium für Gesundheit). During the conference mentioned above a board of experts was constituted. Its task is to work on German guidelines on palliative care for children with cancer.

Ad 3 and 4: International cooperation and the visits of numerous institutions providing palliative care in Germany or abroad have led to the establishment of recommendations on how to organize and finance domestic palliative care for chil-

	dren with cancer. Ad 5: PATE is working on a tool for the documentation of therapies and adverse effects during pediatric palliative care similar to the one already established in German adult palliative care <u>Telemedicine</u> What is the experience with telemedicine today? A metaanalysis done by the Cochrane Library 2 years ago comprising 7 clinical studies with a total of 800 patients (all studies except one had but small case numbers) failed to show any significant superiority of telemedicine to standard care. However, the telemedicine technique was feasible and reliable. Telemedicine was well accepted by the patients. Since the publication of the Cochrane Library more than 1400 studies on the issue have been published. The next metaanalysis is eagerly awaited. A recently performed Irish study on 100 patients with rheumatoid arthritis could show that visiting the doctor „by television“ was reliable at reasonable costs (Leggett et al. 2001). Image-based patient-doctor interactions were more effective than contacts merely done by phone. After video conferencing just 6 percent of the patients had to visit their doctor in person versus 75 percent after telephone contact. The 97 percent diagnostic accuracy after television contact compared favorably with the 71 percent diagnostic accuracy after telephone contact. Often the health assessment of children during their palliative phase of life is very difficult to perform for a general pediatrician who is not especially trained in that field. Our own experience shows that it is not uncommon that children are assessed as „prefinal” who in fact are well under the circumstances and lived for another several months. On the other hand major symptoms go unreported, for instance complete paraplegia/paralysis. To clear up misunderstandings is one of the main issues this project TOPP was designed for. Several model projects of palliative care using telemedicine are already working successfully, for instance in the U.S.A (Cook et al. 2001) and at the Milano Istituti Tumori, Italy. A close cooperation with the latter institution has already been established. A German nationwide survey was able to show that most German pediatric oncologists are confident that the introduction of telemedicine will improve the quality of care of children with cancer (Graf et al. 2002).
C.3	**Aims** The aim of the model project TOPP is to evaluate the potential of telemedicine with respect to home care for children with cancer during their end-of-life period. At first the quantity and quality of infrastructure (hard- and software) needed and its handling will be evaluated at a level three hospital, i.e. the University Children’s Hospital Münster, Germany (UKM). The resulting know-how will be transferred to a medium-sized Pediatric Oncology (Vestische Kinderklinik Datteln, Witten/Herdecke University; Germany). Datteln has been chosen for reasons of its proximity to and an already established tight cooperation with Münster. In Münster regularly 10 patients at a time are in palliative care. Each year 30-40 children with cancer die. In Datteln there are 2 to 4 patients in palliative care at a time.

C.4 **Methodological approach**

Each patient's family will be provided with a notebook computer, web cam, and ISDN internet connection. The University Children's Hospital Münster and the Vestische Kinderklinik Datteln are either already provided with sufficient internet technology (see telemedicine project of Prof. Jürgens and Dr. Paulussen), or the technique will be provided in the near future. By this means the pediatric patient and his parents as well as the local pediatrician or general practitioner involved and the nursing home care team are able to contact the pediatric oncologist if they feel the necessity to do so. The primary care providers may even establish regular screen-based visitations during the visitation in the patients' home.

Telemedicine will be used in order to establish communication lines and to reach its' aims by the following means:

Communication Partners		Aim(s)
Pediatric oncologist	Family	Á Direct assessment of the health status independent of a third party's judgement (e.g. effectiveness of analgesia; fatigue; level of activity; adverse effects of therapy; advance of disease) Á Regular assessment of family needs Á Improved security by regular health reports Á Help in the assessment of acute events Á Teaching and supervising (e.g. change of dressing)
Pediatric oncologist	Local pediatrician or home care team member while visiting the patient	Á Discussion of treatment details under direct visualization of the patient (e.g. decubitus, shortness of breath, obstructions of any kind, vigilance, mood, etc.) Á Teaching and supervising (e.g. change of drainage devices, change of patient-controlled-analgesia (PCA) medication, change of PCA parameters, or other problem solving)
Local pediatrician or nursing team member	TOPP Team	Á Providing of documentation tools, address files, proposals on symptom control and control of adverse effects, etc. Á Discussion of difficult matters

C.5	**Work plan** The data of all patients cared for by TOPP will be collected by a standardized documentation system developed in their own projects. Pediatricians who are actively involved in palliative care are under the impression that during the end-of-life period children have a great need of analgesics, anticonvulsants, or neuroleptic drugs, exceeding by far all recommendations given in textbooks. The documentation system will help in the prospective evaluation of therapies and adverse effects. On the long run the aim is to improve the care of dying children. <u>Scientific project evaluation</u> In cooperation with Dr Joanne Wolfe (Harvard Medical School, Boston) we are currently performing a survey with bereaved parents who lost their child to cancer. Using a validated interview we are collecting data on symptoms, adverse effects of therapy, availability of care, satisfaction with the medical and psychosocial team, and circumstances of death (historical control). The same interview schedule will be used to evaluate the telemedicine setting, using the same historical control (for details of the interview see Wolfe et al. 2000). At the end of the project, all participating local pediatricians and general practitioners will be asked to participate in a survey by standardized questionnaire on the quality of the patient care, telemedicine technique, cooperation quality, etc. This questionnaire will be developed and validated during the TOPP project phase to improve construct validity.
C.6	**Networking** TOPP is a network of competence which coordinates the horizontal scientific network and the vertical network of investigation and care. <u>Horizontal scientific network</u> Results from other pediatric palliative projects will be transferred to the physicians of the TOPP project. Technical know how from the other telemedicine project of Prof. Jürgens (see above) should help to fasten the development of a functioning video conferencing between patient and TOPP team. <u>Vertical network of investigation and care</u> Documentation sheets, guidelines etc. recently developed will directly influence patient care. In two model institutions (Münster and Datteln) TOPP will coordinate and network local pediatricians and members of the home care team with their corresponding cancer wards, outpatient hospitals and day care centers. Therefore, an aim of TOPP is to evaluate the feasibility of vertically connecting experts in Pediatric Oncology/palliative care with the home care physician.

Part D- Requested Funding for the Project

D.1 **Salaries**

- 1/2 Pediatrician post (Münster) BAT IIa for 2 years:
  2003: 30.000 €
  2004: 31.000 €
- 1/4 Pediatrician post (Datteln) BAT IIa for 1 year:
  2004: 16.000 €
- 1/2 Post of a medical informatics technician for 2 years:
  2003: 30.000 €
  2004: 31.000 €

Tasks

In the first year development and support of the telemedicine technique in Münster. In the second year transfer of the system to Datteln, system support in Datteln and Münster. Thus, identical workload during both the years 2003, and 2004.

D.2 **Consumables**

Server costs, maintenance, service, internet costs (2 years): 30000 €

D.3 **Investments**

8 laptops suitable for telemedicine application (2270 € each): 18160 €

Cooperations with Deutsche Telekom and Siemens AG are planed in order to reduce the costs of technical devices. First very promising contacts with these companies are already established.

Laptop

In order to allow for mobility of the computer work place there is need for a notebook computer (as opposed to a tower model).

Type of processor and size of memory: Internet data rate is the technical bottle neck of life cam data transfer. Using a 56k modem or ISDN technology a processor speed of 300 MHz and a RAM size of 64 MB are sufficient. Using DSL technology a 700 MHz processor is recommended. Hence, a today's standard laptop would meet requirements.

Graphic board: With modern laptops the choice of the graphic board is of no importance for the discussed purpose. The cameras' maximum resolution and frame rate are of interest only for the local work place. The H.323 standard defines CIF (common interface format) as the standard video format for video conferences. This format is incompatible with common graphic board accelerators. CIF resolution is 352 x 288 pixels, a resolution that is processed by nearly every modern graphic board without any loss in speed or quality.

Sound board: Minimal requirement is Duplex mode (transceiving simultaneously). For an acceptable quality of sound the full Duplex sampling rate should be higher

than 8 kHz. Any modern sound board matches these requirements.

Network abilities: In order to establish the communication link with the patient and the Pediatric Oncology hospitals, there is need for at least a 56k modem and ISDN ability. In order to allow for DSL networking, a network card should be provided.

Data storage: During each session, all video data will be recorded on hard disk. Later, data will be transferred to CD-ROM by means of an internal CD-Rom burner.

Web Cam

There are huge quality differences in the Web Cams on the market. High sensitivity and high contrast are the paramount parameters for network applications in the proposed project. The mode of camera fixation to the laptop is critical. Most camera models are not provided with a laptop-compatible fixation device. The Kodak DVC325 Digital seems to be a suitable choice.

Internet gate

Using hardware as described above, internet connection is uncritical. Each private internet gate should be suitable as should be even one of those internet-by-call gates free of a monthly basis charge (connection via modem or ISDN).

Software

Operating system: Most laptops are delivered with a preinstalled operating system. For the sake of hardware and software compatibility and feasibility our choice is Windows ME or XP (Microsoft Inc., U.S.A.).

Video conferencing software: Netmeeting (Microsoft Inc, U.S.A.) is recommended for video conferencing. It is provided free of charge.

Backup software: For backup purposes special software is needed which is capable to backup, and restore, whole hard disc partitions. In case of accidental data or program corruption even an ignorant user must be able to easily reconfigure the laptop from CD-ROM. Our choice is Drive Image rel. 5.

Costs of a single work place (computer hard- and software)

Technique	estimated cost
Web Cam (Kodak DVC325 Digital):	90 €
Laptop (Fujitsu-Siemens Lifebook C-6387):	2000 €
ISDN adapter for PCMCIA-slot:	110 €
Backup software (Drive Image):	70 €
Total	2270 €

Not included are the costs for the installation of the internet gateway and for centralized service and support (see below).

D.4	**Other Costs** Scientific interchange with a similar Italian project in adults The Milano Instituti Tumori in Milano, Italy, has successfully established a telemedicine project in adult palliative care. To prepare the implementation of TOPP, members of our team (including Dr. med. Christine Wamsler, qualified Italian interpreter) will exchange ideas and participate in the Italian telemedicine project. The aim is to learn from the Italian experiences and study the technical and human resources necessary for such a project. Travel expenses will be 10000 €. Further material Office equipment etc.: 5000 €. Courses / Conferences Costs of courses and conferences on Pediatric Palliative Care in order to improve the medical knowledge and skills of the TOPP team members comprising fees, accommodation and travel expenses: 10000 €.

(End of the Midterm Report. Annex follows.)

BMBF COMPETENCE NETWORKS

Annex

to the

Speaker’s Midterm Report on the

Competence Network

Pediatric Oncology and Hematology

Contents – Overview

This annex comprises additional data and original material, which complement specific questions and answers of the Speakers' Midterm Report (MR) section 1.

* Referring to section 3, part C.3 of project proposals.

** Referring to section 3, part B.4 of project proposals.

A.1 c) Full index of network-related English papers in reviewed journals (published or in press)

Columns of the table:

Number of the reference

a) Publication represents joint activities of two or more network groups (referring to section 3, B.4 in the Midterm Report).

b) Publication involved at least three network partners from different universities or non-university research institutions (referring to label "**b**" of section 1, question A.1 in the Midterm Report).

c) Publications together with (an) international partner(s) (referring to label "**c**" of section 1, question A.1 in the Midterm Report).

P Project(s) affiliation

#P Number of reference within project

#	a)	b)	c)	P	#P	Reference
1	X	X		A I	1	Langer T, Henze G, Beck J.D. Basic methods and the developing structure of a late effects surveillance system (LESS) in the long-term follow-up of pediatric cancer patients in Germany. Med Pediatric Oncology 34: 348-351, 2000
2	X	X		A K	2	Löning L, Zimmermann M, Reiter A, Kaatsch P, Henze G, Riehm H, Schrappe M. Secondary neoplasms subsequent to Berlin-Frankfurt-Münster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 95: 2770-2775, 2000
3				B/1	1	Knaup P, Harkener S, Ellsässer K.-H, Haux R, Wiedemann T. On the necessity of systematically planning clinical tumor documentation. Meth. Inform. Med 2001;40, 90-98
4				B/1	2	Merzweiler A, Knaup P, Creutzig U, Ehlerding H, Haux R, Mludek V, Schilling FH, Weber R, Wiedemann T. (2000). Requirements and Design Aspects of a Data Model for a Data Dictionary in Paediatric Oncology. In: Hasman, A, Blobel, B, Dudeck, J. et al. (Hrsg.). Medical Infobahn for Europe, 696-700. Amsterdam: IOS Press.
5	X	X		B/1	3	Knaup P, Mludek V, Wiedemann T, Bauer J, Haux R, Kim L, Schilling FH, Selle B. (2000). Integrating Specialized Application Systems into Hospital Information Systems -Obstacles and Factors for Success. In:Hasman, A, Blobel, B, Dudeck, J. et al. (Hrsg.). Medical Infobahn for Europe, 890-894. Amsterdam: IOS Press.
6				B/1	4	Merzweiler A, Knaup P, Weber R, Ehlerding H, Haux R, Wiedemann, T. (2001). Recording clinical data - from a general set of record items to case report forms (crf) for clinics. In: Patel, V, Rogers, R, Haux, R. (Hrsg.). MEDINFO 2001. Proceedings of the 10th World Congress on Medical Informatics, 653-657. Amsterdam: IOS.
7	X	X		B/1	5	Weber R, Knaup P, Knietig R, Haux R, Merzweiler A, Mludek V, Schilling FH, Wiedemann T. (2001). Object-oriented business process analysis of the Cooperative Soft Tissue Sarcoma Trial of the German Society for Paediatric Oncology and Haematology (GPOH). In: Patel, V, Rogers, R, Haux, R. (Hrsg.). MEDINFO 2001. Proceedings of the 10th World Congress on Medical Informatics, 58-62. Amsterdam: IOS.
8	X			D	1	Strauß G, Osen W, Debatin K-M. Clin. Exp. Induction of apoptosis and modulation of activation and effector function in T cells by immunosuppressive drugs. Immun. 200, In Press
9	X			D	2	Wuchter C, Ruppert V, Schrappe M, Dorken B, Ludwig WD, Karawajew L. In vitro susceptibility to dexamethasone- and doxorubicin-induced apoptotic cell death in context of maturation stage, responsiveness to IL-7 and early cytoreduction in vivo in childhood T-ALL. Blood 2002, in press
10	X			D	3	Stahnke K, Fulda S, Friesen C, Strauss G, Debatin KM Activation of apoptosis pathways in peripheral blood lymphocytes by in vivo chemotherapy Blood 2001,98:3066-7330
11	X			D	4	Herr I, Debatin K-M . Cellular stress response and apoptosis in cancer therapy. Blood 2001,98: 2603-2614

#	a)	b)	c)	P	#P	Reference
12	X			D	5	Wuchter C, Krappmann D, Cai Z, Rup-pert V, Scheidereit C, Dorken B, Ludwig WD, Karawajew L. In vitro susceptibility to TRAIL-induced apoptosis of acute leukemia cells in the context of TRAIL receptor gene ex-pression and constitutive NF-kappa B activity. Leukemia 2001,15:921-8
13	X			D	6	Cai Z, Lin M, Wuchter C, Ruppert V, Dorken B, Ludwig WD, Karawajew L. Apoptotic response to homoharring-tonine in human wt p53 leukemic cells is independent of reactive oxygen spe-cies generation and implicates Bax translocation, mitochondrial cytochrome c release and caspase activation. Leukemia 2001;15:567-74
14	X			D	7	Wuchter C, Karawajew L, Ruppert V, Schrappe M, Harbott J, Ratei R, Dorken B, Ludwig WD. Constitutive expression levels of CD95 and Bcl-2 as well as CD95 func-tion and spontaneous apoptosis in vitro do not predict the response to induction che-motherapy and relapse rate in child-hood acute lymphoblastic leukaemia. Br J Hae-matol 2000;110:154-60
15	X			D	8	Karawajew L, Ruppert V, Wuchter C, Kosser A, Schrappe M, Dorken B, Ludwig WD. Inhibition of in vitro spontaneous apop-tosis by IL-7 correlates with bcl-2 up-regulation, cortical/mature immunophe-notype, and better early cytoreduction of childhood T-cell acute lymphoblastic leukemia. Blood 2000;96:297-306
16	X			D	9	Fulda S, Meyer E, Debatin KM. Metabolic inhibitors sensitize for CD95 (APO-1/Fas)-induced apoptosis by down-regulating Fas-associated death domain-like interleukin 1-converting enzyme inhibitory protein expression. Cancer Res 2000;60:3947-56
17	X			D	10	Beltinger C, Fulda S, Kammertoens T, Uckert W, Debatin KM. Mitochondrial amplifi-cation of death signals determines thymidine kinase/ganciclovir-triggered activation of apoptosis. Cancer Res 2000;60:3212-7
18				E	1	Tschan CA, Pilz C, Zeidler C, Welte K, Germeshausen M. Time course of increasing numbers of mutations in the granulocyte colony-stimulating factor receptor gene in a patient with congenital neutropenia who developed leukemia. Blood 97: 1882-84, 2001.
19		X		E	2	Germeshausen M, Ballmaier M, Schulze H, Welte K, Flohr T, Beiske K, Storm-Mathisen I, Abrahamsen TG. Granulocyte colony-stimulating factor receptor muta-tions in a patient with acute lymphoblastic leukemia secondary to severe congenital neutropenia. Blood 97: 829-830, 2001.
20				E	3	Germeshausen M, Ballmaier M, Welte K. Implications of mutations in hematopoietic growth factor receptor genes in congenital cytopenias. Ann NY Acad Sci 938: 305-21, 2001.
21				E	4	Jung A, Ruckert S, Frank P, Brabletz T, Kirchner T. 7-deaza-2`-deoxyguanosine allows PCR and sequencing from CpG islands. Mol Path 55, 55-57, 2001.
22				E	5	Rischewski J, Schneppenheim R. Screening strategies for a highly polymorphic gene: DHPLC analysis of the Fanconi anemia group A gene. J Biochem Biophys Methods 30;47:53-64, 2001.
23			X	E	6	Hasle H, Niemeyer CM. Myelodysplastic syndrome and juvenile myelomonocytic leukemia in children. In: Trends in Molecular Medicine (formerly: Molecular Medicine Today) 2: 468-457, 2002
24				F	1	Eckert C, Landt O, Taube T, Seeger K, Beyermann B, Proba J, Henze G. Potential of LightCycler technology for quantification of minimal residual disease in childhood acute lymphoblastic leukemia. Leukemia 2000;14:316-323
25			X	F	2	Eckert C, Biondi A, Seeger K, Cazzaniga G, Hartmann R, Beyermann B, Pogodda M, Proba J, Henze G. Prognostic value of minimal residual disease in relapsed child-hood acute lymphoblastic leukaemia. Lancet 2001;358:1239-1241
26				F	3	Nakao M, Janssen JW, Bartram CR. Duplex PCR facilitates the identification of im-munoglobulin kappa (IGK) gene rearrangements in acute lymphoblastic leukemia. Leukemia 2000;14:218-219
27				F	4	Nakao M, Janssen JW, Flohr T, Bartram CR. Rapid and reliable quantification of minimal residual disease in acute lymphoblastic leukemia using rearranged immu-noglobulin and T-cell receptor loci by LightCycler technology. Cancer Res 2000;60:3281-3289
28				F	5	Seeger K, Buchwald D, Peter A, Taube T, von Stackelberg A, Schmitt G, Henze G. TEL-AML1 fusion in relapsed childhood acute lymphoblastic leukemia. Blood 1999;94:374-376

#	a)	b)	c)	P	#P	Reference
29				F	6	Seeger K, Buchwald D, Taube T, Peter A, von Stackelberg A, Schmitt G, Kochling J, Henze G. TEL-AML1 positivity in relapsed B cell precursor acute lymphoblastic leukemia in childhood. Berlin-Frankfurt-Munster Study Group. Leukemia 1999;13:1469-1470
30				F	7	Seeger K, Kreuzer KA, Lass U, Taube T, Buchwald D, Eckert C, Korner G, Schmidt CA, Henze G. Molecular quantification of response to therapy and remission status in TEL-AML1-positive childhood ALL by real-time reverse transcription polymerase chain reaction. Cancer Res 2001;61:2517-2522
31				F	8	Seeger K, Taube T, Eckert C, Hanel C, Pogodda M, Henze G. Unusual T-cell receptor-delta gene rearrangement patterns revealed by screening of a large series of childhood acute lymphoblastic leukaemia by multiplex polymerase chain reaction. Br J Haematol 2001;113:318-322
32	X	X	X	F	9	Seeger K, Viehmann S, Buchwald D, Harbott J, Schrappe M, Stary J, Henze G, Trka J. Treatment response and residual-disease monitoring in initial and relapsed TEL-AML1 positive childhood ALL. Leukemia 2001;15:280-282
33	X	X		F	10	zur Stadt U, Harms DO, Schluter S, Schrappe M, Goebel U, Spaar H, Janka G, Kabisch H. MRD at the end of induction therapy in childhood acute lymphoblastic leukemia: outcome prediction strongly depends on the therapeutic regimen. Leukemia 2001;15:283-285
34				F	11	zur Stadt U, Rischewski J, Schneppenheim R, Kabisch H. Denaturing HPLC for identification of clonal T-cell receptor gamma rearrangements in newly diagnosed acute lymphoblastic leukemia. Clin Chem 2001;47:2003-2011
35				G	1	Otano-Joos M, Mechtersheimer G, Ohi 2, Wilgenbus KK, Scheurlen W, Lehnert T, Willeke F, Otto HF, Lichter P, Joos S. Detection of chromosomal imbalances in leiomyosarcoma by comparative genomic hybridization and interphase cytogenetics. Cytogenet Cell Genet 2000; 90:86-92
36				G	2	Granzow M, Popp S, Weber S, Hager HD, Boschert J, Scheurlen W, Jauch A. Multiplex-FISH classifies chromosome rearrangements in a child with intracranial ependymoma. Cancer Genet. Cytogenet (in press)
37			X	G	3	Schulz S, Becker KF, Braungart E, Reichmuth C, Klamt B, Atkinson M, Gessler M, Hofler H. Molecular analysis of E-cadherin-11 in Wilm's tumours. J Pathol 2000; 191:162-169
38		X		G	4	Hartmann W, Waha A, Koch A, Albrecht S, von Schweinitz D, Pietsch T. p57-KIP2 is not mutated in hepatoblastoma but shows increased transcriptional activity - a comparative analysis of three imprinted genes p57-KIP2, IGF2 and H19. Am J Pathol 2000; 157:1393-403
39		X		G	5	Weber RG, Pietsch T, von Schweinitz D, Lichter P. Characterization of chromosomal imbalances in hepatoblastomas: a role for gains on 8q and 20 as predictors of outcome. Am J Pathol 2000; 157:571-578
40				G	6	Bühren J, Christoph AHA, Buslei R, Albrecht S, Wiestler OD, Pietsch T. Expression of the neurotrophin receptor p75-NTR in medulloblastomas is correlated to distinct histological and clinical features: Evidence for a medulloblastoma subtype derived from the external granule cell layer. J Neuropathol Exp Neurol 2000; 59:229-40
41				G	7	Herms J, Neidt I, Lüscher B, Sommer A, Schürmann P, Schröder T, Bergmann M, Wilken B, Probst-Cousin S, Hernaiz-Driever P, Behnke J, Hanefeld F, Pietsch T, Kretzschmar HA. c-myc expression in medulloblastoma and its prognostic value. Int J Cancer 2000; 89:395-402.
42		X		G	8	Koch A, Waha A, Tonn JC, Sörensen N, Berthold F, Hartmann W, Friedl W, Reifenberger G, Wiestler OD, Pietsch T. Mutations of components of the wingless/WNT signaling pathway in sporadic primitive neuroectodermal tumors. Int J Cancer 2000; 93:445-9.
43			X	G	9	Kraus JA, de Millas W, Sörensen N, Herbold C, Schichor C, Tonn JC, Wiestler OD, von Deimling A, Pietsch T. Evidence for a tumor suppressor gene at 22q11-q12 involved in the pathogenesis of human ependymomas and distinct form hSNF5/INI1. Acta Neuropathol 2001; 102:69-74.
44				G		Söling A, Schurr P, Berthold F. Expression and clinical relevance on NY-ESO1, MAGE-1 and MAGE-3 in neuroblstoma. Anticancer Res 1999; 19:2205-09.
45				G	10	Müller S, van den Boom D, Zirkel D, Köster H, Berthold F, Schwab M, Westphal M, Zumkeller W. Retention of imprinting of the human apoptosis-related gene TSSC2 in human brain tumors. Hum Mol Gen 2000; 9:757-763.

#	a)	b)	c)	P	#P	Reference
46		X		G	11	Poremba CH, Hero B, Heine B, Scheel CH, Schaefer KL, Christiansen H, Berthold F, Kneif S, Stein H, Juergens H, Boecker W, Dockhorn-Dworniczak B. Telomerase is a strong indicator for assessing the proneness to progression in neuroblastomas. Med Pediat Oncol 2000; 35:651-655.
47		X	X	G	12	Poremba C, Scheel C, Hero B, Christiansen H, Schaefer K, Nakayama J, Berthold F, Juergens H, Boecker W, Dockhorn-Dworniczak B. Telomerase activity and telomerase subunits gene expression patterns in neuroblastoma: A molecular an immunhistochemical study establishing prognostic tools for fresh-frozen and paraffin-embedded tissue. J Clin Oncol 2000; 18:2582-2592.
48		X	X	G	13	Ladenstein R, Ambros IM, Poetschger U, Amann G, Urban C, Fink FM, Schmitt K, Jones R, Slociak M, Schilling F, Ritter J, Berthold F, Gadner H Ambros PF. Prognostic significanes of DNA Di-tetraploidy in neuroblastoma. Med Pediat Oncol 2001; 36:83-92.
49		X		G	14	Theobald M, Christiansen H, Schmidt A, Malekian B, Wolkewitz N, Christiansen N, Brinkschmidt C, Berthold F, Lampert F. Sublocalization of putative tumor suppressor gene loci on chromosome arm 14q in neuroblastoma. Genes, Chromosomes & Cancer 1999; 26:40-46.
50			X	G	15	Bown N, Cotterill S, Lastowska M, O´Neill S, Pearson ADJ, Plantaz D, Meddeb M, Danglot G, Brinkschmidt C, Christiansen H, Laureys G, Spelemann F. Gain of chromosome arm 17q and adverse outcome in patients with neuroblastoma. N Eng J Med 1999; 340:1951-1962.
51		X		G	16	Poremba C, Willenbring H, Hero B, Christiansen H, Schäfer KL, Brinkschmidt C, Jürgens H, Böcker W, Dockhorn-Dworniczak B. Telomerase activity distinguishes between neuroblastomas with good and poor prognostic. Ann Oncol 1999; 10:1-7.
52				G	17	Dötsch J, Harmjanz A, Christiansen H, Hänze J, Lampert F, Rascher W. Gene expression of neuronal nitric oxide synthase and adrenomedullin in human neuroblastoma using real-time PCR. Int J Cancer 2000; 88:172-175.
53				G	18	Brinkschmidt C, Christiansen H, Terpe HJ, Simon R, Lampert F, Böcker W, Dockhorn-Dworniczak B. Distal chromosome 17 gains in neuroblastomas detected by comparative genomic hybridisation (CGH) are associated with a poor clinical outcome. Med Pediat Oncol 2001; 36:11-13.
54			X	G	19	Vandesompele J, Speleman F, van Roy N, Laureys G, Brinkschmidt C, Christiansen H, Lampert F, Lastowska M, Bown N, Pearson A, Nicholson JC, Ross F, Combaret V, Delattre O, Feuerstin BG, Plantaz D. Multicentre analysis of patterns of DNA gains and losses in 204 neuroblastoma tumors: How many genetic subgroups are there. Med Pediat Oncol 2001; 36:5-10.
55				G	20	Bergmann E, Wanzel M, Weber A, Shin I, Christiansen H, Eilers M. Expression of p27Kip1 is prognostic and independent of MYCN amplification in human neuroblastoma. Int J Cancer 2001; 95:176-183.
56				G	21	Dötsch J, Repp R, Rascher W, Christiansen H. Diagnostic and scientific applications of TaqMan real-time PCR in neuroblastomas. Expert Rev Mol Diagn 2001; 1:233-238.
57			X	G	22	O'Neill S, Estrom L, Lastoska M, Robets P, Brodeur GM, Kees UR, Schwab M, Bown N. MYCN Amplification and 17q in neuroblastoma: Evidence for structural association. Genes, Chromosomes & Cancer 2001, 30:87 .
58			X	G	23	Boon K, Caron HN, van Asperen R, Velantijn L, Hermus MC, van Sluis P, Roobeek I, Weis I, Voute PA, Schwab M, Versteeg R. N-myc enhance the expression of a large set of genes functioning in ribosome biogenesis and protein synthesis. EMBO Journal 2001; 20:1-11.
59				G	24	Savelyeva L, Schwab M. Amplification of oncogenes revisited: From expression profiling to clinical application. Cancer Letters 2001; 167:115-123.
60		X	X	G	25	Khan J, Wei JS, Ringner M, Saal LH, Ladanyi M, Westermann F, Berthold F, Schwab M, Antonescu CR, Peterson C, Meltzer PS. Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural networks. Nature Medicine 2001; 7:673-679.
61		X		G	26	Bauer A, Savelyeva L, Claas A, Praml C, Berthold F, Schwab M. Smallest region of overlapping deletion in 1p36 human neuroblastoma: A 1-Mbp cosmid and PAC contig. Genes, Chromosomes & Cancer 2001; 31:228-239.
62			X	G	27	Hing S, Lu YJ, Summersgill B, King-Underwood L, Nicholoson J, Grundy P, Grundy R, Gessler M, Shipley J, Pritchard-Jones K. Gain of 1q is associated with adverse outcome in favourable histology Wilm´s tumors. Am J Pathol 2001; 158:393-8.

#	a)	b)	c)	P	#P	Reference
63		X		G	28	Przkora R, Meyer-Puttlitz B, Schmitt O, Berthold F, Nöthen M, Krauss J, Tonn JC, von Deimling A, Wiestler OD, Pietsch T. Analysis of the TSC2 gene in human medulloblastoma. Acta Neuropathol 2001; 102:380-4.
64		X		G	29	Dahmen RP, Koch A, Denkhaus D, Tonn JC, Sörensen N, Berthold F, Behrens J, Birchmeier W, Wiestler OD, Pietsch T. Deletions of AXIN1, a component of the WNT/wingless pathway, in sporadic medulloblastomas. Cancer Res 2001; 61:7039-43.
65		X		H	1	Bader P, Stoll K, Huber S, Geiselhart A, Handgretinger R, Niemeyer C, Einsele H, Schlegel PG, Niethammer D, Beck J, Klingebiel T: Characterization of line-age-specific chimaerism in patients with acute leukaemia and myelodysplastic syndrome after allogeneic stem cell transplantation before and after relapse. Br J Haematol 108:761, 2000
66				H	2	Borgmann A, Baldy C, von Stackelberg A, Beyermann B, Fichtner I, Nurnberg P, Henze G: Childhood all blasts retain phenotypic and genotypic characteristics upon long-term serial passage in NOD/SCID mice. Pediatr Hematol Oncol 17:635, 2000
67		X		H	3	Bornhauser M, Theuser C, Soucek S, Holig K, Klingebiel T, Blau W, Fauser A, Runde V, Schwinger W, Rutt C, Ehninger G: Allogeneic transplantation of G-CSF mobilized peripheral blood stem cells from unrelated donors: a retrospective analysis. Haematologica 85:839, 2000
68		X		H	4	Burdach S, van Kaick B, Laws HJ, Ahrens S, Haase R, Korholz D, Pape H, Dunst J, Kahn T, Willers R, Engel B, Dirksen U, Kramm C, Nurnberger W, Heyll A, Ladenstein R, Gadner H, Jurgens H, Goebel U: Allogeneic and autologous stem-cell transplantation in advanced Ewing tumors. An update after long-term follow-up from two centers of the European Intergroup study EICESS. Stem-Cell Trans-plant Programs at Dusseldorf University Medical Center, Germany and St. Anna Kinderspital, Vienna, Austria. Ann Oncol 11:1451, 2000
69			X	H	5	Burdach S, Baersch G, Hansen G: Immunogenetherapy with IL-2 or IL-7 trans-fected Ewing tumor cells in NOD/SCID mice. Med Ped Onc 37(3):178 2001
70			X	H	6	Deeg HJ, Amylon ID, Harris RE, Collins R, Beatty PG, Feig S, Ramsay N, Territo M, Khan SP, Pamphilon D, Leis JF, Burdach S, Anasetti C, Hackman R, Storer B, Mueller B: Marrow transplants from unrelated donors for patients with aplastic anemia: minimum effective dose of total body irradiation. Biol Blood Marrow Transplant 7:208, 2001
71			X	H	7	Felzmann T, Buchberger M, Jechlinger M, Kircheis R, Wagner E, Gadner H: Xenogenization by tetanus toxoid loading into lymphoblastoid cell lines and pri-mary human tumor cells mediated by polycations and liposomes. Cancer Lett 161:241, 2000
72			X	H	8	Felzmann T, Buchberger M, Lehner M, Printz D, Kircheis R, Wagner E, Gadner H, Holter W: Functional maturation of dendritic cells by exposure to CD40L trans-genic tumor cells, fibroblasts or keratinocytes. Cancer Lett 168:145, 2001
73			X	H	9	Fisch P, Moris A, Rammensee HG, Handgretinger R: Inhibitory MHC class I receptors on gammadelta T cells in tumour immunity and autoimmunity. Immunol Today 21:187, 2000
74				H	10	Hattenhorst U, Glynne R, Murray R, Burdach S: Differential gene expression analysis in pediatric c-ALL versus normal pre-B-cells and bone marrow DNA-microarrays. Blood 96(11):107a, 2000
75			X	H	11	Heinsohn S, Scholz RB, Weber B, Wittenstein B, Werner M, Delling G, Kempf-Bielack B, Setlak P, Bielack S, Kabisch H: SV40 sequences in human osteosar-coma of German origin. Anticancer Res 20:4539, 2000
76				H	12	Khan J, Wei JS, Ringner M, Saal LH, Ladanyi M, Westermann F, Berthold F, Schwab M, Antonescu CR, Peterson C, Meltzer PS: Classification and diagnostic prediction of cancers using gene expression profiling and artificial neural net-works. Nat Med 7:673, 2001
77				H	13	Kroger N, Zabelina T, Kruger W, Renges H, Stute N, Durken M, Graf von Finkenstein F, Erttmann R, Kabisch H, Schafhausen P, Jaburg N, Loliger C, Zander AR: Anti-thymocyte-globulin as part of the preparative regimen prevents graft failure and severe graft versus host disease (GvHD) in allogeneic stem cell transplanta-tion from unrelated donors. Ann Hematol 80:209, 2001
78				H	14	Kurre P, Burdach S: A potential role for leukemia inhibitory factor in the increased clonogenicity of human fetal progenitor cells. Blood 96:1199, 2000

#	a)	b)	c)	P	#P	Reference
79				H	15	Packer RJ, Raffel C, Villablanca JG, Tonn JC, Burdach SE, Burger K, LaFond D, McComb JG, Cogen PH, Vezina G, Kapcala LP: Treatment of progressive or recurrent pediatric malignant supratentorial brain tumors with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration. J Neurosurg 92:249, 2000
80				H	16	Ottinger HD, Muller C, Schmitz N, Kubanek B, Arnold R, Ebell W, Eberhard HP, Ehninger G, Fronz U, Goldmann S, Grosse-Wilde H, Havers W, Klingebiel T, Kolb HJ, Seeber S, Schaefer UW, Baldomero H, Gratwohl A: Transplant activities in Germany in 1998--a survey facilitated by the National Registry for Hemopoietic Stem Cell Transplantation. Ann Hematol 79:437, 2000Schilbach KE, Geiselhart A, Wessels JT, Niethammer D, Handgretinger R: Human gammadelta T lympho-cytes exert natural and IL-2-induced cytotoxicity to neuroblastoma cells. J Immu-nother 23:536, 2000
81			X	H	17	Packer RJ, Raffel C, Villablanca JG, Tonn JC, Burdach SE, Burger K, LaFond D, McComb JG, Cogen PH, Vezina G, Kapcala LP: Treatment of progressive or recurrent pediatric malignant supratentorial brain tumors with herpes simplex virus thymidine kinase gene vector-producer cells followed by intravenous ganciclovir administration. J Neurosurg 92:249, 2000Schilbach K, Geiselhart A, Handgret-inger R: Induction of proliferation and augmented cytotoxicity of gammadelta T lymphocytes by bisphosphonate clodronate. Blood 97:2917, 2001
82			X	H	18	Peters C, Minkov M, Gadner H, Klingebiel T, Vossen J, Locatelli F, Cornish J, Ortega J, Bekasi A, Souillet G, Stary J, Niethammer D: Statement of current ma-jority practices in graft-versus-host disease prophylaxis and treatment in children. Bone Marrow Transplant 26:405, 2000Schlegel PG, Eyrich M, Bader P, Handgretinger R, Lang P, Niethammer D, Klingebiel T: OKT-3-based recondition-ing regimen for early graft failure in HLA-non-identical stem cell transplants. Br J Haematol 111:668, 2000
83				H	19	Rischewski J, Bismarck P, Kabisch H, Janka-Schaub G, Obser T, Schneppen-heim R: The common deletion 657del5 in the Nibrin gene is not a major risk fac-tor for B or T cell non-Hodgkin lymphoma in a pediatric population. Leukemia 14:1528, 2000Schwinger W, Urban C, Lackner H, Kerbl R, Benesch M, Dorn-busch HJ, Sovinz P, Schauenstein K, Schumm M, Handgretinger R: Unrelated peripheral blood stem cell transplantation with 'megadoses' of purified CD34+ cells in three children with refractory severe aplastic anemia. Bone Marrow Transplant 25:513, 2000
84		X		I	1	Marx M, Beck JD, Grabenbauer GG, Dörr HG. Spontaneous nocturnal growth hormone secretion in children after medulloblastoma therapy. Med Pediatr Oncol 36:494
Wd hlg.		X		I A	2	Langer T, Henze G, Beck JD. Basic methods and the developing structure of a late effects surveillance system (LESS) in the long-term follow-up of pediatric cancer patients in Germany. For the German Late Effects Study Group in the German Society Pediatric Oncology and Hematology (GPOH). Med Pediatr Oncol;34:348-51, 2000
85		X		I	3	Langer T, Martus P, Ottensmeier H, Hertzberg H, Beck JD, Meier W. CNS late-effects after ALL-therapy in childhood Part III: Neuropsychological performance in long-term survivors of childhood ALL. Impairments of distractibility, attention and memory and its interferences to CNS morphology. Med Pediatr Oncol. In Press
86				K	2	Kaatsch P, Rickert CH, Kühl J, Schüz J, Michaelis J. Population-based epidemiological data on brain tumors in German children. Cancer 92: 3155-3164, 2001.
Wd hlg.	X	X		K A	1	Löning L., Zimmermann M., Reiter A., Kaatsch P., Henze G., Riehm H., Schrappe M. Secondary neoplasms subsequent to Berlin-Frankfurt-Münster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. Blood 95: 2770-2775, 2000.

A.2 b) Patents applied for within the network

Title	Prospective Patent Holder	Medical Research Network Project	Implications and planned usage	Patent Status
Tumor Box	F. Berthold	G – Embryonal Tumors	General use for safe transport of frozen and non-frozen fresh tissue samples.	Application submitted on 25.06.2001, Application number A2 10131828.6
Method of detecting release of substances from cell organells by means statuteof flow cytometry	K.-M. Debatin	D – Apoptosis and Drug Resistence		Applications submitted on 13.11.2001, (1) US Application number US-09-987,206 (2) German Application Number 10155518.0

Gesellschaft für Pädiatrische Onkologie und Hämatologie

Statut des Aufsichtsrates
für die Pädiatrische Tumorgewebebank "Embryonale Tumoren"

Zweck

Ziel der Pädiatrischen Tumorgewebebank für embryonalen Tumoren ist es, Tumorgewebe in hoher Qualität zu sammeln, zu lagern und für Forschungsprojekte zur Verfügung zu stellen. Dadurch sollen besonders biologische, immunologische und molekulargenetische Erkenntnisse zur Verbesserung des Krankheitsverständnisses, der Diagnostik und der Behandlungsmöglichkeiten gewonnen werden.

Rahmen

Die dezentralen Tumorbanken werden im Rahmen des Kompetenznetzes Pädiatrische Onkologie und Hämatologie Teilprojekt G "Klinische Relevanz molekularbiologischer Marker bei embryonalen Tumoren" etabliert und gefördert.

Derzeitige Standorte:

Neuroblastom, seltene Tumoren:	Universitätskinderklinik, Köln
Nephroblastom:	Institut für physiologische Chemie der Universität Würzburg
Hepatoblastom, Hirntumoren:	Institut für Neuropathologie der Universität, Bonn

Verteilung des Tumorgewebes

1. Automatische Verteilung:

   Gewebeproben für patientenrelevante Untersuchungen im Rahmen laufender Therapiestudien werden automatisch nach vorgegebenem Zeittakt (z. B. 1x /Woche) an die kooperierenden Labors weitergegeben bzw. von den sammelnden Einrichtungen selbst bearbeitet. Die einsendenden Kliniken können auf dem Einsendeschein Prioritäten des Labors festlegen.

Einrichtungen mit automatischer Belieferung sind z. Zt.

Neuroblastom:

DKFZ Heidelberg (Prof. Schwab)
Universitätskinderklinik Marburg (PD Christiansen)
Universitätskinderklinik Köln (Prof. Berthold)

Hepatoblastom:

Institut für Neuropathologie der Universität Bonn (Prof. Wiestler)

Hirntumoren:

Institut für Neuropathologie der Universität Bonn (PD Pietsch)
Universitätskinderklinik Mannheim (PD Scheurlen)

Nephroblastom:

Institut für physiologische Chemie Universität Würzburg (Prof. Gessler)

Der Aufsichtsrat legt die Institutionen mit automatischer Zusendung alle zwei Jahre fest.

2. Verteilung auf Antrag:

Anträge auf Tumorgewebe werden an die zuständige Tumorbank gerichtet und mit einem Vermerk der zuständigen Tumorbank über die Verfügbarkeit des Materials an den Aufsichtsrat weitergeleitet.

Der Aufsichtsrat bewertet die Anträge, bestimmt über Ablehnung oder Bewilligung und legt Prioritäten fest.

Der jeweilige Studienleiter sollte einen Kommentar zu den beantragten Projekten bzw. Material abgeben, er hat jedoch kein Entscheidungsrecht.

Vorgegebene allgemeine Prioritäten sind:

1. Priorität

Wissenschaftlich begutachtete Forscher mit bewilligter Förderung

2. Priorität

neue Forscher oder Forscher bei der Entwicklung neuer Forschungsgebiete

3. Priorität

andere Forscher.

4. Priorität

Anträge von Forschern aus dem Ausland können im Rahmen von Kooperationen mit deutschen Gruppen gestellt werden.

Die Forscher, die Material bzw. Tumorproben erhalten haben, sollen einen Ergebnisbericht über das Projekt verfassen.

Zusammensetzung und Bestellung des Aufsichtsrates

mindestens 5, maximal 7 Mitglieder

davon a) 2-3 pädiatrische Onkologen mit Interesse an experimenteller Forschung

b) 2-3 Grundlagenforscher mit Interesse an pädiatrisch-onkologischer Forschung

c) 1 Tumorbankbetreiber

Derzeitige Vorschläge für

a) Prof. Treuner, Stuttgart
Prof. Mittler, Magdeburg
PD Schweigerer, Essen

b) Prof. Schmidt, Mannheim
Prof. Bartram, Heidelberg
Prof. Lichter, Heidelberg

c) Prof. Berthold, Köln

Die Mitglieder des Aufsichtsrates werden für drei Jahre vom GPOH-Vorstand bestellt. Jeweils 40-50% des Aufsichtsrates werden nach Abschluß einer Wahlperiode durch neue Mitglieder ersetzt. Welche Mitglieder des Aufsichtsrates nach der ersten Wahlperiode ausscheiden, wird durch das Losverfahren bestimmt.

Vorgaben für die Arbeit des Aufsichtsrates

- Vergabe des Tumorgewebes nach Kriterien der Wissenschaftlichkeit und der klinischen Relevanz
- Entscheidungen je nach Bedarf, mindestens aber 2 x jährlich
- Koordination der Arbeit des Aufsichtsrates durch einen Tumorbankbetreiber
- Der Aufsichtsrat ist rechenschaftspflichtig gegenüber der Leitgruppe "Kompetenznetz Pädiatrische Onkologie und Hämatologie" und dem GPOH-Vorstand

Änderungen des Statuts werden vom GPOH-Vorstand beschlossen.

Berlin, den .....

GPOH-Vorsitzender

B.4 c), C.9 c) Clinical Trials of the Society of Pediatric Oncology and Hematology e.V. (GPOH)

The following table lists co-operative multicentric clinical trials which are conducted with the approval of the GPOH, were initiated by the investigators, are funded completely independent from industry, succeeded to include almost all eligible patients suffering from the disease entity listed, provide comprehensive medical counselling, and constitute the state-of-the-art of diagnosis and therapy ("Therapieoptimierungsstudie").

These trials are not financially supported by the competence network, but are listed here to explain the existing structures of medical quality assurance.

#	Short Title	Disease Entity	Principle Investigator	City of Trial Office
1	SIOP 93-01/GPOH	Nephroblastoms (Wilm's-Tumor)	Prof. Dr. Graf	Homburg/Saar
2	COSS 96	Osteosarcoma	Prof. Dr. Bielack	Münster
3	EURO-E.W.I.N.G. - 99	Ewing tumur	Prof. Dr. Jürgens	Münster
4	CWS-96	Soft tissue sarcoma	Prof. Dr. Treuner	Stuttgart
5	HB 94	Hepatoblastoma	Prof. Dr. von Schweinitz	Basel
6	SIOP CNS GCT 96	Intracranial germ cell tumors	Prof. Dr. Göbel Dr. Calaminus	Düsseldorf
7	MAKEI 96	Malignant Germ cell tumors	Prof. Dr. Göbel Dr .Calaminus	Düsseldorf
8	NB 97	Neuroblastoma	Prof. Dr. Berthold	Köln
9	HIT 2000	Primitive neuro ectodermal tumors of the CNS and Ependymomas	PD Dr. Kühl	Würzburg
10	HIT-ENDO	Kraniopharyngeoma	PD Dr. Müller	Oldenburg
11	HIT-GBM:	Glioblastoma	Prof. Dr. Wolff	Regensburg
12	HIT-LGG	Low grade glioma	Dr. Gnekow	Augsburg
13	GPOH HD-95	Morbus Hodgkin	N/A since 2002	
14	AML-BFM 98	Acute myeloblastic leukemia	Prof. Dr. Creutzig	Münster
15	ALL-BFM 2000	Acute lymphoblastic leuekemia	Prof. Dr. Schrappe	Hannover
16	COALL-06-97	Acute lymphoblastic leuekemia	Prof. Dr. Janka-Schaub	Hamburg
17	NHL-BFM 95	Non-Hodgkin Lymphome	Prof. Dr. Reiter	Gießen
18	ALL-REZ BFM 96	Acute lymphoblastic leukemia - Relapse	Prof. Dr. Henze	Berlin
19	LCH-II	Langerhans cell histiocytosis	Prof. Dr. Gadner	Wien
20	CML-päd 95/96	Chronic myeloblastic leukemia	PD Dr. Suttorp	Dresden
21	EWOG-MDS 98	Myelodysplastic Syndrome	Prof. Dr. Niemeyer	Freiburg
22	MET 97	Malignant endocrine tumors	Prof. Dr. Bucsky	Lübeck
23	SAA 94	Severe aplastic anemia	Dr. Führer	München
24	Carcinoma of the nasopharynx	Carcinoma of the nasopharynx	Dr. Mertens	Aachen
				Sum

The total annual incidence of the diseases listed is approximately 1800, according to the German Children's Cancer Registry 2000. The relative frequency of clinical trial patients among all registered patients is 92%.

There are more clinical trials conducted in pediatric oncology and hematology. These address special scientific diagnostic and therapeutic questions and thus include only subsets of patients.

Kompetenznetz Pädiatrische Onkologie

Merkmale des Basisdatensatzes der GPOH

Version 2.0

Stand: 02/2002

Hinweise zur Verwendung dieses Dokuments

Dieses Dokument enthält die Auflistung der Merkmale des Basisdatensatzes der GPOH. Datenbankrelevant sind der angegebene Datentyp, die Länge des entsprechenden Datenfeldes und die Codeziffern zur Verschlüsselung. Die Tabellenanordnung stellt jedoch keine Abbildung eines Datenbankschemas dar.

Kursiv gedruckte Begriffe sind im Glossar definiert.

Erklärung der Spalteninhalte

Kontext(e):	In der Spalte "Kontext" stehen ein oder mehrere Kontexte. Mehrere Kontexte sind durch Spiegelstriche getrennt. Unter "Kontext" wird ein Gliederungsbereich auf einem Erhebungsformular verstanden. Inhaltlich zusammengehörige Merkmale stehen in einem Kontext. Mehrere durch Spiegelstriche getrennte Kontexte bilden verschachtelte Kontexte (eine Kontexthierarchie), wobei ein Kontext den nachfolgenden Kontext enthält. Um eine gute Übersichtlichkeit zu erreichen, wurde hier nicht die vollständige Kontexthierarchie widergegeben.
Merkmalsart:	Die Spalte "Merkmalsart" enthält die Bezeichnung des Merkmals auf einem Erhebungsformular. Zusammen mit der Kontexthierarchie, in der das Merkmal steht, wird der Inhalt des Merkmals eindeutig.
Typ:	Datentyp und Feldlänge Datentypen: A (): alphanumerisch (Anzahl Zeichen) D (): Datum (Anzahl Zeichen) I (): numerisch Integer (Anzahl Ziffern) R (): numerisch Real (Anzahl Vorkommastellen, Nachkommastellen)
Verschlüsselung/Optionen:	Verschlüsselung (Codierung) der auswählbaren Optionen bei Optionsmerkmalen. Bei Schlüsseln mit vielen Optionsausprägungen dient der unterstrichene Schlüsselname als Verweis auf die Verschlüsselungstabellen. In der Regel kann immer nur eine Option gewählt werden, es sei denn, der Zusatz "(mehrfach)" zeigt an, dass beliebig viele Optionen gewählt werden können. Abkürzungen: k.A.: keine Angabe n.s./n.e.: nicht sinnvoll/nicht erhebbar
Datumsformat/Einheit:	Genauigkeit des Datums oder Einheit. Datumsformate: TT: Tag, 2stellig MM: Monat, 2stellig JJJJ: Jahr, 4stellig ss Stunde, 2stellig mm Minute, 2stellig
lfd. Nr.	Nummerierung der Merkmale in diesem Dokument.

Gliederung

1 Stammdaten des Patienten

1.1 Angaben zur Person

Kontext(e)	Merkmalsart	Typ	Verschlüsselung/Optionen/Datumsformat/Einheit	lfd. Nr.
Stammdaten der Person	Name	A 50		1
	Vorname	A 50		2
	Geburtsname	A 50		3
	Geschlecht	I 1	-1 = k.A. 1 = männlich 2 = weiblich	4
	Geburtsdatum	D 8	TTMMJJJJ	5
	Geburtsland	I 2	Geburtsland	6
	Geburtsort	A 50		243

1.1.1 Identifikationszahlen

Kontext(e)	Merkmalsart	Typ	Verschlüsselung/Optionen/Datumsformat/Einheit	lfd. Nr.
Gültiger PID der GPOH	ID	A 8		7
Aktuelles Primärmalignom – Gültige Identifikationszahl vom *IMBEI*	siehe Kapitel 2, Merkmal 33			
Aktuelles Sekundärmalignom – Gültige Identifikationszahl vom *IMBEI*	siehe Kapitel 5, Merkmal 215			
Identifikationszahl von der Klink	siehe Kapitel 2.2, Merkmal 42			
Identifikationszahl von der *Studie*	siehe Kapitel 2.8.3, Merkmal 126			

1.2 Gültige Privatadresse

Kontext(e)	Merkmalsart	Typ	Verschlüsselung/Optionen/Datumsformat/Einheit	lfd. Nr.
Gültige Privatadresse	Straße	A 50		8
	PLZ	A 10		9
	Ort	A 50		10
	Land	A 50		11
Telefonanschluss Hinweis: Es können beliebig viele Nummern erfasst werden.	Nummer	A 25		12
	Art	I 1	-1 = k.A. 1 = Festnetz 2 = Fax 3 = Mobil	244

Begriffsordnungssystem

Synonyme Bezeichn.: Begriffssystem
Unterbegriffe: ICD-10, Version 2.0, ICD-O-3 international, OPS-301, Version 2.1, Toxizitätskriterien der GPOH, Version 2.0
Definition: Als Begriffsordnungssystem werden im Basisdatensatz Klassifikationen, Nomenklaturen und sonstige Verschlüsselungssysteme bezeichnet, die bestimmten Begriffen oder Klassen Codierungen (oder Scores) zuweisen.

ICD-10, Version 2.0

Synonyme Bezeichn.: Internationale Klassifikation der Krankheiten, 10. Revision, Version 2.0, ICD-10-SGB-V, Version 2.0
Überbegriffe: Begriffsordnungssystem
Definition: Internationale Klassifikation der Krankheiten, 10. Revision in der deutschen SGB-V-Fassung, Version 2.0.

ICD-O-3 international

Synonyme Bezeichn.: International Classification of Diseases for Oncology, third edition
Überbegriffe: Begriffsordnungssystem
Definition: Mit "ICD-O-3 international" wird im Basisdatensatz die englischsprachige Originalfassung der Internationalen Klassifikation der Krankheiten für die Onkologie in der 3. Auflage bezeichnet. Die deutsche Ausgabe (ICD-O-DA) soll im Basisdatensatz nicht verwendet werden.

OPS-301, Version 2.1

Synonyme Bezeichn.: Operationenschlüssel nach Paragraph 301 SGB V
Überbegriffe: Begriffsordnungssystem
Definition: Operationenschlüssel nach Paragraph 301 SGB V, erstellt vom Deutschen Institut für Medizinische Dokumentation und Information (DIMDI) in der Version 2.0.

Toxizitätskriterien der GPOH, Version 2.0

Synonyme Bezeichn.: Toxizitätsscores der GPOH, Version 2.0, Toxizitätsskalen der GPOH, Version 2.0
Überbegriffe: Begriffsordnungssystem
Definition: Die Toxizitätskriterien der GPOH, Version 2.0 umfassen die Toxizitässcores (einschliesslich der Skala für den Allgemeinzustand), die im Basisdatensatz, Version 2.0 (Februar 2002), enthalten sind. Diese Toxizitätskriterien sind an die Common Toxicity Criteria (CTC), Version 2.0 des NCI angelehnt, jedoch nicht immer mit Ihnen identisch.

Bereitschaft der Eltern bzw. des Patienten zur Studienteilnahme

Synonyme Bezeichn.: Einverständnis der Eltern bzw. des Patienten zur Studienteilnahme, Einwilligung der Eltern bzw. des Patienten zur Studienteilnahme
Definition: Die Bereitschaft der Eltern bzw. des Patienten zur Studienteilnahme ist gegeben, wenn die Eltern, bzw., bei ausreichender Einsichtsfähigkeit, der Patient selbst ihr/sein schriftliches Einverständnis zur Studienteilnahme gegeben haben/hat.

Toxizitätskriterien der GPOH, Version 2.0

(153)

Angelehnt an die Common Toxicity Criteria (CTC), Version 2.0 des NCI

Abkürzungen:
N: Altersnorm
EF: ejection fraction, Auswurffraktion
SF-LV: shortening fraction, linksventrikuläre Verkürzungsfraktion

Allgemeinzustand (modifizierter Karnofski-Index)

(75, 152)

Code	Klartext
-1	k.A.
1	Normale Aktivität, keine Beeinträchtigung
2	Geringe Beeinträchtigung der Aktivität, jedoch keine zusätzliche Hilfe erforderlich
3	Altersentsprechende Aktivität stark eingeschränkt (z.B. kein regelmäßiger Kindergarten- bzw. Schulbesuch möglich)
4	Bettlägerig, pflegebedürftig
5	Intensive Behandlung notwendig, schwerstkrank, moribund

Toxizitätsscores Gastrointestinaltrakt

Grad	0	1	2	3	4
Übelkeit	keine	ausreichende Nahrungsaufnahme	kann essen, aber deutl. verminderte Aufnahme	praktisch keine Nahrungsaufnahme	TPN erforderlich
Erbrechen [Anzahl Episoden in 24 h]	0	1	2 – 5	6 – 10	> 10 oder TPN erforderlich
Stomatitis	keine	schmerzlose Ulzera, Erythem	schmerzendes Erythem oder Ulzerationen, kann aber essen	schmerzendes Erythem oder Ulzerationen, kann nichts mehr essen	TPN wegen Stomatitis erforderlich
Diarrhoe [Stuhlfrequenz/Tag]	keine	2 – 3	4 – 6 oder nächtl. Stuhl oder leichte Bauchkrämpfe	7 – 9 oder Inkontinenz oder starke Bauchkrämpfe	>= 10 oder blutiger Durchfall oder TPN erforderlich

Toxizitätsscores Hämatologie

Grad	0	1	2	3	4
Hämoglobin [g/dl]	Altersnorm (N)	10.0 – < N	8.0 – < 10.0	6.5 – < 8.0	< 6.5
Leukozyten [g/l]	>= 4.0	3.0 – < 4.0	2.0 – < 3.0	1.0 – < 2.0	< 1.0
Granulozyten [g/l]	>= 2.0	1.5 – < 2.0	1.0 – < 1.5	0.5 – < 1.0	< 0.5
Thrombozyten [g/l]	>= 100	75 – < 100	50 – < 75	10 – < 50	< 10

Toxizitätsscores Haut

Grad	0	1	2	3	4
Hautveränderungen	keine	Erythem	trockene Desquamation, Vaskulitis, Pruritus	feuchte Desquamationen, Ulzerationen	Exfoliative Dermatitis, Nekrosen

Toxizitätsscores Herz

Grad	0	1	2	3	4
Arrhythmie	keine	Asympt., keine Therapie	rekurr./persist. keine Therapie	Therapie erforderlich	Hypotension, ventr. Arrhyt., Defibrillation
Herzfunktion	Normal	asymptomat. EF↓ (Ruhe) >= 10% aber < 20% vom Ausgangswert	asymptomat. aber EF↓ (Ruhe) unter dem unteren Normwert für EF (Arbeit) oder EF↓ >= 20% vom Ausgangswert	Milde CHF, therapeutisch kompensiert	Schwere / refraktäre CHF oder Notwendigkeit der Intubation
Echocardio: LV-SF (%)	>= 30	>= 24 – < 30	>= 20 – < 24	> 15 – < 20	<= 15

Toxizitätsscores Infektion

Grad	0	1	2	3	4
Infektion	keine	leicht	mäßig; ohne Erregernachweis; i.v.-Antibiotika	schwer; mit Erreger-nachweis; i.v.-ATB	lebensbedrohlich, mit Hypotonie
Fieber [°C]	< 38	38 – 39	> 39 – 40	> 40 für < 24 Std.	> 40 für >= 24 Std.

Toxizitätsscores Leber

Grad	0	1	2	3	4
Bilirubin	Altersnorm (N)	> N – 1.5 x N	> 1.5 – 3.0 x N	> 3.0 – 10.0 x N	> 10.0 x N
S-GOT/S-GPT	Altersnorm (N)	> N – 2.5 x N	> 2.5 – 5.0 x N	> 5.0 – 20.0 x N	> 20 x N

Toxizitätsscores Nieren

Grad	0	1	2	3	4
Creatinin	Altersnorm (N)	> N – 1.5 x N	> 1.5 – 3.0 x N	> 3.0 – 6.0 x N	> 6.0 x N
Proteinurie [g/l]	keine	< 3	3 – 10.0	> 10.0	Nephrot. Syndrom
Hämaturie	keine	mikroskopisch	makroskop. ohne Koagel	makroskop. mit Koagel	Transfusion erforderlich
Creatinin-Clearence [ml/Min./1,73m²]	>= 90	60 – 89	40 – 59	20 – 39	<= 19

Toxizitätsscores Neurologie

Grad	0	1	2	3	4
Zentrale Neurotoxizität	keine	vorübergehende Lethargie	Somnolenz < 50% der Zeit; mäßige Desorientierung	Somnolenz ≥ 50% der Zeit, erhebl. Desorientierung, Halluzination.	Koma, Krämpfe
Periphere Neurotoxizität	keine	Parästhesien	schwere Parästhesien und/oder milde Schwäche	unerträgliche Parästhesien, deutl. motorische Verluste	Paralyse

C.7 Matrix of cooperation within the network and with external partners

Category	Project Name	A	B/1	B/2	C	D	E	F	G	H	I	K	T
This network's projects	A – coord./man. group		X	X	X	X	X	X	X	X	X		X
	B/1 – "DOSPO"			X	X				X			X	
	B/2 – IT-Security				X				X			X	X
	C – Telemedicine												X
	D – Molec. Apotsosis									X			
	E – Preleukemic dis.							X	X			X	
	F – MRD												
	G – Embryon. tumors									X			
	H – Imm./gene ther.												
	I – QoL, vert. netwk.												
	K – Sec. malig. neopl.												
	T – Tele palliat. ped.												
		A	**B/1**	**B/2**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**K**	**T**
Central Institutions	KKR		X		X		X		X				
	KTR								X				
	PRST	X				X	X					X	
	ALL-Bank					X		X	X				
	Reference labs for immunophenotyping					X	X	X	X				
	Clinical Pharmacology, PedNet Modul	X								X			
	LESS								X		X		
Hospitals	(participating in trials)	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Trials	ALL-BFM		X	X		X	X	X			X		
	CoALL		X			X	X	X			X		
	ALL-REZ		X				X	X		X			
	AML		X			X	X	X					
	NHL							X					
	NB (Neuroblastoma)								X				
	WT (Wilm's tumor)		X		X				X				
	HIT MED				X				X		X		
	EURO-E.W.I.N.G.				X								
	CWS												
	COSS												
	MAKEI												
	HB								X				
	SAA/FA						X					X	
Other	DKKS (DLFH)	2											X
	Deutsche Krebshilfe								4				
	Telematics P. (TMF)	1		3	X				X				
	Other competence networks	X		X			X	X					
	Research groups								5				

Legend

X: Cooperation without separate/special funding.

1: BMBF-grant “Telemedizinische Infrastuktur (TMI)” (cooperation with the TMF and three other networks)

2: “Publikation strukturierter Dokumente zur Patienten- und Angehörigeninformation bei onkologischen und hämatologischen Erkrankungen” (planned DKKS/KPOH cooperative project)

3: BMBF-grants „Einrichtung eines Pseudonymisierungsdienstes“ and „Sicherheitsinfrastruktur (PKI)“

4: Deutsche Krebshilfe grant "SAGE analysis in neuroblastoma"

5: Five DFG-grants: "CGH in Wilm's tumors", "LOH in Wilm's tumors", "Components of the patched signalling pathway", "Molecular genetics of ptc+/- mouse tumors", "IGF in hepatoblastoma" (cooperations with the University of Bonn)

C.9 b) List of clinical multi-center studies performed in the network

##	#	Short Title	Project classification[+]	Network members involved	New substantial cooperations with	New study groups
1	D	Drug Resistance	Basic science study accompanying CoALL and ALL-BFM studies[+]	Ludwig Janka-Schaub	MDC Berlin, AG Experimental Pharmacology, I. Fichtner	–
2	E	Pre-Leukemic Bone Marrow Disorders	Basic science study accompanying SAA, SCN, FA, AML studies[+]	Welte Bender-Götze Ebell Harbott Schneppenheim Baumann Schmitt-Gräf Kaatsch Creutzig	–	"Congenital bone marrow failure disorders" "Acquired aplastic anemia" (subprojects of the competence network program "Rare diseases")
3	F	Minimal residual disease	Applied biomedical science study accompanying CoALL, AML, ALL-REZ BFM, ALL-BFM and NHL-BFM studies[+]	Kabisch Reinhardt Seeger Reiter Schrappe Bartram Griesinger	European Project for standardization of RQ-PCR EuropeanMRD task force project	European Group for MRD in ALL by phenotyping
4	G	Embryonal tumors	Basic science and applied biomedical science study accompanying NB, HB, HIT MED and Nephroblastoma studies[+]	Berthold Christiansen	Multi-center trial MAKEI[+] Multi-center trial CWS[+]	–
5	I [1]	Late Effects and Quality of Life	Clinical study accompanying ALL BFM and HIT MED studies+	Kühl Ottensmeier Beck Ravens-Sieberer Creutzig	APRO (Arbeitsgemeinschaft Pädiatrische Radioonkologie)	Prospective evaluation of neuropsychology and QoL in craniopharyngeoma Cross-sectional evaluation of QoL in AML patients in Gemany and Spain

* Newly initiated since the network exists.

\+ As explained in the following table.

C.10 International Partners performing together with network projects

#	Subproject	International Partner(s)	City, Country
A	Education program pediatric oncology and hematology	JR Mann, SIOPE/ESPHI	Birmingham, UK
E	Classifications of myelodys-plastic syndromes	H. Hasle, G. Kerndrup, Skejby Hospital J.M. Bennett, University of Rochester J. Chessells, Camelia Botnar Laboratories D. Head, Department of Pathology, Vanderbilt University	Aarhus, Denmark Rochester, NY, USA London, Great Britain Nashville, USA
F	MRD in AML	M. Dworzak, St. Anna Kinderspital O. Hrusak, Charles University	Wien, Austria Prag, Czech Republic
G	Embryonal and rare tumors	Institute of Cancer Research European Wilm's tumors trial University of Queensland National Cancer Institute Karolinska Institute National Cancer Institute	Sutton, UK Amsterdam, NL Australia Bethesda, USA Stockholm, Sweden Bethesda, USA
I	Late effects Quality of life	Jankovicz, ELTEC group Health act, Dr. Jeanne Landgraf, Boston QoL unit EORTC Brussels Dr. Colin Kennedy, University of Southhampton Prof, Ortega, University of Barcelona Prof. Strömberg, University of Göteborg Dr. Perilongo, University of Padova	Monza, Italy Boston, USA Brussels, Belgium Southhampton, UK Barcelona, Spain Göteborg, Sweden Padova, Italy
T	Exchange on adult palliative care telemedicine	Milano Instituti Tumori	Milano, Italy

Legend:

Project of the competence network Pediatric Oncology and Hematology.

The projects mentioned above involve at least three network partners from different universities.
In the table, only the additional international partners/groups involved are listed.

D.14 Presentations of this network and its projects to the public (sorted by month, meeting, and year)

D.14Presentations of the network

Month	Meeting	Year	Title of presentation	Type of presentation	Scientist (project)
01	Telekom-Workshop "Sicherheitsinfrastruktur"	2000	Kompetenznetz für die Pädiatrische Onkologie und Hämatologie.	Oral Presentation	Pommerening K
03	Annual status meeting of the Society for Pediatric Oncology and Hematology (GPOH)	2000 2001 2002	News and recent advances – status report about the competence network to the society	Oral presentations	Creutzig U
05	Semi-annual scientific meeting of the GPOH	2000 2001 2002	News and recent advances – status report about the competence network to the society	Oral presentations	Henze G, Creutzig U
03	Deutscher Krebskongress (Berlin)	2002	Personal attendance, poster display „Pädiatrische Onkologie und Hämatologie, ‚Ihr Kind hat Krebs.' – diese Nachricht trifft jährlich 2000 Eltern. Aus Angst und Hoffnung wird Heilung – immer mehr."	Exhibition (three days)	Herold R
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2001	Das Kompetenznetz Pädiatrische Onkologie und Hämatologie	Oral presentation	Henze G
10	Science Street Gürzenich köln	2001	Personal attendance, poster display, alternately representation of all medical competence networks	Exhibition (one day)	Herold R
11	Semi-annual scientific meeting of the GPOH	2001	News and recent advances – status report about the competence network to the society	Oral presentation	Henze G, Creutzig U
12	Management-Symposium Darmstadt, Kompetenznetztreffen	2001	Kompetenznetz Pädiatrische Onkologie und Hämatologie	Oral presentation	Creutzig U

Presentation of this network's projects

Month	Meeting	Year	Title of Presentation	Type of Presentation	Scientist (project)
02	4. Kongreß des Tumorzentrums (Freiburg)	2000	Myelodysplastische Syndrome im Kindes- und Jugendalter	Oral presentation	Niemeyer CM
02	Kongress der Gesellschaft für Arbeitswissenschaft	2002	Prozessorientierte Arbeitsorganisation im Krankenhaus	Oral presentation	Dickhoff A, Friesdorf W, Herold R, Henze G et al.
03	Annual Meeting of the European Group for Blood and Marrow Transplantation	2001	Stem cell transplantation for children with Juvenile Myelomonocytic Leukemia (JMML): interim analysis of a multicenter study of the European Working Group of MDS in childhood (EWOG-MDS) and the EBMT	Oral presentation	Niemeyer C et al.
03	Annual Meeting of the European Group for Blood and Marrow Transplantation	2001	Busulfan, cyclophosphamide and melphalan as preparative regimen to allogeneic stem cell transplantation in childhood MDS: results of the second interim analysis of the EBMT/EWOG-MDS study	Oral presentation	Locatelli F, Niemeyer C et al.

Month	Meeting	Year	Title of Presentation	Type of Presentation	Scientist (project)
03	Annual Meeting of the European Group for Blood and Marrow Transplantation	2001	Relapse after allogeneic stem cell transplantation for juvenile myelomonocytic leukemia: are there still options?	Oral presentation	Bierings M, Niemeyer C et al.
03	Deutscher Krebskongress (Berlin)	2000	Sekundäre maligne Neoplasien nach Krebserkrankungen im Kindesalter	Oral presentation	Klein G, Kaatsch P Michaelis J
03	Deutscher Krebskongress (Berlin)	2002	Assistants in Clinical Research and Quality Assurance	Invited oral Presentation	Herold R
03	Deutscher Krebskongress (Berlin)	2002	Minimal residual disease	Oral presentation	HarbottJ
03	Deutscher Krebskongress (Berlin)	2002	Health-related quality of life and the network for follow-up	Oral presentation	Calaminus G
03	Deutscher Krebskongress (Berlin)	2002	Embryonal tumors	Oral presentation	Berthold F
03	Jahrestagung der Deutschen Gesellschaft für Humangenetik (Lübeck)	2000	Discrepancy between cytogenetic findings and the result of a cell-cycle analysis in a patient with Fanconi Anemia, secondary malignancy and clonal disease	Oral presentation	Rischewski J
03	Semi-annual meeting of the network members	2002	Qualifizierung von Kliniken; Qualitätsindikatoren, Möglichkeiten des Auditings von Kliniken; Datenqualität und Möglichkeiten, die Dokumentationsmenge zu reduzieren	Oral presentation	Creutzig U
03	Semi-annual meeting of the network members	2002	Öffentlichkeitsarbeit und Internetportal “kinderkrebsinfo.de”	Oral presentation	Herold R
03	Semi-annual meeting of the network members	2002	Vertikale Vernetzung	Oral presentation	Calaminus G
03	Semi-annual meeting of the network members	2002	Erleichterung/Verbesserung der Studiendokumentation durch Koordination der Aktenführung	Oral presentation	Laupert A
03	Semi-annual meeting of the network members	2002	Telemedizin – Vernetzung vor Ort: praktische Erfahrungen	Oral presentation	Graf N
03	TMF-Workshop	2002	PID-Dienst und PKI im Kompetenznetz POH	Oral presentation	Pommerening K
04	DNA 2000 Symposium (Boston)	2000	Screening strategies for a highly polymorphic gene: DHPLC-analysis of the Fanconi Anemia Group A Gene	Oral presentation	Rischewski J, Schneppenheim R
04	TMF-AG Datenschutz und -sicherheit	2001	"Aufbau einer Sicherheitsinfrastruktur für die TMF" and "PID-Erzeugung (Pseudonymisierungsdienst)"	Oral presentation	Pommerening K
05	2nd International Symposium on Myelodys-plastic Syndromes in Childhood (Funen DK)	2000	Cytogenetic evaluation of children with MDS and juvenile myelomonocytic leukemia (JMML) - Results of the European Working of Childhood MDS (EWOG-MDS)	Oral presentation	Harbott J, Zimmermann M, Niemeyer C et al.
05	2nd International Symposium on Myelodys-plastic Syndromes in Childhood (Funen DK)	2000	Detection of monosomy 7 and trisomy 8 in childhood MDS and JMML by fluorescence in situ hybridization (FISH)	Oral presentation	Pils S, Roitzheim B, Niemeyer C, Harbott J
05	2nd International Symposium on Myelodys-plastic Syndromes in Childhood (Funen DK)	2000	Acquired chromosomal aberrations in children with Down syndrome and myelodysplatic syndrome (MDS) or acute myeloid leukemia (AML)	Oral presentation	Teigler-Schlegel A, Baumann M, Creutzig U, Niemeyer C, Harbott J

Month	Meeting	Year	Title of Presentation	Type of Presentation	Scientist (project)
05	2nd International Symposium on Myelodysplastic Syndromes in Childhood (Funen DK)	2000	Morphological and histopathological features in childhod MD and JMML: Experience of the EWOG-MDS Morphology board	Oral presentation	Baumann I, Niemeyer CM et al.
05	I-BFM (International BFM-Study group)	2002	Presentation of results on MRD (F)	Oral presentation	Harbott J
05	International Symposium on Myelodysplastic Syndromes in Childhood)	2000	Refractory anemia in childhood: a study of the European Working Group of MDS in Childhood (EWOG-MDS)	Oral presentation	Kardos G, Niemeyer C, Zimmermann M et al.
05	International Symposium on Myelodysplastic Syndromes in Childhood)	2000	International prognostic scoring system for childhood MDS and JMML	Oral presentation	Hasle H, Harbott J, Nöllke P, Niemeyer CM et al.
05	International Symposium on Myelodysplastic Syndromes in Childhood)	2001	Primary MDS in childhood: AML-like chemotherapy prior to stem cell transplantation (SCT) does not improve event-free survival	Oral presentation	Niemeyer CM, Locatelli F, Nöllke P
05	International Symposium on Myelodysplastic Syndromes in Childhood)	2001	Juvenile myelomonocytic leukemia (JMML) in the presence of other congenital abnormalities	Oral presentation	Büchner J, Niemeyer CM et al.
05	International Symposium on Myelodysplastic Syndromes in Childhood)	2001	MDS in Childhood and Adolescence: When to treat and how to treat	Oral presentation	Niemeyer C
05	Kinderärztekongreß	2000	Phänotyp-Genotyp-Vergleich einer deutschen Patientin mit Fanconi Anämie (Fanc) der Gruppe C	Oral presentation	Rischewski J, Clausen H, Leber V, Suttorp M, Schnepenheim R
05	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH)	200!	Stammzelltransplantation für myelodysplastische Syndrome (MDS): Risikofaktoren für Rezidiv und toxische Todesfälle	Oral presentation	Niemeyer C, Fischer A, Harbott J, Nöllke P
05	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH)	2000	Die Behandlung von Kindern und Jugendlichen mit myelodysplastischem Syndrom (MDS) – Zwischenbericht zur Therapieoptimierungsstudie EWOG-MDS 98	Oral presentation	Niemeyer C, Rogge T, Fischer A, Nöllke P
05	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH)	2000	Charakterisierung hypoplasticsher Knochenmarkerkrankungen bei Kindern und Jugendlichen	Oral presentation	Baumann I, Harbott J, Führer M, Niemeyer C
05	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH)	2000	Kann eine intensive Chemotherapie vor Stammzelltransplantation (SZT) bei Kindern und Jugendlichen mit myelodysplastischem Syndrom die Heilungsrate verbessern?	Oral presentation	Kontny U, Duffner U, Nöllke P, Niemeyer C
05	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH)	2000	Falsch negative Fanconi-Anämie-Diagnostik bei gleichzeitigem Vorliegen eines MDS	Oral presentation	Rischewski J, von Bismarck P, Janka G, Schindler D, Schneppenheim R
05	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH)	2000	Indikationen zur allogenen Stammzelltransplantation (SZT) bei Kindern und Jugendlichen mit nächtlicher paroxysmaler Hämoglobinurie (PNH)	Oral presentation	Strahm B, Kontny U, Duffner U, Niemeyer C

Month	Meeting	Year	Title of Presentation	Type of Presentation	Scientist (project)
06	5th Annual Meeting of the European Haematology Association (EHA, Birmingham)	2000	Children and adollescents with primary myelodysplastic syndromes (MDS): should they receive intensive chemotherapy prior to stem cell transplantation (SCT)?	Oral presentation	Niemeyer C, Duffner U, Locatelli LF, Zecca M, Rogge T, Fischer A, Nöllke P
06	Jahrestagung der Kind-Philipp-Stiftung für Leukämie-Forschung	2000	Fanconi anemia group G mutations in pediatric patients with myeloid malignancies	Oral presentation	Lever V., Rischewski, J., Niemeyer, C., Schinder, D., Schneppenheim, R
06	Jahrestagung der Kind-Philipp-Stiftung für Leukämie-Forschung	2000	Semiautomatized screening for Fanconi Anemia gene mutations using DHPLC	Oral presentation	Rischewski J, Wierzbinski J., Schneppenheim R
08	Porzer Gespräche "Gesundheitstelematik" IGD/DLR	2000	Datenschutz und IT-Sicherheit der Telematik im Gesundheitswesen	Oral presentation	Pommerening K
08	Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS) and International Congress of the European Federation for Medical Informatics	2000	Integrating Specialized Application Systems into Hospital Information Systems –Obstacles and Factors for Success	Oral presentation	Mludek V, Knaup P, Wiedemann T, Bauer J, Haux R, Kim L, Schilling FH, Selle, B
08	Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS) and International Congress of the European Federation for Medical Informatics	2000	Data Protection and Security Aspects in Medical Research Networks	Oral presentation	Pommerening K
09	TMF-Tagung (BMBF Telematics Platform)	2000	PGP und SSL in den medizinischen Forschungsnetzen	Oral presentation	Pommerening K
09	World Congress on Medical Informatics (Medinfo)	2001	Object-oriented business process analysis of the cooperative soft tissue sarcoma trial of the german society for paediatric oncology and haematology (GPOH)	Oral presentation	Weber R, Knaup P, Knietig R, Haux R, Merzweiler A, Mludek V, Schilling FH, Wiedemann T
09	World Congress on Medical Informatics (Medinfo)	2001	Recording clinical data - from a general set of record items to case report forms (crf) for clinics	Oral presentation	Weber R, Merzweiler A, Knaup P, Ehlerding H, Haux R, Wiedemann T
09	Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS)	2001	Systematische Remodellierung eines bundesweiten Dokumentations- und Therapieplanungssystems mit UML	Poster presentation	Garde S, Knaup P, Baumgarten B, Haux R, Merzweiler A, Weber R
09	Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS)	2001	Ein Pseudonymisierungsdienst für Medizinische Forschungsnetze	Oral presentation	Pommerening K
09	Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS)	2001	A reusable pseudonymization interface for epidemiologic research	Poster presentation	Wagner M

Month	Meeting	Year	Title of Presentation	Type of Presentation	Scientist (project)
09	Jahrestagung der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS)	2001	Aufbau eines Telemedizinnetzwerkes im Rahmen multizentrischer Therapiestudien der pädiatrischen Onkologie	Oral presentation	Ganslandt T, Huf T, Graf N, Prokosch HU, Jürgens H, Paulussen M
09	European Congress of Pathology	2001	Clinical Interoperability: Taking Telepathology to the Next Level	Oral presentation	Ganslandt T, Korsching E, Prokosch HU, Herbst H, Böcker W, Senninger N, Spiegel HU
09	Jahrestagung der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin	2001	Elektronische Erfassung von Diagnosen und Prozeduren in der Pädiatrischen Onkologie und Hämatologie	Oral presentation	Herold R
09	Jahrestagung der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin	2001	Erkennung von Fanconi Anämie Mutationen mittels DHPLC als halbautomatisches Screeningverfahren	Oral presentation	Rischewski J, Wierzbinski J., Schneppenheim R
09	Jahrestagung der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin	2001	Paroxysmale nächtliche Hämoglobinurie (PNH): Krankheitsverlauf und therapeutische Möglichkeiten anhand von zwei Fallbeispielen	Oral presentation	Strahm B, Kontny H U, Duffner U, Niemeyer CM
09	Jahrestagung der Deutschen Gesellschaft für Kinderheilkunde und Jugendmedizin	2001	Inzidenz und Management von Zweitmalignomen	Oral presentation	Niemeyer C
09	Symposium "Telemedizin und Robotik"	2001	Telemedizin und Qualitätssicherung in der Onkologie	Oral presentation	Rube Ch, Graf N
10	World Congress of High Tech Medicine	2000	Data Security and Data Protection in Medical Research Networks	Oral presentation	Pommerening K
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2001	Minimal residual disease	Oral presentation	Harbott J
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2001	Telemedicine communication in the GPOH Pediatric Oncology competence net: Evaluation of expectations and infrastructure	Oral presentation	Paulussen M
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2001	Aufbau eines Wissensservers für die Pädiatrische Onkologie und Hämatologie	Oral presentation	Herold R
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2001	Indications for allogeneic stem cell transplantation (SCT) in two adolescent patient with paroxysmal nocturnal hemoglobinuria (PNH)	Oral presentation	Strahm B, Kontny H U, Duffner U, Niemeyer C M
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2001	Stem cell transplantation (SCT) in children and adolescents with myelodysplastic syndromes (MDS): Impact of prior chemotherapy and karyotype	Oral presentation	Niemeyer CM et al.
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2001	Activation of p21ras in MDS, AML, JMML and other haematopoeitic malignancies measured by a quantitative and non-radioactive method	Oral presentation	Scheele J, Niemeyer C et al.
10	Jahrestagung Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO)	2000	Prospective study on stem cell transplantation (SCT) for children and adolescents with MDS	Oral presentation	Niemeyer C et al.

Month	Meeting	Year	Title of Presentation	Type of Presentation	Scientist (project)
10	Meeting of the International Society of Pediatric Oncology (SIOP)	2000	AML-like chemotherapy prior to Stem cell transplantation does not improve event-free survival in children's and adolescents with MDS	Oral presentation	Niemeyer CM, Locatelli F, Nöllke P
10	Meeting of the International Society of Pediatric Oncology (SIOP)	2001	The Meta-EICESS Protocol For Patients With Primary Multifocal And Early Relapsed Ewing Tumors: Results After 5 Years	Oral presentation	Burdach St
10	Meeting of the International Society of Pediatric Oncology (SIOP)	2001	Immunogene Therapy with IL2 or IL7 transfected Ewing Tumor Cells in NOD/SCID Mice	Oral presentation	Burdach St
10	Meeting of the International Society of Pediatric Oncology (SIOP)	2001	Allogeneic stem cell transplantation for juvenile myelomonocytic leukaemia	Oral presentation	Bierings M, Niemeyer C et al.
11	Telemed 2001	2001	Automatische Korrektur fehlerhafter Patientenzuordnungen im Rahmen von medizinischen Forschungsnetzen	Oral presentation	Pommerening K
11	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH, Berlin)	2000	Versorgung von Kindern und Jugendlichen mit angeborenen Erkrankungen mit Knochenmarkversagen	Oral presentation	Niemeyer C, Ebell W, Welte K
11	Wissenschaftliche Halbjahrestagung der Gesellschaft für Pädiatri-sche Onkologie und Hämatologie (GPOH, Berlin)	2001	Telemedizin im Kompetenznetz Pädiatrische Hämatologie und Onkologie - Ein Zwischenbericht	Poster Presentation	Paulussen M, Graf N, Huf Th, Ganslandt Th
11	Medica (industrial fair)	2001	Interoperabilität: Telepathologie auf dem nächsten Level	Presentation	Ganslandt T, Korsching E, Prokosch HU, Spiegel HU
12	Annual Meeting of the American Society of Hematology (ASH)	2000	Elevated frequency of the mutation 657del5 within the NBS1 gene in childhood acute lymphoblastic leukemia	Oral presentation	Rischewski J et al.
12	Annual Meeting of the American Society of Hematology (ASH)	2000	Evolution of severe congenital neutropenia (CN) to chronic myelomonocytic leukemia (CMML) associated with expression of a truncated G-CSF receptor in leukemic blasts and an activating NRAS mutation	Oral presentation	Germeshausen M et al.
12	Annual Meeting of the American Society of Hematology (ASH)	2000	Development of glomerulonephritis in patients (pts) with severe chronic neutropenia (SCN)	Oral presentation	Boxer L, Welte K, Dale DC et al.
12	Annual Meeting of the American Society of Hematology (ASH)	2000	AML-Type intensive chemotherapy prior to stem cell transplantation (SCT) does not improve survival in children and adolescents with primary myelodysplastic syndromes (MDS)	Oral presentation	Niemeyer C, Duffner U, Bender-Götze C, Dini G, Ebell W et al.
12	Annual Meeting of the American Society of Hematology (ASH)	2001	International Prognostic Scoring System (IPSS) for Childhood Myelodysplastic Syndrome (MDS) and Juvenile Myelomonocytic Leukemia (JMML)	Oral presentation	Hasle H, Niemeyer CM et al.

Month	Meeting	Year	Title of Presentation	Type of Presentation	Scientist (project)
12	Annual Meeting of the American Society of Hematology (ASH)	2001	Allogeneic Stem cell Transplantation in Children with Juvenile Myelomonocytic Leukemia: Results of a Prospective Study of the EWOG-MDS/EBMT Groups	Oral presentation	Locatelli F, Niemeyer C et al.
12	Annual Meeting of the American Society of Hematology (ASH)	2001	The Outcome of Hepatitis-Associated Aplastic Anemia (AA)Treated with Immunosuppressive Therapy (IST) or Bone Marrow Transplantation (BMT) – The Experience of the German/Austrian Pediatric AA Study Group	Oral presentation	Führer M, Rampf U, Niemeyer C, Bender-Götze C
12	Annual Meeting of the American Society of Hematology (ASH)	2001	Clinical outcome in myelokathexis: A report of 6 patients enrolled in the Severe Chronic Neutropenia International Registry	Oral presentation	Bonilla MA, Welte K et al.
12	Annual Meeting of the American Society of Hematology (ASH)	2001	Long term treatment of chronic idiopathic neutropenia in women with G-CSF	Oral presentation	Bolyard AA, Welte K, Dale DC et al.
12	Management-Symposium Darmstadt – Kompetenznetztreffen	2001	Vertikale Vernetzung in der Pädiatrischen Onkologie	Oral presentation	Neubauer M, Calaminus G
12	Management-Symposium Darmstadt – Kompetenznetztreffen	2001	Strategies for the persistance of medical competence networks	Chairing workshop, oral presentation	Herold R

D.15 Media coverage – collection of media reports on this network

Paper end electronic press, radio and TV reports

The following list includes the media reports featuring our competence network.
The press conference took place on 23.11.2001, immediately before the society's semi-annual meeting.
Thirty-three media representatives requested press information.

#	Date	Medium	Name – Format	Report Title	Author
1	01.03.2001	Press	targetForum	Forschung in Deutschland – Kompetenz vernetzt	C. Vetter
2	09.03.2001	Electronic press	BerliNews	Genomforschung an Mikroorganismen: BMBF fördert drei Kompetenznetze	
3	22.11.2001	Press	AFP Agence France-Presse	Announcement of press conference	
4	23.11.2001	Press	dpa Deutsche Presse-Agentur	Jährlich sterben in Deutschland 500 Kinder an Krebs	bb
5	23.11.2001	Press	Neue Ruhr Zeitung	Jährlich sterben in Deutschland 500 Kinder an Krebs	
6	23.11.2001	Press	Ostthüringer Zeitung	Jährlich sterben in Deutschland 500 Kinder an Krebs	
7	23.11.2001	Press	Potsdamer Neueste Nachrichten	Ein Netz der Hoffnung. Kliniken organisieren sich im Kampf gegen Kinderkrebs	
8	23.11.2001	Electronic press	Potsdamer Neueste Nachrichten online	Ein Netz der Hoffnung. Kliniken organisieren sich im Kampf gegen Kinderkrebs	bas
9	23.11.2001	Press	Thüringer Allgemeine Zeitung	Jährlich sterben in Deutschland 500 Kinder an Krebs	
10	23.11.2001	Electronic press	web.de	Jährlich sterben in Deutschland 500 Kinder an Krebs	
11	23.11.2001	Radio	Radio Hundert, 6 – Kompakt am Mittag	Summary of the press conference and interview with Prof. Henze (total, 6 minutes, start 12:40)	
12	23.11.2001	Radio	Sender Freies Berlin Stadtradio 88,8 – Berolina	Interview with Prof. Henze (total, 3,5 minutes, start 12:20)	
13	24.11.2001	TV	tv.Berlin	Interview with Prof. Henze (total, 1,5 minutes, start 19:14) and visit to a pediatric oncology ward	
14	27.11.2001	Electronic press	BertelsmannSpringer Medizin Online	Das Kompetenznetz Pädiatrische Onkologie und Hämatologie	P. Düker
15	26.11.2001	Press	Der Tagesspiegel	Ein Netz der Hoffnung. Kliniken organisieren sich im Kampf gegen Kinderkrebs	bas
16	26.11.2001	Electronic press	Der Tagesspiegel online	Ein Netz der Hoffnung. Kliniken organisieren sich im Kampf gegen Kinderkrebs	bas
17	27.11.2001	Electronic press	bsmedic-Berlin (HOS-Multimedica)	Das Kompetenznetz Pädiatrische Onkologie und Hämatologie	
18	27.11.2001	Press	Frankfurter Rundschau	Unterstützung bei unsicherer Diagnose. Weil Krebs bei Kindern selten vorkommt, brauchen nicht nur Laien, sondern auch Ärzte Rat/Hilfe per Telefon und Internet	R. Jung
19	09.12.2001	TV	ZDF 3sat – Teletipps vom Hausarzt	NewsEcke: Pointers to the competence network	
20	07.01.2002	Press	Deutsches Ärzteblatt	Kompetenznetzwerke: Eine Struktur gewinnt allmählich Inhalte	V. Zylka-Menhorn
21	09.01.2002	Press	Berliner Morgenpost	Krebs bei Kindern ist anders. Fortschritte in der Therapie retten die meisten der kleinen Patienten	A. Schrum

22	09.01.2002	Electronic press	Berliner Morgenpost online	Krebs bei Kindern ist anders. Fortschritte in der Therapie retten die meisten der kleinen Patienten	A. Schrum
23	13.02.2002	Press	Frankfurter Allgemeine Zeitung	Kompetenznetze verbessern Krankenversorgung. Mehr Kommunikation zwischen Forschung und Praxis/Effektivere klinische Studien	H. Kaulen

Internet links to this network

On March 24th, 2002, the search engine http://www.google.de/ searching for “kompetenznetz pädiatrische onkologie” retrieved 610 documents in the internet that linked to this competence network’s pages. The following are links found on endorsed documents:

Title	**URI**
Yahoo! > Gesundheit > Medizin > Kinderheilkunde	http://de.dir.yahoo.com/Gesundheit/Medizin/kinderheilkunde/
Yahoo! > Gesundheit > Krankheiten und Beschwerden > Krebs > Kinder	http://de.dir.yahoo.com/Gesundheit/Krankheiten_und_Beschwerden/Krebs/kinder/
Onkologie Online (DKFZ)	http://www.dkfz-heidelberg.de/tzhdma/tzlinks.htm
Deutsche Zentralbibliothek für Medizin	http://www.zbmed.de/a_digit/disziplin/haem.html
Deutsche Gesellschaft für Kinderheilkunde und Jugendmedizin e.V.	http://www.dgkj.de/kammerntext.htm
INKA – Das Informationsnetz für Krebspatienten und Angehörige: Krebstherapie: Therapiestudien	http://www.inkanet.de/info/krebstherapie/studien.htm
Kompetenznetze.de des BMBF	http://www.kompetenznetze.de/
InternetRatgeber Gesundheit	http://www.amgen.de/internet/tx_irg_kinder.htm
Klinikbibliothek Schnarrenberg und Datenbankdienste	http://www.medizin.uni-tuebingen.de/~webbibl/neues.htm
Nordwestdeutsche Gesellschaft für ärztliche Fortbildung e.V.	http://www.westerland-symposium.de/linksammlung.htm
Community of Knowledge	http://www.community-of-knowledge.de/cp_artikel.htm?artikel_id=80
Medknowledge Suchkatalog für Medizin	http://www.medknowledge.de/fach/kinderheilkunde_onkologie.htm
Selbstfindung TopNews	http://www.vkdnet.de/website/news/texte/ps_topn.htm
Wyeth Pharma GmbH Patienteninfo	http://www.krebs-webweiser.de/krebs-webweiser1101.pdf

E.20 List of Guidelines in Pediatric Oncology and Hematology and internet start page (AWMF)

The following guidelines are published on the internet (http://www.awmf-leitlinien.de/) under the auspices of the AWMF (working group of the scientific medical specialty societies in Germany). The AWMF definition of step 1 is: „A representatively composed group of experts of a AWMF Specialty Society informally consents on a guideline which is passed by the society's board of directors." In addition, "+IDA" refers to accomplishment of an interdisciplinary agreement.

The guidelines were also published on paper:

- Leitlinien für die Diagnostik und Therapie in der Pädiatrischen Onkologie, Creutzi U and Henz G (eds.). Reihe „Qualitätssicherung in der Onkologie", Zuckschwerdt Stuttgart 2nd ed. 2001
- Leitlinien für die Diagnostik und Therapie in der Pädiatrischen Onkologie, in: Leitlinien Kinderheilkunde und Jugendmedizin, Reinhardt D, Böhles H, Creutzig U, Kies W, Korinthenberg R, Luthard T, Michal D, Poets CF and Ulmer (eds.), Urban&Fischer München 2001
- Leitlinien für Diagnostik und Therapie, Informationszentrum für Standards in der Onkologie (ISTO), Onkologie/Deutsche Krebsgesellschaft (#4 to #15, also on the internet http://www.krebsgesellschaft.de/)

#	Guideline	English translation	Step (see top of page)	Number of persons within the network involved	Date of publication	Last revision
1	Grundlagen der Therapie von Tumoren und malignen Systemerkrankungen des Kindes	Basics of the therapy of tumors and malignant systemic diseases in childhood	1	2	13.01.1997	
2	Psychosoziale Standards für die Pädiatrische Onkologie	Psychosocical standards in pediatric oncology	1	2	13.01.1997	
3	Prinzipien zur Erfassung von Spätfolgen	Priciples of late effect surveillance	1	2	13.01.1997	
4	Nephroblastom	Nephroblastoma	1+IDA	1	13.01.1997	01.11.1999
5	Osteosarkome	Osteosarcoma	1+IDA	1	13.01.1997	01.11.1999
6	Ewing-Sarkome und PNET	Ewing-Tumors and PNET	1+IDA	2	13.01.1997	01.11.1999
7	Weichteilsarkome	Soft tissue sarcomas	1+IDA	1	13.01.1997	01.11.1999
8	Neruoblastoma	Neruoblastoma	1+IDA	2	13.01.1997	01.11.1999
9	Medulloblastom	Medulloblastoma	1+IDA	2	13.01.1997	01.11.1999
10	Keimzelltumoren	Germ cell tumors	1+IDA	2	13.01.1997	01.04.2000
11	Hepatoblastom	Hepatoblastoma	1+IDA	2	13.01.1997	01.11.1999
12	Morbus Hodgkin	Hodgkin's Disease	1+IDA	2	13.01.1997	01.11.1999
13	Non-Hodgkin Lymphome	Non-Hodgkin Lymphomas	1+IDA	2	13.01.1997	01.11.1999
14	Akute lymphoblastische – (ALL) und akute myeloische Leukämie (AML)	Acute lymphoblastic and myeloblastic leukemia	1+IDA	2	13.01.1997	01.11.1999
15	Langerhanszell-Histiozytose (LCH)	Langerhans Histocytosis	1+IDA	0	13.01.1997	01.06.2000
16	Sichelzellanämie	Sickle cell disease	1	0	13.01.1997	01.01.2001
17	Thalassämie	Thalassemia	1	2	13.01.1997	01.01.2001
18	Hereditäre Sphärozytose	Spherocytosis	1	0	13.01.1997	01.01.2001
19	Aplastische Anämie	Aplastic Anemia	1	0	13.01.1997	01.01.2001
20	Eisenmangelanämie	Iron-deficit anemia	1	2	01.06.2000	
21	Lymphknotenvergrößerung	Enlarged lymph node	1	0	13.01.1997	

Leitlinien für Diagnostik und Therapie

Pädiatrische Onkologie und Hämatologie

Die Gesellschaft für Pädiatrische Onkologie und Hämatologie hat im Rahmen der Deutschen Gesellschaft für Kinderheilkunde bzw. der Deutschen Krebsgesellschaft Leitlinien für folgende Diagnosetypen im Schwerpunkt Onkologie / Hämatologie erarbeitet:

Zurück zur Titelseite "Leitlinien"
Zurück zur Liste der Leitlinien
Zurück zur AWMF-Leitseite im WWW

Zuletzt aktualisiert am 06.03.01 13:28:40

Kompetenznetz Pädiatrische Onkologie
Studienunterstützung

Auswertung der Befragung der dokumentierenden Mitarbeiter in den Kliniken

durchgeführt im Januar 2001
vom Arbeitsprojekt Studienunterstützung

Dokumentation der Studiendaten

Hannover, Juli 2001

A.U. Diers

J. Hannemann

1. Ziel und Zweck der Befragung der Dokumentierenden in den Kliniken

Das Arbeitsprojekt Studienunterstützung führte im Januar 2001 eine Befragung unter den dokumentierenden Mitarbeitern in den Studienkliniken durch. Vorausgegangen war eine Befragung der Mitarbeiter in den Studienzentralen im Herbst 2000, bei der als Hauptprobleme die Kommunikation mit unterschiedlichen Mitarbeitern in den Kliniken und die qualitativ heterogene Dokumentation in den Kliniken herausgestellt wurden.
Um einen genaueren Überblick über den aktuellen Zustand und über bestehende Probleme der Dokumentation in der Klinik zu bekommen, wurde der neue Fragebogen (s. Anhang) konzipiert. Ein weiteres Ziel war es, Probleme in der Dokumentation und Kommunikation aus Kliniksicht aufzuzeigen, bei deren Lösung das Arbeitsprojekt Studienunterstützung helfend eingreifen kann.

Aktuell ist geplant, Lösungsvorschläge zu erarbeiten, um Strukturen und Prozesse im Dokumentationsablauf zu verbessern.

2. Zusammenfassung

Von 54 angeschriebenen Kliniken erhielten wir 42 Fragebögen zurück. Insgesamt fällt auf, daß 20 Befragte (48%) eine Vereinheitlichung der Studien erwarten. Dies bezieht sich sowohl auf eine einheitliche Verwendung von Begriffen als auch auf die Vereinheitlichung der Protokolle und Erhebungsbögen.
Für eine Reduktion von Merkmalen sprechen sich immerhin 12 (29%) der Antwortenden aus. Sieben (17%) bemängeln, daß Protokolle zum Teil nur in englischer Sprache vorliegen, was immer wieder zu Verständnisschwierigkeiten führt.

Durch die Art der Fragen und der Fragestellung wurde versucht, auf mögliche Schwierigkeiten genauer einzugehen. Es zeigte sich aber, daß der Spielraum der bewußt allgemein gehaltenen Fragen leider zu wenig genutzt wurde, um eigene Vorstellungen zu vermitteln und konkrete Hinweise zu geben.

Für das Arbeitsprojekt ergeben sich trotz der Allgemeinheit der Aussagen durchaus Konsequenzen zur Unterstützung der Studien. Es ist geplant, Protokolle und Erhebungsbögen, die besonders positiv oder negativ bewertet wurden, noch einmal gesondert von ausgewählten Dokumentaren und Ärzten beurteilen zu lassen. Aus diesen Bewertungen soll dann ein Empfehlungskatalog zusammengestellt werden, der aufführt, was bei der Neuerstellung von Protokollen besonders zu beachten ist.
Weiterhin wird sich das Arbeitsprojekt Studienunterstützung mit der Erstellung von „strukturierten Arbeitsanweisungen“ sog. Standard Operating Procedures (SOP) zur Bearbeitung von Dokumentationsbögen beschäftigen.

Acht Befragte (19%) hielten keine generellen Verbesserungen an den Erhebungsbögen für notwendig; 16 (38%) machten zu dieser Frage keine Angaben.

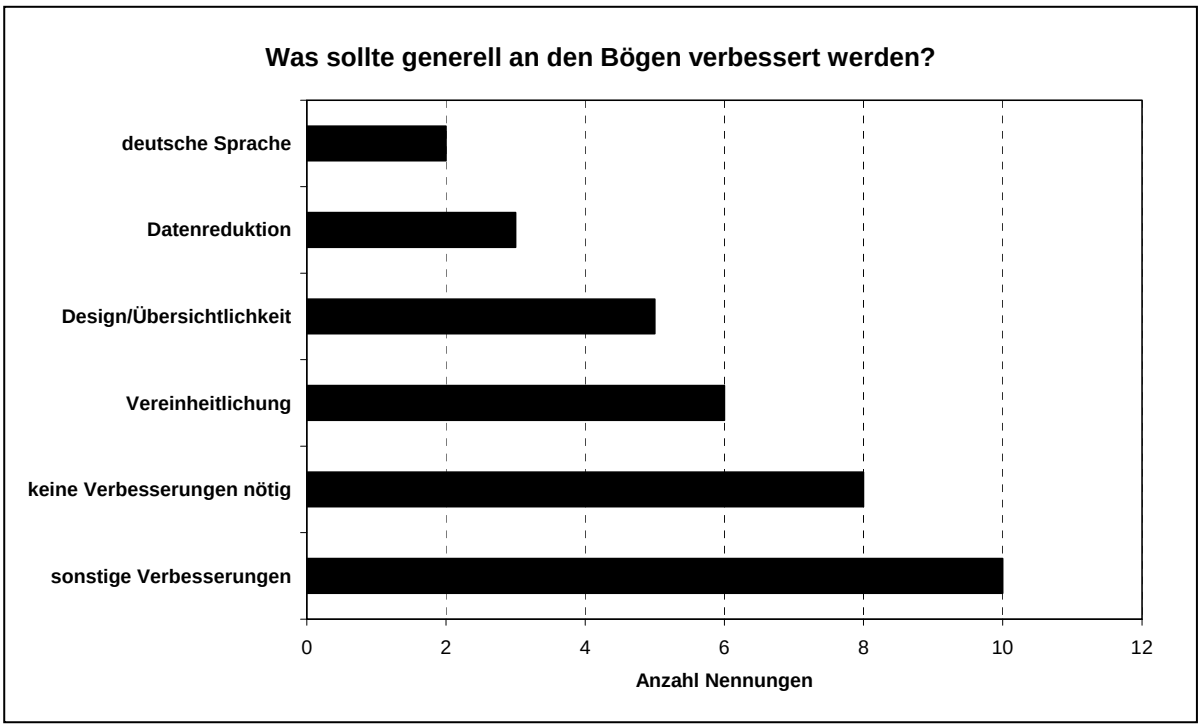


Abbildung 3: Verbesserungsvorschläge zu den Erhebungsbögen (Zahl Nennungen: 34, Mehrfachnennungen möglich)

Frage 21

Auf welche Weise haben Sie Zugang zu den Protokollen?

Insgesamt verfügten 29 (69%) aller Befragten über eigene Exemplare, wobei sich folgende Verteilung ergab: 13 (65%) Ärzte, sechs (60%) Dokumentare und sieben (88%) FSA.
27 Befragte (64%) hatten Zugang zu Protokollen in einem Arztzimmer.
Sechs Personen gaben unter „sonstiges“ an, daß Protokolle im Stationszimmer für jeden zugänglich sind oder, daß Protokolle als Datei im Computer zur Verfügung stehen.
Dreimal wurden zu dieser Frage keine Angaben gemacht.

Frage 22

Haben Sie Verständnisschwierigkeiten in bezug auf die Protokolle?

Von 20 Dokumentierenden (48%) lösten jeweils neun ihre Verständnisprobleme bei Protokollen durch Anrufe in der Studienzentrale bzw. durch Nachfragen bei den Ärzten in der Klinik. Probleme gab es vielfach bei Protokollen, die ausschließlich in englischer Sprache vorliegen und bei Verwendung einer uneinheitlichen Nomenklatur (z.B. gleiche Abkürzung mit unterschiedlichen Bedeutungen in den verschiedenen Protokollen). Informationen sind teilweise nur verstreut im Protokoll zu finden.
18 Befragte (43%) hatten keine Probleme mit dem Verständnis der Protokolle.

Frage 23

Ist die Uneinheitlichkeit der Protokolle der Therapieoptimierungsstudien ein Problem für Sie?

Auf diese Frage antworteten 22 Befragte (52%) mit „ja“, 17 stellten besondere Probleme mit den Protokollen fest. Hauptsächlich wurden die unterschiedlichen Empfehlungen zu Chemotherapie und Supportivtherapie kritisiert. Es fielen die Nennungen für unterschiedliche Applikationsvorschriften, Dosismodifikationen und Lösungsmittel (n=8) auf. Hier wurde eine einheitliche Handhabung gewünscht.
17 Dokumentierende (41%) hatten mit der Uneinheitlichkeit der Protokolle keine Probleme.

Die Fragen 22 und 23 wurden im folgenden zusammen ausgewertet, um feststellen zu können, ob die Verständnisprobleme in bezug auf die Protokolle in einem Zusammenhang mit deren Uneinheitlichkeit stehen. Bei 40% der Mitarbeiter bestand sowohl ein Problem mit dem Verständnis als auch mit der Uneinheitlichkeit (z.B. bezüglich Aufbau, Gestaltung, Sprache) der Protokolle (Tabelle 3). 29% gaben an, weder Verständnisprobleme noch Probleme mit der Uneinheitlichkeit der verschiedenen Protokolle zu haben.

			Uneinheitlichkeit		
			ja	**nein**	**Gesamt**
Verständnis-probleme	**ja**	**n**	15	5	**20**
		%	40	13	**53**
	nein	**n**	7	11	**18**
		%	18	29	**47**
	Gesamt	**n**	**22**	**16**	**38**
		%	**58**	**42**	**100**

Tabelle 3: Verständnisprobleme und Uneinheitlichkeit der Protokolle (k.A.=4)

Frage 24

Was könnte an den Protokollen verbessert werden?

Die im folgenden angesprochenen Verbesserungsvorschläge sind in einigen Studien-protokollen bereits seit einiger Zeit realisiert.

Von 24 Mitarbeitern in den Kliniken (57%) wurden folgende Vorschläge unterbreitet:

- Einheitliche Gliederung für alle Studienprotokolle (n=14)
- Einheitliches Stichwort- und Abkürzungsverzeichnis im Anhang (n= 5)
- Dokumentationsanleitungen zu verschiedenen Bögen (n= 4)
  angelehnt an Standard Operating Procedures (SOP)

weitere interessante Vorschläge:

- Dokumentationsbögen als abtrennbare Kopiervorlage im Anhang
- Therapiepläne auf der Umschlagseite der Protokolle
- Übersichtliche Erklärung und Definition der Stadieneinteilung
- Updates nicht als lose „Zettelsammlung“ (oder zumindest durchnumerieren)

Für vier Personen (10%) waren keinerlei Verbesserungen an den Protokollen notwendig; 14 (33%) machten zu dieser Frage keine Angaben.

Frage 25
Welche Hilfsmittel im Umgang mit den Protokollen wünschen Sie sich?

29 Befragte (69%) machten diesbezüglich verschiedene Vorschläge (Mehrfachnennungen):
- Ablaufpläne zur Dokumentation: (n=17)
- Vorgaben zum Ausfüllen der Bögen (SOP): (n=13)
- Übersichten: (n=11)

weitere Hilfsmittel:
- Weiterbildung über die Inhalte der Protokolle
- Ablaufschemata für Infusionen
- Protokoll: Register, Abkürzungsverzeichnis, Extraseite für Kritik und Verbesserungen
- aktualisierte Software

Vier (10%) der Dokumentierenden gaben an, daß keine zusätzlichen Hilfsmittel gewünscht werden; neun (21%) haben zu dieser Frage keine Angaben gemacht.

Frage 26
Welche Verbesserungsvorschläge haben Sie bezüglich Art und Vorgehen für Follow-up-Anfragen?

Bei der Anfrage von Daten für das Follow-up wählen die Studienzentralen unterschiedliche Methoden. Die wichtigsten Anregungen von 15 Dokumentierenden (36%) bezogen sich auf die folgenden Bereiche:
- Angabe des Datums der letzten Information vom Patienten auf der Follow-up-Anfrage
- keine doppelten Anfragen (Mainz, Studienzentrale, LESS)
- Anfrage weniger, relevanter Daten
- durch das Lesen der Arztbriefe erübrigen sich manche Anfragen
- Auflistung aller Ereignisse des Patienten (Rezidiv, Metastase, Zweitmalignom, Spätfolgen) jeweils mit Datum
- eindeutige Vorgabe von Nachsorgeuntersuchungen in Zeit und Umfang („Nachsorgeprogramm“)

10 (24%) aller Antwortenden hatten keine Verbesserungsvorschläge; 17 (40%) machten keine Angaben.

Frage 27

Sollten Follow-up Anfragen besser über das Jahr verteilt oder gesammelt in einem bestimmten Zeitraum gestellt werden?

Die Antworten auf diese Frage führten zu keiner Übereinstimmung zwischen Ärzten, Dokumentaren und FSA. Die Hälfte aller Antwortenden wünschte sich, daß die Follow-up-Anfragen über das Jahr verteilt erfolgen, ebenso viele sprachen sich für gesammelte Anfragen zu bestimmten Zeitpunkten aus (Tabelle 4). Dabei war die berufsgruppenspezifische Verteilung interessant:
Bei den Ärzten waren 47% für eine verteilte und 53% für eine gesammelte Follow-up-Anfrage. 60% der als „Dokumentare" gruppierten Mitarbeiter sprachen sich für gesammelte Follow-up-Anfragen aus, während 71% der FSA über das Jahr verteilte Anfragen bevorzugen.

		Zeitpunkt Follow-up		
		verteilt	**gesammelt**	**Gesamt**
Arzt	**n**	8	9	**17**
	%	47	53	**100**
Dokumentar	**n**	4	6	**10**
	%	40	60	**100**
FSA	**n**	5	2	**7**
	%	71	29	**100**
andere	**n**	2	2	**4**
	%	50	50	**100**
Gesamt	**n**	**19**	**19**	**38**
	%	**50**	**50**	**100**

Tabelle 4: Aufgabe in der Klinik und gewünschter Zeitpunkt zu Follow-up-Anfragen (k.A.=4)

Fragen 28/29

28.) Bearbeiten Sie die Verlaufsdokumentation (auch Therapie und Toxizität) selbständig?
29.) Werden ihre Angaben noch einmal vom zuständigen Arzt überprüft?

Die Fragen 28 und 29 richteten sich an die Dokumentationskräfte. Für die Auswertung wurden daher nur deren Angaben bewertet. Sieben (39%) der Dokumentare und FSA gaben an, die Dokumentation der Verlaufsdaten selbständig durchzuführen, wobei eine nachträgliche Überprüfung durch einen Arzt erfolgt.
Die Hälfte (n=9) der Gruppe bearbeitete die Verlaufsdokumentation und Therapie selbständig ohne nochmalige Überprüfung durch einen Arzt, z.T. allerdings mit Ausnahme der Toxizitätsdaten. Zwei führten die Dokumentation nicht selbständig durch.

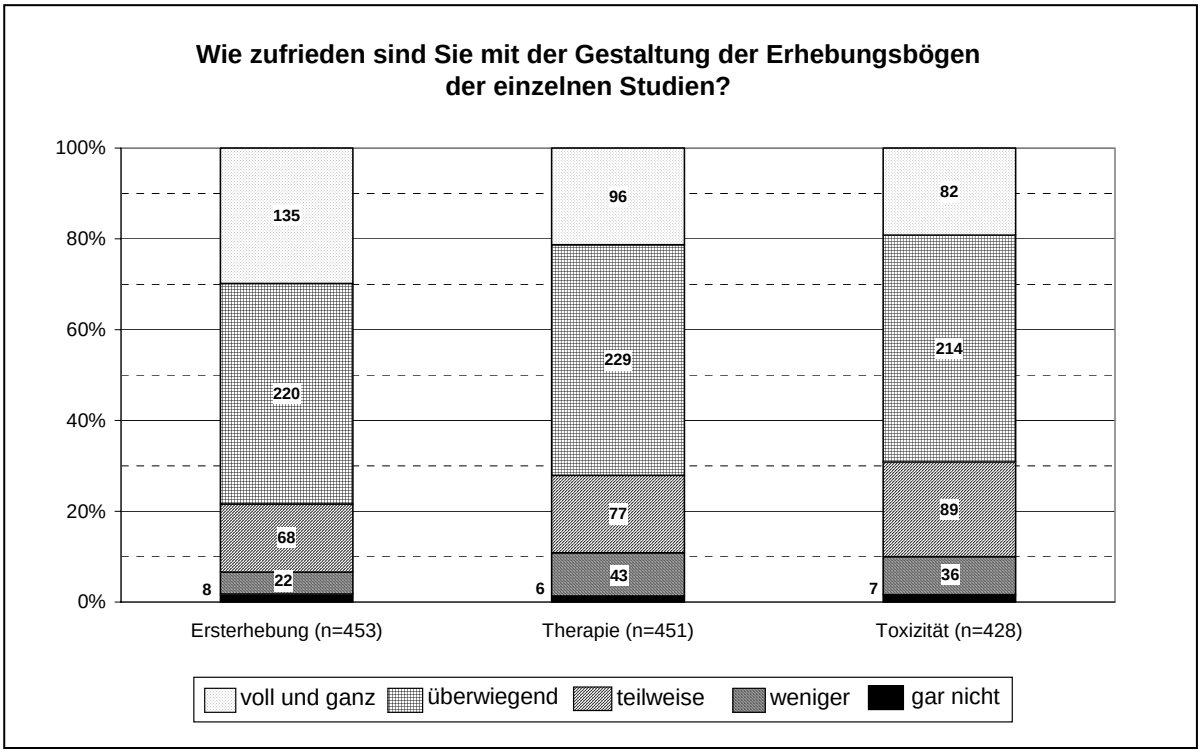


Abbildung 5: Zufriedenheit mit der Gestaltung der Erhebungsbögen der Ersterhebung, Therapie- und Toxizitätsdokumentation; Häufigkeiten prozentual und absolut

4. Fazit

Die Befragung unter den dokumentierenden Mitarbeitern in den Studienkliniken hat wertvolle Anregungen gebracht, wie die Arbeit in den Kliniken vereinfacht werden könnte. Es zeigte sich, daß nicht nur seitens der Studienzentralen Verbesserungen nötig sind, sondern ebenfalls in den Kliniken Bedarf für Veränderungen besteht. Dies betrifft in erster Linie die Zusammenarbeit zwischen Ärzten und Dokumentaren sowie die Dokumentation der Patientenakten.

Die Befragung bot die Möglichkeit, gerade in bezug auf Protokolle und Erhebungsbögen, Ärgernisse zu nennen und so auf die Erstellung neuer Protokolle positiv einzuwirken. Leider wurde die Chance, Anregungen und Verbesserungsvorschläge an die Studienzentralen zu geben, nur von wenigen genutzt.

Zu guter Letzt möchten wir uns ganz herzlich bei allen bedanken, die mit viel Engagement und Zeit ihre Ideen eingebracht haben.

U. Creutzig
A. U. Diers
J. Hannemann
M. Zimmermann
Hannover, 07/2001

Frage 30

Für welche Studien haben Sie bisher die Dokumentation bearbeitet und

a) Welche Studien schätzen Sie als besonders aufwendig/zeitintensiv in bezug auf die Daten der Ersterhebung, der Therapie und der Toxizität ein?

Etwa 40% der Studien wurden als (sehr) aufwendig eingeschätzt (vgl. Abbildung 4). Ein geringer bis sehr geringer Aufwand traf lediglich auf 25% der Studien (Toxizität=18%) zu. Bei dieser Frage gab es sehr unterschiedliche Einschätzungen, was die einzelnen Studien angeht. Allerdings wurden einige Studien auch nur sehr selten genannt (s. studienspezifischer Anhang).

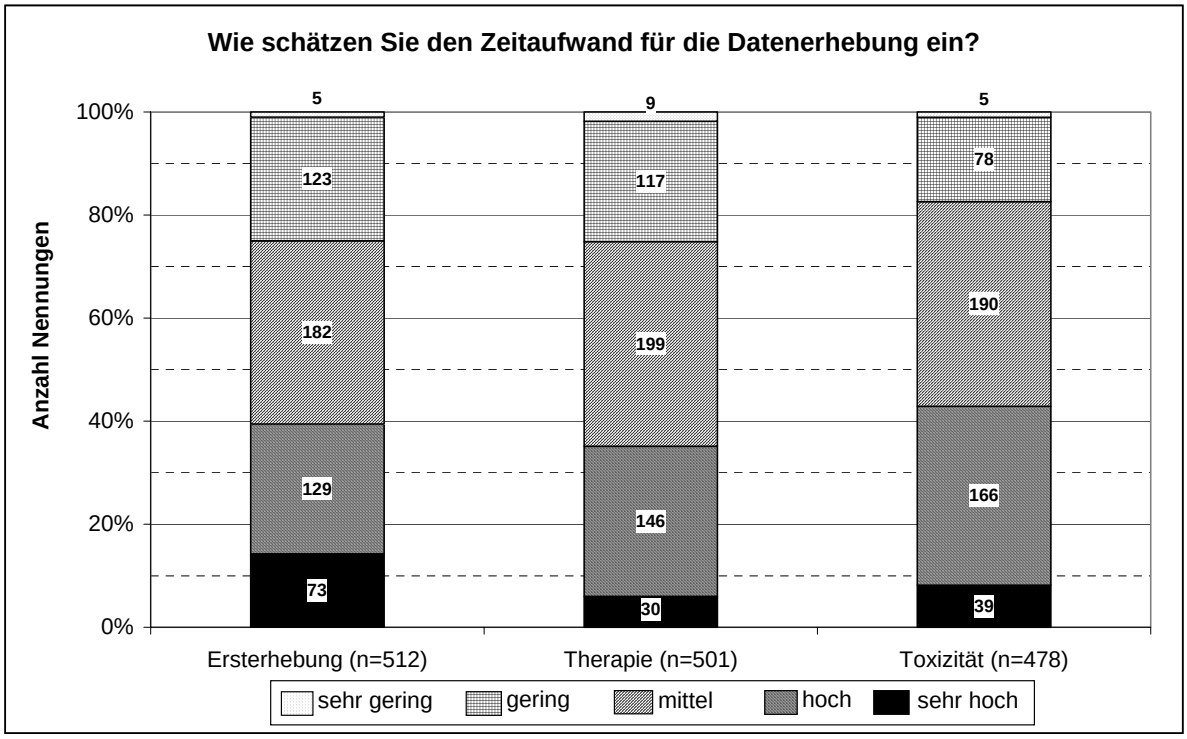


Abbildung 4: Zeitaufwand für die Datenerhebung über alle Therapieoptimierungsstudien; Häufigkeiten prozentual und absolut

b) Wie zufrieden sind Sie generell mit der Gestaltung (unter den Aspekten der Handhabung, Verständlichkeit) der Ersterhebungsbögen sowie der Bögen zur Therapie- und Toxizitätsdokumentation der einzelnen Studien?

Die Befragten waren mit 30% der Ersterhebungsbögen und ca. 20% der Therapie- und Toxizitätsdokumentation „voll zufrieden“ (vgl. Abbildung 5). Etwa die Hälfte aller Erhebungsbögen wurde mit „überwiegend zufrieden“ bewertet. Lediglich knapp 10% aller Nennungen entfielen auf „weniger“ bis „gar nicht“ zufrieden.

List of network and/or GPOH working groups (excerpt)

#	Working group Name	Subject	Number of Members (Network members)	Affiliation with the network
4	AG DRG	Classification, documentation of medical and psychosocial diagnoses and procedures	10 (4)	Network provides work force, exchange with other groups
5	GPOH-Beratungsgremium für Teilprojekt K	Medizinisches Ratgebergremium	5 (2)	Network provides Topic (Secondary Malignancies)
6	Standardisierungsgruppe	Erstellung und Verabschiedung des Basisdatensatzes der GPOH	8 (6)	Support of B/1
1	DOSPO Task Force	Controlling the DOSPO development	10 (8)	Support of B/1, problem solution introduced by A
2	AK Medizinische Informatik der GPOH und der GMDS	General discussion of IT usage for Pediatric Oncology	12 (6)	Exchange with A, B/1, B/2, C

C.3 Project work plans and milestones (referring to section 3, part C.3 of project proposals)

Project A: Coordination and management group

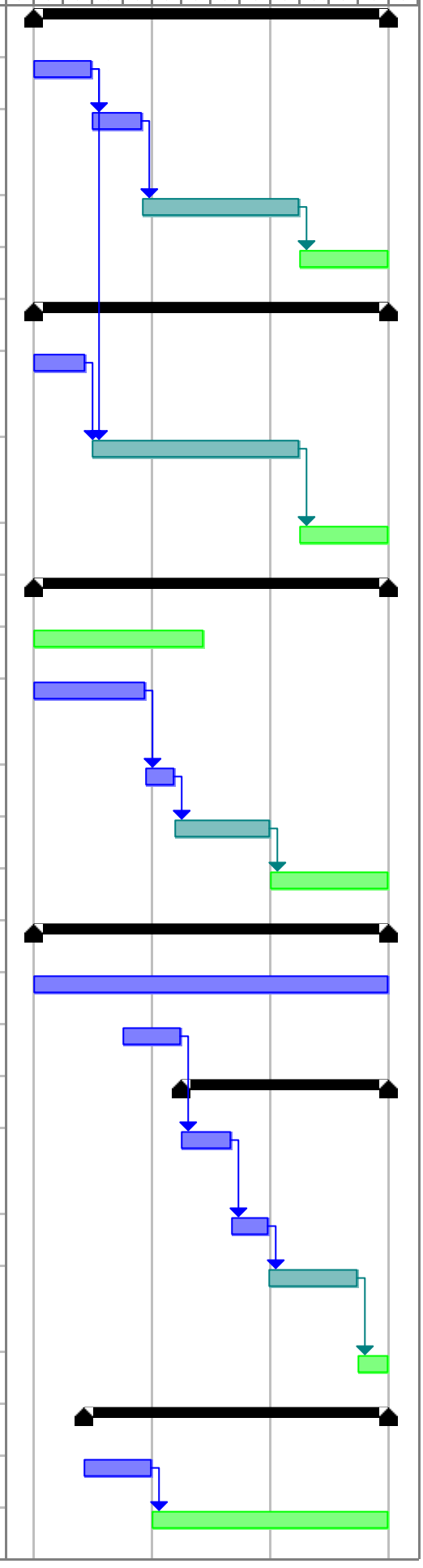
	2002		2003				2004			
Task	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Network organisation										
Annual status meeting of the GPOH and the network members			X				X			
Anual scientific meeting of the network members		X				X				X
Meetings of all medical documentarists in Pediatric Oncology and Hhematology				X				X		
Annual meetings of clinical trial offices' staff	X				X				X	
Management										
Request and process status reports of network projects	X		X		X		X		X	
Conduct workshop on project management, transfer of research results and marketing/PR employment				X						
Visibility										
Internet portal launched and relauchend	X					X				
Number of diseases and clinical trials included in the information server				10				18		
Press conferences, preceding press releases				X				X		
Exposition of the network at fairs and science meetings	X			X				X		
News letter "DIE MITTEILUNGEN"										
Informationbrochure revised and distributed						X				
Transfer into health care										
Training meetings of FSA	X			X			X			X
Local auditing of FSAs, site visits	x	x	x	x	x	x	x	x	x	x
Certification concept completed and agreed upon with members of relevant other bodies and organizations				X						
Certification of FSA							X	X	X	
Evaluation										
Questionings								X		
Interviews				X				X		
Internal decision report		X				X			X	
Final report on the project A										X
Sustainability – Quality control system										
Final, management and implementation concept completed	X									
Quality criteria agreed among the specialist society anf the network, including piloting in one institution			X							
Pilotinvestigation TOPICS completed and reported		X								
Proposal submission to BMG				X						
Inclusion of a first trial into this system						X				
Participation of hospitals		2			5			12		

Project B/1: Computer-based application systems

Please, see the following pages.

Appendix: DOSPO Work Plan

		2002				2003				2004				20
		Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
1	**Integration in hospital information systems**														
2	Developing HL7-Interface for Patient data + Piloting in 3 hospitals														
3	Developing HL7-Interface for Diagnoses and Procedures + Piloting in 3 hospitals														
4	Rollout HL7-Interface (Patient data / Diagnoses + Procedures)														
5	Change to routine operation														
6	**Documentation of diagnoses and procedures**														
7	Adapting documentation of diagnoses and procedures to new legal requirements and supporting introduction (without interfaces)														
8	Rollout documentation of diagnoses and procedures in combination with the HL7-Interfaces														
9	Change to routine operation														
10	**Therapy Planning**														
11	Supporting clinics in the current therapy planning module														
12	Realizing improvements of the protocol definition and therapy planning modules in close cooperation with pilot clinics														
13	Piloting of the modules in the pilot clinics														
14	Rollout improved therapy planning														
15	Change to routine operation														
16	**Miscellaneous functionality (report writing, scheduling, analysis, ...)**														
17	continuous maintenance of the modules and supporting their introduction														
18	**Integrating the revised basic data set**														
19	**Interface to the Childhood Cancer Registry**														
20	Realizing computer-based workflow-support (electronic signature of the clinician, automatic sending, checking for completeness, ...)														
21	Piloting in 2 user clinics and the Childhood Cancer Registry														
22	Comprehensive introduction of electronic reporting to the Childhood Cancer Registry														
23	Change to routine operation														
24	**Setting up routine operation**														
25	Setting up technical and organizational requirements														
26	Routine hotline-support														



Appendix: Terminology Server - Work Plan

Nr.		2002				2003				2004				20
		Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
1	**Extending the terminology server: integrity constraints**														
2	Extending and adapting the data model														
3	Specifiying extended functionality of the application system														
4	Devolping extendend functionality														
5	Inputting integrity constraints of already covered items														
6	**Extending the terminology server: versioning management**														
7	Extending and adapting the data model														
8	Specifiying extended functionality of the application system														
9	Devolping extendend functionality														
10	Inputting versioning information of already covered items														
11	**Evaluating terminology server using the SIOP 2001-trial**														
12	Modelling terminology of SIOP 2001														
13	Inputting trial into terminology server														
14	Gathering suggestions for improvement														
15	Specifiying improved functionality of the application system														
16	Developing improved functionality														
17	Evaluating improvement of degree of standardization														
18	**Modelling and inputting terminology of further trials**														
19	Modelling terminology														
20	Inputting terminology														

Project C: Evaluation of Telemedicine

		Respon	2002		2003				2004			
	Deliverables	**sibility**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
	Point-to-point telemedicine applications											
I	Installation and test of teleradiology systems in 5 participating institutions		X	X	X	X	X					
1	Installation of test systems	all	X	X								
2	Technical tests	all	X	X	X							
3	Practical tests in clinic routine	all	X	X	X	X	X					
4	Feasibility report, implementation suggestions	MS					X	X				
	Central electronic image clearing institution concept											
II	Evaluation of acceptance; organizational co-ordination		X	X	X	X	X	X	X			
1	Definition of expectations, tasks and structure	MS	X	X	X	X						
2	Co-ordination with telematic-platform	B			X	X	X	X	X			
3	Co-ordination with DOSPO (project B)	HO			X	X	X	X	X			
4	Co-ordination with network co-ordination centre and research assistant project („Forschungs-und Studienassistenten“, project A)	B			X	X	X	X	X			
5	Co-ordination with telemedicine projects of other competence networks	B	X	X	X	X	X	X	X			
6	Acceptance report, suggestions for implementation	MS						X	X			
III	Analysis of technical requirements for set-up and maintenance		X	X	X	X						
1	Information technology (hardware, software, data flow, backup, network security, data security and confidentiality, ...)	MS	X	X	X	X						
2	Staff	MS	X	X	X	X						
3	Finances	MS			X	X						
4	Technical feasibility report, suggestions for implementation	MS					X					
IV	Test installation of central electronic image clearing institution functionality for a limited number of participants						X	X	X	X	X	X
1	Technical set-up (server, software, connectivity, safety)	MS					X	X				
2	Function tests („phantom data“)	all						X	X			
3	Practical evaluation („real medical data“)	all							X	X	X	
4	Feasibility report, suggestions for implementation	MS									X	X
V	Remote Data Entry (RDE) for GPOH Trials		X	X	X	X	X	X	X	X	X	X
1	Analysis of available RDE systems	HO	X	X								
2	Test implementation of an RDE system for the SIOP2001/GPOH study	HO	X	X	X							
3	Evaluation of DOSPO (project B) compatibility	HO	X	X	X	X						
4	Evaluation of RDE for SIOP2001/GPOH study	HO		X	X	X	X					
5	Evaluation of RDE for other GPOH trials	HO				X	X	X	X	X	X	
6	Feasibility report, suggestions for implementation	HO									X	X

Project D: Molecular parameters of drug resistance

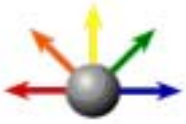
Task	**2003**				**2004**			
Quarter of year	**I**	**II**	**III**	**IV**	**I**	**II**	**III**	**IV**
1 – Analysis of constitutive apoptosis sensitivity								
Standardization of chemical stress assay	X	X						
Application in study laboratories		X	X	X	X	X	X	
Establishment of database for experimental data	X	X	X					
Implementation of clinical data and analysis							X	X
Development of tools for data analysis				X	X	X	X	X
2 – Analysis of drug sensitivity								
Optimization casp-3/cyto-c assay for T-ALL/AML	X	X						
Application in study laboratories			X	X	X	X	X	X
Implementation of clinical data and analysis							X	X
Development of assay for B precursor ALL	X	X	X	X				
Application in study laboratories				X	X	X	X	X
3 – Bax and related genes mutation analysis								
Analysis of Bax mutation on RT-PCR level				X	X	X	X	
4 – Expression analysis of apoptosis genes								
Validation of apoptosis gene array	X	X						
Modification of procedures with primary samples			X	X	X			
Standardization of RNA preparation				X	X			
Aquisition of RNA in study laboratories					X	X		
Analysis of expression in primary leukemia cells					X	X	X	X
Development of tools for data analysis				X	X	X	X	X
Implementation of clinical data and analysis							X	X
5 – Analysis of apoptosis during chemotherapy								
Standardization of p53 measurement (FCM)	X	X						
p53 measurement during chemotherapy (HH,UL)			X	X	X	X	X	X
Development of assays for apoptosis related changes	X	X	X	X				
Application on leukemia cells during chemotherapy				X	X	X	X	X
6 –Drug induced apoptosis in leukemia stem cells								
Establishment of hu Leukemia on NOD/SCID	X	X	X	X	X	X		
Analysis of engraftment properties upon treatment					X	X	X	X
7 – Establishment of central database								
Definition of database variables	X	X						
Establishment of database		X	X	X				
Data entry experimental data				X	X	X	X	X
Import of clinical data							X	X

Project K: Second malignant neoplasms after childhood cancer

Task	Time
Continuation of the documentation	
Validation of new cases in cooperation with clinical trials	Ongoing
Sending documentation forms for SMN patients to clinical trials or clinics	Ongoing
Coding and data entry of documentation form	Ongoing
Conducting the case-control study	
Sending out documentation forms for controls sampled until 1999	Apr 2002
Check data for completeness, coding and data entry for controls	May – Dec 2002
Sample controls for the 2000 to 2002–cases	Apr 2003
Sending out documentation forms for controls sampled for 2000 – 2002	Apr/May 2003
Check data for completeness, coding and data entry for control data	May – Sep 2003
If necessary, sample further controls	Jul 2003
Processing of further controls	Aug – Oct 2003
Data exchange with PRST	
Documentation of the therapy data of the SMN cases with SCT we currently know by the PRST (about 20)	Jan – May 2002
Documentation of the therapy data of new SMN cases with SCT by the PRST	Ongoing
Documentation of the therapy data of controls with SCT by the PRST	May 2002 – Dec 2003
Cooperations regarding genetic aspects	
Contacting potential cooperation partners	Mar – May 2002
Resulting activities	Jun 2002 – Oct 2003
Data processing and evaluation of the study	
Finalize plausibility checks, consistency checks, correct data errors	Dec 2003
Evaluate study	Jan – May 2004
Matching data with state cancer registries	
Establish regular data exchange with all registries	until Dec 2003
Working out recommendations for post treatment care for former patients	
Based on the results of the case-control study (as described, we expect not to be able to do this within the project period)	2004/2005
Meeting the board of consultants one or twice a year	
Depends on the state of the study	to be discussed
Publications on the case-control study	
Final report	Jun – Dec 2004
Final scientific publication	Jun – Dec 2004

Pädiatrisches Register für StammzellTransplantationen

PRST



Kooperatives

Pädiatrisches Register für StammzellTransplantationen

Deutschland - Österreich

Das PRST erfaßt zeitnah Transplantationen hämatopoetischer Stammzellen bei Kindern zu Zwecken der Qualitätssicherung und Förderung der Wissenschaft im Bereich Pädiatrie.

Der vorgesehene Ablauf der Meldungen an das PRST ist im folgenden beschrieben, dort sind auch die benötigten und bisher vorhandenen Formulare zu finden.

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Gefördert von der Deutschen Krebshilfe

und dem Kompetenznetz - Pädiatrische Onkologie und Hämatologie

Besucher seit dem 1.1.2000 auf dieser Seite: 

Zurück zum Anfang

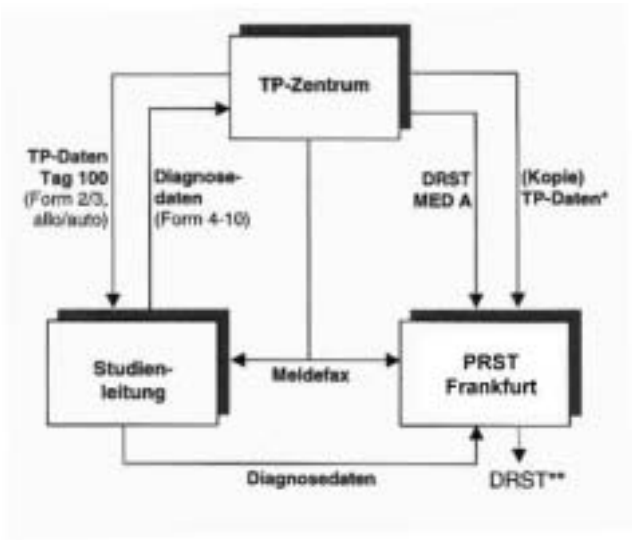
Letzte Aktualisierung: 18. Oktober 2001.

Pädiatrisches Register für StammzellTransplantationen

PRST

Dokumentationsablauf und Formulare

Stand Dezember 1999



Das Meldefax....

...wird von den transplantierenden Zentren bei Patientenaufnahme an die entsprechenden Studienleitungen***** und an das PRST in Frankfurt geschickt.

Die Diagnosedaten,....

...Informationen zur Primärerkrankung, werden von den Studienleitungen an die transplantierenden Zentren und an das PRST nach Frankfurt geschickt.

Die DRST-MED-A-Formulare....

...First Report/Follow up werden von den transplantierenden Zentren bei Entlassung/nach Wiedervorstellung der Patienten **direkt zum PRST nach Frankfurt** geschickt. Von dort werden die Daten an das DRST weitergeleitet. *****neu*****

Die Transplantationsdaten....

...(Form 2/3) werden von den transplantierenden Zentren für jeden Patienten am Tag 100 an die entsprechenden Studienleitungen***** und **in Kopie (***neu***)** zum PRST nach Frankfurt geschickt

* Ist der Patient an keiner Therapieoptimierungsstudie beteiligt, werden alle Daten direkt Frankfurt übermittelt.
Erfaßt die Studienleitung die Daten mit eigenen Bögen (z.B. MDS-Studie), müssen nur diese ausgefüllt werden.

****** Das DRST leitet, falls gewünscht, die Daten an EBMT/IBMT-R weiter. Ob und wohin die Daten weitergeleitet werden können, wird im Meldefax angegeben.

Anmerkung: Die Formulare sind **!!!Ersatz!!!** für EBMT-MED **B**-Formulare.

Doppeltes Ausfüllen erfolgt auf freiwilliger Basis!

Besucher seit dem 1.1.2000 auf dieser Seite: 284

Letzte Aktualisierung: 10. Oktober 2001.

Pädiatrisches Register für StammzellTransplantationen

PRST-Tübingen

Startseite | Dokumentationsablauf | New Chronol. Liste der Änderungen
Teilnehmer | Formulare

Inhaltsverzeichnis:

Download von Acrobat Reader Vers. 4.0 der Firma Adobe:

Download aller o.g. Formulare im PDF-Format: PDF-Forms.ZIP

Um die beiden o.g. Dateien zu "entzippen" benötigen Sie ein Dekomprimierprogramm wie z.B. "Winzip"

Besucher seit dem 1.1.2000 auf dieser Seite:

Letzte Aktualisierung: 07. September 2000.

Projekt A: Koordinationszentrale und Mantelantrag im Kompetenznetz Pädiatrische Onkologie und Hämatologie

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Startseite des Mantelantrags und der Koordinationszentrale –

- willkommen zum Projekt A im Kompetenznetz Pädiatrische Onkologie und Hämatologie, Projektleiter Prof. Henze. Das Forschungsnetz geht von der Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) aus. Das Bundesministerium für Bildung und Forschung (BMBF) und der Projektträger Gesundheitsforschung (DLR) fördern dieses und andere Netze.

Ziel und Aufgabe

In den zehn Projekten dieses Kompetenznetzes werden Krebskrankheiten und Erkrankungen des blutbildenden Systems bei Kindern und Jugendlichen spezifisch, mit übergreifenden Ansätzen und auf der Basis eines intensivierten Zusammenwirkens der Experten und der Strukturen untersucht.

Das Arbeitsprogramm unseres Projekts A läuft vom 01.07.1999 bis vorerst zum 30.06.2002, u.a. zu Themen wie Datenverbesserung und Informationstransfer: Wie auch in anderen Kompetenznetzen in der Medizin sollen klinische und Grundlagen- Forschung so effektiv gefördert werden, daß neue Ergebnisse zügig in die klinische Praxis und zum Nutzen der Betroffenen vermittelt werden.

Informationsaustausch

Allgemeine Informationen zu den Erkrankungen sind über die Internet-Seiten auf diesem und auf dem Wissensserver zu erhalten. Informationen für Ärzte sind zur Zeit Vorträge über die Kompetenznetz-Projekte sowie Diavorlagen zu Krebskrankheiten und anderen Erkrankungen des blutbildenden Systems bei Kindern und Jugendlichen. Zum Ausprobieren: Klicken Sie **JOIN** zum Einschreiben an, um Nachrichten und Dateien anderen bereitzustellen. Die Koordinationszentrale erweitert Ihre Zugriffsrechte.

Kompetenznetz Pädiatrische Onkologie

Nachrichten
Aktuelle Veranstaltungen...
Neue Seiten...

Eine Initiative der

GESELLSCHAFT FÜR PÄDIATRISCHE ONKOLOGIE UND HÄMATOLOGIE GPOH

Gefördert vom

Bundesministerium für Bildung und Forschung

Projekt A: Koordinationszentrale und Mantelantrag im Kompetenznetz Pädiatrische Onkologie und Hämatologie

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FSA: Hintergrund zum Tätigkeitsprofil.

Das folgende Tätigkeitsprofil für Forschungs- und Studienassistenten (FSA) wurde von der Koordinationszentrale Ende 1999 zusammen mit der erweiterten Leitgruppe des Kompetenznetzes abgestimmt und verabschiedet. Es ist eine verbindliche Obermenge aller konkreten Tätigkeiten, die die FSA am jeweiligen Einsatzort ausüben. Das Tätigkeitsprofil ist Bestandteil der Vereinbarungen zwischen der Koordinationszentrale und den örtlichen FSA-Verantwortlichen über den Einsatz der FSA.

Text des Tätigkeitsprofils

Die Mitarbeiter haben im Kompetenznetzwerk ihre zentrale Aufgabe in der praktischen Umsetzung, der Koordinierung und der Durchführung der Belange von klinischen Studien und wissenschaftlichen Teilprojekten in pädiatrisch-onkologischen Abteilungen und Zentren. Sie unterstützen den verantwortlichen Arzt bei der Organisationsplanung und Durchführung von Studien an Patienten oder Patientenmaterialien. Sie sind Mitarbeiter im interdisziplinären wissenschaftlichen Team.

Der Aufgabenbereich umfaßt:

- Unterstützung bei der Durchführung von klinischen Studien
  - Registrierung von Studienpatienten
  - Berücksichtigung und Dokumentation von Ein- und Ausschlußkriterien sowie Steuerungsregeln von Studien, damit konkrete Hilfe bei der Umsetzung verschiedener Studienprotokolle vor Ort
  - Berücksichtigung und Dokumentation des Studienablaufs und Therapieplans
  - Vorbereitung von verschiedenen lokalen Untersuchungen einschließlich bildgebender Verfahren und lokaler Laboruntersuchungen
- Laborlogistik
  - Gewinnung, Portionierung/Aliquotierung, Konservierung, Asservierung von Blut, Urin, Liquor, Knochenmark, Biopsiematerial etc.
  - Selbständige Durchführung von Blutentnahmen
  - Selbständige Übernahme der Versandlogistik für die termingerechte Materialbereitstellung und Versendung zur Durchführung von Basis- und weiterführenden Untersuchungen
  - Nachfragen nach adäquatem Eintreffen und Einholen von daraus gewonnenen Befunden
- Dokumentation
  - Schriftlich und elektronisch mit Hilfe von DOSPO (PC-Programm)
  - Termingerechte Bereitstellung und Erhebung der Studiendaten mit Patientenfragebögen,
  - Auch für Nachsorge und Lebensqualitätsmessung
  - Selbständige telefonische und elektronische Kommunikation in Material- Befund- und Dokumentationsbelangen zwischen Kliniken, KMT-Zentren, Kindertumorregister, Referenz- und Forschungslaboratorien
  - Begleitende Erstellung einer zu überlassenden Dokumentation über klinikspezifische, studienspezifische und allgemeine Vorgehensweisen (z.B. im Aktenordnerformat)
- Hinweise

  Mögliche Voraussetzungen hierfür sind eine abgeschlossene Ausbildung (z.B. Dokumentar, Krankenpflege, MTA, Arzthelfer) und vorhandene Erfahrungen in onkologischen Arbeitsbereichen.

  Fortbildungsseminare sind zunächst 3x pro Jahr vorgesehen, mit Erfahrungsaustausch für die Mitarbeiter.

Interviews of the RAs - Summary

Research assistants (RAs) are now employed by hospitals that operate within the paediatric oncology and hematology network and have a minimum annual caseload of 22 patients. This project is intended to improve collaboration between hospitals and central research institutes and should relieve hospital staff from research-related work that was carried out before on top of the usual workload.

We carried out informal 1-hour interviews with four groups, each with between four and eight RAs, to gather information about their working conditions, the type of work and how it is being carried out.

Despite this early phase of the project, RAs were able to comment on the following aspects of their job:

- Collaboration with central research institutes has improved considerably. More data are collected and these are transmitted faster than before, requests from central research institutes could be answered faster and information is processed in a speedier fashion.

- Collaboration with reference laboratories has improved and has led to a noticeable reduction in the loss of specimens.

- Several RAs commented that relieving hospital staff by transferring information processing and data management tasks to RAs has meant a higher recognition for this type of work, and the RA position itself

- The appointment of RAs has led to a clearer definition of responsibilities with an elimination of grey areas in responsibilities. Studies are now coordinated by one person and thus easier to access. The amount of suggestions for improvements on the part of RAs demonstrates the advantage of specifically dedicating study management to RAs.

However, infrastructure at the hospital sites was, and still is, often unfavourable, particularly in the beginning stage of this project. This particularly relates to offices and technical equipment, but also to the not often seemless integration into the day-to-day operation of the hospitals and their staff.

There is a considerable need to improve the conditions for introducing electronic data management, the inadequacy of which makes tasks, such as double data entry, time-consuming for physicians and study personnel. The double documentation required initially means additional work for the doctors.

CWS-96 Checkliste – Initiale Maßnahmen

Name: Vorname: Geb.-Datum

Stationäre Aufnahme: Diagnose-Datum: Abteilung:

	Datum/Handzeichen			
Labor- und klinische Diagnostik	**geplant**	**durchgeführt**	**Befund gesehen**	**CAVE**
1) Anamnese				
2) Aufklärungsgespräch				
3) Einwilligungserklärungen (KMP, Stanze, Transfusion, HIV, Chemotherapie, KKR, Studien)				
4) Psychosoziale Anamnese				
5) Klinische Untersuchung				
6) Blutentnahmen, Urin (Protokoll S. 41)				
7) Hausintern:				
Bildgebende + apparative Diagnostik (Protokoll S. 40/41)	**geplant**	**durchgeführt**	**Befund gesehen**	**CAVE**
1) Tumorregion MRT				
2) LK-Stationen Sono				
3) LK-Stationen MRT/CT (nach Sono-Befund)				
4) Thorax-Röntgen in 2 Ebenen				
5) Thorax-CT, Spiral-CT (falls verfügbar)				
6) Cerebrales MRT oder CCT				
7) Skelettszintigraphie				
8) EKG				
9) Echokardiographie				
10) EEG				
11) LUFU				
12) Augenhintergrund				
13) Audiometrie				
14) Hausintern:				
Invasive Diagnostik (Protokoll S. 119-122)	**geplant**	**durchgeführt**	**Befund gesehen**	**CAVE**
1) Initiale OP / Biopsie				
2) Materialversand **extern**: ü Frisches Tumorgewebe in RPMI (Kiel)				
ü EDTA-KM (Kiel, Studienzentrale)				
ü EDTA-Blut + Ausstriche (?)				
3) Materialversand **intern**: ü Frisches Tumorgewebe in RPMI (Patho)				
ü EDTA-KM + Stanze (Patho/Labor)				
ü EDTA-Blut + Ausstriche (Patho/Labor)				
4) Fakultative Diagnostik (Seite 41)				
5) Hausintern:				
Dokumentation	**geplant**	**durchgeführt**	**Befund gesehen**	**CAVE**
Fax-Meldung Studienzentrale: Vor Beginn Chemotherapie incl. OP-Bericht, Histologie, Referenzhistologie, MRT-/CT-Befunden				
Meldung KKR				
Hausintern:				

CWS-Checkliste – Verlaufsdiagnostik

Name: Vorname: Geb.-Datum:

		Datum/Handzeichen			
Zeitpunkt	**Untersuchungen (Protokoll S. 42/131/138)**	**geplant**	**durchgeführt**	**Befund gesehen**	**CAVE**
Woche 3* Datum	Primärtumorsitz-Sono				
	Echo				
	Labor				
Woche 6* Datum	Primärtumorsitz-Sono				
	Echo				
	Labor				
Woche 9 (Response) Datum**	**Primärtumorsitz: MRT + KM**				
	Thorax-Röntgen in 2 Ebenen				
	Abdomen-/Becken-Sono				
	EKG				
	Echo				
	Labor				
Woche 12* Datum	Primärtumorsitz-Sono				
	Echo				
	Labor				
Woche 15* Datum	Primärtumorsitz-Sono				
	Echo				
	Labor				
Woche 18 (CR ?) Datum**	**Primärtumorsitz: MRT + KM**				
	Thorax-Röntgen in 2 Ebenen				
	Abdomen-/Becken-Sono				
	EKG				
	Echo				
	Labor				
Woche 21* Datum	Abdomen-/Becken-Sono				
	Echo				
	Labor				
Woche 24* Datum	Abdomen-/Becken-Sono				
	Echo				
	Labor				
Woche 27 (Therapieabschluß) Datum**	**Primärtumorsitz: MRT + KM**				
	Primärtumor-Sono				
	Cerebrales MRT / CCT				
	Thorax-CT				
	Thorax-Röntgen in 2 Ebenen				
	Abdomen-/Becken-Sono/regionäre LK-Stationen (?)				
	Skelettszintigraphie				
	EKG				
	Echo				
	EEG				
	Augenhintergrund				
	Audiometrie				
	KM – initialer Befall				
	Liquor – initialer Befall				
	Labor				
	Klinische Untersuchung				
	Neurolog. Untersuchung				
Hausintern					
Dokumentation**	**Ersterhebung**				
	Therapiedokumentation				
	Therapieabschlußdokumentation				
	LESS + Nachsorgedokumentation				

* = Fakultativ / ** = Obligat

„IHR KIND HAT KREBS."

Pädiatrische Onkologie und Hämatologie

INFORMATIONEN ÜBER KREBSERKRANKUNGEN IM KINDES- UND JUGENDALTER

www.kinderkrebsinfo.de

DIE KRANKHEIT HINTER DER MASKE

„Ihr Kind hat Krebs." Jedes Jahr hören 2.000 Eltern in Deutschland diesen furchtbaren Satz. Bilder mit tapfer lächelnden Gesichtern zwischen Apparaturen und Schläuchen gehen durch den Kopf. Bisher sind mehr als 20 Krebsarten bei Kindern bekannt. Jede hat ihre ganz individuelle Gestalt, ihr eigenes Gesicht. Eine frühzeitige Diagnose ist der wichtigste Schritt auf dem Weg der Heilung. Bei Kindern kann sich die bösartige Erkrankung hinter einer harmlosen „Maske" verstecken. Häufig auftretende Kopfschmerzen, Blässe, Schmerzen in den Knochen oder blaue Flecken und Fieber können schon erste Anzeichen einer Krebserkrankung sein. Doch oft wird diese Diagnose von Anfang an ausgeschlossen: „Krebs wird es schon nicht sein." Die gemeinschaftliche Sorge um die Kinder, die der Ärzte und die der Eltern, sollte so früh wie möglich beginnen.

Im Jahr 2010 wird jeder 250. junge Erwachsene ein Überlebender einer Krebskrankheit im Kindesalter sein – die gesundheitsbezogene Lebensqualität und die Spätfolgenreduktion werden immer wichtiger.

Kinder sind keine kleinen Erwachsenen

In der Behandlung der Krankheit treten zahlreiche Hürden auf. Ein Beispiel: Viele der Medikamente sind für Kinder gar nicht zugelassen. Die Pädiatrische Onkologie und Hämatologie muss bisher auf die Pharmaprodukte der Erwachsenenmedizin zurückgreifen. Doch diese Medikamente sind in zahlreichen Studien und Forschungsreihen auf die Krankheiten und Organismen der Erwachsenen, nicht auf die von Kindern abgestimmt. Und mit einer kleineren Dosierung ist es nicht getan. Für eine erfolgreiche Behandlung ist die Frage „Was und wieviel gibt man wann?" die alles entscheidende.

Kinder sind dankbare Patienten. Der Umgang mit der Krankheit ist direkter als bei Erwachsenen, ohne Umschweife. Die Belastungsprobe, auf die sie zusammen mit ihren Eltern gestellt werden, ist immens. Geduld ist das oberste Gebot. Die größte Sorge der Patienten ist die Rückkehr der Erkrankung.

Der Heilung ein grosses Stück näher

Entgegen gängiger Meinung spielt das Thema „Krebs bei Kindern" nur eine untergeordnete Rolle auf der Agenda der medizinischen Fachwelt. Dies hängt zum einen mit der glücklicherweise relativ geringen Zahl von etwa 2.000 Erkrankungsfällen pro Jahr zusammen (zum Vergleich: Jährlich erkranken über 40.000 Frauen an Brustkrebs), zum anderen aber auch mit einem hohen Maß an Unsicherheit und Unwissenheit. Auch bei Ärzten in Kliniken und Praxen. Zu speziell ist das Wissen, das benötigt wird, um Krebs bei Kindern rechtzeitig zu erkennen und vor allem anschließend erfolgreich zu behandeln.

Dabei haben sich in den letzten Jahren und Jahrzehnten rasante Fortschritte gezeigt. Die Überlebensraten konnten – je nach Art der Erkrankung – auf durchschnittlich 75 Prozent gesteigert werden. Hinter dieser Zahl stehen viele Einzelschicksale, die der Krankheit zunächst mit Angst und Ohnmacht gegenüberstehen, die den Kampf gegen den Krebs aber immer häufiger gewinnen. Zu verdanken ist dieser Erfolg einer stark verbesserten Entwicklung der Chemotherapie, der Laborforschung und der Klinischen Forschung.

Der status quo kann nur ein Zwischenschritt sein. Ziel auch aller künftigen Anstrengungen ist es, die Heilungsrate zu erhöhen und die Lebensqualität der Betroffenen zu steigern. Die Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH), der alle führenden Ärzte und Kliniken angehören, die die Kinder und Jugendlichen behandeln, hat in den letzten Jahren dafür gesorgt, dass über 90 Prozent aller Betroffenen in Deutschland nach einheitlichen Ablaufplänen untersucht und behandelt werden. Die in Deutschland erreichten Behandlungsergebnisse bei krebskranken Kindern und Jugendlichen zählen zu den besten der Welt.

Um das Wissen aller Beteiligten über die Krankheit optimal zu vernetzen, hat die GPOH 1999 das „Kompetenznetz Pädiatrische Onkologie und Hämatologie" gegründet. Das Netzwerk soll für „Mehr Wissen, besseres Verstehen und gezielteres Behandeln" sorgen und einen Qualitätsstandard für alle Fragen rund um Krebs bei Kindern festlegen. Eltern und Kinder, Ärzte und Kliniken, Forschung und Pharmaunternehmen, Presse und Öffentlichkeit sind in einem Netz. Die elf spezifisch ausgerichteten Aufgabenstellungen schaffen ein Know-how, das nur zusammen generiert werden kann.

Die Ergebnisse des „Kompetenznetz Pädiatrische Onkologie und Hämatologie" kommen den Betroffenen schnell zu Gute. Damit aus Angst und Ohnmacht immer mehr Hoffnung und Heilung wird. Denn es gibt nicht das eine Medikament gegen den Krebs, sondern umfassende Konzepte zur Behandlung von Krebskrankheiten.

BESSERE ERGEBNISSE DURCH KOOPERATION

Die folgenden Forschungsschwerpunkte und Projekte werden realisiert im Kompetenznetz Pädiatrische Onkologie und Hämatologie

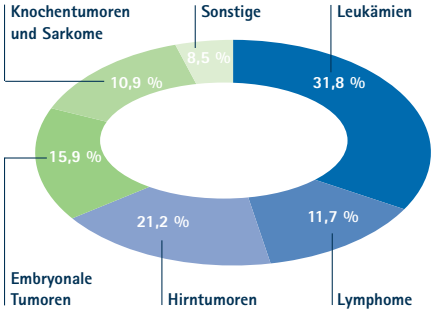
Projekt	Leitung	Telefon
Koordinationszentrale	Prof. Dr. med. Dr. h.c. Günter Henze, Berlin	+49 (30) 45 05-6 60 32
Rechnerbasierte Anwendungssysteme	Dipl.-Inform. Med. Ulrike Kutscha, Heidelberg	+49 (62 21) 56-54 81
Datenschutz/Datensicherheit	Prof. Dr. rer. nat. Klaus Pommerening, Mainz	+49 (61 31) 17-31 06
Telemedizin	Prof. Dr. med. Norbert Graf, Homburg Dr. med. Michael Paulussen, Münster	+49 (68 41) 16-2 83 97 +49 (2 51) 8 35-28 01
Molekulare Parameter der Zytostatikaresistenz	Prof. Dr. med. Klaus Debatin, Ulm	+49 (7 31) 5 02-77 00
Präleukämische Knochenmarkerkrankungen	Prof. Dr. med. Charlotte Niemeyer, Freiburg	+49 (7 61) 2 70-21 05
Molekulare Veränderungen bei embryonalen Tumoren	Prof. Dr. med. Frank Berthold, Köln	+49 (2 21) 4 78-43 80
Lebensqualität und Spätfolgen	Dr. med. Gabriele Calaminus, Düsseldorf	+49 (2 11) 8 11-76 80
Minimale Resterkrankung	Prof. Dr. med. Jochen Harbott, Gießen	+49 (6 41) 99-4 34 26
Sekundärmalignome nach Krebserkrankungen im Kindesalter	Dr. rer. physiol. Peter Kaatsch, Mainz	+49 (61 31) 17-31 11
Immun- und Gentherapie	Prof. Dr. med. Stefan Burdach, Halle	+49 (3 45) 5 57-23 88

GROSSE FORTSCHRITTE
FÜR KLEINE PATIENTEN

Das jahresbezogene Auftreten von Krebserkrankungen im Kindes- und Jugendlichenalter ist seit 20 Jahren konstant: Es erkranken 14 von 100.000, das waren 1.838 unmittelbar Betroffene im Jahr 2000 (jeweils bezogen auf unter 15jährige Kinder und Jugendliche).

75% der Erkrankten werden in 32 speziellen Kliniken betreut.
Neu durch das Kompetenznetz Pädiatrische Onkologie und Hämatologie: An den meisten Kliniken schaffen Forschungs- und Studienassistenten eine neue Daten- und Materiallogistik.

Krebserkrankungen im Kindes- und Jugendalter weisen eine besondere Verteilung und charakteristische Tumorarten auf, die beispielsweise aus Geweben entstehen, die krankhafterweise in einem embryonalen Stadium verblieben sind.
Drei von vier Patienten werden geheilt, aber ungefähr 500 Kinder und Jugendliche sterben jedes Jahr an der Krebserkrankung. Zum Vergleich: In dieser Altersgruppe sind nur Unfalltodesfälle häufiger.



EIN PROJEKT DER GESELLSCHAFT FÜR PÄDIATRISCHE ONKOLOGIE UND HÄMATOLOGIE GPOH

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

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Kinderkrebs-Informationsportal: www.kinderkrebsinfo.de

Kompetenznetz Pädiatrische Onkologie und Hämatologie

Erfolg der Behandlung von Kindern mit Krebserkrankungen durch einheitliche und konsequente Diagnostik und Therapie in Therapieoptimierungsstudien während der letzten 20 Jahre

U. Creutzig [1], G. Henze [2], H. Jürgens [3]
für die Gesellschaft für Pädiatrische Onkolgie und Hämatologie
unter Mitarbeit von S. Bielack [4], P. Kaatsch [5], J. Klussmann [6], N. Graf [7], D. Reinhardt [4], M. Schrappe [8], M. Zimmermann [8]

[1] Geschäftsführerin der GPOH und Leiterin der Koordinationszentrale Kompetenznetz Pädiatrische Onkologie und Hämatologie; [2]Sprecher des Kompetenznetzes Pädiatrische Onkologie und Hämatologie, Berlin; [3]Vorsitzender der GPOH, Münster; [4]Pädiatrische Hämatologie/Onkologie Universitäts-Kinderklinik, Münster; [5]Deutsches Kinderkrebsregister, Mainz; [6]Stud. med., Göttingen; [7]Universitäts-Kinderklinik, Homburg/Saar; [8]Kinderklinik der MHH, Hannover

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Die Diagnose „Krebs“ bedeutete noch bis in die 60er und 70er Jahre auch bei Kindern ein nahezu sicheres Todesurteil. Im Folgenden soll die Entstehung und Entwicklung der pädiatrischen Onkologie in Deutschland dargestellt werden, die heute bei etwa 75% aller Kinder mit bösartigen Erkrankungen eine Heilung ermöglicht.

Epidemiologie

Maligne Erkrankungen sind insgesamt bei Kindern selten. Die altersstandardisierte Inzidenz zwischen 1991-2000 lag bei 13,7 Neuerkrankungen pro 100.000 unter 15jährigen Kindern pro Jahr. (1).Wichtig für die möglichst vollständige Erfassung aller Erkrankungsfälle war die Gründung des Kinderkrebsregisters am Institut für Medizinische Statistik und Dokumentation in Mainz am 1. Januar 1980. Das Deutsche Kinderkrebsregister ist heute mit etwa 30 000 erfassten Erkrankungen das größte seiner Art. Seit 1991, als mit der Erweiterung der Bundesrepublik die Erfassung ausgedehnt wurde, kommen jährlich bei einer Bevölkerung von 13,0 Millionen Kindern etwa 1800 Neuerkrankungen pro Jahr hinzu.

Abbildung 1 zeigt die relative Häufigkeit der l991 bis 2000 gemeldeten Patienten nach den häufigsten Diagnosegruppen (nur Patienten unter 15 Jahren) (1). Der Vergleich der relativen Häufigkeit bösartiger Neubildungen bei Kindern und Erwachsenen zeigt, daß im Kindesalter praktisch ausschließlich Malignome mesodermalen Ursprungs auftreten im Gegensatz zu der Dominanz epi- und endodermaler Neoplasien im Erwachsenenalter. Die Leukämien und malignen Lymphome überwiegen mit 47%, gefolgt von ZNS-Tumoren, embryonalen Neoplasien und Sarkomen des

Bindesgewebes und Knochens, während Karzinome außerordentlich selten sind (1%). Damit bestehen grundlegende Unterschiede in der absoluten und relativen Häufigkeit der Malignome bei Kindern und Erwachsenen (> 90% Karzinome).

Ein großer Teil der Tumoren im Kindesalter ist pränatal angelegt; sie werden als embryonale Tumoren bezeichnet (Neuroblastom, Nephroblastom, Medulloblastom, Retinoblastom, embryonales Rhabdomyosarkom, Keimzelltumoren, Hepatoblastom). Diese Tumoren werden meist bereits in den ersten fünf Lebensjahren diagnostiziert. Bei den übrigen Malignomen ist die Altersverteilung zum Teil sehr unterschiedlich. Die akute lymphoblastische Leukämie (ALL), die häufigste Einzeldiagnose, betrifft überwiegend 1 bis 6 Jahre alte Kinder, während bei älteren Kindern Knochentumoren und Lymphome eine vergleichsweise hohe Inzidenz aufweisen (1).

Zusammenarbeit in der Pädiatrischen Onkologie im Rahmen von Therapieoptimierungsstudien

Angesichts der Seltenheit von malignen Erkrankungen im Kindesalter haben sich die Pädiatrischen Onkologen schon in den siebziger Jahren zusammengeschlossen, um ausreichende Erfahrung in der Therapie so seltener Erkrankungen zu generieren.
Sechs Jahre nachdem Donald Pinkel 1968 (Memphis/USA) auf einem Vortrag in München seine Heilungsergebnisse bei Kindern mit ALL vorstellte (s.u.), wurden nahezu gleiche Ergebnisse innerhalb einer ersten gemeinsamen Therapiestudie zur Behandlung der ALL in Deutschland (2) erreicht. Die 1976 von H. Riehm gegründete BFM (Berlin, Frankfurt, Münster)-Studiengruppe ist durch ihr Behandlungskonzept (s.u.) und die erreichten hohen Heilungsraten bei der ALL international bekannt geworden (3). Heute beteiligen sich pädiatrisch-onkologisch tätige Ärzte an über 70 deutschen, österreichischen und schweizerischen Kliniken an dieser Kooperation. Am internationalen Standard gemessen sind dadurch beispielgebende Behandlungsergebnisse erzielt worden (s. Abb.2).

Die „Deutsche Arbeitsgemeinschaft für Leukämie-Forschung und -Behandlung im Kindesalter (DAL) wurde 1966 gegründet, 1973 folgte die Gesellschaft für Pädiatrische Onkologie (GPO) mit dem Ziel, auch die Tumorkrankheiten im Kindesalter zu erforschen und gemeinsam zu behandeln. GPO und DAL tagten seitdem gemeinsam halbjährlich. Ihre wichtigsten Projekte sind die Durchführung von multizentrischen Therapiestudien, deren Überwachung, Auswertung und kontinuierliche Aktualisierung. Beide Arbeitsgemeinschaften wurden 1991 zur Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH) vereinigt.
In Deutschland werden derzeit über 90% der an Krebs erkrankten Kinder und Jugendlichen in 23 aktiven Therapiestudien eingeschlossen und einheitlich behandelt (s. Tab. 1). Nach Angaben des Deutschen Kinderkrebsregisters (s.u.) liegt der relative Anteil von Studienpatienten je nach Diagnose zwischen 92% und 100%. Der hohe Anteil der in Therapiestudien erfassten und dokumentierten Patienten hat Deutschland im internationalen Vergleich eine herausragende Stellung in der Qualität von klinischer Krebsforschung und Krebsbehandlung im Kindesalter verschafft. Die Spitzenstellung geht zurück auf die Behandlungslogistik der Pädiatrischen Onkologie und die weitgehende Konzentrierung der Behandlung auf spezialisierte Zentren. So werden ca. 75% der krebskranken Kinder und Jugendlichen an den 30 größten Zentren in Deutschland behandelt.
Therapieoptimierungsstudien in der Pädiatrischen Onkologie beinhalten Aspekte der klinischen Forschung und dienen der Verbesserung der Behandlungsqualität der betroffenen Kinder. Referenzlaboratorien innerhalb der Studien sind ein elementares qualitätssicherndes Element. So ist die Etablierung innovativer diagnostischer Methodik nur über Referenzlaboratorien möglich.

Zwischen den Studienleitungen und dem Kinderkrebsregister findet ein regelmäßiger Informationsaustausch über Initial- und Verlaufsdaten statt. Dieser Austausch trägt zu einer gegenseitigen Qualitätssicherung der Daten bei.

Therapiekonzepte

Den Therapikonzepten bei soliden Tumoren liegt die Kombination einer intensivierten, systemisch wirkenden Polychemotherapie mit einer stetig weiterentwickelten lokalen operativen und/oder strahlentherapeutischen Behandlung zugrunde. Fast alle malignen Tumoren und hämatologischen Systemerkrankungen im Kindesalter sprechen auf eine Behandlung mit Zytostatika an. Aus diesem

Grund steht die Chemotherapie, von wenigen Ausnahmen abgesehen, im Mittelpunkt oder sie ist wesentlicher Bestandteil der kombinierten Behandlungsstrategie. Mit der Chemotherapie wird bei soliden Tumoren die Zerstörung und partielle Devitialisation des Primärtumors und von bereits zum Zeitpunkt der Diagnose vorhandenen Mikrometastasen angestrebt. Die definitive lokale Behandlung des Tumors erfolgt durch Operation und Strahlentherapie.
Die Kombination von Chemo- und Strahlentherapie wird prätherapeutisch (neoadjuvant) oder postlokaltherapeutisch (adjuvant) eingesetzt. Chemo- und Strahlentherapie wird auch gleichzeitig (synchron) oder hintereinandergeschaltet (sequentiell) durchgeführt.

Therapieerfolge

Die 5-Jahres-Überlebensraten für alle malignen Erkrankungen des Kindesalters sind von weniger als 10%-20% in den 50er und 60er Jahren heute auf ca. 75% angestiegen (s. Abb. 3). Sie betragen über 90% für den Morbus Hodgkin und das Retinoblastom, 80% für die akute lymphatische Leukämie, das Non-Hodgkin-Lymphom, den Wilms-Tumor und Keimzelltumoren, 60% für die Weichteilsarkome und 55% für die Erkrankung mit der derzeit noch ungünstigsten Prognose im Kindesalter, der akuten myeloischen Leukämie. Bei Hirntumoren liegen die Überlebensraten bei 67% (s. Tab.2).

5-Jahres Überlebensraten sind angesichts der Tatsache, dass Rezidive bösartiger Erkrankungen im Kindesalter meist innerhalb der ersten zwei bis drei Jahre nach Diagnosestellung eintreten, fast identisch mit Heilungsraten. Nach erfolgreicher Therapie ist ein bei den meisten Kindern weitgehend normal verlaufendes Leben zu erwarten. Die Langzeitüberwachung ehemaliger krebskranker Kinder und Jugendlicher ist notwendig, auch um Spätfolgen und die Entwicklung möglicher Zweittumoren erkennen zu können. Sie ist angesichts der hohen Heilungsraten und der langen Lebenserwartung nach geheilter Krebserkrankung auch eine Aufgabe, die über die Kinderheilkunde hinausgeht und entsprechend zu strukturieren ist.

An den ständig angestiegenen Überlebensraten bei den Krebserkrankungen der Kinder und Jugendlichen haben die bundesweiten multizentrischen Therapieoptimierungsstudien einen erheblichen Anteil. Durch sie wurde der Standard für Diagnostik und Therapie definiert und weiter entwickelt.

Vergleich der Situation der pädiatrisch-onkologischen Studien in Deutschland und in anderen Ländern Europas

Die Situation in Deutschland unterscheidet sich von den meisten anderen Ländern Europas und auch den USA dadurch, dass hierzulande grundsätzlich fast alle Kinder mit einer Krebserkrankung innerhalb von Therapieoptimierungsstudien einheitlich für die jeweilige Krankheit behandelt werden. Es ist davon auszugehen, dass über 95% aller Patienten zentral dem Kinderkrebsregister gemeldet werden. Eine landesweite Erfassung erfolgt sonst nur in Skandinavien (Norwegen, Schweden, Finnland, Dänemark und Island) im Rahmen der NOPHO-Studien. In Großbritannien werden etwa 2/3 der pädiatrischen Patienten innerhalb von Studien behandelt. In Frankreich und Italien nimmt nur eine begrenzte Zahl von Kliniken an den Studien teil (Ausnahme nationale ALL Studie in Italien).
Bedingt durch die landesweite Ausdehnung in Deutschland nehmen auch kleinere Kliniken mit geringeren Patientenzahlen an den Therapieoptimierungsstudien teil. Dadurch wird die gesamte Patientengruppe mit einer bestimmten Krankheit erfaßt und einheitlich behandelt. Damit werden Selektionen vermieden, z.B. Begrenzung auf bestimmte Krankheitsstadien oder bestimmte Kliniken oder Ausschluß von Patienten mit Begleiterkrankungen.
Die deutschen Studien zeichnen sich zusätzlich durch die Beratungsleistung der Studienzentralen aus, die durch die zeitnahe Dokumentation und Information über die einzelnen Patienten möglich ist.
Es ist hinzuzufügen, dass eine zunehmende Internationalisierung in der Pädiatrischen Onkologie zu verzeichnen ist und mehrere internationale Studien von Deutschland ausgehen. Dazu gehören die EURO-EWING-, Wilms-Tumor-(SIOP)-, Hepatoblastom- und Keimzelltumor-Studien, sowie die Studie zur Behandlung der Low-grade-Gliome und die EWOG-MDS-Studie. Bei den Leukämien und Non-Hodgkin-Lymphomen gibt es einen Verbund der BFM-Studien unter Einschluss von Österreich, Tschechien und einem Teil der Schweiz, bei der ALL-Studie eine direkte Kooperation mit Italien.

Beispiele von Therapie- und Prognoseverbesserung bei Leukämien und Tumoren

Akute Leukämien

Akute lymphoblastische Leukämien (ALL) und akute myeloische Leukämien (AML) sind mit etwa 600 Neuerkrankungen/Jahr in Deutschland die häufigsten bösartigen Neuerkrankungen bei Kindern. Ohne Behandlung führen sie innerhalb weniger Monate zum Tod. Heute werden mit modernen Kombinationschemotherapien, bestehend aus Induktions-, Konsolidierungs- und Dauertherapie mit Zytostatika insgesamt über 80% der Kinder mit ALL und über 50% der Kinder mit AML geheilt.

Akute lymphoblastische Leukämie

In den 50er Jahren wurden erstmals Medikamente zur Behandlung von Leukämien mít mäßigem Erfolg eingesetzt. Durch Einführung der Dauertherapie wurde die mittlere Lebensdauer zwischen 1963 und 1967 in einer deutschen Studie auf 17 Monate angehoben. Die erste erfolgreiche Leukämietherapie, mit der Überlebensraten von 30% im St. Jude Childrens Research Hospital in Memphis erreicht wurden (4), bestand neben der Induktionstherapie aus einer präventiven Behandlung des zentralen Nervensystems und aus einer Dauertherapie mit mehreren Zytostatika. Diese Therapiestrategie wurde 1971 von Lampert bundesweit erfolgreich eingeführt (2). Etwa parallel dazu entwickelte H. Riehm eine intensive Kombinationstherapie, die zunächst von 1970 an in einer Westberliner Pilotstudie eingesetzt wurde (5). Dieser Therapieplan enthielt alle bis dahin bekannten bei der ALL wirksamen Mittel in einer Zusammensetzung, die bis an die therapeutische Toleranzgrenze ging und wegen der erhöhten Toxizität erheblich kritisiert wurde. Nachdem verbesserte Überlebensraten (über 50%) erkennbar wurden, schlossen sich weitere Kliniken an (Frankfurt und Münster). 1976 wurde dann die BFM (Berlin, Frankfurt, Münster)-Studiengruppe gegründet.
Die Überlebensrate stieg auf 55%, und im weiteren Verlauf wurden die Ergebnisse innerhalb von bisher 6 aufeinanderfolgenden Studien, an denen jetzt immer mehr Kinderkliniken in Deutschland teilnahmen, weiter gesteigert (Abb. 2). Durch Risikoadaptierung wurde die Therapie für Patienten mit Standardrisiko massvoll gestaltet, während sie bei Kindern mit mittleren und hohem Risiko weiter intensiviert wurde. In den aufeinanderfolgenden Studien konnte immer mehr die präventive Schädelbestrahlung durch eine auf das Zentralnervensystem ausgerichtete Chemotherapie ersetzt werden.

Im Rahmen der Studien wurde der Prognosefaktor Ansprechen auf eine Vorphase mit Prednison etabliert. Die etwa 10% der Patienten, die unzureichend auf die initiale einwöchige Prednisontherapie ansprachen, zeigten ein ereignisfreies Überleben von unter 40% im Vergleich zu den gut ansprechenden Patienten 65% (Studie ALL-BFM 83).
Die Hochdosistherapie mit Methotrexat führte in der Studie ALL-BFM 86 zu einer Verbesserung der Überlebensraten bei Kindern mit T-ALL. Zugleich kam es zu deutlich weniger Rezidiven im Zentralnervensystem. In den 90er Jahren war das Ziel, die Spätfolgen bei Patienten mit einem guten Ansprechen auf Prednison zu reduzieren. Die Anthrazyklindosen wurden reduziert und die Strahlentherapie auf Hochrisikopatienten und T-ALL begrenzt. Heute wird die Therapie auch nach dem Ergebnis der molekularen Untersuchungen zur „minimalen Resterkrankung“ (MRD) gesteuert.

Insgesamt konnte an Erkenntnissen gewonnen werden:

1. die Reintensivierung der Chemotherapie ist auch bei Patienten mit einem niedrigen Risiko eines Rückfalls ein entscheidender Teil der Behandlung
2. die Intensität der präventiven Strahlentherapie des ZNS kann gesenkt oder komplett durch eine systemische und intrathekale Chemotherapie ersetzt werden
3. eine 24-monatige Erhaltungstherapie verhindert eine höhere Anzahl von Rückfällen im Vergleich zu einer 18- monatigen Behandlung
4. das frühe Ansprechen ermöglicht die Zuordnung zu Risikogruppen.

Heute sind die BFM-ALL-Studien weltweit anerkannt. In den USA wurden wesentliche

Therapieelemente übernommen. Die Studie wird heute gemeinsam mit Österreich und Italien durchgeführt und in weiteren Studiengruppen in Osteuropa, Mittel- und Südamerika zum Teil in adaptierter Form durchgeführt.
In der zweiten in Deutschland laufenden Studie CoALL wurden ähnliche Ergebnisse mit einer etwas anders gestalteten Intensivphase erzielt.

Akute myeloische Leukämie

Akute myeloische Leukämien (AML) sind bei Kindern deutlich seltener als die ALL (nur 20% aller Leukämien im Kindesalter). 1978 wurde in Deutschland die erste kooperative Therapiestudie bei Kindern mit AML durchgeführt (6). Die Therapiestrategie war ähnlich aufgebaut wie die der ALL, wobei Substanzen, die bei der AML wirksamer sind, verstärkt angewandt wurden. Dazu gehören insbesondere die Medikamente Cytosinarabinosid und die Anthrazykline. Wie bei der ALL wurde auch bei der AML eine präventive Schädelbestrahlung und eine Erhaltungstherapie durchgeführt.
Mit Hilfe der Anfangstherapie (Induktion) erreichten 1978 fast 80% der Patienten eine Remission, und die 5-Jahres-Überlebensrate konnte von unter 10% auf 40% angehoben werden.

In den weiteren Studien wurde die Therapie deutlich intensiviert und optimiert, so dass heute eine 5-Jahresüberlebensrate von 60% erreicht worden ist. Die schematische Entwicklung in der Struktur der AML-BFM-Studien wird in Abbildung 4 aufgeführt.

Die Erfahrungen der Vorgängerstudie wurden jeweils zur Optimierung der folgenden Studie genutzt. Dieses Vorgehen hat entscheidend, zusammen mit der Verbesserung der supportiven Therapie und dem Erfahrungsgewinn der Teilnehmer, zu einem Anstieg der Überlebensraten in den vier aufeinanderfolgenden AML-BFM Therapiestudien geführt.

Osteosarkome

3% aller bösartigen Neuerkrankungen bei Kindern und Jugendlichen sind Osteosarkome. Damit gehören Osteosarkome zu den häufigsten bösartigen Knochentumoren in dieser Altersgruppe. Sie sind meist in den Wachstumsfugen der langen Röhrenknochen lokalisiert und kommen häufiger bei Jungen vor.

Bei etwa 70% der Patienten mit Osteosarkom wird davon ausgegangen, dassMikrometastasen zum Zeittpunkt der Diagnose vorliegen“. Durch eine präoperative Therapie werden diese Mikrometastasen frühzeitig behandelt und der Tumor wird partiell devitalisiert. Bei gutem Ansprechen auf die Chemotherapie werden oft extremitätenerhaltende Operationen möglich. Aus dem Ansprechen können auch Prognose und weiteres Vorgehen abgeleitet werden. Nach der Operation wird die Chemotherapie fortgesetzt (7). Die Bestrahlung spielt in der Lokaltherapie wegen der hohen Resistenz der Osteosarkomzellen eine untergeordnete Rolle.

Die deutsch, österreichisch, schweizerische Studiengruppe COSS führt seit 1977 multizentrische Studien zur Behandlung von Osteosarkomen durch. Während das erste Protokoll COSS-77 auf einer postoperativen adjuvanten Chemotherapie basierte, beinhalteten alle Studienprotokolle nach 1980 eine neoadjuvante Chemotherapie.
Der Zusammenhang zwischen Tumorgröße, dem Ansprechen auf die Chemotherapie und dem rückfallfreien Überleben wurde in der COSS-80-Studie etabliert.

Insgesamt stieg die Wahrscheinlichkeit für ein ereignisfreies Überleben nach 10 Jahren von 46% in der Studie COSS-77 auf 66% in der Studie COSS-86 an (s. Abb. 5). Mit der Studie COSS-96 wird an die guten Ergebnisse der COSS-86-Studie angeknüpft und gleichzeitig versucht, die Nebenwirkungen und Spätfolgen der Therapie zu minimieren.

Wilms-Tumor (Nephroblastom)

Der Wilms-Tumor (Nephroblastom) gehört zu den embryonalen Tumoren. Assoziationen mit Mißbildungssyndromen (Hemi-hypertrophie, Wiedemann-Beckwith Syndrom, urogenitale Fehlbildungen, Aniridie) sind bekannt. 70% der an Wilms-Tumoren neu erkrankten Kinder sind zwischen 1 und 5 Jahren alt. Säuglinge sind zu etwa 15% betroffen. Bei 10% der Patienten wird der Tumor bei einer Vorsorgeuntersuchung als tastbarer Bauchtumor festgestellt .Die Diagnose beruht wesentlich auf bildgebenden Untersuchungen (abdominelle Sonographie, CT oder MRT).
Die Behandlung besteht aus einer Kombination von Operation, Chemotherapie und evtl. Bestrahlung. Sie wird nach dem Alter, dem Stadium (I bis V) und dem histologischem Subtyp, einem der wesenlichen Prognosefaktoren beim Wilms-Tumor, stratifiziert. Das Ziel der Operation ist immer eine radikale Entfernung des Tumors und dessen Metastasen und eine genaue Bestimmung des Stadiums (8).

Die Durchführung der Chemotherapie und Strahlentherapie wird in Abhängigkeit von unterschiedlichen Risikofaktoren stratifiziert. Weltweit sind hier die prospektiven, randomisierten, multizentrischen Studien der NWTSG (National Wilms Tumor Study Group) in den USA und der SIOP (International Society of Paediatric Oncology), vorwiegend in Europa, führend. Hauptziele dieser Studien sind, durch risikoadaptierte Behandlung hohe Heilungsraten zu erzielen, akut- und Spätfolgen zu reduzieren und die Belastung durch die Therapie zu minimieren.
Innerhalb der SIOP wurde insbesondere die Wertigkeit einer präoperativen Behandlung analysiert. Diese führt zu einer Reduktion des Tumorvolumens und bewirkt ein sogenanntes "downstaging" des Tumors nach Operation. Die operative Entfernung des geschrumpften Tumors wird dadurch erleichtert und das Risiko von Tumorrupturen deutlich vermindert. Gleichzeitig werden Mikrometastasen ohne Verzögerung behandelt und das Ansprechen auf die präoperative Therapie kann gemessen und zur Stratifizierung der postoperativen Therapie herangezogen werden.

Die wichtigsten Ergebnisse von insgesamt sechs SIOP-Studien sind:

- SIOP 2 Studie: Signifikant weniger intraoperative Tumorrupturen bei präoperativer Bestrahlung und präoperativer Therapie mit Actinomycin D im Vergleich zur sofortigen Operation.
- SIOP 5 Studie (1977): Kein Unterschied in den Überlebensraten und im ereignisfreien Überleben mit präoperativer Chemotherapie oder Radiotherapie. Seitdem ist die präoperative Chemotherapie über 4 Wochen mit Actinomycin D und Vincristin Standard.
- SIOP 6 Studie (1980): Eine reduzierte postoperative Behandlung, abhängig vom lokalen Stadium, wurde mit der damaligen postoperativen Standardtherapie verglichen um Spätfolgen zu senken. Das Ergebnis zeigte für das Stadium I keine Prognoseverschlechterung durch Therapiereduktion, jedoch in den Stadien II und III. Daraufhin wurde die Behandlung für diese Stadien in der folgenden Studie SIOP 9 intensiviert (Überlebensraten s. Abb. 6).
- SIOP 9 Studie: Beim Vergleich einer verlängerten präoperativen Chemotherapie (4 gegen 8 Wochen) ergab sich zwar eine weitere Tumorvolumenreduktion aber keine Erniedrigung des postoperativen Stadiums. Die postoperative Chemotherapie bestand aus Vincristin und Actinomycin D und wurde im Stadium II und III durch Doxorubicin ergänzt. Die lokale Radiotherapie wurde auf wenige Indikationen reduziert, so dass nur noch 18% aller Patienten bestrahlt wurden. Die ereignisfreie Überlebensrate betrug 84% und die Überlebensrate 90% nach jeweils fünf Jahren.
- SIOP 93 Studie: Eine weitere Therapiereduktion im Stadium I wurde prospektiv randomisiert geprüft. Vorläufige Ergebnisse zeigen, dass die postoperative Therapie im Stadium I auf 4 Wochen ohne Prognoseverschlechterung reduziert werden kann. Dafür konnte die Prognose bei Hochrisikopatienten mit einem Klarzellensarkom durch eine weitere Intensivierung der Therapie verbessert werden.

In zukünftigen Studien zum Wilmstumor sollen unter Einbeziehung von molekularbiologischen Untersuchungen weitere Risikofaktoren ermittelt werden, um die Behandlung noch besser dem jeweiligen Risiko anzupassen.

Hirntumoren

Die Tumoren des Zentralnervensystems sind mit ca. 20 % aller Krebserkrankungen im Kindesalter die größte Diagnosegruppe unter den soliden Tumoren. Dies sind in Deutschland jährlich ca. 380

neuerkrankte Kinder und Jugendliche. Das mittlere Erkrankungsalter liegt bei 6½ Jahren. Astrozytome sind mit ca. 50% aller Hirntumoren die größte Gruppe. Es folgen Medulloblastome mit 20%, Ependymome mit 10% und Kraniopharyngeome mit 8%. Zwei Drittel der Tumoren betreffen das Kleinhirn. Das biologische Verhalten der Tumoren und die Prognose hängt vom feingeweblichen Typ, aber auch von der Lokalisation und Operabilität des Tumors und dem Alter des Kindes ab. Häufig führen neurologische, intellektuelle, hormonelle und psychosoziale Defizite zu einer Beeinträchtigung der Lebensqualität.

Medulloblastome

Das Medulloblastom entsteht durch eine Störung der normalen Kleinhirnentwicklung. Der Tumor kann in angrenzende Strukturen hineinwachsen, z.B. in den Hirnstamm, aber auch in den 4. Ventrikel und entlang der Liquorwege.
Die Anamnese ist aufgrund der Bösartigkeit der Medulloblastome meist kurz. Kopfschmerzen und Erbrechen sind typisch, ebenso mentale oder emotionale Veränderungen, Gleichgewichtsprobleme oder Störung der Feinmotorik. Bildgebende Verfahren wie Computertomographie oder Magnetresonanztomographie bestätigen die Diagnose und ermöglichen eine genaue Lokalisation des Tumors.

Die Prognose von Kindern mit einem Medulloblastom war noch in den 80er Jahren schlecht. In Deutschland überlebten damals die Hälfte der Kinder fünf Jahre und nur 39% zehn Jahre. Die körperliche und geistige Entwicklung sowie das psychosoziale Verhalten der geheilten Kinder wurde häufig durch die Tumorerkrankung, aber auch durch die Therapie, insbesondere die Bestrahlung von Kopf- und Spinalkanal, erheblich beeinträchtigt. Das Ziel der bundesweiten HIT(**Hi**rn**t**umor)-Studien der GPOH war daher nicht nur die Heilung möglichst vieler Kinder, sondern auch die Verringerung der therapiebedingten Spätfolgen und damit die Steigerung der Lebensqualität der Langzeitüberlebenden.
Durch eine adjuvante Chemotherapie in Ergänzung zu Operation und Bestrahlung wurde die Prognose von Kindern mit hohem Rezidivrisiko, d.h. ausgedehntem Tumor, inkompletter Resektion, Metastasen und niedrigem Alter, deutlich verbessert. Die Standardkombination besteht aus Cisplatin, CCNU und Vincristin. Bei Kindern ohne primäre Metastasierung können mit kombinierter postoperativer Strahlen- und Chemotherapie Heilungsraten von über 60% erwartet werden (9).

Die multizentrische Therapiestudie HIT 2000 verfolgt das Ziel einer möglichst individuellen, dem Rückfall- und Spätfolgenrisiko angepassten Therapie. Die Zuordnung zu einer bestimmten Therapiegruppe erfolgt anhand von Risikomerkmalen wie zum Beispiel Alter bei Diagnose und Stadium der Metastasierung. Mehr als in den vorangegangen Studien sollen die Aspekte der Spätfolgen sowie der Lebensqualität bearbeitet werden, um so die Grundlage für eine adäquate Rehabilitation ehemals an einem Hirntumor erkrankter Kinder zu schaffen.

Infrastruktur und Förderung von Studien

Mehr als 90% aller Kinder mit malignen Erkrankungen werden in Deutschland innerhalb von Therapieoptimierungsstudien behandelt. Somit stellen die Therapieoptimierungsstudien z.Zt. den Standard in der Pädiatrischen Onkologie und Hämatologie dar. Sie haben erheblich zur Verbesserung der Überlebenschancen von Kindern mit malignen Erkrankungen beigetragen und sind ein positives Beispiel für gut funktionierende interdisziplinäre Zusammenarbeit.

In den Therapieoptimierungsstudien werden neue Therapieansätze verfolgt. Bei diesen Studien geht es nicht primär um die Zulassung von neuen Medikamenten sondern um die Weiterentwicklung von interdisziplinären multimodalen Therapieansätzen. Überwiegend wird eine modifizierte Therapie mit einer Standardbehandlung hinsichtlich Verbesserung der Prognose und Verminderung von Nebenwirkungen verglichen. Gleichzeitig wird im Rahmen dieser Studien ein erheblicher Beitrag zur Qualitätssicherung geleistet (Qualität der Diagnose, Beratung der teilnehmenden Ärzte, Dokumentation der Prozess- und Ergebnisqualität).
Innerhalb dieser Therapieoptimierungsstudien müssen oft für das Kindesalter nicht zugelassene Medikamente verabreicht werden. Viele Medikamente bleiben in ihrer Zulassung auf häufige Indikationen beschränkt, auch wenn der Stand der medizinischen Wissenschaft den Zulassungsrahmen

überschritten hat. Auch ist in den seltensten Fällen das Kindesalter bei der Indikation berücksichtigt. Die Verwendung außerhalb der registrierten Indikation bei seltenen Krankheiten und für Kinder als Altersgruppe ist somit ein zentrales Problem in der Pädiatrischen Onkologie, dem nur durch die Behandlung innerhalb von Therapieoptimierungsstudien, die sich nach dem internationalen Standard ärztlichen Wissens ausrichten, begegnet werden kann. Nur so ist für alle krebskranken Kinder und Jugendliche eine qualitätsgesicherte Therapie gewährleistet.
Ein erheblicher Klärungsbedarf besteht in Hinblick auf die Stellung solcher Studien im Rahmen des Arzneimittelgesetzes, auch um den damit verbundenen logistischen Überbau zu definieren und diese Studien durchführbar und finanzierbar zu halten.

Da Tumorerkrankungen im Kindesalter selten sind, können nur bundesweite, teils sogar nur internationale Studienkonzepte die notwendigen Daten und die Evidenz für eine Verbesserung in der Behandlung generieren.

Kostenanalyse

Die Abschätzung der Behandlungskosten einer malignen Erkrankung im Kindesalter ist komplex, da sowohl direkte Kosten wie Medikamenten-, Personal-, Geräte- oder Gebäudekosten berücksichtigt werden müssen, zum anderen aber auch die indirekten Folgekosten durch Arbeitsunfähigkeit, Beitragsausfälle (Eltern und Kinder). Bislang wurden nur in wenigen Analysen die Kosten für die Behandlung maligner Erkrankungen untersucht.
In einer finnischen Kostenanalyse im Kuopio University Hospital zwischen 1991 und 1994 wurden die durchschnittlichen direkten Kosten einer ALL-Behandlung bei Kindern auf US $103.250 (US $55.196-166.039) kalkuliert.
Die Patienten wurden vor ihrer Behandlung in drei Gruppen (Standardrisiko SR, mittleres Risiko IR, hohes Risiko HR) je nach ihrem Rückfallrisiko eingeteilt. Nach der Einteilung richtete sich auch die Behandlung und dementsprechend waren die Kosten stark von der Risikogruppe abhängig (SR: $74.342, IR:$91.207, HR: $136.973).
In den direkten Kosten sind die üblichen Krankenhauskosten (Bettkosten, Personalkosten etc.) und die patientenspezifischen Kosten enthalten. Zu den patientenspezifischen Kosten zählen alle Kosten, die einem einzelnen Patienten angerechnet werden können, wie z.B. Kosten, die das Labor, die Radiologie und die Therapie (Chemotherapie, Bestrahlung, Operation, Transfusionen, Antibiotika, Antimykotika etc.) betreffen. Die indirekten Kosten wie z.B. Verdienstausfälle der Eltern und Fahrtkosten sind nicht mit einbezogen.

In einer derzeitig dualen Finanzierung sind die mit der pädiatrischen Onkologie verbundenen Behandlungskosten durch die Krankenversicherungsträger gedeckt, der mit den Therapie-optimierungsstudien verbundene analytische Überbau ist fremd finanziert. Der weitaus größte Anteil entfällt dabei auf die Deutsche Krebshilfe, der so der wesentliche und nicht wegdenkbare Verdienst um die Strukturentwicklung in der Pädiatrischen Onkologie zuzuerkennen ist. Für den Konsiliarteil und qualitätssichernde Aspekte sind jedoch neue Finanzierungsmodelle vordringlich. Angemessen wäre aus unserer Sicht die Kalkulation von Qualitätssicherungsanteilen an den Therapieoptimierungsstudien und die Übernahme von so ermittelten Kosten für Konsiliarleistungen, Dokumentation und Qualitätssicherung und Referenzlaboratorien durch die Krankenversicherungen, die für die Qualitätssicherung der medizinisch erforderlichen Behandlung zuständig sind. Ein Merkmal der Therapieoptimierungsstudien ist auch, dass diese geradezu exemplarisch eine "Evidenz-basierte" Medizin darstellen. Nach den§§ 2, 70, 72, 135 SGB Vhat der Patient ein Anrecht auf die Weiterentwicklung der Qualität der Behandlung und die Krankenhäuser sind verpflichtet, sich an einrichtungsübergreifenden Massnahmen der Qualitätssicherung zu beteiligen. Förderungsmittel der Deutschen Krebshilfe wie auch der Deutschen Kinderkrebsstiftung können dann verstärkt dem eigentlichen Zweck der Förderung von Grundlagenforschung, Transferforschung und Klinischer Forschung zugeführt werden. Nur so kann langfristig eine hoch qualifizierte, Evidenz-basierte, aktuelle Forschungsergebnisse berücksichtigende Medizin in der Pädiatrischen Onkologie in Deutschland gesichert werden. Dies ist auch primäres Ziel des Förderprogramms "Kompetenznetze in der Medizin" des Bundesministeriums für Bildung und Forschung (BMBF) und des Kompetenznetzes Pädiatrische Onkologie und Hämatologie im Rahmen dieses strukturellen Förderprogramms.

Literatur

(1) Kaatsch P, Spix C, Michaelis J. German Childhood Cancer Registry - Annual Report 2000 (Jahresbericht 2000 des Deutschen Kinderkrebsregisters). Deutsches Kinderkrebsregister, editor. 2002. Institut für Medizinische Biometrie, Epidemiologie und Informatik.

(2) Henze G, Langermann HJ, Lampert F, Neidhardt M, Riehm H. Die Studie zur Behandlung der akuten lymphoblastischen Leukämie 1971-1974 der Deutschen Arbeitsgemeinschaft für Leukämie-Forschung und -Behandlung im Kindesalter e.V. Klin Pädiatr 1979; 191(2):114-126.

(3) Schrappe M, Reiter A, Zimmermann M, Harbott J, Ludwig WD, Henze G, Gadner H, Odenwald E, Riehm H. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995. Berlin-Frankfurt-Munster. Leukemia 2000; 14(12):2205-2222.

(4) Pinkel D, Simone J, Omar Hustu H, Aur R.J.A. Nine years experience with "total therapy" of childhood acute lymphocytic Leukemia. Pediatrics 1972; 50(2):246-251.

(5) Riehm H, Gadner H, Welte K. [The west-berlin therapy study of acute lymphoblastic leukemia in childhood--report after 6 years]. Klin Padiatr 1977; 189(8):89-102.

(6) Creutzig U, Ritter J, Riehm H, Langermann H-J, Henze G, Kabisch H, Niethammer D, Jürgens J, Stollmann B, Lasson U, Kaufmann U, Löffler H, Schellong G. Improved treatment results in childhood acute myelogenous leukemia: A report of the German cooperative study AML-BFM-78. Blood 1985; 65:298-304.

(7) Bielack S, Flege S, Kempf-Bielack B. Behandlungskonzept des Osteosarkoms. Onkologe 2000; 6:747-759.

(8) Gutjahr P. Krebs bei Kindern und Jugendlichen. Alzen G, Bode U, Fleischhack G, Graf N, Gummich R, Haas RJ, Hasan C, Henze G, Hertl M, Humpl T, Keber W, Kontny U, Kovar H, Kühl J, Kutzner J, Lion T, Niemeyer C, Schmid I, Schmitt H-J, Stachel D, Weinmann G, editors. Klinik und Praxis der Pädiatrischen Onkologie. 24-611. 1999.

(9) Kühl J, Müller HL, Berthold F, Kortmann R.D., Deinlein F, Maaß F, Graf N, Gnekow A, Scheurlen W, Göbel U, Wolff J, Bamberg M, Kaatsch P, Kleihues P, Rating D, Sörensen N, Wiestler OD. Pre-radiation chemotherapy of children and young adults with malignant brain tumors: results of the German pilot trial HIT `88/`89. Klin Pädiatr 1998; 210:227-233.

(10) Graf N, Tournade MF, de Kraker J. The role of preoperative chemotherapy in the management of Wilms' tumor. The SIOP studies. International Society of Pediatric Oncology. Urol Clin North Am 2000; 27(3):443-454.

Tabelle 1: Studien und Projekte der Gesellschaft für Pädiatrische Onkologie und Hämatologie

	Projekt/Studienbezeichnung	***Leitung***
Studien		
(1)	Akute lymphoblastische Leukämie – ALL-BFM 2000	Prof. Dr. med. M. Schrappe, Kinderklinik der MHH, Hannover
(2)	Akute lymphoblastische Leukämie – COALL-06-97	Frau Prof. Dr. med. G. Janka, Univ.-Kinderklinik Hamburg
(3)	Akute lymphoblastische Leukämie-Rezidive ALL-REZ BFM 96	Prof. Dr. med. G. Henze, Univ.-Kinderklinik Berlin (Charité)
(4)	Akute Myeloische Leukämie AML-BFM 98	Prof. Dr. med. J. Ritter, Frau Prof. Dr. med. U. Creutzig, Univ.-Kinderklinik Münster
(5)	Schwere Aplastische Anämie SAA94	Frau Dr. M. Führer, Frau Prof. Dr. med. Ch. Bender-Götze, Univ.-Kinderklinik München
(6)	Chronische myeloische Leukämie bei Kindern CML-päd 95/96	Prof. Dr. med. M. Suttorp, Univ.-Kinderklinik Dresden
(7)	Ewing-Sarkom EUROpean Ewing tumour Working Initiative of National Groups – EURO-E.W.I.N.G. - 99	Prof. Dr. med. H. Jürgens, Univ.-Kinderklinik Münster
(8)	Hepatoblastom HB 94	Prof. Dr. med. D. von Schweinitz, Univ.-Kinderklinik Basel
(9)	Hirntumoren Medulloblastome (HIT MED)	PD Dr. med. J. Kühl, Univ.-Kinderklinik Würzburg
(10)	Kraniopharyngeom (HIT-ENDO)	PD Dr. med. Hermann Müller, Städt. Kinderklinik Oldenburg
(11)	Glioblastome hoch maligne (HIT – GBM)	PD Dr. J.E.A. Wolff, Kinderklinik. St. Hedwig, Regensburg
(12)	Glioblastome niedrig maligne (HIT-LGG)	Frau Dr. Astrid K. Gnekow, Kinderklinik Augsburg (Zentralklinik)
(13)	Morbus Hodgkin Therapiestudie für den Morbus Hodgkin bei Kindern und Jugendlichen – GPOH HD-2002 in Planung	Z. Zt. nicht besetzt
(14)	Maligne nichttestikuläre Keimzell-Tumoren MAKEI 96	Prof. Dr. med. U. Göbel, Univ.-Kinderklinik Düsseldorf
(15)	Testikuläre Keimzelltumoren MAHO 98	Prof. Dr. med. U. Göbel, Univ.-Kinderklinik Düsseldorf
(16)	Maligne endokrine Tumoren MET 97	Prof. Dr. med. P. Bucsky, Univ.-Kinderklinik Lübeck
(17)	Myelodysplastische Syndrome (einschl. CMML) –98 EWOG-MDS 98	Frau Prof. Dr. med. Ch. Niemeyer, Univ.-Kinderklinik Freiburg i. Breisgau

	Projekt/Studienbezeichnung	**Leitung**
Studien		
(18)	Nephroblastom (Wilms-Tumor) Nephroblastom-Studie SIOP 2002/GPOH	Prof. Dr. Norbert Graf, Univ.-Kinderklinik Homburg/Saar
(19)	Non-Hodgkin-Lymphom NHL-BFM 95	Prof. Dr. med. A. Reiter, Univ.-Kinderklinik Giessen
(20)	Neuroblastom NB 97	Prof. Dr. med. F. Berthold, Univ.-Kinderklinik Köln
(21)	Osteosarkom COSS 96	PD Dr. med. Stefan Bielack, Univ.-Kinderklinik Münster
(22)	Weichteilsarkome CWS-96	Prof. Dr. med. J. Treuner, Kinderklinik Stuttgart (Olgahospital)
(23)	Nasopharynx-Karzinom (98)	Dr. med. R. Mertens, Univ.-Kinderklinik Aachen
Zentrale Einrich-tungen und Projekte	Deutsches Kinderkrebsregister	Prof. Dr. med. J. Michaelis, Dr. P. Kaatsch, Univ. Mainz (IMBEI)
	Rechnerunterstütze Therapieplanung und Dokumentation (DOSPO)	Frau Dr. U. Kutscha, Univ. Heidelberg (Abteilung Medizinische Informatik)
	Projekt Spätfolgen (LESS)	Prof. Dr. med. J.D. Beck, Univ.-Kinderklinik Erlangen
	Cooperatives Pädiatrisches Stammzelltransplantations-Register	Prof. Dr. med. T. Klingebiel, Univ.-Kinderklinik Frankfurt
Referenz-Zentren	Immunphänotypisierung	Charite, RRK Berlin-Buch (Med. Klinik)
	Zytogenetik/ Molekulargenetik	Univ.-Kinderklinik Giessen
	Zentrales Kinder-Tumorregister	Univ. Kiel (Pathologie)
	Zentrales Lymphknotenregister	Univ. Kiel (Pathologie)
	Hirntumor-Referenzzentrum	Univ. Bonn (Neuropathologie)
	Knochenmark ALL / ALL Rez(BFM)	Univ.-Kinderklinik Hannover / Berlin
	Knochenmark ALL(COALL)	Univ.-Kinderklinik Hamburg
	Knochenmark MDS	Univ.-Kinderklinik Freiburg
	Knochenmark AML / CML	Univ.-Kinderklinik Münster

Abkürzungen: Univ. Universität, IMBEI: Institut für Medizinische Biometrie, Epidemiologie und Informatik

Tabelle 2: 3-, 5-, 10- und 15-Jahres-Überlebenswahrscheinlichkeit und Wahrscheinlichkeit ereignisfreien Überlebens (Sterbetafelverfahren ergänzt nach (1)) für die häufigsten Diagnosen (1980-2000)

Diagnose	Patienten zahl	Wahrscheinlichkeit Ereignisfreie Überlebensrate			Überlebensrate		
		3 Jahre	5 Jahre	10 Jahre	3 Jahre	5 Jahre	10 Jahre
Retinoblastom	449	94	94	92	97	97	95
Morbus Hodgkin	1462	87	86	84	97	95	93
Keimzelltumore	899	81	78	76	89	87	85
Nephroblastom	1661	80	80	79	87	86	85
Non-Hodgkin-Lymphom	1768	80	79	76	84	82	81
Akute lymphoblastische Leukämie	7945	77	71	68	85	81	76
Astrozytom	1855	72	68	61	78	77	74
Neuroblastom	2423	62	59	57	70	66	63
Osteosarkom	763	63	58	54	75	67	62
Rhabdomyosarkom	1004	58	55	53	69	63	60
Ewing-Sarkom	542	61	55	51	71	64	58
Periphere neuroektodermale Tumore	1148	51	46	40	58	52	43
Akute myeloische Leukämie	1509	41	39	38	49	45	43
Alle Erkrankungen	26609	70	66	63	78	74	70

Abbildungen

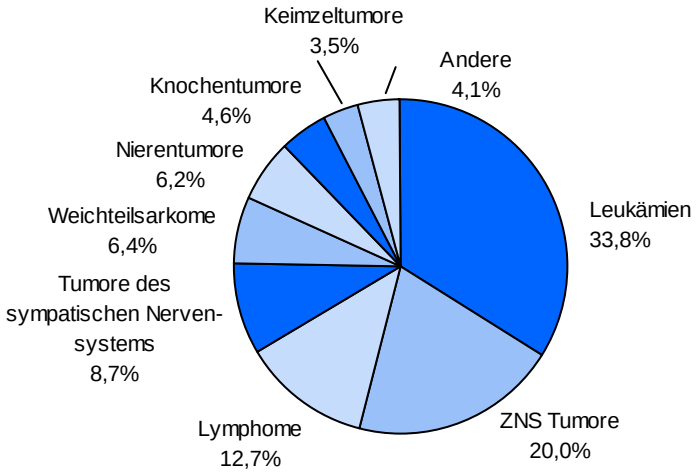

Abbildung 1: Relative Häufigkeit der gemeldeten Patienten nach den häufigsten Einzeldiagnosen (1991-2000)

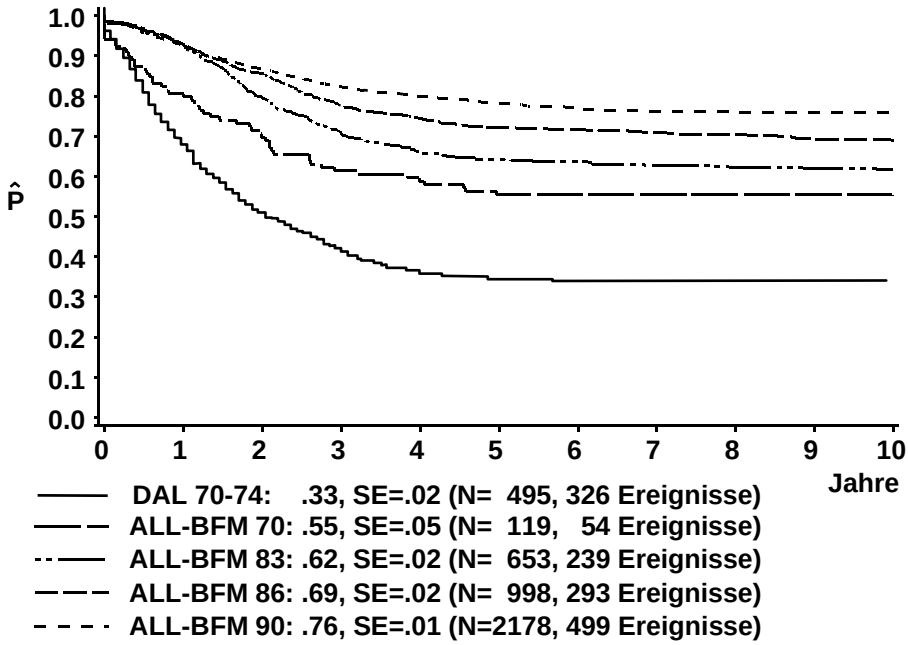

Abbildung 2: Anstieg der Wahrscheinlichkeit des Ereignisfreien Überlebens von Kindern und Jugendlichen mit mit akuter lymphoblastischer Leukämie

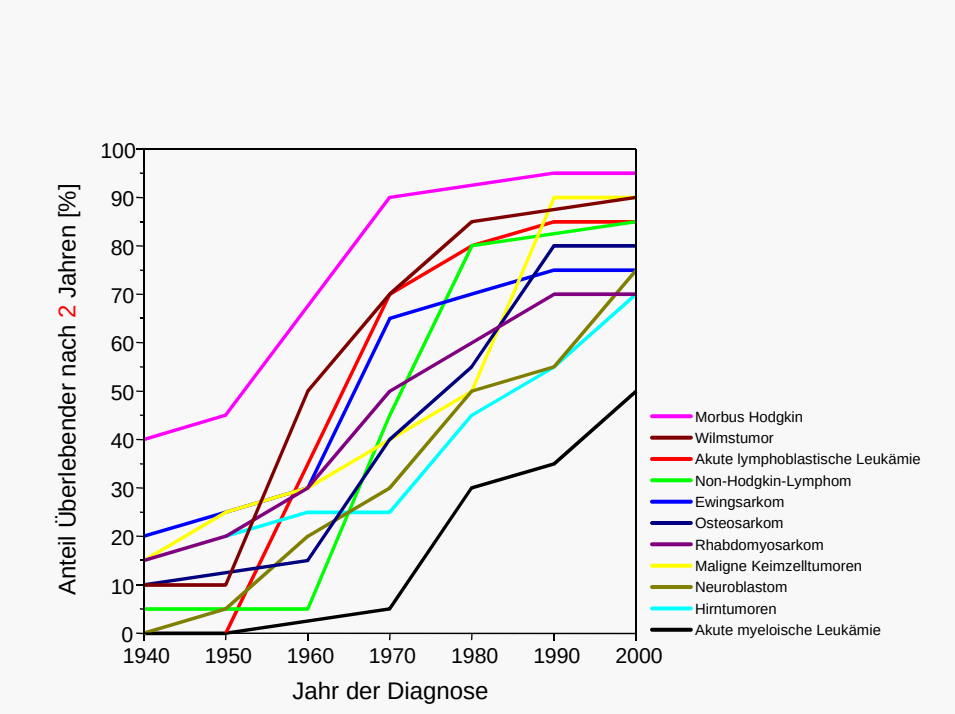

Abbildung 3: Anstieg der Überlebensraten von Kindern und Jugendlichen mit bösartigen Erkrankungen seit 1940 (es wird nur eine 2 Jahres Überlebensrate angegeben, da es vor 1970 keine längeren Verlaufsdaten gibt)

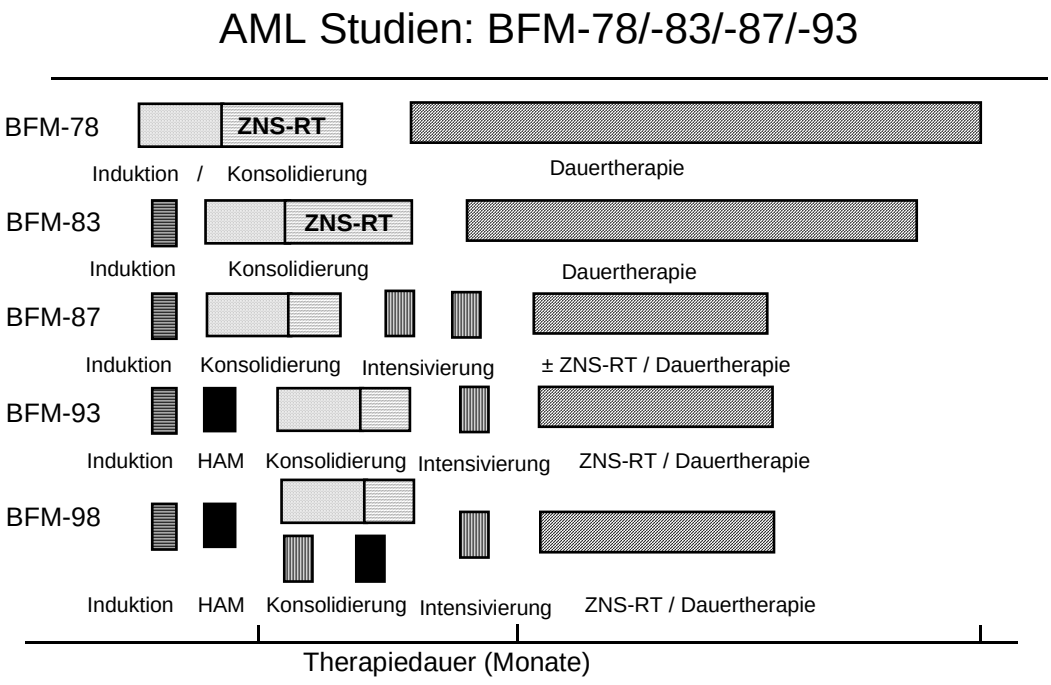

Abbildung 4: Schematische Darstellung von aufeinander folgenden Therapiestudien am Beispiel der AML BFM Studien

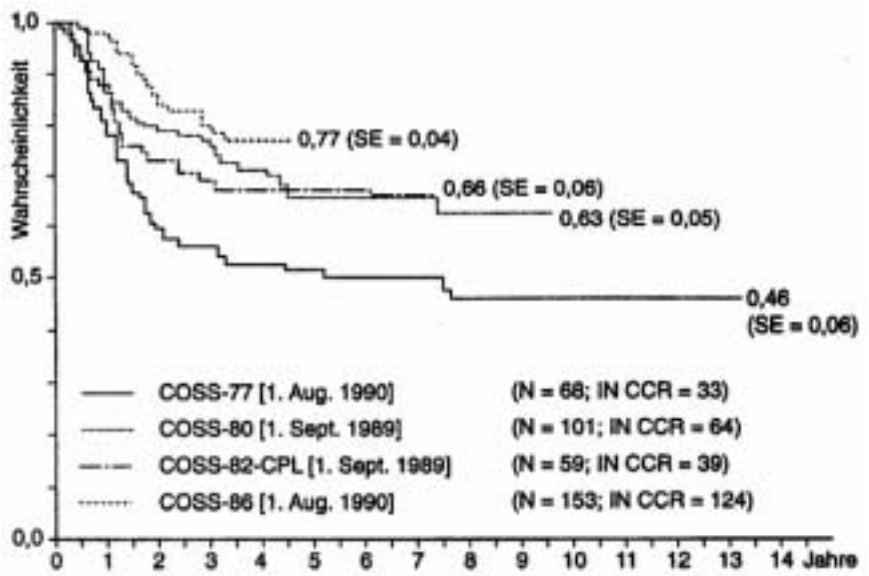

Abbildung 5: Analyse des metastasenfreien Überlebens: Vergleich der Studien COSS-77, COSS-80, COSS-82-CPL und COSS-86

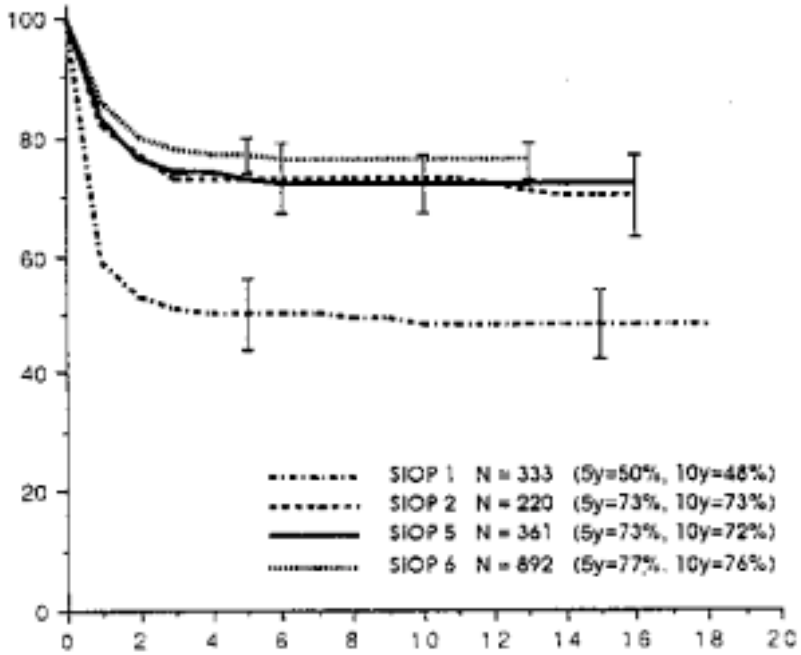

Abbildung 6: Wahrscheinlichkeit für das Ereignisfreie Überleben der Studienpatienten mit Nephroblastomen in Jahren
(10)

B.4 Abstracts of publications of network projects (published, in press or submitted)

P	Reference	Abstract
A I	Creutzig U, Calaminus G. Vertikale Vernetzung in der Pädiatrischen Onkologie. Onkologe 6: 814-188, 2000	Die Strukturierung der medizinischen Versorgung bedarf einer Neuorientierung. Dies findet bereits im Bemühen der Gesundheitsreformer wie auch der Politik darin Ausdruck,Versorgungsnetzwerke zu errichten, die eine Zusammenführung von Kompetenzen und die Förderung des Aufbaus übergeordneter Funktionen ermöglichen. Ziel ist es, sowohl eine bessere horizontale Vernetzung der Fachdisziplinen, die in die Behandlung von Patienten involviert sind, zu erhalten, als auch den Informationsfluss über Erkrankung, Therapie und den Erfolg der Rehabilitation – z.B. nach einer Krebserkrankung – für den nachbetreuenden Arzt abrufbar zu machen.Dies betrifft sowohl die Information über den individuellen Patienten als auch generell Informationen zum Erkrankungsbild und dem „state of art“ der Diagnostik und Behandlung. Diese Aspekte werden mit dem Begriff der vertikalen Vernetzungumschrieben. In der Patientenversorgung wird hierunter die Verbindung zwischen der spezialisierten medizinischen Versorgung und dem medizinischen Alltag verstanden. Spezialwissen soll für die niedergelassenen Fachdisziplinen einfach und schnell erhältlich sein. Für die Pädiatrische Onkologie und Hämatologie ist die Bedeutung dieser vertikalen Vernetzung für die Gestaltung der generellen Patientenversorgung weniger entscheidend als für andere spezielle Fachgruppen, bei denen große Patientenzahlen betroffen sind.
B/1	Knaup P, Harkener S, Ellsässer K.-H, Haux R, Wiedemann T. On the necessity of systematically planning clinical tumor documentation. Meth Inform Med 2001;40, 90-98	Tumor documentation is an important task for both clinical research and patient care. Documentation systems designed for this purpose should be goal-oriented and must be planned systematically. We applied the so-called 'standardized documentation protocol' method to the systematic planning of two documentation systems in oncology: one for the tumor center Heidelberg/Mannheim, and the other for a nationwide project in the field of documentation and therapy planning in pediatric oncology. The method proved to be helpful in both cases, even though the resulting documentation protocols are completely different and served different objectives. Therefore, the aim of this paper is to help medical informatics professionals and motivate them to systematically plan other documentation systems by using this method.
B/1	Merzweiler A, Ehlerding H, Creutzig U, Graf N, Hero B, Kaatsch P, Zimmermann M, Weber R, Knaup P. (2002) Terminologiestandardisierung in der Pädiatrischen Onkologie - der Basisdatensatz. Klinische Pädiatrie (submitted)	Background: Within the scope of more than 20 therapy-optimizing clinical studies in pediatric oncology, extensive documentation and vast amounts of case report forms have been developed within the past 20 to 25 years. Within these studies, information is often captured in different terminological ways, making patient documentation in clinics more difficult. Method: The terminology used in therapy-optimizing clinical studies of the German Society for Pediatric Oncology and Hematology (GPOH) is to be standardized by a central „standards committee“. Result: As a first result, the basic data set of the GPOH was revised and made available via http://www.dospo.uni-hd.de. Conclusion: The base for a unique documentation language in pediatric oncology has been made available to German speaking institutions.
B/1	Merzweiler A, Knaup P, Creutzig U, Ehlerding H, Haux R, Mludek V, Schilling FH, Weber R, Wiedemann T. (2000). Requirements and Design Aspects of a Data Model for a Data Dictionary in Paediatric Oncology. In: Hasman, A, Blobel, B, Dudeck, J. et al. (Hrsg.). Medical Infobahn for Europe, 696-700. Amsterdam: IOS Press.	German children suffering from cancer are most often treated within the framework of multi-centered clinical trials. Extensive information and knowledge exchange is important in conducting these trials, which should be based on a standardized documentation. To support this effort, a nationwide project aims to define a standardized terminology that should be used for therapy documentation in clinical trials. In order to support terminology maintenance, we are currently developing a data dictionary. In this paper, we will describe the requirements and design aspects of the data model used for the data dictionary as first results of our research. Also, we will compare it to other terminology systems.
B/1	Knaup P, Mludek V, Wiedemann T, Bauer J, Haux R, Kim L, Schilling FH, Selle B. (2000). Integrating Specialized Application Systems into Hospital Information Systems -Obstacles and Factors for Success. In:Hasman, A, Blobel, B, Dudeck, J. et al. (Hrsg.). Medical Infobahn for	Hospital information systems are often huge and heterogeneous systems. To support physicians in their daily clinical work, dedicated application systems are being developed for particular medical fields or tasks. These systems must be integrated into the standing hospital information systems. The integration process is quite complicated, because it makes the information system's infrastructure even more heterogeneous. We have developed an application system for documentation and therapy planning in pediatric oncology (DOSPO). We have introduced the system in the Department of Pediatric Oncology of Heidelberg University Hospital. The fact that DOSPO has been developed as a universal system for nation-

P	Reference	Abstract
	Europe, 890-894. Amsterdam: IOS Press.	wide use made the integration process more difficult. In any case, the introduction of specialized application systems must be systematically planned in advance. Special, regard must be given the available resources and established processes of the prevailing information system. To simplify the integration process, comprehensive future electronic patient records should be designed in a way that allows easy enhancement of new clinical functions.
B/1	Merzweiler A, Knaup P, Weber R, Ehlerding H, Haux R, Wiedemann, T. (2001). Recording clinical data - from a general set of record items to case report forms (CRF) for clinics. In: Patel, V, Rogers, R, Haux, R. (Hrsg.). MEDINFO 2001. Proceedings of the 10th World Congress on Medical Informatics, 653-657. Amsterdam: IOS.	Standardizing a documentation language only makes sense if it is used consequently for documentation. An example from German pediatric oncological is the development of a procedure that generates CRFs from a documentation language. The introduced procedure has proven feasible in practice. With it, we can support developers of documentation systems in creating CRFs. Through guaranteed use of the documentation terminology, we further achieve that information recorded with the created CRFs can be analyzed statistically across different institutions.
B/1	Weber R, Knaup P, Knietig R, Haux R, Merzweiler A, Mludek V, Schilling FH, Wiedemann T. (2001). Object-oriented business process analysis of the Cooperative Soft Tissue Sarcoma Trial of the German Society for Paediatric Oncology and Haematology (GPOH). In: Patel, V, Rogers, R, Haux, R. (Hrsg.). MEDINFO 2001. Proceedings of the 10th World Congress on Medical Informatics, 58-62. Amsterdam: IOS.	The German Society for Pediatric Oncology and Hematology (GPOH) runs national multi-centered clinical trials to improve the treatment of children suffering from malignant diseases. Our goal is to provide methods and tools to support the trial centers in developing study-specific modules for the computer-based DOcumentation System for Paediatric Oncology (DOSPO). For this purpose, we have carried out an object-oriented business process analysis of the Cooperative Soft Tissue Sarcoma Trial at the Olga Hospital for Child and Adolescent Medicine, Stuttgart, Germany. A comprehensive business process model resulted consisting of UML diagrams and use case specifications. We recommend object-oriented business process analysis as a method for defining requirements of information processing projects in the general field of clinical trials. Our model could serve as a basis for this purpose, because only slight adjustments are required for each type of clinical study.
B/2	Pommerening K. IT-Sicherheit in medizinischen Netzen -- aktuelle Probleme und Lösungsansätze. Zentralbl Gynakol 122: 658-662, 2000.	Designers and users of medical networks have to face strong requirements for data protection and security. Professional discretion and data protection laws allow the transfer of or access to patient data only in a therapeutic context. These data should also be protected from the network provider. Patients should be safe from any harm by faulty data or buggy procedures. On the other hand the security of the most used software products gets worse and worse. The use of the internet more and more endangers the integrity of the user's computer. The security requirements can be met only through strict care in planning, building, and configuring the infrastructure. Some concrete recommendations and guiding principles can immediately be realized. If these recommendations are followed, the internet can be of immense value for health care.
D	Stahnke K, Mohr A, Liu J, Schneider M, Debatin KM: Flowcytometric detection of mitochondrial cytochrome c release identifies deficient mitochondrial apoptosis signaling in leukemia cells	Deficient activation of apoptosis signaling pathways may be responsible for drug resistance and treatment failure of malignant diseases. We developed a method for the detection of cytochrome c release in intact cells by flow cytometry. In Jurkat T cell leukemia cells mitochondrial cytochrome c release could be detected in CD95 receptor or cytotoxic drug induced apoptosis. A good correlation was found to results obtained in conventional immunoblotting and fluorescence microscopy. Differential requirement for mitochondrial signaling in CD95 induced apoptosis in SKW (type I) and Jurkat (type II) was detected by the method. By simultaneous measurement of cytochrome c release and active caspase-3 in multicolor flowcytometry, we identified deficient mitochondrial apoptosis signaling in the presence of caspase-3 activation in Jurkat cells overexpressing Bcl-2. In addition, we found the method to be applicable for analysis of primary leukemia cells identifying heterogeneous patterns of mitochondrial signaling and caspase activation. Flowcytometric analysis of mitochondrial cytochrome c release is a valuable tool for the analysis of mitochondrial apoptosis resistance mechanisms in leukemia.
D	Stahnke K, Eckhoff S, Mohr A, Debatin KM: Chemotherapy induces depletion and apoptosis predominantly in a CD34 positive subset of leukemia cells	The initial response to induction chemotherapy is one of the major prognostic factors in acute leukemia. Chemotherapy in vivo eliminates leukemia cells from bone marrow and peripheral blood possibly by induction of apoptosis. It has recently been shown that leukemia arises from immature leukemia stem cells positive for CD34 and negative for CD38. We therefore analyzed depletion and induction of apoptosis in the subset of CD34

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		positive in peripheral blood leukemia cells from patients with ALL and AML undergoing first cycle chemotherapy. We found expression of CD34 on leukemic blasts in 23 of 24 cases analyzed. The proportion of leukemia cells expressing CD34 varied from 0% to 87% in AML and 1.5% to 74.5% in ALL patients. During induction chemotherapy, CD34+ leukemia cells were more rapidly depleted than CD34- cells. Furthermore, in vivo chemotherapy induced a significant increase of in vitro apoptosis after 24hours in this immature subpopulation. Interestingly, without differentiating mature and immature leukemia cells according to their CD34 status, no effect on in vitro apoptosis could be detected during in vivo chemotherapy. In vitro treatment with cytarabin again resulted in predominant induction of apoptosis in CD34 positive leukemia cells in ALL and AML samples. CD95 expression and sensitivity on both CD34 positive and negative subpopulations remained low during in vivo chemotherapy and upon in vitro drug treatment, suggesting induction of apoptosis independent of the CD95 system. Thus induction of apoptosis by in vivo chemotherapy targets an immature subpopulation of leukemia cells during remission induction. Analysis of differential chemosensitivity of leukemia cell subpopulations could enhance the predictive value of in vitro drug testing assays for response to treatment.
D	Wuchter C, Ruppert V, Schrappe M, Dorken B, Ludwig WD, Karawajew L. In vitro susceptibility to dexamethasone- and doxorubicin-induced apoptotic cell death in context of maturation stage, responsiveness to IL-7 and early cytoreduction in vivo in childhood T-ALL. Blood 2002, in press	Within childhood T-ALL, patients with a cortical (CD1a positive) immunophenotype have been identified as a subgroup with favorable outcome in the ALL-BFM, COALL and POG studies. We investigated in leukemic samples of children with T-ALL (n=81) whether the different in vivo therapy response could be linked to differential in vitro susceptibility to apoptotic cell death. The extent of dexamethasone- as well as doxorubicin-induced apoptosis, detected by annexin V-staining, positively correlated with the expression levels of CD1a (Spearman correlation coefficient, rs = 0.3 and 0.4, respectively; p<0.01). When compared to cortical T-ALL, mature (CD1a negative, surface CD3 positive) T-ALL were significantly more resistant to doxorubicin, and immature, pro-/pre-T-ALL were more resistant to both drugs (p<0.05). Apoptosis-related parameters (Bax, Bcl-2, CD95 and CD95-induced apoptosis) did not account for differential susceptibility to drug-induced apoptosis. By contrast, an IL-7 induced rescue of leukemic cells from spontaneous apoptosis, recently proposed to reflect distinct developmental stages and apoptotic programs in T-ALL, was highly associated with susceptibility to dexamethasone- but not doxorubicin-induced apoptosis (p<0.001 vs. p=0.08). Analysis of clinical data showed that in vitro susceptibility to dexamethasone (but not to doxorubicin) closely correlated with early in vivo therapy response characterized by percentages of blast cells in bone marrow on day 15 (rs = -0.46, p=0.001). Taken together, the in vitro assessment of drug-induced apoptosis revealed maturation-dependent differences within childhood T-ALL. The enhanced sensitivity to both drugs in cortical T-ALL might account for the better in vivo treatment response of this prognostically favorable T-ALL subgroup.
D	Stahnke K, Fulda S, Friesen C, Strauss G, Debatin KM Activation of apoptosis pathways in peripheral blood lymphocytes by in vivo chemotherapy Blood 2001,98:3066-7330	In addition to myelosuppression, anticancer drugs cause rapid and persistent depletion of lymphocytes, possibly by direct apoptosis induction in mature T and B cells. Induction of apoptosis regulators was analyzed in peripheral blood lymphocytes from pediatric patients undergoing first-cycle chemotherapy for solid tumors. In vivo chemotherapy induced a significant increase in lymphocyte apoptosis ex vivo. The activation of initiator caspase-8 and effector caspase-3 and the cleavage of caspase substrates was detected 12 to 48 hours after the onset of therapy. Caspase inhibition by Z-VAD-fmk did not reduce ex vivo lymphocyte apoptosis in all patients, indicating the additional involvement of caspase-independent cell death. No evidence for the involvement of activation-induced cell death was found in the acute phase of lymphocyte depletion as analyzed by activation marker expression and sensitivity for CD95 signaling. Lymphocyte apoptosis in vivo appeared to be predominantly mediated by the mitochondrial pathway because a marked decrease of mitochondrial membrane potential (DeltaPsi(M)) was detected after 24 to 72 hours of treatment, preceded by the increased expression of Bax. Interestingly, despite the use of DNA-damaging agents, p53 remained completely undetectable throughout treatment. In contrast, in vitro treatment with cytarabine and etoposide induced p53 protein, CD95 receptor expression, CD95 sensitivity, and CD95 receptor-ligand interaction in stimulated cycling lymphocytes, but no such induction was seen in resting cells. These data suggest that chemotherapy-induced lymphocyte deple-

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		tion involves distinct mechanisms of apoptosis induction, such as direct mitochondrial and caspase-dependent pathways in resting cells and p53-dependent pathways in cycling lymphocytes.
D	Wuchter C, Krappmann D, Cai Z, Ruppert V, Scheidereit C, Dorken B, Ludwig WD, Karawajew L In vitro susceptibility to TRAIL-induced apoptosis of acute leukemia cells in the context of TRAIL receptor gene expression and constitutive NF-kappa B activity. Leukemia 2001,15:921-8	The TNF-related apoptosis-inducing ligand (TRAIL) is currently under evaluation as a possible (co-)therapeutic in cancer treatment. We therefore examined 129 cell samples from patients with de novo acute leukemia as to their constitutive susceptibility to TRAIL-induced apoptosis In vitro. Only 21 (16%) cell samples revealed at least 10% TRAIL-susceptible cells/sample as detected by flow cytometric annexinV staining after 24 h culture compared with medium control. Precursor B cell ALL samples (11 (27%) of 41) were more TRAIL-susceptible compared with AML (5 (9%) of 54; P < 0.05) but not compared with precursor T cell ALL (5 (15%) of 34; P = 0.20). Furthermore, we examined constitutive mRNA expression levels of TRAIL receptors R1-R4 by semi-quantitative RT-PCR (n = 58). Expression levels were heterogeneous, however, there was no significant correlation between the expression of the signal-transducing receptors (R1, R2) as well as of the decoy receptors (R3, R4) and TRAIL sensitivity in this series. Constitutive NF-kappa B activity has been shown to influence TRAIL susceptibility of leukemic cells. In 39 leukemic cell samples examined, we found a generally high NF-kappa B activity as detected by electrophoretic mobility shift assay which did not differ between TRAIL-susceptible and TRAIL-resistant cases. Finally, 49 acute leukemic cell samples were coincubated with doxorubicin in vitro. Doxorubicin sensitized four of 35 initially TRAIL-resistant samples and augmented TRAIL-induced apoptosis in two of 14 TRAIL-susceptible samples. In summary, constitutive TRAIL susceptibility differs between leukemia subtypes and does not correlate with mRNA expression levels of the TRAIL receptors R1-R4 as well as constitutive NF-kappa B activation status. The observed sensitization of leukemic cells to TRAIL by doxorubicin in vitro indicates that TRAIL should be further evaluated as to its possible role as an in vivo cotherapeutic in acute leukemia.
D	Cai Z, Lin M, Wuchter C, Ruppert V, Dorken B, Ludwig WD, Karawajew L Apoptotic response to homoharringtonine in human wt p53 leukemic cells is independent of reactive oxygen species generation and implicates Bax translocation, mitochondrial cytochrome c release and caspase activation. Leukemia 2001;15:567-74	In the present study, we investigated the in vitro apoptotic response of leukemic cells to the cellular stress induced by homoharringtonine (HHT), a plant alkaloid with antileukemic activity which is currently being tested for treatment of acute and chronic leukemias. A comparison of leukemic cell lines with different p53 gene status revealed a considerably higher sensitivity to HHT-induced apoptosis in the cells with a wt p53, and apoptotic events in wt p53 leukemia cells (MOLT-3 cell line) were studied in more detail. To this end, we examined components of apoptotic cascades including Bax expression and its intracellular localization, changes of mitochondrial membrane potential (MMP), reactive oxygen species (ROS) levels, cytochrome c release from mitochondria and activation of caspases. Bax protein levels did not increase despite an up-regulation of bax at mRNA level. However, Bax translocation from cytosol towards mitochondria was observed. In addition, we observed a release of cytochrome c from the mitochondria, and the localization changes of both Bax and cytochrome c were found already at the early, annexin V-negative stage of HHT-induced apoptosis. HHT-treated MOLT-3 cells revealed loss of MMP as well as activation of caspases demonstrated by DEVD-, IETD- and LEHD-tetrapeptide cleavage activity in the cell lysates. ROS levels only slightly increased in HHT-treated cells and antioxidants did not prevent apoptosis and MMP changes. Therefore, wt p53 leukemic cells respond to HHT-specific cellular stress by induction of ROS-independent apoptotic pathway characterized by translocation of Bax, mitochondrial cytochrome c release and activation of caspases.
D	Wuchter C, Karawajew L, Ruppert V, Schrappe M, Harbott J, Ratei R, Dorken B, Ludwig WD. Constitutive expression levels of CD95 and Bcl-2 as well as CD95 function and spontaneous apoptosis in vitro do not predict the response to induction chemotherapy and relapse rate in childhood acute lymphoblastic leukaemia Br J Haematol 2000;110:154-60	CD95 (Fas/APO-1) expression and function and Bcl-2 expression, as well as spontaneous apoptosis in vitro, have been shown to be predictive markers for the in vivo response to chemotherapy in acute myeloid leukaemia (AML). To determine the clinical significance of apoptosis-regulating factors in acute lymphoblastic leukaemia (ALL), we investigated cell samples of children with ALL who had been included in the German ALL Berlin-Frankfurt-Munster (BFM) study using flow cytometry for constitutive expression levels of CD95 (n = 110) and Bcl-2 (n = 110). Furthermore, we determined the extent of spontaneous apoptosis in vitro (n = 102) and susceptibility to anti-CD95-induced apoptosis (CD95-sensitivity) (n = 97). We correlated these findings with the functional activity of the multidrug resistance (MDR)-associated P-glycoprotein (P-gp), as detected by the rhodamine123 efflux test, immunophenotype, cytogenetics and clinical data of the patients examined. Good responders to initial

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		prednisone therapy ('prednisone response') revealed significantly higher Bcl-2 expression levels [5.4 +/- 3.4 relative fluorescence intensity (RFI), n = 68] than poor responders (3.7 +/- 2.6 RFI, n = 42; P = 0.002). There was no significant correlation between the other investigated parameters and prednisone response. Moreover, neither the CD95 and Bcl-2 expression levels nor the extent of spontaneous apoptosis in vitro, CD95 sensitivity or P-gp function were correlated with the response to induction chemotherapy or relapse rate, either for B-cell precursor ALL or T-cell ALL. No consistent pattern of change in CD95 (n = 10) and Bcl-2 expression (n = 9) was noted in cases studied at both initial diagnosis and relapse. In conclusion, our findings underline the different cell biological features of primary AML and ALL cells.
D	Karawajew L, Ruppert V, Wuchter C, Kosser A, Schrappe M, Dorken B, Ludwig WD. Inhibition of in vitro spontaneous apoptosis by IL-7 correlates with bcl-2 up-regulation, cortical/mature immunophenotype, and better early cytoreduction of childhood T-cell acute lymphoblastic leukemia. Blood 2000;96:297-306	In normal T-cell development, IL-7 plays a nonredundant role as an antiapoptic factor by regulating Bcl-2 expression in pro-T cells. In the current study, we addressed the roles of IL-7 and related cytokines as apoptosis-modulating factors in precursor T-cell acute lymphoblastic leukemia (T-ALL). To this end, leukemic blasts from pediatric patients with T-ALL were prospectively investigated as to their responsiveness to IL-7, IL-4, and IL-2 (in terms of modulation of spontaneous apoptosis, assessed by flow cytometry), cytokine receptor expression profiles, and expression levels of Bcl-2 and Bax proteins. IL-7, in contrast to IL-4 and IL-2, was highly efficient in apoptosis inhibition, and this effect correlated with the expression levels of IL-7Ralpha chain and with the up-regulation of Bcl-2 protein expression (P <.0001). Subclassification of T-ALL samples (n = 130) according to their in vitro IL-7 responses revealed that IL-7 refractory samples were more frequently positive for CD34 (P <.0001) and the myeloid-associated antigen CD33 (P =.01), whereas IL-7 responsiveness was associated with an expression of more mature differentiation-associated T-cell antigens (CD1a, surface CD3, CD4/8; P <.05). Furthermore, the extent of apoptosis inhibition by IL-7 in vitro quantitatively correlated with early cytoreduction as determined by the prednisone peripheral blood response on day 8 and cytoreduction in the marrow on day 15 (n = 87; P <.05). Multivariate analysis of the apoptosis-related parameters investigated, including spontaneous apoptosis, its inhibition by IL-7, and expression levels of Bcl-2 and Bax, showed that only IL-7 responsiveness has an independent impact on early cytoreduction (P <. 05), thus indicating a potential prognostic relevance of IL-7 sensitivity in T-ALL.
D	Fulda S, Kufer MU, Meyer E, van Valen F, Dockhorn-Dworniczak B, Debatin KM. Sensitization for death receptor- or drug-induced apoptosis by re-expression of caspase-8 through demethylation or gene transfer. Oncogene 2001;20:5865-77	Resistance of tumors to treatment with cytotoxic drugs, irradiation or immunotherapy may be due to disrupted apoptosis programs. Here, we report in a variety of different tumor cells including Ewing tumor, neuroblastoma, malignant brain tumors and melanoma that caspase-8 expression acts as a key determinant of sensitivity for apoptosis induced by death-inducing ligands or cytotoxic drugs. In tumor cell lines resistant to TRAIL, anti-CD95 or TNFalpha, caspase-8 protein and mRNA expression was decreased or absent without caspase-8 gene loss. Methylation-specific PCR revealed hypermethylation of caspase-8 regulatory sequences in cells with impaired caspase-8 expression. Treatment with the demethylation agent 5-Aza-2'-deoxycytidine (5-dAzaC) reversed hypermethylation of caspase-8 resulting in restoration of caspase-8 expression and recruitment and activation of caspase-8 at the CD95 DISC upon receptor cross-linking thereby sensitizing for death receptor-, and importantly, also for drug-induced apoptosis. Inhibition of caspase-8 activity also inhibited apoptosis sensitization by 5-dAzaC. Similar to demethylation, introduction of caspase-8 by gene transfer sensitized for apoptosis induction. Hypermethylation of caspase-8 was linked to reduced caspase-8 expression in different tumor cell lines in vitro and, most importantly, also in primary tumor samples. Thus, these findings indicate that re-expression of caspase-8, e.g. by demethylation or caspase-8 gene transfer, might be an effective strategy to restore sensitivity for chemotherapy- or death receptor-induced apoptosis in various tumors in vivo.
D	Fulda S, Meyer E, Debatin KM. Metabolic inhibitors sensitize for CD95 (APO-1/Fas)-induced apoptosis by down-regulating Fas-associated death domain-like interleukin 1-converting enzyme inhibitory protein expression. Cancer Res 2000;60:3947-56	Protein or RNA synthesis inhibitors are known to sensitize some resistant cells for death receptor-induced apoptosis. However, the molecular mechanism(s) involved in sensitization have not yet been defined exactly. Here, we report that metabolic inhibitors such as cycloheximide (CHX) or actinomycin D (ActD) sensitize for CD95-induced apoptosis by strongly down-regulating FLIP and RIP expression. Metabolic labeling studies revealed that CHX or ActD inhibited protein or RNA synthesis at concentrations required for sensitization. In contrast to Fas-associated death domain (FADD) or caspase-8, FADD-like interleukin 1-converting en-

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		zyme-inhibitory protein (FLIP) and RIP protein levels rapidly decreased upon treatment with CHX or ActD, indicating that both molecules have a high turnover rate. Selective down-regulation of FLIP expression by FLIP antisense oligonucleotides sensitized for CD95-induced apoptosis. Reduction of FLIP levels resulted in undetectable amounts of FLIP at the CD95 death-inducing signaling complex (DISC) upon CD95 stimulation, thereby enhancing the recruitment of caspase-8 to the DISC and caspase-8 activation. CHX- or ActD-mediated sensitization to CD95-induced apoptosis was predominantly found in type I cells in which FADD and caspase-8 are recruited to CD95 upon stimulation but not in type II cells in which no DISC formation is detected. Pretreatment with CHX or ActD sensitized for subsequent CD95 stimulation compared with cells without pretreatment. CHX or ActD also reduced XIAP expression and similarly sensitized for tumor necrosis factor-related apoptosis-inducing ligand- or tumor necrosis factor-alpha-induced apoptosis. Because blockade of death receptor triggering by FLIP overexpression has recently been implicated in tumorigenesis and treatment resistance in vivo, strategies to inhibit FLIP expression, e.g., by metabolic inhibitors, may prove to be a useful complementary tool for the treatment of cancer.
D	Beltinger C, Fulda S, Kammertoens T, Uckert W, Debatin KM. Mitochondrial amplification of death signals determines thymidine kinase/ganciclovir-triggered activation of apoptosis. Cancer Res 2000;60:3212-7	Previous clinical experience shows that the efficacy of suicide gene transfer in tumor therapy is limited, resulting from inefficient gene transfer or alternatively, from intrinsic resistance of the tumor in vivo. Herpes simplex virus thymidine kinase/ganciclovir (TK/GCV), a paradigmatic suicide gene therapy system, has been described to exert its cytotoxic effect, at least in part, by inducing apoptosis in target cells. Here, we report that mitochondria amplify TK/GCV-induced apoptosis by regulating p53 accumulation and the effector phase of apoptosis. Treatment with TK/GCV led to mitochondrial perturbations including loss of the mitochondrial membrane potential and release of cytochrome c from mitochondria into the cytosol, inducing caspase activation and nuclear fragmentation. Inhibition of TK/GCV-induced mitochondrial perturbations by Bcl-2 overexpression or by the mitochondrion-specific inhibitor bongkrekic acid also strongly inhibited TK/GCV-induced activation of caspases and apoptosis. TK/GCV-induced mitochondrial perturbations depended on caspase activity possibly initiated by death receptor signaling. Perturbation of mitochondrial function mediated accumulation of wild-type p53 protein, since Bcl-2 overexpression, bongkrekic acid, or inhibition of mitochondrial protein synthesis with chloramphenicol strongly reduced TK/GCV-induced accumulation of wild-type p53 protein. These findings suggest that TK/GCV therapy may be less efficient in tumors in which the mitochondrial amplification of TK/GCV-induced apoptosis is blocked, e.g., by Bcl-2 overexpression. Given the low efficacy of currently used gene therapy systems, our data on molecular mechanisms that regulate sensitivity or resistance toward TK/GCV-induced cytotoxicity might have important implications to improve the clinical application of suicide gene therapy.
E	Tschan CA, Pilz C, Zeidler C, Welte K, Germeshausen M. Time course of increasing numbers of mutations in the granulocyte colony-stimulating factor receptor gene in a patient with congenital neutropenia who developed leukemia. Blood 97: 1882-84, 2001	Point mutations in the granulocyte colony-stimulating factor receptor (G-CSFR) gene have been linked to the development of secondary leukemia in patients with congenital neutropenia (CN). This report presents data on a now 18-year-old patient with CN who has received G-CSF treatment since 1989 and who developed acute myeloid leukemia (AML) in 1998. To evaluate whether there is an association between the occurrence of point mutations of the G-CSFR gene and development of secondary AML, DNA/messenger RNA of neutrophils and mononuclear cells from this patient were analyzed at different time points by polymerase chain reaction and subsequent cloning by DNA sequencing of representative numbers of individual clones. Findings suggest an increasing instability of the G-CSFR gene in time as judged by increasing numbers of mutations proposed to be one important step in the development of AML in this patient.
E	Germeshausen M, Ballmaier M, Welte K. Implications of mutations in hematopoietic growth factor receptor genes in congenital cytopenias. Ann NY Acad Sci 938: 305-21, 2001	Mutations in the genes of hematopoietic growth factor receptors as a cause of congenital cytopenia, such as congenital amegakaryocytic thrombocytopenia (CAMT) or severe congenital neutropenia (CN), are discussed. There are striking differences in the relevance of receptor mutations in these diseases. CAMT is a rare disease characterized by severe hypomegakaryocytic thrombocytopenia during the first years of life that develops into pancytopenia in later childhood. In patients with CAMT, we found inherited mutations in c-mpl, the gene coding for the thrombopoietin receptor, in 8 out of 8 cases. The type of mutation seems to correlate with the clinical course seen in the patients. Functional studies

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		demonstrated defective thrombopoietin (TPO) reactivity in hematopoietic progenitor cells and platelets in CAMT patients. CN is a group of hematopoietic disorders characterized by profound, absolute neutropenia due to a maturation arrest of myeloid progenitor cells. About 10% of all patients develop secondary MDS/leukemia. The malignant progression is associated with acquired nonsense mutations within the G-CSF receptor gene that lead to the truncation of the carboxy-terminal cytoplasmic domain of the receptor protein involved in maturation of myeloid progenitor cells. This seems to be one important step in leukemogenesis in CN patients. CAMT is caused by inherited mutations in c-mpl, the gene for the thrombopoietin receptor, which lead to reduced or absent reactivity to TPO. In contrast, mutations in the G-CSF receptor in CN are acquired and are most probably connected with progression of the neutropenia into MDS/leukemia as a result of a loss of differentiation signaling.
E	Jung A, Ruckert S, Frank P, Brabletz T, Kirchner T. 7-deaza-2`-deoxyguanosine allows PCR and sequencing from CpG islands. Mol Path 55, 55-57, 2001	CpG islands are GC-rich sequences which are found in many promoters of higher eukaryotes. They contain CG dinucleotides at high frequency which are substrates for DNA methylases. Methylation leads to transcriptional silencing of promoters. Due to the high GC content CpG islands exhibit strong base-base interactions which lead to super-structures and consequently to regions with higher melting temperatures. Therefore, Taq-polymerases and especially sequenases fall of their templates causing premature termination of PCR or sequencing reactions. The results from such reactions are thus insufficient for further analysis. We have therefore evaluated the usage of 7-deaza-2´-deoxyguanosine for PCR amplification of the human p16INK4A promoter and sequencing of HUMARA exon 1 PCR products. Our results show that addition of 7-deaza-2´-deoxyguanosine significantly improves results particularly when small amounts of poor quality DNA are available as starting material.
E	Rischewski J, Schneppenheim R. Screening strategies for a highly polymorphic gene: DHPLC analysis of the Fanconi anemia group A gene. J Biochem Biophys Methods 30;47:53-64, 2001	Introduction: Patients with Fanconi anemia (Fanc) are at risk to develop leukemia. Mutations of the group A gene (FancA) are most common. A multitude of polymorphisms and mutations within the 43 exons of the gene are described. To examine the role of heterozygosity as a risk factor for malignancies, a partial automatized screening method to identify aberrations was needed. We report on our experience with DHPLC (WAVE (Transgenomic)). Methods: PCR amplification of all 43 exons from one individual is done on one microtiter plate on a gradient thermocycler. DHPLC analysis conditions were established via melting curves, prediction software, and test runs with aberrant samples. PCR-products are analyzed twice: Native, and after adding a WT- PCR product. Retention patterns are compared to previously identified polymorphic PCR products or mutants. Results and discussion: We defined the mutation screening conditions for all 43 exons of FANCA using DHPLC. So far, 40 different sequence variations could be detected in more than 100 individuals. The native analysis identifies heterozygous individuals, the second run detects homozygous aberrations. Retention patterns are specific for the underlying sequence aberration, thus reducing sequencing demand and costs. DHPLC is a valuable tool for reproducible recognition of known sequence aberrations and screening for unknown mutations in the highly polymorphic FANCA gene
E	Rischewski J, Clausen H, Leber V, Niemeyer C, Ritter J, Schindler D, Schneppenheim R: A heterozygous frameshift mutation in the Fanconi anemia C gene in familial T-ALL and secondary malignancy. Klin Padiatr 212:174-6, 2000	Background: Patients with Fanconi Anemia (FANC) have a well documented increased risk to develop malignancies, especially Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS). The risk for heterozygous individuals is not clear, epidemiological data are inconsistent. If the risk for heterozygous individuals to develop malignancies was increased, they should be found in groups of patients with AML or MDS at higher proportion than in the normal population. We are currently screening a pediatric population with hematologic malignancies for mutations in the FANCA, FANCC and FANCG gene, and report here on siblings carrying a heterozygous frameshift mutation in the FANCC Gene. Patients and Methods: Using PCR based single strand conformational analysis we screened the DNA from pediatric patients suffering from 1° or 2° MDS, CMML / JMML or AML for mutations in the FANCA (43 exons), FANCC (14 exons) and FANCG (14 exons) gene, and included one patient with refractory T-ALL, being the brother of a patient with T-ALL and MDS transforming into AML. Aberrant PCR products were directly sequenced. Flowcytometric measurement of mitogen- sensitivity and G2-phase arrest is used to evaluate cultured stimulated lymphocytes from individuals carrying FANC- mutations. Results: A novel heterozygous frameshift mutation, 377-378delGA in the FANCC gene was found in 2 siblings, both

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		suffering from T-ALL with subsequent MDS transforming to AML in one of them. No other mutation was found by direct sequencing of the complete FANCC gene. Both patients died under therapy. The parents (first degree cousins) and one healthy brother are also carriers. Their lymphocytes show a higher mutagen sensitivity than normal, but do not get blocked in G2 phase as being typical for Fanconi Anemia. Conclusion: As the mutation causes a premature Stopcodon within exon 4 of the FANCC gene it has to be regarded as a causal FANCC gene defect. The findings within this family support the hypothesis of an increased risk to develop malignancies in heterozygous carriers of FANC- mutations. A systematic screening of further patients is needed, and we are currently examining a larger cohort to get a better estimate of the true risk of heterozygosity.
	Rischewski J, Schindler D, Ziegler K, Janka-Schaub G, Schneppenheim R: Discrepancy of diagnostic hallmarks of Fanconi anemia in a patient with myelodysplastic syndrome. Klin Padiatr. 2002, in press.	Abstract: Background: Patients with Fanconi anemia (FA) are well-documented of facing increased risk for developing malignancies, foremost acute myelogenous leukemia (AML) that often evolves from preceding myelodysplastic syndrome (MDS). The diagnosis FA is based on the greatly elevated sensitivity of the patient´s cells to mitomycin C (MMC) and diepoxybutan (DEB), conspicuous in the analysis of metaphase chromosomes, in reduced cellular survival rates, and in the accumulation of live cells in the G2/M phase of the cell cycle. However, the diagnosis FA cannot savely be made from blood cells in case of high-grade somatic mosaicism of hematopoetic cells or (pre)leukemic conditions, no matter what type of analysis is used. Patient, Methods and Results: An one year old patient displayed morphological features of FA. The diagnosis was confirmed by high breakage rates of metaphase chromosomes using DEB challenge of peripheral blood lymphocytes (PBL). At age two years, he developed abdominal B-cell non-Hodgkin lymphoma responsive to chemotherapy. At age four years, he presented with a medulloblastoma. At that time, cell cycle analysis failed to show G2/M accumulation in mononuclear blood cells, whereas the analysis of metaphase chromosomes from PBL detected a subset of cells with increased breakage and rearrangements typical of FA. Likewise, the diagnosis FA was confirmed with cultured fibroblasts by their oxygen hypersensitivity and disproportionately reduced growth rates in the presence of MMC. Six months later, bone marrow studies were indicative of MDS type RAEBt, which developed towards overt leukemia. Another month later, the patient died from increased cranial pressure caused by relapse of the medulloblastoma. Conclusion: False-negative results of FA testing using chromosome analysis and cell cycle studies with blood have been reported when mosaicism of hematopoetic cells or (pre)-leukemia was present. In particular, FA testing with (pre)-leukemic blood represents a diagnostic pitfall. Improved statistics by the high number of cells anlyzed with the flow assay normally forms an advantage, but the detection of increased breakage in a subset of cells at a single cell basis may be helpful in the above conditions, although this assumption reportedly does not always apply in a (pre)-leukemic status. In the present patient, evidence of MDS was gained, assumedly responsible for negative testing in cell cycle studies. The diagnosis of FA in patients with discrepant diagnostic results in PBL should be evaluated by a fibroblast MMC challenge, and a bone marrow aspirate should be performed to exclude the existence of MDS.
E	Hasle H, Niemeyer CM, Baumann I, Bennett JM, Chessells J, Kerndrup G, Head D. Proposal for the classification of myelodysplastic diseases in children. Submitted	Abstract: Myelodysplasia is rare in childhood and there is no widely accepted system for its diagnosis and classification. We propose minimal diagnostic criteria and a simple classification scheme which, while based on accepted morphological features, allows for the special problems of myelodysplastic diseases in childhood. This new classification recognizes three major diagnostic groups: 1) juvenile myelomonocytic leukemia (JMML), previously named chronic myelomonocytic leukemia (CMML), or juvenile chronic myeloid leukemia (JCML) 2) MDS/AML of Down syndrome, a disease with distinct clinical and biological features, is referred to as myeloid leukemia of Down syndrome 3) MDS occurring both de novo and as a complication of previous therapy or pre-existing bone marrow disorder (secondary MDS). The main proposed subtypes of MDS are: refractory cytosine (RC) and refractory anemia with excess of blasts (RAEB). There remains uncertainty about the value of retaining the subtype of RAEB-T with 20-30% blasts in the marrow, abolished by the recent WHO classification. Cytogenetics and serial assessments of the patients are essential adjuncts to morphology both in diagnosis and classification.

P	Reference	Abstract
E	Kardos G, Baumann I, Passmore J, Locatelli F, Hasle H, Schulz J, Starý J, Schmitt-Graef A, Fischer A, Harbott J, Webb D, Chessels J, Fenu S, Cantú Rajnoldi A, Kerndrup G, van Wering E, Nöllke P, Niemeyer CM. Refractory cytopenia in childhood. A Retrospective analysis of 67 cases. Submitted	Abstract: Refractory cytopenia (RC) is an uncommon diagnosis in childhood. In an attempt to identify prognostic factors influencing outcome we analyzed retrospectively the data of 67 children with RA. Median age at diagnosis was 8.3 years. Only 24% of children had hypercellular bone marrow at diagnosis. Dysplasia of the erythopoetic line was most often seen. Of the 66 patients with karyotypic analysis, 32 had monosomy seven (- 7). Overall survival at 15 years was 0.48 (± 0.19). 20 children progressed to advanced form of MDS. Median time to progression was 1,7 years. The probability of progression was much higher in patients with monosomy 7 as compared to those with other chromosomal abnormalities or a normal karyotype (0.91 at 6 years v. 0.39 and 0.16). 41 children were transplanted, 17 with an HLA compatible family donor (MFD) and 24 with an unrelated donor (MUD). Probability of survival at 10 years was 0.64 (± 0.17) with no significant difference between MFD and MUD transplants. Children transplanted after progression had a significantly worse survival (0.76 v 0.36). Stem cell transplantation improved survival significantly in children with -7, but not in the others (0.42 v 0.27 and 0.77 v 0.64). Relapse after stem cell transplantation was only seen in patients with monosomy 7 and more advanced MDS at the time of transplantation. A high progression rate and a short survival were observed in children with RA and monosomy 7 with conservative therapy. Early bone marrow transplantation before progression seems to be the treatment of choice.

Anforderung eines Patienten-Identifikators (PID)

Erklärung/Hilfe [Vor der ersten Verwendung unbedingt lesen!]

Identifizierende Angaben		**Wie sicher ist der Name?**	○ **sicher** ◉ **unsicher**
Nachname:		Vorname:	
früherer Nachname:		Geburtsdatum	TT: MM: JJJJ:
Ergänzende Angaben			
Geschlecht:	○ weiblich ○ männlich ◉ unbekannt		
Postleitzahl:		Wohnort:	
		Staat:	

Bevor Sie das Formular abschicken, vergewissern Sie sich bitte noch einmal, ob alle Einträge korrekt sind.

PID anfordern

Formular zurücksetzen

Falls Sie als Reaktion nicht einen PID oder eine verständliche Fehlermeldung zurück erhalten, wenden Sie sich per E-Mail an webmaster@gpoh.de.

drescher KONZEPT
GRAFIK
konzept
DESIGN

Charité/Campus Virchow-Klinikum
Dr. Ralf Herold • Koordinator
Augustenburger Platz 1

13353 Berlin

Kostenangebot Marketing KPOH 2. Phase

09/04/2002

Sehr geehrter Herr Herold,

vielen Dank für Ihre Anfrage bezüglich der Fortführung von Marketingmaßnahmen für das „Kompetenznetz Pädiatrische Onkologie und Hämatologie"(KPOH, 2. Phase).

In der ersten Phase 2001/2002 der Marketingaktivitäten für das KPOH wurden – im Rahmen des Budgets von netto 35.260,00 € – die folgenden Aktivitäten durchgeführt:

- Entwurf und Produktion der Geschäftsausstattung (Briefbögen) des KPOH
- Konzeption, Entwurf und Produktion einer Infobroschüre in Form einer Mappe als Träger weiterführender Informationen von thematisch unterschiedlichen Einlegeblättern (derzeit in Arbeit)
- Marketingkonzept zur professionellen Öffentlichkeitsarbeit (derzeit in Arbeit)
- Presseaktivitäten: Pressekonferenz November 2001, Kontakte zu TV-Stationen
- Entwurf, Strukturierung (Sitemap) und programmiertechnische Umsetzung des Internet-Auftritts für das Kinderkrebs-Info-Portal
- Strukturierung (Sitemap) des Internet-Auftritts für das KPOH

Mit den genannten Aktivitäten sind erste Schritte in Richtung eines einheitlichen und professionellen Auftritts in Sachen Öffentlichkeitsarbeit getan. Dies mit dem Ziel, (a) die „eigenen Reihen" mit professionellem Informationsmaterial auszustatten, (b) die Belange des KPOH in der Öffentlichkeit durchzusetzen und um (c) eine Basis für die Eigenständigkeit des Netzes ab 2005 zu legen.

Ziel der Aktivitäten in der folgenden Phase ist, das KPOH marketingstrategisch als **Kompetenz-Qualitätsmarke** gegenüber Krankenkassen/Krankenhäusern, Betroffenen und der allgemeinen Öffentlichkeit zu positionieren.
Das KPOH wird künftig offensiv die Belange der Pädiatrischen Onkologie und Hämatologie in der Öffentlichkeit thematisieren, um so die wissenschaftliche Arbeit und die Behandlung der Kranken auf eine stabilere Grundlage zu stellen (Stichworte „Finanzierung – weg von Charity" und „Medikamente für Kinder").

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Im Zeitraum 2003-2004 sehen wir dafür – im Rahmen des Budgets von 80.000 € – die folgenden Aktivitäten:

KONZEPT:

In Fortführung des „Marketingkonzeptes 2002" wird das KPOH zu einer bundesweit bekannten Marke ausgebaut. Dieser Prozess wird konzeptionell begleitet und ständig auf dem Laufenden gehalten. Als „Produkte" werden wir aktualisierte Powerpoint- (bzw. ähnlich strukturierte) – Folien liefern und aktualisieren, die die Mitglieder des KPOH in Vorträgen verwenden können. Wir stellen uns vor, diese Marketing-Folien im Internet bereitzuhalten, so dass diese jederzeit aktuell z.B. in Berlin, Hannover oder Münster abgerufen werden können.

Zeitgleich wird der Verselbstständigungsprozess konzeptionell begleitet und ebenfalls durch Folien unterlegt.

PRINTPRODUKTE:

Träger der Basisinformationen wird auch in den Jahren 2003 – 2004 die Infobroschüre sein. Diese hatten wir so angelegt, dass sie jederzeit durch „Einlegeblätter" modular erweiterbar ist. Konzeption, Gestaltung, Text und Produktion der Einlegeblätter werden wir weiterführen.

Die Infobroschüre wird – allein aus Kostengründen – kein Massenstreumedium sein können. Daher schlagen wir einen Flyer vor (in Leporello-Form), der auf Messen oder ähnlichen öffentlichkeitsstarken Versammlungen distribuiert werden kann. Der Flyer wird auch als „Tür" zum Web-Auftritt im Internet dienen.

Mit dem Ziel, die Meinungsbildner aktuell über das KPOH auf dem Laufenden zu halten (insbesondere im Hinblick auf den Verselbstständigungsprozess), schlagen wir einen 4-seitigen Newsletter vor (empfohlenes Format A4), der im Zeitraum 2003 – 2004 zwei Mal als Print-Version erscheinen soll und selbstverständlich auch im Internet abgerufen werden kann.
Im Jahr 2004 schlagen wir eine konzeptionelle und grafische Überarbeitung der Infobroschüre vor.

MESSEAUFTRITT:

In der Vergangenheit hat sich gezeigt, dass Messeauftritte hervorragende Gelegenheiten sind, um mit der dort versammelten Presse gezielt in Kontakt zu kommen.
Wir werden daher eine für den flexiblen Einsatz geeignete KPOH-Messewand konzeptionell und grafisch vorbereiten und produzieren lassen.

INTERNET-SEITEN

Die Gestaltung der KPOH Seiten auf Basis des Corporate Designs der vorhandenen Produkte (Kinderkrebs-Info-Portal, Info-Mappe, Geschäftsausstattung) sollte in 2003 geschehen.
Eine Aktualisierung/Überarbeitung der Bilddaten und Farbwelt der Seiten KPOH und Info-Portal erfolgt in 2004.
Die ständige inhaltliche Aktualisierung erfolgt über das KPOH und wird konform mit der Grafik umgesetzt.

PR

Die Thematisierung der KPOH-Belange in der Presse wird weiter und offensiv fortgesetzt. Wir schlagen hierzu die Erstellung eines PR-Verteilers für ca. 50 Journalisten, die regelmäßige Herausgabe von Pressemitteilungen, die Initialisierung von weiteren TV-Kontakten sowie eine jährliche Pressekonferenz vor. Außerdem werden die PR-Aktivitäten rund um Messeauftritte verstärkt.

Die aufgeführten Vorschläge würden wir gern mit Ihnen in einen „Marketing-Fahrplan" einarbeiten.
In einem ersten (groben) Schritt stellen wir diese Maßnahmen wie folgt dar:

	Print	**Konzept**	**Messeauftritt**	**Internetseiten**	**PR**
2003:	Einlegeblätter Image-Flyer Newsletter Nr. 1 (Konzeption + Gestaltg./Druck)	Markenkonzept Detailliertes Marketingkonzept Privatisierung	Prod. einer mobilen Messewand (Konzeption + Gestaltg.)	Gestaltung KPOH-Seiten	PR-Verteiler Pressekonferenz TV-Auftritte Pressemitteilungen
2004:	Newsletter Nr. 2 Überarbeitung der Info-Broschüre (Konzeption + Gestaltg./Druck)	Fortsetzung		Web-Relaunch Info-Portal KPOH-Seiten	Pressekonferenz TV-Auftritte Pressemitteilungen
Budget	**ca. 25.000 €**	**ca. 7.500 €**	**ca. 7.500 €**	**ca. 10.000 €**	**ca. 30.000 €**

Dieses Angebot versteht sich zuzüglich der gesetzlich geltenden Mehrwertsteuer.

Aufwendungen für Bildrechte sowie Illustratorenkosten sind nicht Bestandteil dieses Angebotes.
Diese werden Ihnen bei Bedarf avisiert.

Für weitere Gespräche stehen wir Ihnen gern zur Verfügung.
Wir freuen uns auf eine spannende Zusammenarbeit!

Mit besten Grüßen

Claudia Drescher

Angebot zur Evaluation und Prozessbegleitung des Kompetenznetzes Pädiatrische Onkologie und Hämatologie

2. Phase: 2000 - 2004

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1. Vorbemerkung

WIAD und Prognos haben in der ersten Phase der wissenschaftlichen Begleitung des Kompetenznetzes eine "Bestandsaufnahme der Vernetzung in der Pädiatrischen Onkologie und Hämatologie" durchgeführt, deren Ergebnisse mit einem Abschlussbericht im Juni 2000 vorgelegt wurden. Diese Bestandaufnahme bildet die Grundlage für die Fortsetzung und Erweiterung der Prozessbegleitung und Evaluation in der 2. Phase in den Jahren 2000 bis 2004, für die hiermit ein Angebot unterbreitet wird.

In diese 2. Phase treten neben die Aufgaben der wissenschaftlichen Begleitung im engeren Sinne auch

- die Unterstützung bei der Steuerung des Gesamtvorhabens und der Teilprojekte,
- die Unterstützung bei der Öffentlichkeitsarbeit und Ergebnisverwertung sowie
- Evaluations- und Methodenberatung,

Aufgaben, die im wesentlichen im Rahmen von Tagungen bzw. Workshops abzuleisten sind.

In der nachstehenden Leistungsbeschreibung werden die anstehenden Aufgabenpakete modulartig dargestellt.

2. Evaluationsdesign und Methoden

<u>Arbeitsmodul 1:</u> Untersuchung der Kooperations- und Informationsstrukturen zwischen Studienzentralen, Referenzlaboratorien und Kliniken

Arbeitsmodul 1 knüpft an die übergeordnete Zielsetzung des Kompetenznetzes Pädiatrische Onkologie an, nämlich den Aufbau einer effizienten Forschungskooperation durch Verbindung von Klinik, zentralen Einrichtungen und Forschungslaboratorien. Geplant ist in diesem Kontext die Etablierung neuer, netzwerkübergreifender Strukturen zur Verbesserung des Informationsflusses, der Kooperation und der Interaktion zwischen den Partnern aus Klinik und Forschung, wie zum Beispiel:

- eine zentrale Forschungskoordination,
- die flächendeckende Einführung von rechnerbasierten Anwendungssystemen und telemedizinischen Verfahren,
- die Optimierung der Logistik für den Materialversand und
- die Bereitstellung von Informationen und Wissen zur Realisierung der vertikalen Vernetzung.

Die wissenschaftliche Begleitung der neuen Kooperations- und Informationsstrukturen wird sich hauptsächlich an den folgenden Untersuchungsbereichen bzw. Leitfragen orientieren:

- **Wissenstransfer innerhalb der Pädiatrischen Onkologie und Hämatologie** *(Untersuchungsbereich 1)*
  Welche Informationsquellen werden zum Wissenserwerb/-transfer genutzt?
  Wie werden diese Quellen hinsichtlich Anwendung und Relevanz von den Beteiligten bewertet?
  Wie kann der Wissenstransfer optimiert werden?
  Wie kann der Wissensserver des Kompetenznetzes in den Transfer eingebunden werden?

- **Informationslieferung der Kliniken an die Studienzentralen bzw. Referenzlaboratorien** *(Untersuchungsbereich 2)*
  Wie hoch ist der Aufwand der Kliniken für die Lieferung von Material und Daten an die Studienzentralen bzw. Referenzlaboratorien?
  Wie wird der Informationsaustausch von den Beteiligten bewertet?
  Gibt es Optimierungsmöglichkeiten bei Materialasservierung und -versand?
  Welche neuen Dokumentationsmedien kommen zum Einsatz?

- **Informationsempfang der Kliniken von den Studienzentralen bzw. Referenzlaboratorien** *(Untersuchungsbereich 3)*
  In welcher Form empfangen die Kliniken Informationen von den Studienzentralen bzw. Referenzlaboratorien (Studienprotokolle, Beratungen etc.)?
  Wie werden diese Informationsquellen bewertet und wo sind Optimierungspotentiale?

- **Einsatz der Forschungs- und Studienassistenten** *(Untersuchungsbereich 4)*
  Welche Kenntnisse und Fähigkeiten werden von den Forschungs- und Studienassistenten erwartet?
  Welche Verbesserungen in der Zusammenarbeit mit den Studienzentralen werden durch den Einsatz von Forschungs- und Studienassistenten erwartet?
  Welche Verbesserungen wurden erzielt?
  Wie gestaltet sich das Aufgabenspektrum der Forschungs- und Studienassistenten?

Zur Bearbeitung der genannten Untersuchungsbereiche sind zwei schriftliche Befragungen von Klinikärzten geplant:

- Befragung 1 erstreckt sich auf die Untersuchungsbereiche 1 bis 3. In diese Befragung sollen alle diejenigen Kinderkliniken einbezogen werden, die pro Jahr mehr als zehn onkologische bzw. hämatologische Neuerkrankungen behandeln. Hierzu zählen gegenwärtig etwa 50 Kliniken.
- Befragung 2 erstreckt sich auf den Untersuchungsbereich 4. Für diese Befragung kommen alle diejenigen Kinderkliniken in Betracht, die einen Forschungs- und Studienassistenten beschäftigen. Hierzu zählen gegenwärtig etwa 30 Kliniken mit jeweils mehr als 25 Neuerkrankungen.

Beide Befragungen wurden bereits einmal im Jahre 1999 durchgeführt. Sie sollen während des Förderzeitraums noch zweimal durchgeführt werden, um die Vernetzungsfortschritte angemessen evaluieren zu können.

Arbeitsmodul 2: Vertiefende Untersuchung des Einsatzes der Forschungs- und Studienassistenten

Zur Weiterentwicklung der Vernetzungs- und Kooperationsstrukturen zwischen Kliniken, Studienzentralen und Referenzlaboratorien fördert das Bundesministerium für Bildung und Forschung die Beschäftigung sog. Forschungs- und Studienassistenten. Ihre Aufgaben liegen schwerpunktmäßig in den nachstehenden Bereichen:

- Unterstützung der verantwortlichen Ärzte bei der Organisation und Durchführung von klinischen Studien
- Entnahme, Aufbereitung und Versand von Patientenmaterialien/Laborlogistik
- Dokumentation und Kommunikation mit anderen Forschungseinrichtungen

Die Arbeitsfelder und das Tätigkeitsspektrum der Forschungs- und Studienassistenten sollen einer gesonderten Betrachtung unterzogen werden. Im Vordergrund stehen hierbei die folgenden Fragen:

- Welche unterschiedlichen Aufgaben/Tätigkeiten werden von den neuen Mitarbeitern wahrgenommen?
- Mit welchen Zeitanteilen werden diese Aufgaben/Tätigkeiten wahrgenommen?

- Welche anderen Klinikmitarbeiter werden durch den Einsatz der Forschungs- und Studienassistenten in welchem Umfang entlastet?
- Wie sind die Forschungs- und Studienassistenten in die Aufbau- und Ablauforganisation der Kliniken eingebunden?
- Mit wem kommunizieren die neuen Mitarbeiter (intern und extern)? Was sind die Hauptgegenstände der Kommunikation, was die Kommunikationsmedien?
- Welche Fähigkeiten, Kenntnisse und formalen Qualifikationen besitzen die eingestellten Forschungs- und Studienassistenten?
- Welche Veränderungen lassen sich in den Bereichen „Durchführung von Studien", „Laborlogistik" und „Dokumentation" während des Förderzeitraums nachweisen?

Zur Beantwortung dieser Fragestellungen ist ein zweigleisiger Instrumenteneinsatz geplant:

- Schriftliche Befragungen der ca. 30 Forschungs- und Studienassistenten sind in den Jahren 2001 sowie 2004 vorgesehen.
- Mündliche Befragungen der Forschungs- und Studienassistenten sind in den Jahren 2000, 2002 und 2004 vorgesehen. Hierzu sollen die regelmäßig stattfindenden Gruppentreffen dieser Mitarbeiter genutzt werden. Anläßlich dieser Gruppentreffen sind alternativ auch Diskussionen mit einem größeren Kreis von Forschungs- und Studienassistenten möglich.

Arbeitsmodul 3: Dokumentation und Präsentation der Ergebnisse

Die Dokumentation der Ergebnisse erfolgt gemeinsam mit der Koordinationszentrale des Kompetenznetzes. Insgesamt sind ein Zwischenbericht im Jahre 2001 nach Durchführung und Auswertung der ersten Erhebungswelle sowie ein abschließender Bericht zum Ende des Jahres 2004 geplant.

Die Ergebnisse sowohl des Zwischen- als auch des Endberichtes werden einem vom Auftraggeber zu bestimmenden Kreis oder Gremium präsentiert und zur Diskussion gestellt.

Arbeitsmodule 4-6: Unterstützungs- und Beratungsleistungen

Für Unterstützungs- und Beratungsleistungen im Rahmen der Module 4 bis 6 kann der Auftraggeber jährlich auf 10 bis 15 Personentage zurückgreifen. Die Leistungen können sich auf die nachstehend genannten Felder erstrecken:

- **Projektmanagement**
  Das Kompetenznetz Pädiatrische Onkologie stellt ein Projekt dar, das innerhalb bestehender Organisationsstrukturen parallel zum medizinischen Routinebetrieb zu bewältigen ist. Es weist eine Reihe von Merkmalen auf, die die Steuerung nicht einfach machen und das Management vor besondere Herausforderungen stellen. Zu nennen ist in diesem Zusammenhang die Vielzahl externer Beteiligter aufgrund der Einbindung in übergeordnete Programmstrukturen (Bundesministerium als Förderer, Projektträger, acht weitere Kompetenznetze, zahlreiche übergeordnete Gremien und Projekte). Zu nennen sind des weiteren die

Vielzahl interner Beteiligter aufgrund von neun Unterprojekten und die hohe Eigenständigkeit der Unterprojekte mit zum Teil heterogenen Zielsetzungen und Selbstevaluation.

Managementaufgaben stellen sich sowohl auf der Ebene der einzelnen Teilprojekte als auch auf der Ebene der Zusammenführung der Teilprojekte zum gemeinsamen Kompetenznetz Pädiatrische Onkologie. Die angebotenen Beratungsleistungen können sich in diesem Kontext auf alle Teilbereiche des klassischen Projektmanagements erstrecken: auf die Projektplanung und -organisation, auf das Informationsmanagement und die Projektdokumentation sowie auf die Projektsteuerung und -kontrolle. Für den Know-how-Transfer sind verschiedene Wege denkbar: regelmäßige Arbeitssitzungen mit den Projektverantwortlichen, Weitergabe von Informationen zum Thema Projektmanagement über das Intranet des Kompetenznetzes, Erarbeitung von Projektplänen, Ablaufdiagrammen, Pflichtenheften etc. gemeinsam mit den Projektverantwortlichen.

- **Evaluation**
  Ist wie im vorliegenden Fall eine interne Evaluation vorgesehen, muß diese in die Planung, das Informationsmanagement und die Steuerung des Projektes mit einbezogen werden. Festzulegen sind insbesondere die Ziele der Evaluation, die zum Einsatz kommenden Methoden und Erhebungsinstrumente, die Aufbauorganisation, d. h. wer für welche Aufgaben im Rahmen der Evaluation verantwortlich ist, der zeitliche Rahmen sowie die Form der Dokumentation der Ergebnisse.

  Die angebotenen Unterstützungsleistungen könnten sich hierbei insbesondere auf die Methodenwahl und die Instrumentenentwicklung beziehen. Know-how steht in den Bereichen empirische Sozialwissenschaften, Epidemiologie, Biostatistik und Gesundheitsökonomie zur Verfügung. Auch im Rahmen der Aufbereitung und Darstellung von Evaluationsergebnissen sind Unterstützungsleistungen denkbar (siehe hierzu auch Öffentlichkeitsarbeit und Ergebnisverwertung).

- **Öffentlichkeitsarbeit und Ergebnisverwertung**
  Elementarer Bestandteil des Förderkonzepts der Medizinischen Kompetenznetze ist auch die Vermittlung der Information, was Forschung leistet und für wen. So ist eines der Leitziele die Schaffung einer sowohl für die Fachwelt als auch in besonderem Maße für die Öffentlichkeit erkennbaren Kompetenz. Externe Unterstützungs- und Beratungsleistungen könnten in diesem Kontext die Erarbeitung eines Konzeptes für die Öffentlichkeitsarbeit sowie die mediengerechte Aufbereitung von Ergebnissen für den Transfer in die Öffentlichkeit umfassen.

3. Arbeits- und Zeitplan

Die Leistungsbeschreibung wird in Form eines Arbeits- und Zeitplans vorgelegt, in dem den einzelnen Arbeitsmodulen die jeweiligen Leistungen bzw. Instrumente für den Gesamtzeitraum 2000 bis 2004 zugeordnet sind. Zusätzlich ist der Leistungsaufwand für die einzelnen Arbeitsschritte in Tagen ausgewiesen.

Arbeits- und Zeitplan

Arbeitsmodule	2000	2001	2002	2003	2004	Wissenschaftler-Tage
(1) Untersuchung der Kooperations- und Informationsstrukturen (z.B. Nutzung des Wissensservers, Informationslieferung und –empfang, Einbindung und Vernetzungsbeitrag der Forschungs- und Studienassistenten (FSA), Entwicklung der Vernetzung)						
1.1 Schriftliche Befragung der Studienzentralen und Referenzlaboratorien (n = ca. 30)		■			■	55
1.2 Schriftliche Befragung leitender Klinikärzte (n = ca. 50)		■			■	50
(2) Untersuchung der Arbeitsfelder und der Einbeziehung der FSA in die Aufbau- und Ablauforganisation sowie der Effektivität der FSA						
2.1 Schriftliche Befragung der FSA (n = ca. 30)		■			■	55
2.2 Mündliche Befragung der FSA (n = ca. 30) im Rahmen von Gruppentreffen	■		■		■	45
(3) Berichterstattung gemeinsam mit der Koordinationszentrale (◆), Projektabstimmung, Diskussion und Präsentation der Ergebnisse		◆			◆	85
(4) Unterstützung bei der Steuerung des Gesamtvorhabens und der Teilprojekte	▬	▬	▬	▬	▬	
(5) Evaluations- und Methodenberatung	▬	▬	▬	▬	▬	65
(6) Unterstützung bei Öffentlichkeitsarbeit und Ergebnisverwertung	▬	▬	▬	▬	▬	
	2000	2001	2002	2003	2004	

Die Wissenschaftler-Tage verteilen sich wie folgt auf die kalkulierten Module und Jahre. Diese Leistungsmengen verteilen sich zu gleichen Teilen auf beide Anbieter.

Module	2000	2001	2002	2003	2004	Gesamt
1.1	-	30	-	-	25	**55**
1.2	-	25	-	-	25	**50**
2.1	-	30	-	-	25	**55**
2.2	15	-	15	-	15	**45**
3.	10	20	10	10	25	**75**
4. – 6.	10	15	15	15	10	**65**
Gesamt	**35**	**120**	**40**	**25**	**125**	**345**

4. Kalkulation

Der Kalkulation liegt ein Wissenschaftler-Tagessatz von DM 1.300,- im Jahre 2000 zugrunde, der um jährlich DM 50,- erhöht wird. Die übrigen Kosten werden zu konstanten Preisen kalkuliert. Hiernach ergeben sich folgende Kosten, die netto hälftig auf beide Anbieter entfallen.

Kostenplan WIAD und Prognos	2000	2001	2002	2003	2004	Gesamt
(A) Honorare						
• Wissenschaftler	45.50	162.000	56.00	36.25	187.500	**487.250**
• Projektassistenz	3.0	5.0	3.0	3.0	5.0	**19.00**
• Sekretariat	4.0	12.00	6.0	6.0	15.00	**43.00**
(B) Sachkosten						
• Reisekosten	3.0	8.0	8.0	8.0	8.0	**35.00**
• sonstige Sachkosten	2.0	4.0	3.0	2.0	4.0	**15.00**
Kosten (netto)	**57.50**	**191.000**	**76.00**	**55.25**	**219.500**	**599.250**
MWSt. WIAD (7%)	2.0	6.6	2.6	1.9	7.6	**20.97**
MWSt. Prognos (16%)	4.6	15.28	6.0	4.4	17.56	**47.94**
Gesamtkosten (brutto)	**64.11**	**212.965**	**84.74**	**61.60**	**244.743**	**668.165**

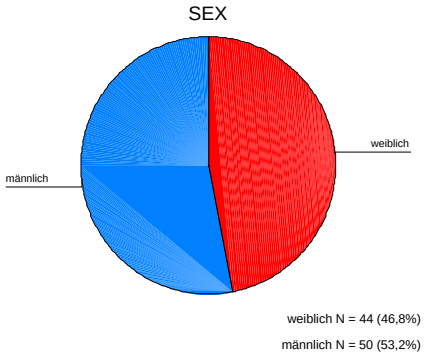
ANNEX 1:

Auswertung der Neuropsychologie

In diesem Anhang wird über die Auswertung der neuropsychologischen Testverfahren berichtet, sofern die vorliegenden Testeregebnisse eine statistische Auswertung (Größe der Stichprobe zuließen).

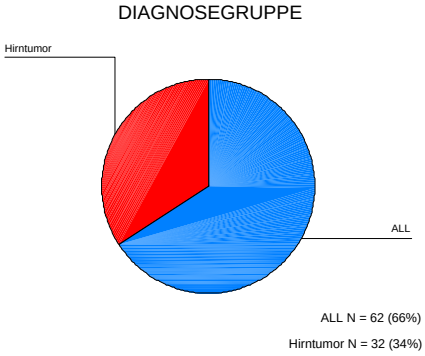
Zur Übersicht zunächst einige Informationen zu der Patientenstichprobe:

	Häufigkeit	Prozent
weiblich	44	46,8
männlich	50	53,2
Gesamt	94	100,0



DIAGNOSEGRUPPE

	Häufigkeit	Prozent
ALL	62	66,0
Hirntu	32	34,0
Gesamt	94	100,0



Im folgenden noch einige Erläuterungen zu den angewandten Testverfahren als Hintergrundinformation:

Eingesetzte Testverfahren:

Intelligenztests

- Kaufman-Assesment-Battery for Children (K-ABC) (Altersstufen 2;6 bis 11;11 Jahre), Individualtest zur Messung von Intelligenz und Fertigkeiten bei Kindern und Jugendlichen von A. S. Kaufman und N. L. Kaufman. Deutsche Bearbeitung von U. Melchers, U. Preuß.
- Kaufman-Adolescent and Adult Intelligence Test (K-TIM) (Altersstufe Ó12;0 Jahre) Individualtest zur Messung von Intelligenz und Fertigkeiten bei Jugendlichen und Erwachsenen von A. S. Kaufman und N. L. Kaufman. Deutsche Bearbeitung von U. Melchers, U. Preuß und S. Schümann. Experimentalversion.

Die K-ABC ist ein Testverfahren, das Intelligenz und Fertigkeiten mißt. Die Grundlage der K-ABC ist die Definition der Intelligenz als Fähigkeit, Probleme durch geistiges Verarbeiten zu lösen. Hierbei steht der Prozeß der Lösungsfindung im Vordergrund. Die Messung intellektueller Fähigkeiten wird von der Messung des Standes erworbener Fertigkeiten getrennt, um diese unterschiedlichen Bereiche mentaler Leistung einzeln und im Vergleich miteinander erfassen zu können. Deshalb ist die K-ABC in vier Skalen gegliedert: „Skala einzelheitlichen Denkens“, „Skala ganzheitlichen Denkens“, „Fertigkeitenskala“ und „Sprachfreie Skala“.
Die K-TIM ist ebenfalls ein Verfahren zur Messung von Intelligenz und Fertigkeiten, jedoch für Jugendliche und Erwachsene. Die Skalen werden anders bezeichnet: „Skala kristalliner Intelligenz“ und „Skala fluider Intelligenz“. Die Skala kristalliner Intelligenz mißt erworbenes Wissen und ist vom Schul- und Ausbildungsstand abhängig. Dagegen mißt die „Skala fluider Intelligenz“ die Fähigkeit, neue Aufgaben und Probleme zu lösen.

Ergänzende Neuropsychologische Verfahren

∉ Developmental Test of Visual-Motor Integration (VMI) (Altersstufen: 2;6 bis 18;0 Jahre) von K. E. Beery.
Der VMI erfaßt die visuomotorische Integrationsleistung. Hierzu sind geometrische Figuren unterschiedlicher Komplexität nachzuzeichnen.
Der Test ist in der Durchführung anwenderfreundlich, die Auswertung bedarf einiger Erfahrung. Aus diesem Grund wird der Test zusätzlich zentral (Erlangen) nachbewertet, um Einflüsse einer subjektiven Testleiterbewertung auszuschließen. Der Test wird in allen Altersklassen angewandt und ist für die Testpersonen nicht belastend. Anwendungszeit 10 min, Auswertungszeit 20 min.

∉ Fragmentierter Bildertest (FBT) (Altersstufen: 10;0 bis 18;0 Jahre) von J. Kessler, A. Schaaf und R. Mielke.

Der Einsatz erfolgt zur Untersuchung der visuellen Informationsverarbeitung und zur Überprüfung von höheren integrativen Wahrnehmungsprozessen. Der FBT, ein auf Gollin zurückgehendes Verfahren, ist ein Wahrnehmungs- und Gedächtnistest, bei dem die Gestalt von 10 konkreten Figuren sukzessive in 5 Stufen vervollständigt wird. Der Patient wird instruiert, die Figuren anhand der Fragmenteso früh wie möglich zu identifizieren und zu benennen.

∉ Differentieller Leistungstest-KE (DL-KE) (Altersstufen: 5;0 bis 6;11 Jahre), Test zur Erfassung des Leistungsverhaltens bei konzentrierter Tätigkeit von E. W. Kleber, G. Kleber und O. Hans.

∉ Differentieller Leistungstest-KG (DL-KG) (Altersstufen: 7;0 bis 8;11 Jahre), Test zur Erfassung des Leistungsverhaltens bei konzentrierter Tätigkeit von E. W. Kleber, G. Kleber und O. Hans.

Beide Verfahren sind Figurendurchstreichtests, die für die Eingangsstufe der Grundschule bzw. für die übrigen Altersgruppen der Grundschule Material auf einem angemessenen Bearbeitungsniveau zur Verfügung stellen. In der Studie wird in Absprache mit den Testautoren eine reduzierte Itemzahl eingesetzt. Dies ist aus testtheoretischer Sicht (Gütekriterien) problematisch (Bortz & Döring, 1995; Krauth, 1995). Es existieren nur grob differenzierende Normen für beide Testverfahren.

∉ Aufmerksamkeits-Belastungstest d2 (Test d2) (Altersstufen: Ó9;0 Jahre), Test zur Erfassung der Aufmerksamkeits- und Konzentrationsleistung von R. Brickenkamp.

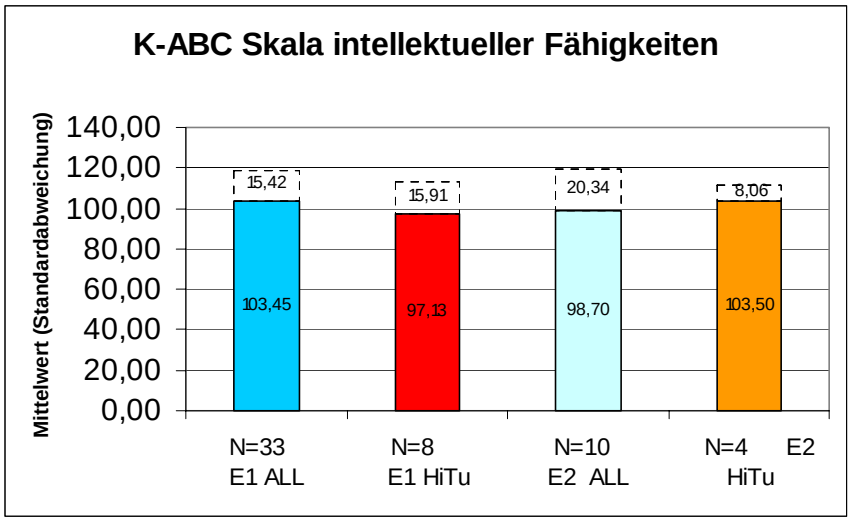
Der Test d2 ist ein Durchstreichtest. Er mißt Tempo und Sorgfalt des Arbeitsverhaltens bei der Unterscheidung ähnlicher visueller Reize (Detail-Diskrimination) und ermöglicht damit die Beurteilung individueller Aufmerksamkeits- und Konzentrationsleistungen.

∉ Tapping-/Reaktionszeitverfahren (Altersstufen: 4;0 bis 18;0 Jahre) von H. Ottensmeier, N. Galley und G. Hopmann, 1997.

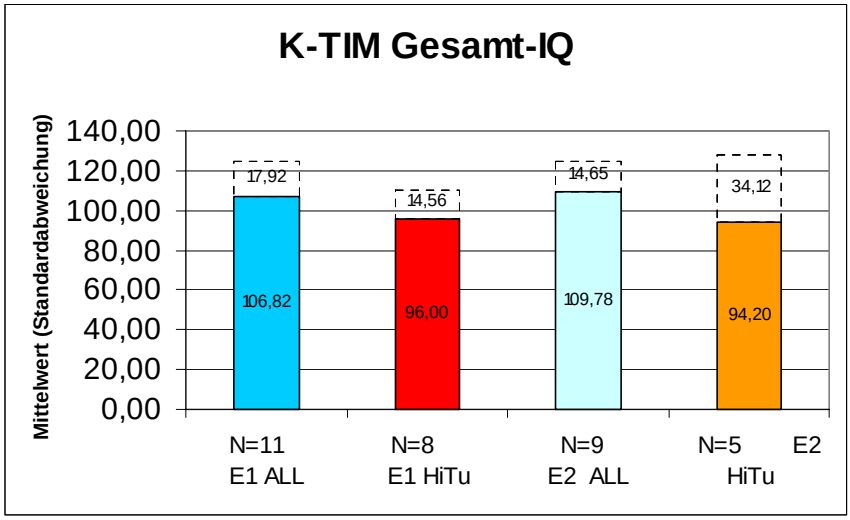
Beim Fingertapping wird die Geschwindigkeit einer basalen motorischen Funktion EDV-gestützt erfaßt. Im Abstand von 10 min werden 2 Untersuchungsgänge durchgeführt. Dazu muß der Patient eine Morsetaste mit dem Zeigefinger bei aufliegendem Handgelenk über einen Zeitraum von 30 Sekunden so schnell wie möglich betätigen. Beim Reaktionszeitverfahren (RT) wird die Latenz der o.b. motorischen Reaktion bei Darbietung eines visuellen und eines akustischen Reizes geprüft. Hierbei ist bei Erscheinen des Reizes der Finger von der gedrückten Morsetaste abzuheben. Es werden 30 Reize angeboten.

Darstellung der Ergebnisse der Neuropsychologie:

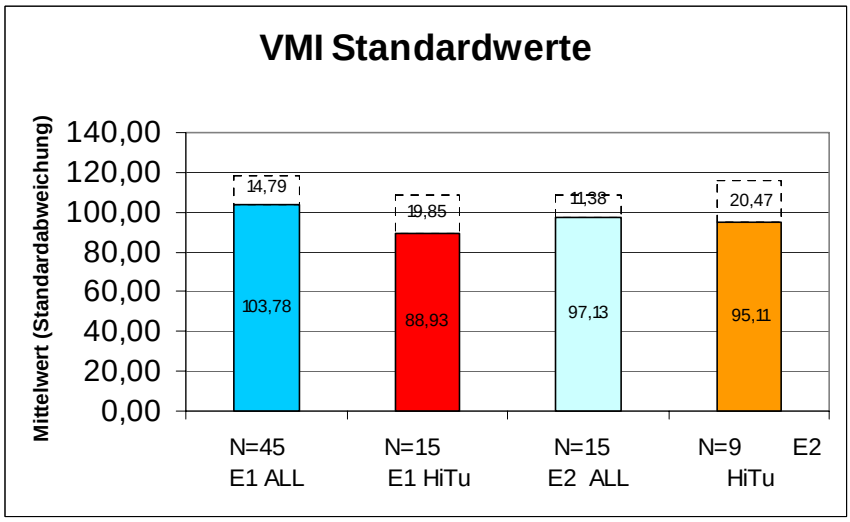
Ausgewertet wurden: der K-ABC, der K-TIM, der D2, DL-KG und DL-KE, sowie der VMI und der FBT. Nicht auswertbar war Tapping/Reaktionszeit, da dazu nur sehr wenige vollständige Datensätze vorlagen, aus denen kein direktes Testergebnis abzulesen ist.



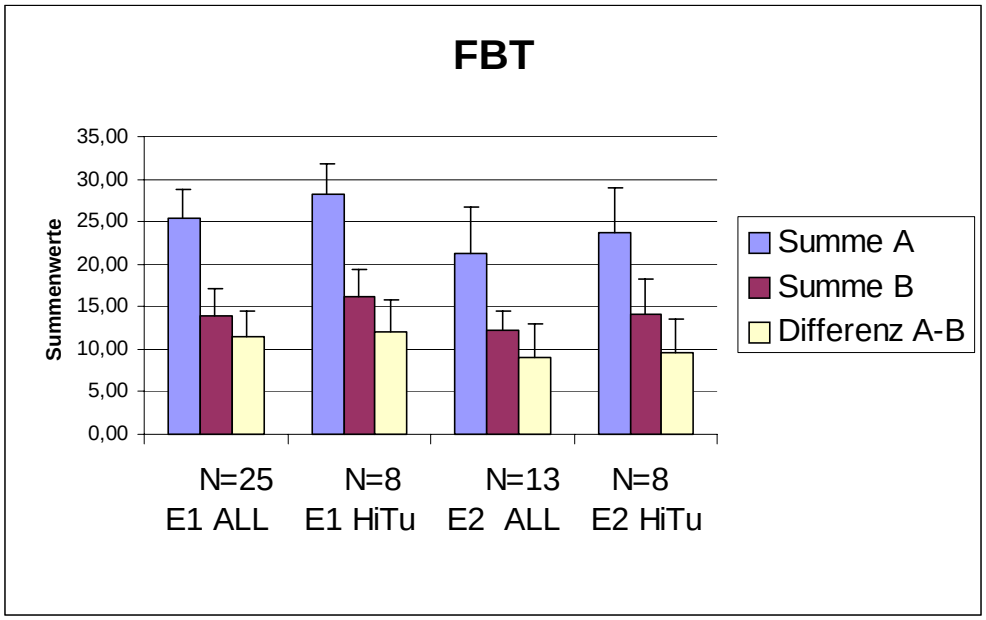
Altersbereich 6 bis 11.11 Jahre, bei Hirntumoren 4.00 bis 11.11 Jahre
Angegeben sind die Mittelwerte und Standardabweichungen der getesteten Studienpatienten. Diese lassen sich mit der Normpopulation (durchschnitt 100, Standardabweichung 15) vergleichen. Dabei schneidet die Gruppe der ALL zum ersten Testzeitpunkt im Durchschnitt etwas besser, die Gruppe der Hirntumorkinder im Durchschnitt etwas schlechter als die Normpopulation ab. Die Standardabweichungen sind vergleichbar. Zum Zweiten Testzeitpunkt kehrt sich dieses Verhältnis dahingehend um, das im Durchschnitt die ALL Kinder etwas schlechter als die Normpopulation sind, die Hirntumorkinder jedoch etwas besser. Allerdings finden sich bei beiden Werten eine geringe Anzahl an getesteten Kindern und eine vergleichsweise hohe Standardabweichung.
Normgruppe: Kinder aus dem deutschsprachigen Raum, mehrere Untersuchungen, Vergleichspopulationen mit Auffälligkeiten, 40 Korrelationsstudien zu anderen Testverfahren



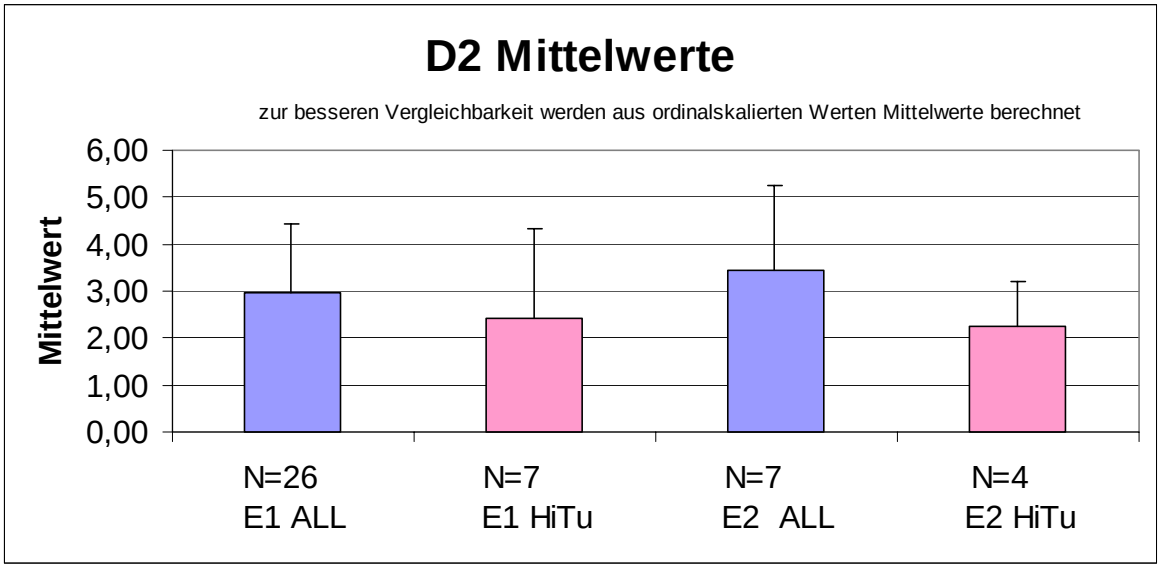
Altersgruppe ab 12 Jahre
Normpopulation aus dem amerikanischen Sprachbereich, keine deutschsprachige Normpopulation. Durchschnitt 100 Standardabweichung 15. Wert entspricht einem IQ
Der Durchschnitt der ALL Patienten unserer Studie liegt zu beiden Testzeitpunkten leicht über dem Durchschnitt der Normpopulation, und steigt vom ersten zum zweiten Zeitpunkt leicht an.
Die Hirntumorpatienten liegen im Durchschnitt leicht unter dem der Normpopulation und werden zum zweiten Testzeitpunkt noch etwas schlechter, allerdings bei sehr geringer Anzahl und steigender Standardabweichung.



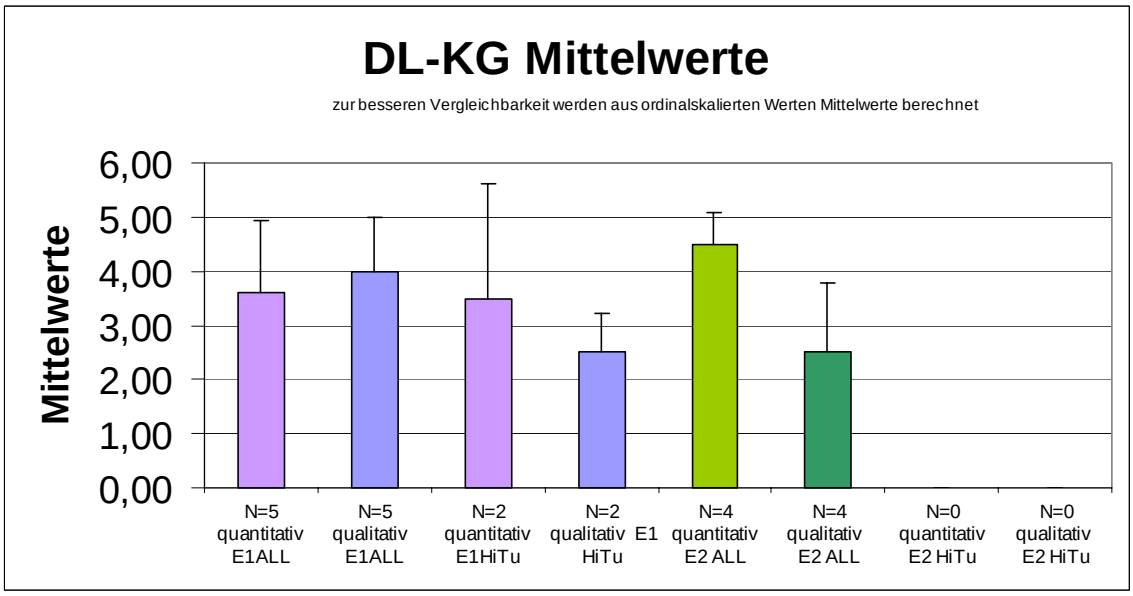
Altersgruppe: ab 6
Normpopulation: Durchschnitt 100+/-15 ; 2614 Testpersonen in der Validierung, mehrfach getestet
Bei E1 ALL im Durchschnitt etwas besser als Normpopulation, Hirntumoren etwas schlechter, bei E2 beide Gruppen im Durchschnitt unterhalb der Normpopulation., Hirntumoren noch deutlicher als ALL, aber besser als zum Zeitpunkt E1(allerdings höhere Standardabweichung)



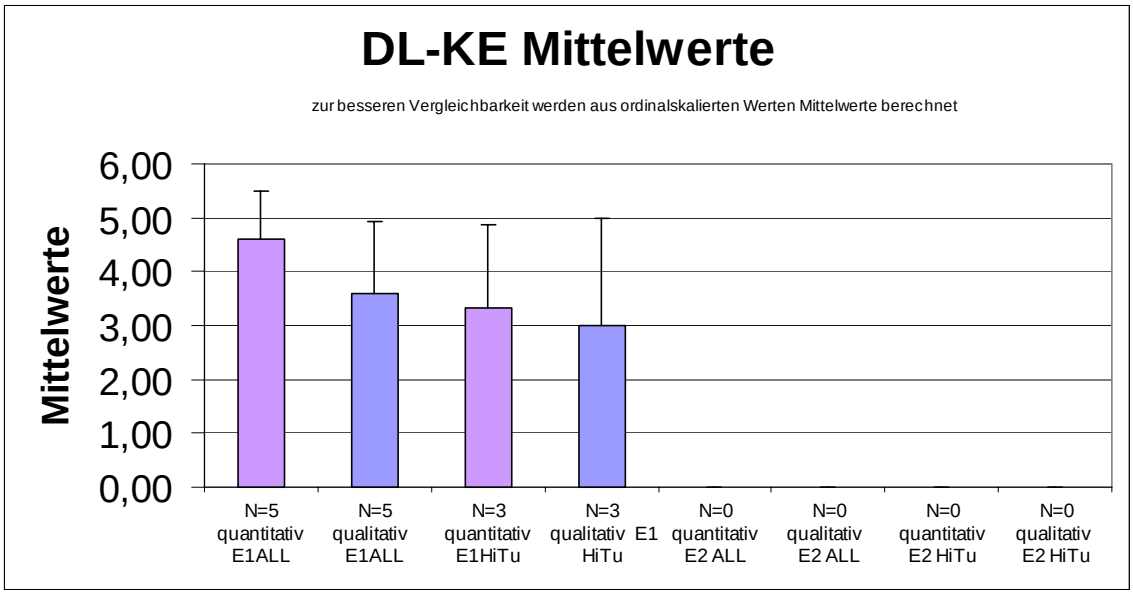
Altersgruppe ab10
Normgruppe: 19 Personen 10-20 Jahre, Durchschnittsalter 16,66
A: 23,73 (3.76), B: 12,42(2.91), A-B: 11,31(2.98)
Ergebnisse unauffällig, deutlich erkennbarer Lerneffekt zum E2 Zeitpunkt
Summe A: erstes Erkennen der Figur- hohe Werte schlecht
Summe B: Wiederholung/ Lerneffekt deutlich durch hohes A-B(kein direkter Vergleich der gelben Säulen möglich, da diese von der Höhe der blauen Säule abhängt!



Normdurchschnitt:3, Alter: ab 9Jahren
1=deutlich unterdurchschnittlich.
2= unterdurchschnittlich.
3=durchschnittlich
4=überdurchschnittlich.
5=deutlich überdurchschnittlich.
ALL wird von E1 zu E2 besser, Hitumore schon zu E1 schlechter als Durchschnitt, wird zu E2 noch etwas schlechter (geringe Personenanzahl!!) Hohe Standardabweichungen in der Population (da ordinalskaliert gibt es keine Standardabweichungen für die Norm)

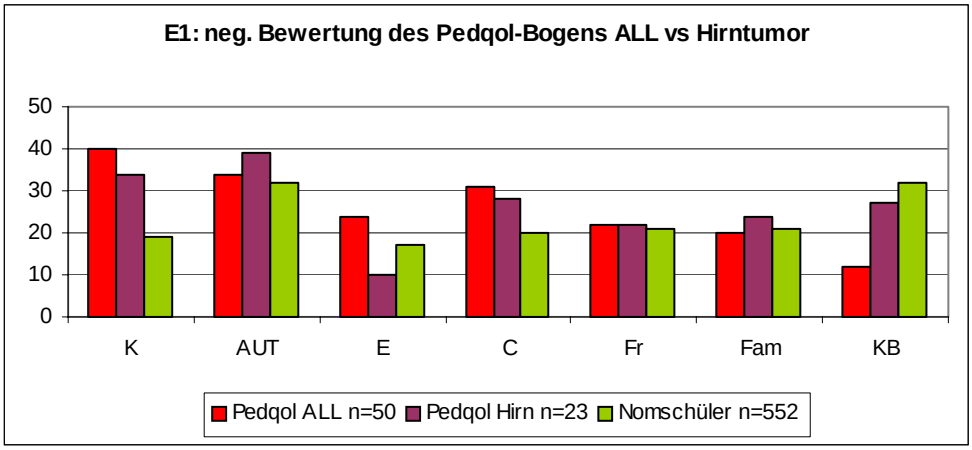


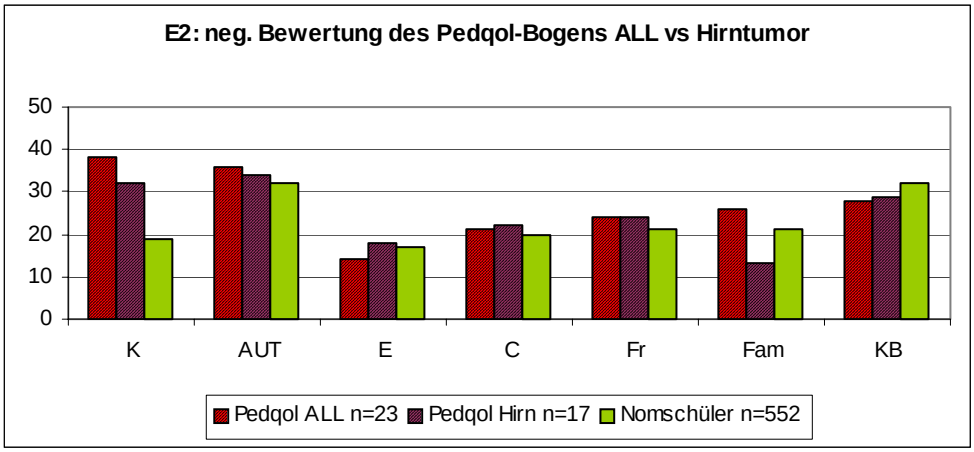
Alter:7-9
Klassifikation siehe oben
Quantitativ: Anzahl aller insgesamt bearbeiteten Zeichen
Qualitativ: Anzahl aller ***richtig*** bearbeiteten Zeichen
unauffällig
Auffällig: qualitative Schwäche bei den HiTu Kindern zum E1 Zeitpunkt
E2 zu wenige Patienten (Gleiche Qualität, geringere Qualität)

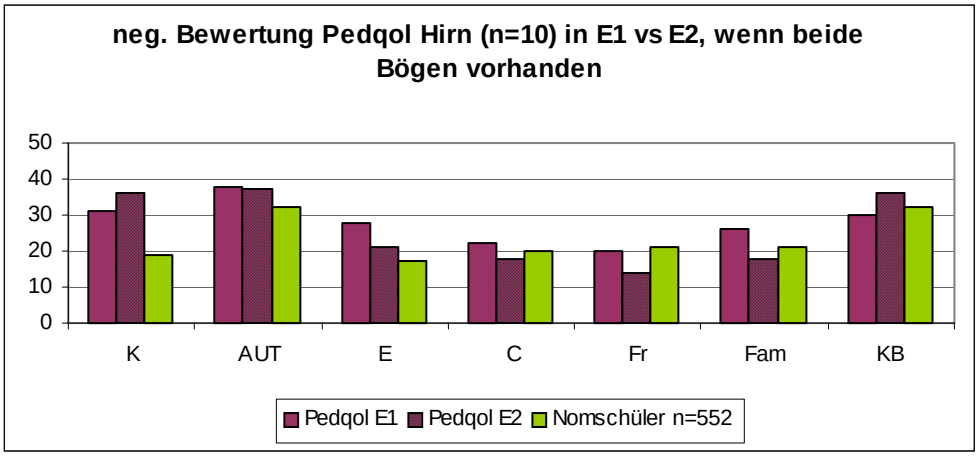


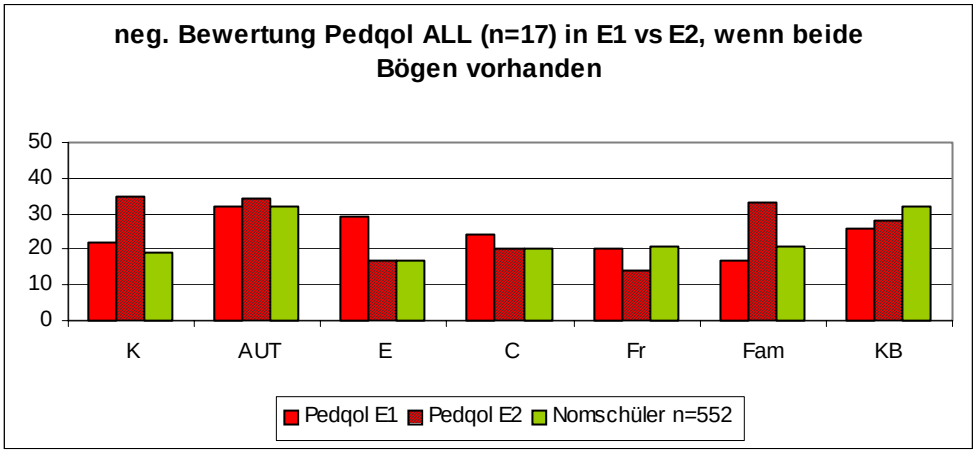
Alter 6-7, minimale Personenzahl, hohe Standardabweichung, Hirntumorpatienten in beiden Bewertungen schlechter als ALL, qualitativ aber deutlich schlechter.

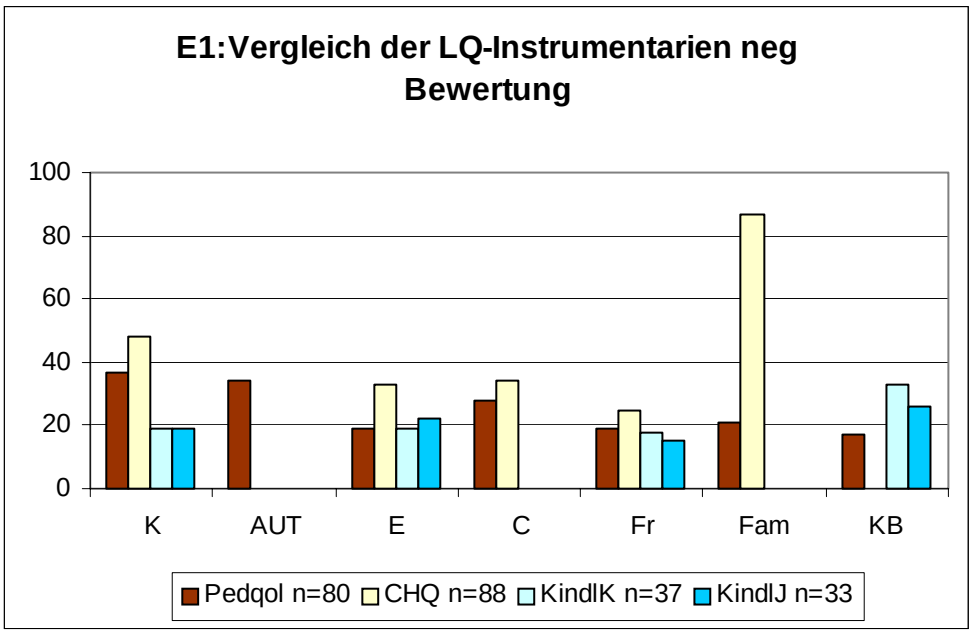
ANNEX 2
Graphische Darstellung der Lebensqualitätsergebnisse, deskriptive Statistik in %

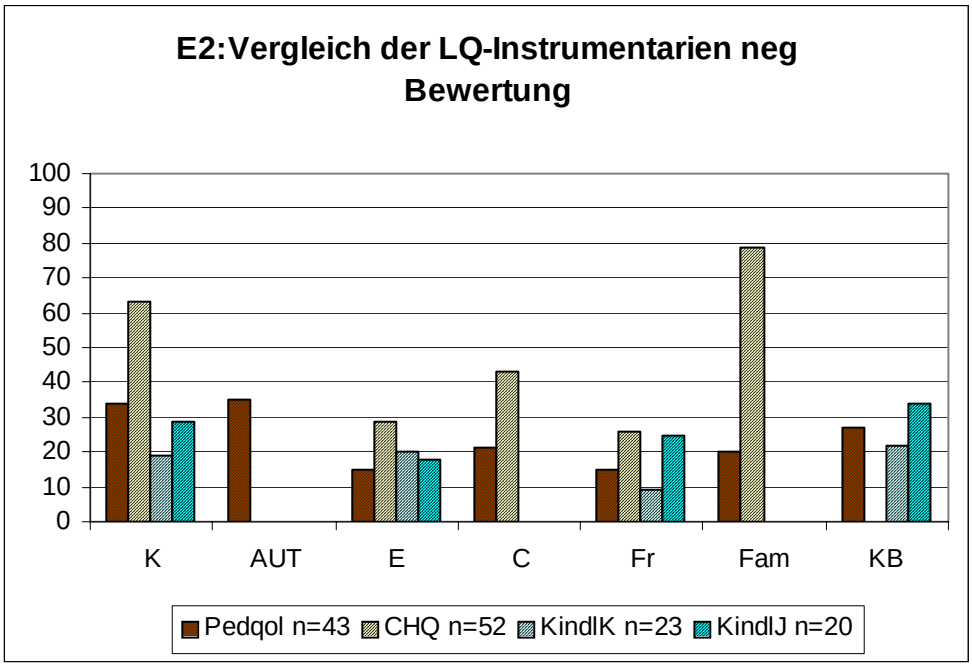






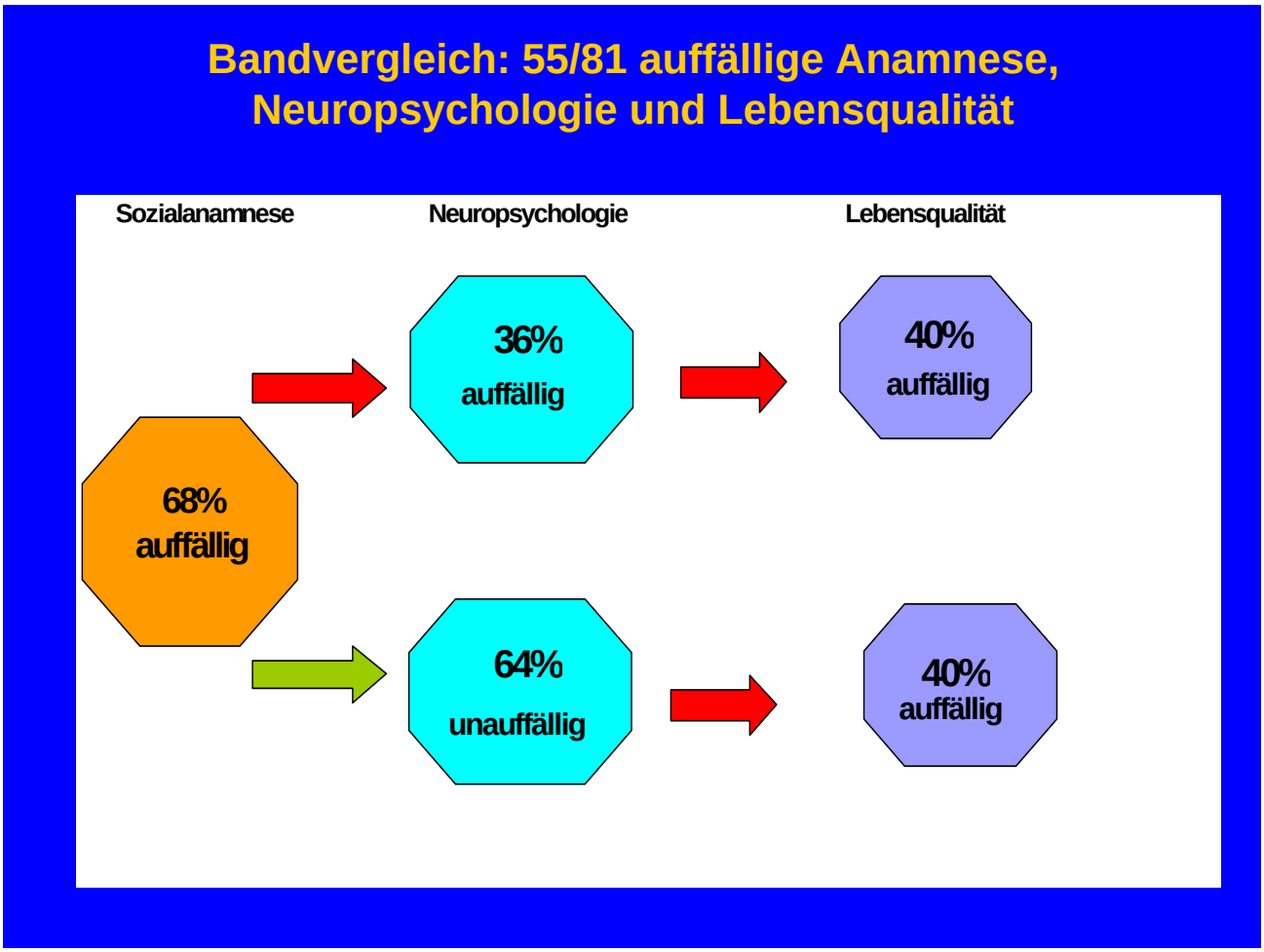






K= Körperliche Funktion
AUT= Autonomie
E= Emotionaler Zustand
C= Kognition
Fr= Soziale Funktion Freunde
Fam: Soziale Funktion Familie
KB= Körperbild

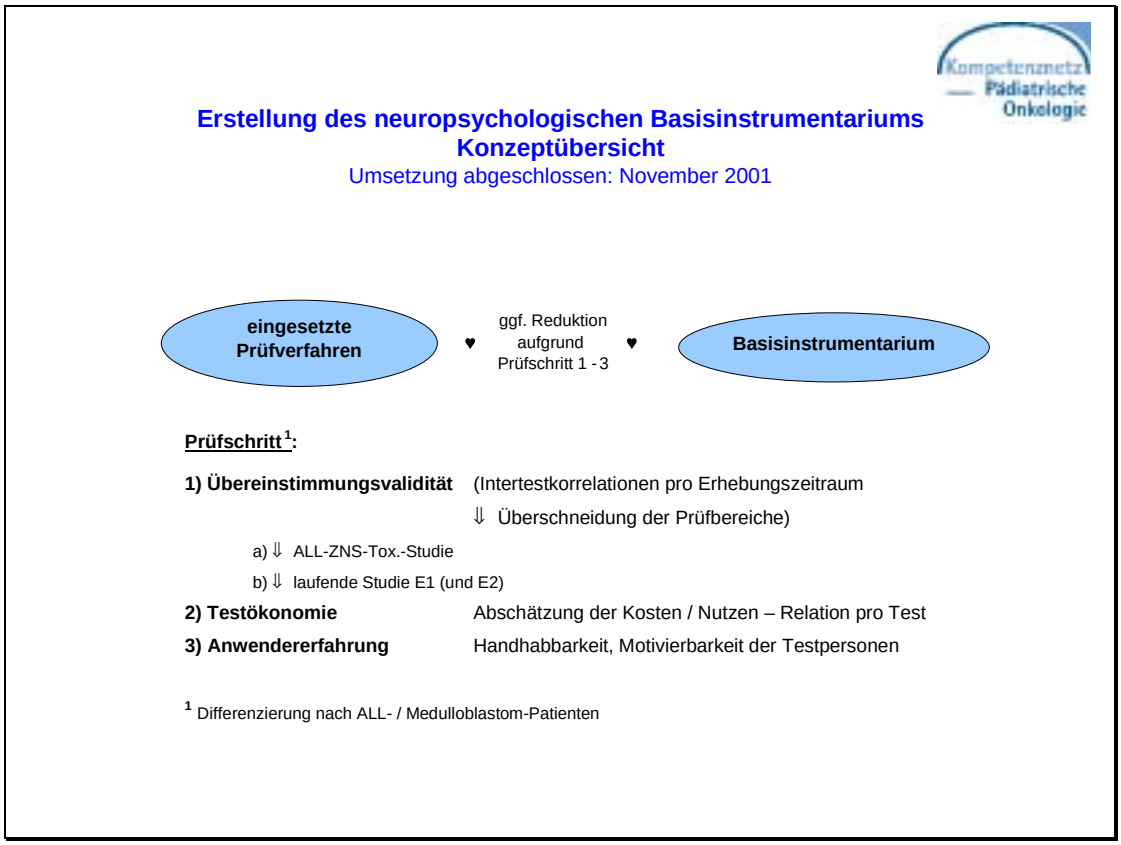
ANNEX 3:
Bandvergleich der psychosozialen, neuropsychologischen und Lebensqualitätsdaten



ANNEX 4: Übereinstimmungsvalididtät der Instrumente, Praktikabilität und Testökonomie

Neuropsychologie:

Im Rahmen des Folgeantrags für das BMBF-Projekt Lebensqualität und Spätfolgen wurden vom Projektträger mit der Weiterförderung des Projektes in der zweiten Förderungsphase bestimmte Auflagen verbunden. Diese umfassen vor allem die Anpassung des Basisinstrumentariums in Form einer möglichen Reduktion.
Zur Erfüllung dieser Auflage wurde in der ersten Phase des Projektes mit den bis 10/2001 vorliegenden Daten ein Prüfverfahren durchgeführt, das verschiedene Schritte umfasste:



Anwenderfreundlichkeit, Praktikabilität und Ökonomie der eingesetzten

Intelligenztests

- Kaufman-Assesment-Battery for Children (K-ABC) (Altersstufen 2;6 bis 11;11 Jahre), Individualtest zur Messung von Intelligenz und Fertigkeiten bei Kindern und Jugendlichen von A. S. Kaufman und N. L. Kaufman. Deutsche Bearbeitung von U. Melchers, U. Preuß.
- Kaufman-Adolescent and Adult Intelligence Test (K-TIM) (Altersstufe Ó12;0 Jahre) Individualtest zur Messung von Intelligenz und Fertigkeiten bei Jugendlichen und Erwachsenen von A. S. Kaufman und N. L. Kaufman. Deutsche Bearbeitung von U. Melchers, U. Preuß und S. Schümann. Experimentalversion.

Bewertung
Die Normgruppendaten des K-TIM entstammen der amerikanischen Validierung. Im Originaltest sind Testungen vorgesehen, die im Vorgang Gelerntes zu einem späteren Zeitpunkt innerhalb der Testung abfragen. Diese werden in der Studienanwendung nicht durchgeführt, da der Test bei wenig belastbaren Patienten nicht aufgesplittet werden kann.
Die Testdurchführung für K-ABC oder K-TIM beträgt rund 120 min., die Auswertungsdauer 45 min.
Eine komplexe Erfassung der Grundintelligenz ist mit beiden Testverfahren möglich. Problematisch ist der benötigte Testmaterialumfang, der vor allem bei Testungen am Patientenbett Umsetzungsprobleme schafft.

Die K-ABC erweist sich als anwenderfreundlich. Beim K-TIM ist mit Einschränkungen der Testobjektivität aufgrund fehlerhaften Test- und Auswertungsmaterials zu rechnen.
Hinsichtlich der Attraktivität der Testverfahren zeigen sich die Kinder bei der Durchführung der K-ABC in der Regel interessiert und gut motivierbar. Demgegenüber bestehen bei der K-TIM durch Eintönigkeit und Aufgabenlänge Probleme.
Auch liegen Hinweise dafür vor, daß im Vergleich zu den Wechslertests (WAIS) beim KAIT (amerikanische Orginalversionen der Tests) im Bereich niedrigerer Intelligenz und der Alterspanne 12 bis 16 Jahre eine ungenauere Differenzierung zu beobachten ist (vgl. Vo et al. 1999).
Der Test ist in der Durchführung anwenderfreundlich, die Auswertung bedarf einiger Erfahrung. Aus diesem Grund wird der Test zusätzlich zentral (Erlangen) nachbewertet, um Einflüsse einer subjektiven Testleiterbewertung auszuschließen

- Fragmentierter Bildertest (FBT) (Altersstufen: 10;0 bis 18;0 Jahre) von J. Kessler, A. Schaaf und R. Mielke.

Bewertung:
Der Test ist anwenderfreundlich und dient der Motivationsförderung bei den Kindern.
Nachteil ist die Beinhaltung einer Wiederholungstestung, die bei weniger belastbaren Kindern zum Testabbruch und einer Nichtauswertbarkeit des Gesamttestes führen kann. Anwendungszeit 2x5 min (plus 10 Min Pause zwischen den Testungen). Auswertungszeit 5 min.

- Differentieller Leistungstest-KE (DL-KE) (Altersstufen: 5;0 bis 6;11 Jahre), Test zur Erfassung des Leistungsverhaltens bei konzentrierter Tätigkeit von E. W. Kleber, G. Kleber und O. Hans.
- Differentieller Leistungstest-KG (DL-KG) (Altersstufen: 7;0 bis 8;11 Jahre), Test zur Erfassung des Leistungsverhaltens bei konzentrierter Tätigkeit von E. W. Kleber, G. Kleber und O. Hans.

Bewertung:
Der Test ist in der Durchführung recht anwenderfreundlich für den Testleiter, für die Testperson ist der Test monoton und anstrengend und führt teilweise zu Frustrationserlebnissen und -äußerungen bzw. Testabbruch bei Kindern mit eingeschränkter Belastbarkeit zum Testzeitpunkt. Anwendungszeit 11 min, Auswertungszeit 45 min.

- Aufmerksamkeits-Belastungstest d2 (Test d2) (Altersstufen: Ó9;0 Jahre), Test zur Erfassung der Aufmerksamkeits- und Konzentrationsleistung von R. Brickenkamp.

Bewertung:
Durch das höhere Alter der Testpersonen treten die für dien DL-Tests beschriebenen Probleme hier weniger auf. Schwierigkeiten werden in der Gruppe der Hirntumorpatienten in der Durchführbarkeit beobachtet. Anwendungszeit 5 min. Auswertungszeit 45 min.

- Tapping-/Reaktionszeitverfahren (Altersstufen: 4;0 bis 18;0 Jahre) von H. Ottensmeier, N. Galley und G. Hopmann, 1997.

Bewertung
Problematisch bei diesem Verfahren ist die Software, die nicht auf gängigen Computern geladen werden kann und somit eines besonderen Equipments bedarf (386/486er Computer). Auch Hardwareprobleme haben dazu geführt, daß über einen längeren Zeitraum die teilnehmenden Kliniken keine funktionsfähigen Tasten zur Verfügung hatten. Die PC-Oberfläche des Programms ist für den Testleiter nicht ausreichend einfach zu bearbeiten. Die Motivation der Probanden ist sehr unterschiedlich aber insgesamt durch die nicht kindgerechte Präsentation beeinflußt. Anwendungsdauer 45 min. Auswertung wird zentral in Würzburg durchgeführt. Auswertungsinformationen sind dem Testleiter nur von dort zugänglich.

Übereinstimmungsvaliditätsuntersuchungen der neuropsychologische Instrumentarien

Datei unter Dateiname “Übereinstimmungsvalidität der Neuropsychologie” Diese datei kann bei Beadrf angefordert werden

Bewertung:
Die untersuchten Testverfahren sind nicht redundant. Es zeigen sich keine Korrelationen. Somit ist aus der Berechnung der Übereinstimmungsvalidität keine Reduktion der Instrumente abzuleiten, sondern nur aus den o.genannten Punkten.

ANNEX 5

Multitrait-Multitemanalyse des PEDQOL und Korrelation zu anderen Instrumenten

Dokumentation zur psychometrischen Analyse des PEDQOL im Projekt „Lebensqualität und Spätfolgen“ des Kompetenznetzes Pädiatrische Onkologie

Datensatz vom 17.01.02, Stand der Auswertung: 13.03.02

Die Ergebnistabellen befinden sich in einer Excel-Datei „Ergebnisse Psychometrische Analyse Pedqol.xls“, der Text dokumentiert die einzelnen Auswertungsschritte. Die Excel Tabellen können bei Bedarf angefordert werden.

Analyse fehlender Werte

(Tabellen „fehlende Werte E1“ und „fehlende Werte E2“)

Zu E1 liegen PEDQOL-Daten zu 73 Kindern bzw. Jugendlichen vor. Bei jeder einzelnen Frage fehlen Antworten von 0 bis 6 Probanden (0 – 8,2 %). Die meisten fehlenden Werte weisen die Items der Skala „Autonomie“ auf, gefolgt von den beiden Zufriedenheits-Items sowie den Items „Angst krank zu werden“ und „lange für Schularbeiten gebraucht“. Die fehlenden Werte auf den beiden letztgenannten Fragen könnten dadurch verursacht sein, dass diese Bedingung auf die Befragten nicht zutraf. Bis zu ca. 2,5 % fehlender Werte können als akzeptabel angesehen werden. Die Frage ist, warum in den beiden Skalen „Autonomie“ und „Global“ durchgängig mehr fehlende Werte auftreten. Dies könnte ein Hinweis darauf sein, dass der Fragebogen insgesamt zu lang ist.

Zu E2 liegen von 28 Kindern bzw. Jugendlichen PEDQOL-Daten vor. Es fehlen zwischen 0 und 6 Angaben (0 – 21,4 %). Besonders viele Angaben fehlen bei Fragen, die sich auf Schule oder auf Aktionen mit Freunden beziehen, vermutlich weil dies in der klinischen Situation nicht zutrifft. Die Skalen „Autonomie“ und „Global“ weisen zu E2 nicht mehr fehlende Werte auf als die anderen Skalen.

Psychometrische Eigenschaften der Einzelitems

(Tabelle „Einzelitems“)

Da die Antwortskala von 1 bis 4 geht, können die einzelnen Items Mittelwerte zwischen 1 und 4 annehmen. Erwünscht sind eine Ausnutzung aller Antwortkategorien und ein Item-Mittelwert möglichst in der Mitte der Skala, hier also etwa zwischen 2 und 3. Items mit zu stark von der Mitte abweichendem Mittelwert produzieren Boden- oder Deckeneffekte und können nicht zwischen Personen mit guter und solchen mit eingeschränkter Lebensqualität differenzieren. Meist ist ihre Streuung auch im Vergleich zu den anderen Items reduziert. Den extremsten Mittelwert weist das Item „alleine“ aus der Skala „Emotional“ auf, gefolgt vom Item „wegen Schmerzen aufgewacht“ aus der Skala „Physisch“ und „gut verstanden mit Eltern“ aus der Skala „Sozial“. Insgesamt zeigen sich keine besonders ausgeprägten Boden- oder Deckeneffekte. Die Ergebnisse zu E2 ähneln denen zu E1.

Die Item-Total-Korrelation gibt an, wie hoch der Zusammenhang jeder einzelnen Frage mit ihrer Subskala, bereinigt um diese Frage, ist. Alle Item-Total-Korrelationen innerhalb einer Subskala sollten von mittlerer bis großer Höhe (r=.40 bis r=.70) und homogen (d.h. etwa gleich hoch) sein. Es gibt mehrere Items mit niedriger bis sehr niedriger Item-Total-Korrelation (in der Tabelle grau markiert). Lediglich die Subskalen „Lernfähig“ und „Global“ sind davon nicht betroffen. Es wäre zu prüfen, ob die Skalenstruktur des Pedqol durch andere Skalenzuordnung einzelner Items oder durch Weglassen derjenigen Items mit besonders niedriger Item-Total-Korrelation verbessert werden kann.

Skalenqualität, interne Konsistenz

(Tabelle „Skalen“)

Ein zentrales Kriterium für die psychometrische Qualität einer Skala ist die interne Konsistenz (Cronbach’s ζ). Sie sollte für alle Subskalen über 0,70 liegen. Bis auf die Skalen „Autonomie“ und „Global“ erfüllen dies für die Gesamtgruppe alle Skalen. Die interne Konsistenz der Gesamtskala kann mit ζ=.93 als sehr gut bezeichnet werden. Betrachtet man die Werte getrennt für die Diagnosegruppen Leukämie und Medulloblastom, ergeben sich kaum relevante Unterschiede, mit Ausnahme einer niedrigeren internen Konsistenz der Skala „Emotional“ in der Medulloblastom-Gruppe. Eine Interpretation ist nicht zuletzt aufgrund der geringen Fallzahl (n = 10) schwierig.

Der Skalenfit gibt an, wie gut die einzelnen Items der angenommenen Skalenstruktur des Instruments entsprechen und wird in prozentualen Werten angegeben. Ein Wert von 90 % wird angestrebt. Der Skalenfit beträgt für die Gesamtskala 79 %, für die Skala „Physisch“ 93 %, für die Skala „Emotional“ 80 %, „Lernfähig“

96 %, „Autonomie“ 68 % und „Global“ 20 %. Hier ist noch Verbesserungspotenzial zu erkennen, z.B. durch Neuzuordnung oder Herausnahme von Fragen mit geringer Item-Total-Korrelation (vgl. oben).

Konvergente Validierung

(Tabelle „Validierung“)

Bei der konvergenten Validierung wird geprüft, ob der PEDQOL die erwarteten Zusammenhänge zu anderen Lebensqualitäts-Messinstrumenten aufweist. Zum einen wird die Korrelation der Gesamt-Summenscores geprüft, zum anderen die korrespondierender Subskalen. Die Korrelation des PEDQOL mit allen Skalen des KINDL und dessen Gesamtscore ist hoch. Dies überrascht nicht angesichts ähnlicher Fragenformulierungen. Teilweise bildet sich auch in beiden Instrumenten eine ähnliche Skalenstruktur ab, allerdings korreliert die Skala „Emotional“ des PEDQOL höher mit der Körper-Skala des KINDL als mit dessen Psyche-Skala. Die Korrelation des PEDQOL mit dem CHQ ist insgesamt wesentlich niedriger, vor allem mit dessen psychosozialer Summenskala. Noch am höchsten korreliert die Skala „Physisch“ des PEDQOL mit der Physischen Summenskala des CHQ.

Änderungssensitivität

(Tabelle “Änderungssensitivität”)

Beim Vergleich der beiden Erhebungszeitpunkte zeigt sich, ob die Instrumente stattgefundene Veränderungen in der Lebensqualität abbilden können. Geprüft wird, ob der t-Test für Mittelwertsveränderungen von E1 nach E2 signifikant ist ($p > .05$) und wie groß der in der Mittelwertdifferenz abgebildete Effekt ist. Effektstärken von 0 bis ∂0,3 sind als klein zu betrachten, von ∂0,4 bis ∂0,7 als mittel und größer als ∂0,8 als groß. Die einzig signifikante Veränderung, die sich von E1 nach E2 zeigt, ist ein Anstieg des PEDQOL-Physischen Skalenwerts mit einer mittleren Effektstärke.

Veränderungen im PEDQOL korrelieren signifikant mit Veränderungen im KINDL und im Veränderungsitem des CHQ.

Zur genaueren Beurteilung der Änderungssensitivität fehlt ein – möglichst objektives – Außenkriterium, an dem die in der Selbst- und Elterneinschätzung beurteilten Veränderungen gemessen werden können. Zudem ist die Fallzahl mit $n = 23$ noch recht klein.

Bewertung:

Der PEDQOL zeigt sich als reliables, sensitives und valides Meßinstrument für die untersuchten Patientengruppen.

Die Instrumente zur Lebensqualität sollten in Ihrer Zusammensetzung weiter angewandt werden. Der Einsatz eines PEDQOL Elternfragebogens als Vergleich zum CHQ erscheint sinnvoll.

ANNEX 7 **Beispiele für Flow-sheets zur Nachsorge**

CoALL-97/AML-BFM 98 follow-up akute lymphatische Leukämie / akute myeloische Leukämie

Patient:_____

	Therapieende	**nach Therapieende**					
	Datum ***__.__.20__***	***1. Jahr*** ***20__***	***2. Jahr*** ***20__***	***3. Jahr*** ***20__***	***4. Jahr*** ***20__***	***5. Jahr*** ***20__***	***- 10. Jahr*** ***- 20__***
Rezidivdiagnostik							
allgem. körperliche Untersuch. + Hoden	1-malig	mtl.	3 mtl.	3 mtl.	4 mtl.	6 mtl.	jährlich
neurologische Unters.	1-malig	mtl.	3 mtl.	3 mtl.	4 mtl.	6 mtl.	jährlich
BB / Diff.-Blutbild / LDH	1-malig	mtl.	3 mtl.	3 mtl.	4 mtl.	6 mtl.	jährlich
Verlaufs- und Spätfolgendiagnostik							
allgem. Blutentnahme[1]	1-malig	1-malig	-	-	-	-	-
Nierenwerte im Serum/Urin[2]	1-malig	4 mtl.	6 mtl.	-	-	-	-
Virusserologie[3]/ Impftiter[4]	1-malig	1-malig	-	-	-	-	-
Blutentnahme-Endokrinologie [5]	1-malig	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich
Perzentilen[6]	1-malig	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich
Tannerstadien/Hodenvol.	1-malig	6 mtl.	6 mtl.	jährlich	jährlich	jährlich	jährlich
Spermiogramm	bei Auffälligkeiten in der Pubertätsentwicklung						
Ophthalmol. Unters.	1-malig	-	-	-	-	1-malig	-
Sonographie-Schilddrüse[7]	1-malig	-	-	-	-	1-malig	1-malig
EKG / (Stress-) Echo-kardiogramm	1-malig	-	-	-	-	1-malig	-
Knochendichtemessung	1-malig	-	1-malig	-	-	-	-
Audiometrie	1-malig	-	-	-	-	1-malig	-
Nachsorge Strahlentherapie	1 x jährlich enstprechend APRO-Richtlinien						
Neuropsych. Testung (Motorik, Koordination, Kognition) ab 4. Lj.	1-malig	-	1-malig	-	-	-	1-malig
Lebensqualität	1-malig	-	1-malig	-	-	-	1-malig
Zweitmalignome							
	Häufigstes Zweitmalignom bei AML: AML und MDS 50% 1.-3. Jahr nach initialer Dx						
	Häufigstes Zweitmalignom bei ALL: Hirntumoren 6.-10. Jahr nach initialer Dx						

[1] **Blutentnahme:** BB, CRP, BSG, Bili, GOT, GPT, #-GT, AP, LDH, ζ-Amylase, Ferritin, Immunglobuline.

[2] **Nierewerte im Serum:** Phosphat, Magnesium, Na, K, Calcium, Kreatinin, Bicarbonat.
Nierewerte im Urin: Urinstatus, Phosphat, Kreatinin, Calcium.

[3] **Virusserologie:** Virus- und Antikörper-Nachweis für HBV, HCV, HIV, CMV, EBV.

[4] **Impftiter:** 6 Monate nach Ende der Therapie bei Pat. mit abgeschl. Grundimmunisierung Auffrischungsimpfung mit folgenden Totimpfstoffen: Td, HBV, Polio-Salk. Weiterführende Impfungen bei nicht abgeschl. Grundimmunisierung. Lebendimpfstoffe gemäß STIKO-Empfehlungen nach 12 Monaten.

[5] **Endokrinologie-Blutentnahme: Sexualhormone:** 1-malig oder bei pathol. Befund in der Pubertätsentwicklung o. den Perzentilen LH, FSH, Prolaktin, bei Jungen zusätzlich Testosteron, bei Mädchen Östradiol (cave Zyklusabhängigkeit), ggf. Stimulationstests. **Schilddrüsenhormone** (nach Bestrahlung im Thorax-/Halsbereich jährlich): fT3, fT4, TSH

[6] Röntgen-Linke-Hand Knochenalterbestimmung bei bei Auffälligkeiten

[7] nach Schädelbestrahlung

MAKEI 96 / MAHO 98-follow-up

extrakranielle Keimzelltumoren / maligne Hodentumoren

Patient: _____

	Therapieende	**nach Therapieende**					
	Datum ***__.__.20__***	***1. Jahr*** ***20__***	***2. Jahr*** ***20__***	***3. Jahr*** ***20__***	***4. Jahr*** ***20__***	***5. Jahr*** ***20__***	***- 10. Jahr*** ***- 20__***
Rezidivdiagnostik							
allgemeine körperliche Unters., Lokalbefund	*1-malig*	mtl.	3 mtl.	3 mtl.	6 mtl.	6 mtl.	jährlich
Blutbild	1-malig	mtl.	3 mtl.	3 mtl.	6 mtl.	6 mtl.	jährlich
AFP / η-HCG	1-malig	mtl.	3 mtl.	3 mtl.	6 mtl.	6 mtl.	jährlich
Röntgen-Thorax[1]	1-malig	-	-	-	-	-	-
CT / Sonographie der prim. Tumorlokalisaton	1-malig	3 mtl.	6 mtl.	jährlich	jährlich	jährlich	jährlich
Verlaufs- und Spätfolgendiagnostik							
allgem. Blutentnahme[2]/ Urinuntersuchung[2]	1-malig	1-malig	-	-	-	-	-
Virusserologie[3]/ Impftiter[4]	1-malig	1-malig	-	-	-	-	-
Blutentnahme-Endokrinologie[5]	1-malig	bei Auffälligkeiten in der Pubertätsentwicklung u./o. nach Bestrahlung jährlich					
Perzentilen[6]	1-malig	jährlich	jährlich	jährlich	jährlich	jährlich	jährlich
Tannerstadien/Hodenvol.	1-malig	6 mtl.	6 mtl.	jährlich	jährlich	jährlich	jährlich
Spermiogramm	bei Auffälligkeiten in der Pubertätsentwicklung u./o. nach Bestrahlung						
EKG/Echokardiogramm	1-malig	-	-	-	-	1-malig	-
Lungenfunktion	1-malig	*jährlich nach Gabe von Bleomycin u./o. nach Bestrahlung*					
Audiometrie	1-malig	-	-	-	-	1-malig	-
Nachsorge Strahlentherapie	1x jährlich entsprechend den APRO-Richtlinien						
Neuropsych. Testung (Motorik, Koordination, Kognition) ab 4. Lj.	1-malig	-	1-malig		-	1-malig	-
Lebensqualität	1-malig	-	1-malig	-	-	1-malig	-
metachrone Erkrankungen							
zwischen 2. bis 10. Jahr nach Diagnose (insbesondere Ovar)							
Zweitmalignome							
Knochentumoren							
ALL, MDS							

[1] bei initialen Metastasen

[2] **allgemeine Blutentnahme:** CRP, BSG, Bili, Harnstoff, Harnsäure Kreatinin, GOT, GPT, #-GT, AP, LDH, ζ-Amylase, Ferritin, Phosphat, Magnesium, Na, K, Calcium, Kreatinin, Bicarbonat.
Urinuntersuchung: Urinstatus, Eiweiß, Glucose, Phosphat, Kreatinin, Calcium.

[3] **Virusserologie:** Virus- und Antikörper-Nachweis für HBV, HCV, HIV, CMV, EBV.

[4] **Impfungen:** 6 Monate nach Ende der Therapie bei Pat. mit abgeschl. Grundimmunisierung Auffrischungsimpfung mit folgenden Totimpfstoffen: Td, HBV, Polio-Salk. Weiterführende Impfungen bei nicht abgeschl. Grundimmunisierung. Lebendimpfstoffe gemäß STIKO-Empfehlungen nach 12 Monaten.

5 **Blutentnahme-Endokrinologie: Sexualhormone:** 1-malig oder bei pathol. Befund in der Pubertätsentwicklung o. den Perzentilen LH, FSH, Prolaktin, bei Jungen zusätzlich Testosteron, bei Mädchen Östradiol (cave Zyklusabhängigkeit), ggf. Stimulationstests. **Schilddrüsenhormone** (nach Bestrahlung im Thorax-/Halsbereich jährlich): gT3, fT4, TSH.

6 incl. Sitzhöhebestimmung bei bestrahlten Patienten. Röntgen-Linke-Hand zur Knochenalterbestimmung bei Auffälligkeiten.