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A Web-based platform for interdisciplinary biomedical research

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1. ABSTRACT

The European Neuroblastoma Group of the International Society for Paediatric Oncology (SIOPEN) is dedicated to the research and treatment of neuroblastoma. The medical research network SIOPEN-R-NET is an extensive web-based European IT network for interdisciplinary biomedical research. The IT infrastructure has been built using state-of-the-art multi-tiered architecture principles. Basic features required for electronic data capture in clinical trials were implemented. Additionally, advanced tools were developed for registration, review, user management, communication and image management. Currently three clinical trials and eight supporting scientific studies are implemented. The medical research network is already in use by 345 active users from 240 institutions in 18 countries. More than 960 000 item entries and 7962 images from 1260 patients are stored. Challenges, which resulted from the fact that only 16 % of the centres had more than 2 patients per year, have been addressed by an intuitive user interface, hierarchical roles, user required features, and experienced support. The system has already been used extensively and has helped to make significant progress in the area of Neuroblastoma research.

2. INTRODUCTION

The core objective of medical research communities is to facilitate close and efficient collaboration between physicians and various supporting disciplines. This in turn will enhance quality and allow for the development of standard operating procedures (SOPs) for the acquisition and evaluation of the diagnostic material and data. Clinical research in oncology is very complex in general because many different medical disciplines are involved. Any information technology (IT) supporting such issues must deal with this complexity, which is further amplified by large-scale research in terms of the number of investigational sites, study physicians, countries, and duration of trials.

Clinical trials and scientific studies are essential for the progress of medicine. A large majority of today's studies follow complex designs, are multi-centric and international with an increasing number of participating institutions. In order to reach a critical mass, international large-scale studies within medical research communities are of utmost importance to facilitate the cooperation of physicians and specialists of associated research fields. To enable cooperation within medical research communities, it

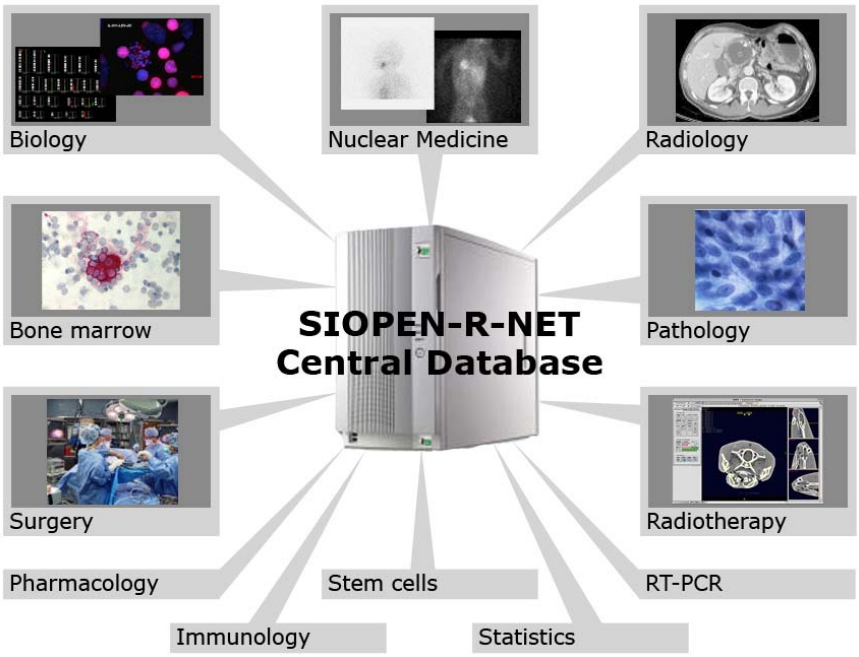

Figure 1. The SIOPEN-R-NET central database facilitates close and efficient collaboration between the oncologists and the various supporting disciplines (scientific committees). Seven out of twelve scientific committees are using the image management module of the medical research network.

is imperative and a prerequisite to establish an electronic network to assure the data flow within the group of partners and to manage all the tasks and requirements of the individuals (1, 2). The Internet and the World Wide Web have been introduced into the management of some aspects of clinical trials, such as data entry on electronic case report forms, electronic data retrieval, remote randomization and the distribution of information on trial progress (3). Data security requirements are also a major concern. A high-quality IT system design of such a web-based medical research network for multi-institutional clinical research projects is essential in order to ensure electronic data confidentiality, security and integrity.

The two most commonly used clinical trials–related software packages, Oracle Corp's Oracle Clinical and Phase Forward's Clintrial, are both designed for use with commercial database systems (4). The US National Institute of Health's National Cancer Institute has a open-source friendly initiative called CaBIG (Cancer Biomedical Informatics Grid), which includes clinical trials management systems, amongst others (5). One of the many projects involved in CaBIG, OpenClinica (6), has used CaBIG as a springboard to launch and maintain a free and open-source clinical trials data-management system. There are also several initiatives in support of clinical research such as the Advancing Clinico Genomic Trials (ACGT) environment for supporting post genomic clinical trials in cancer research (7), the biomedical Informatics Research Network (BIRN) as a geographically distributed virtual community of shared resources offering tremendous potential to advance the diagnosis and treatment of diseases (8), or the INFOBIOMED network supporting the consolidation of biomedical informatics as a crucial scientific discipline for future healthcare (9).

In order to overcome the fragmentation of the European clinical research community in the field of neuroblastoma, the International Society of Paediatric Oncology (SIOP) has started the still-ongoing International Society of Paediatric Oncology European Neuroblastoma Research Network (SIOPEN-R-NET) project within the 5th Framework Program of the European Community 'Quality of Life and Management of living Resources' (EC Grant No. QLRI-CT-2002-01768). It represents a framework that supports clinical trials and integrated research to ultimately improve survival in high risk neuroblastoma, to ensure risk adopted treatment, as well as quality of life in children with low and intermediate risk neuroblastoma. Its inherent aims are to foster collaboration, to support communication and to optimize the use of pre-existing European clinical and research infrastructures in individual countries. Additionally, it strives to improve consistency and complementarities through development of standard operating procedures and quality assurance actions on the European level.

A central objective of the SIOPEN-R-NET has been to facilitate close and efficient collaboration between the oncologists and the various supporting disciplines – called scientific committees (SC). This will increase quality and define specific quality control SOPs for the acquisition and evaluation of the respective diagnostic material and data (Figure 1). The central database facilitates the data management of clinical neuroblastoma trials, which is the major task of the Steering Committee, the European

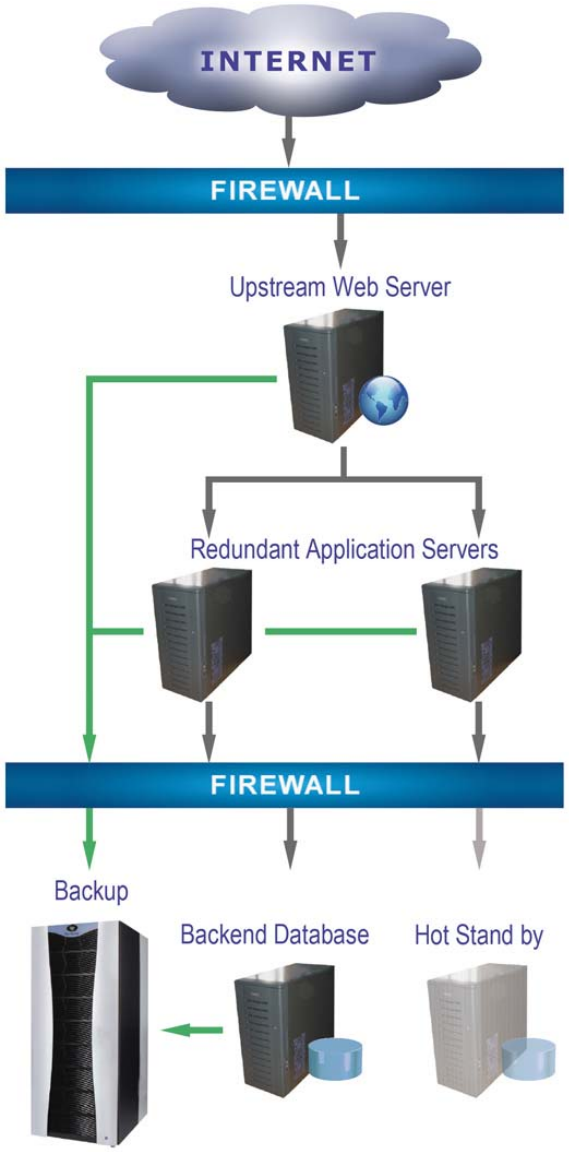

Figure 2. The state-of-the-art multi-tiered IT-Infrastructure architecture comprises an upstream web server handling user request, an application server performing business logic, and a backend relational database system for persistent data storage. All components are separated by firewalls and all critical components are installed twice.

National Co-coordinators and the Statistical SC. In addition it allows data management of the records of each associated research field aiming to ultimately optimize pre-existing therapeutic strategies through drug scheduling (Pharmacological SC), SOPs in stem cell collection including cell therapy (Stem Cell SC) as well as through introduction of new agents and new treatment strategies. More recent therapeutic approaches encompass immunotherapy strategies based on molecularly designed agents, such as specific antibodies or fusion proteins as well as differentiating agents, response modifiers and angiogenesis inhibitors, triggering natural anti-tumour defence mechanisms through tumour vaccination concepts (Immunotherapy SC). Further attention is paid to the development of new diagnostic tests and procedures to detect early markers and weak signals in pathology (Pathology SC), including near-patient tests, nucleic acid diagnostic tests, pharmacological assays and in vivo imaging.

In this paper, we describe and discuss IT aspects for such medical research communities, and present an infrastructure capable of managing the multitude of tasks and requirements of the individuals within the network and ensuring the transfer of knowledge between basic and clinical research.

3. MATERIALS AND METHODS

The main aspects related to design and development of the general IT infrastructure solutions for collaborative research projects such as the SIOPEN-R-NET include the following categories: Regulatory compliance, IT technology and architecture, basic features as required by Electronic Data Capture (EDC) in the conduct of clinical trials, and finally advanced features required beyond EDC to satisfy the requirements of collaborative translational research.

3.1. Regulatory compliance

Basic principles for implementation and operation of the IT-platform for medical research networks are in agreement with principles and detailed guidelines for good clinical practice, recognized specifically in the Commission Directive 2005/28/EC of April 2005 (10) and the ICH (International Conference on Harmonization) Guideline for Good Clinical Practice (11).

3.2. IT technology and general architecture

Data security requirements were a major concern, and were reflected in a state-of-the-art multi-tiered architecture. This results in the separation of components corresponding to their functionality in an upstream web server handling user requests, an application server performing business logic, and a backend relational database system for persistent data storage (Figure 2). Due to the special requirements on system security, all components are additionally separated by means of network security (incorporating firewalls) and are hosted in a secure environment with access limited to qualified personnel only. In order to improve performance and availability of the medical research network services, all critical components are installed twice. This redundancy is either applied to optimize system performance through parallel operation (application server) or as hot-standby servers for an immediate switch-over in case of hardware errors (database server). The majority of server elements are based on open source components and are regularly updated to the latest available version. In addition to the productive system, an identical system without real patient data is available for training purposes.

3.2.1. Web server

The Apache web server (12) represents the front

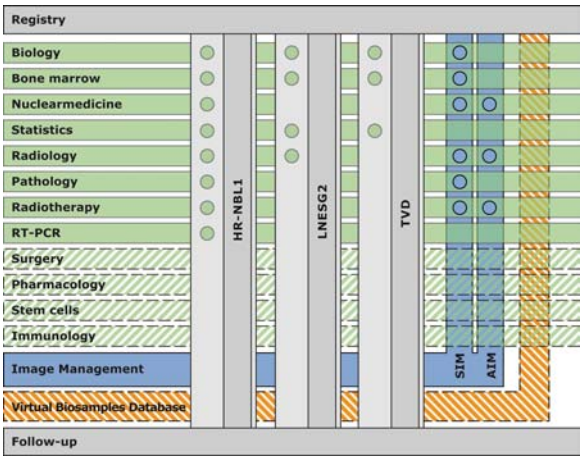

Figure 3. Block diagram of the current extent of the SIOPEN-R-NET IT system. This system comprises of a patient registry common to all three clinical trials and seven so-called scientific studies which are interlinked to the clinical trials. The scientific studies provide services particularly in diagnostic or therapeutic areas. Both the clinical trials and the scientific studies can take advantage of common infrastructure elements, such as the virtual biosamples databank and basic and advanced image management.

end of the medical research network platform and is accessible over the Internet using a standard web browser. The Apache web server handles SSL-encryption to ensure data privacy and provides static content.

3.2.2. Application server

More complex system interactions are processed by a Zope application server (13). The application server handles all business logic as explained in section 3.3 and section 3.4 and manages access to functions, forms and data, based on a fine-grained authorization concept. Furthermore, the application server in combination with the connected database keeps track of all system activities and data manipulation. Audit trails log all transactions of data into and out of the system. These logs include time, date, user ID and records involved in the transaction.

3.2.3. Database server

At the backend of the system data are stored within a relational PostgreSQL database (14). Besides study-specific patient data such as examination results and administered therapies, the database contains all structural information, such as account data, institutional affiliation, and contact details. Moreover, the visibility of patients and their related data as well as authorized access by individual users are controlled by an adequate fine-grained mapping of accounts, groups (institutions), roles and rights within the database. For statistical analyses, selected database content can be exported in various formats including plain text, HTML, Microsoft Excel, and Microsoft Access.

3.2.4. Study design framework

In order to reduce implementation time and improve system quality, a tailored study-design framework was developed, enabling quick and reliable implementation of all relevant application server structures. Additionally, the framework supports a semi-automatic development process of the electronic case report forms (eCRFs) – defined in the clinical trial protocol – and the corresponding data base relations.

3.2.5. Image management server

The image management module allows users to upload and download images from the image data repository via the image data server. The image data server communicates with the research network server.

4. RESULTS

The main goal of the SIOPEN-R-NET project has been achieved, which was the implementation and deployment of a large-scale web-based European Neuroblastoma IT network to facilitate the tasks of the respective medical research community (15).

Figure 3 shows a block diagram of the current extent of the SIOPEN-R-NET IT system, comprising the patient registry common to all clinical trials. The scientific studies are interlinked to the clinical trials and provide services in particularly in diagnostic or therapeutic areas. Both the clinical trials and the scientific studies can take advantage of common infrastructure elements such as basic and advanced image management. So far, three clinical trials and eight scientific studies have been implemented. Six of the scientific studies are using the image management.

4.1. Basic features

In order to efficiently manage processing, collaboration, and communication within the trans-disciplinary groups from several institutions in different countries, the following key features of the medical research network were developed: user management, central database environment, Web-based user interface, patient registry, workflow-support and reminders, remote web-based data entry with audit trail, authentication and authorization checks, study eligibility checks, immediate report of toxicities, data flow confidentiality, data protection and data security features (Figure 4). The medical research network provides online randomization and statistical analyses, embedded computing, online query and SAE (Serious Adverse Event) management.

4.2. Advanced features

In order to support multi-centred interdisciplinary biomedical research, close links were established between the data flow of clinical trials and specific scientific studies. Advanced components – such as registration, review, user management, communication and image management – satisfying the requirements of collaborative translational research are described in the following chapters.

4.2.1. Clinical trials and scientific studies

As the medical research network allows several clinical trials to be conducted simultaneously within one IT

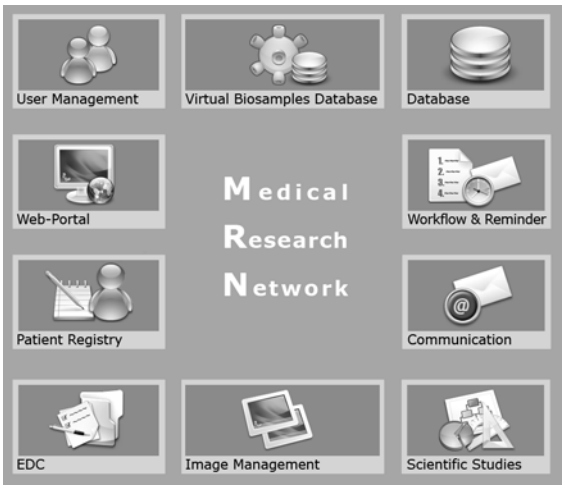

Figure 4. Key features of the medical research network are user management, Web-based user interface, patient registry, electronic data capture (EDC), image management, scientific studies support interlinked to multi-centric clinical trials, communication, workflow-support and reminders, central database, and virtual biosamples database environment.

system dedicated to a particular domain (e.g. neuroblastoma), numerous advantages can be reaped from the synergies between the trials. A common registry as well as a common follow-up section has been implemented.

Each trial may benefit from the various existing scientific specialty groups including, for example, from the domain of biology, pathology and imaging. Patients enrolled in a clinical trial are thus also available in the respective scientific studies. Data entered in the scientific studies can be displayed in the clinical trial eCRFs and vice versa. This streamlines clinical trials as the eCRFs for several domains (e.g. Biology, Pathology, Radiology, etc.) are defined within the scientific studies and thus need not be implement for each trial separately.

4.2.2. Registry

The patient registration process was implemented in two stages:

1. Once a patient is registered in the system a unique patient ID is assigned. As the next step the patient is automatically enrolled in scientific studies that play a role for the pre-study-evaluation.
2. The Agreed Minimum Essential Data (AMED) are entered. Subsequently, the patient can be enrolled in a clinical trial, depending on the inclusion criteria.

During the enrolment process, the patient is assigned to the respective trial in a semiautomatic way according to a predefined decision tree of eligibility criteria. Furthermore the patient is automatically enrolled in the respective scientific studies relevant for a given clinical trial.

4.2.3. Review

In addition to the basic functions of storing and signing data, eCRFs of scientific studies allow reviews. After uploading and signing the data set, specialists are entitled to view the data, to create their own copy for review purposes and to comment or to revise pre-existing information according to strict rules. These reviews can be seen by other specialists. After careful analysis, a specialist with suitable authorisation can approve the one result which is to be used for statistical analysis in the context of the corresponding clinical trial.

4.2.4. User management

The user management is implemented on the basis of account, groups, roles and their respective rights. A user receives an account to which several roles and groups may be assigned. Groups represent the organisational structure of the research community in a hierarchical manner. At the first level there is a master group, which contains one subgroup for each trial/study (second level). At the third level the countries are represented. The fourth level represents the participating institutions. Each role in turn has a set of rights; for example, to edit data, post reviews, use advanced image management, etc. The user may change his / her role in the system provided that he / she has been assigned more than one role. The roles are specific to each study. A user can be assigned the role "clinician" at Institution 1 in the clinical study A as well as “clinician” at Institution 2 in the clinical study B. In each case, the user only has access to data made available to his / her role, for patients assigned to the corresponding group or subgroups.

4.2.5. Communication

The medical research network has been equipped with an internal communication system. Users can exchange messages with each others internally, thus avoiding usage of conventional, non-secure email systems. The user receives merely one external email in which he / she is made aware of an unread item in his / her inbox. To read the email he / she must log into the system. The entire data transfer is encoded by SSL. Additionally, messages can be sent directly from eCRFs regarding updates to the form. These messages automatically contain the receiver’s email address (user who most recently worked on this eCRF), as well as the patient's ID and the appropriate form name. This message system further allows tracing queries and statements made in emails.

4.2.6. Image management

The image management module allows users with a specific role to upload images to eCRFs on to the system, to view these images and to download images stored in the system. The system features two distinct levels. Images can be transferred and viewed either through a HTML based interface (Standard Image Management – SIM), or through an ActiveX plug-in (Advanced Image Management – AIM). Additionally, the ActiveX plug-in offers an image viewing component with the functionality of a PACS (Picture Archiving and Communication System) browser. The SIM module communicates with the research network server, which again communicates with the image

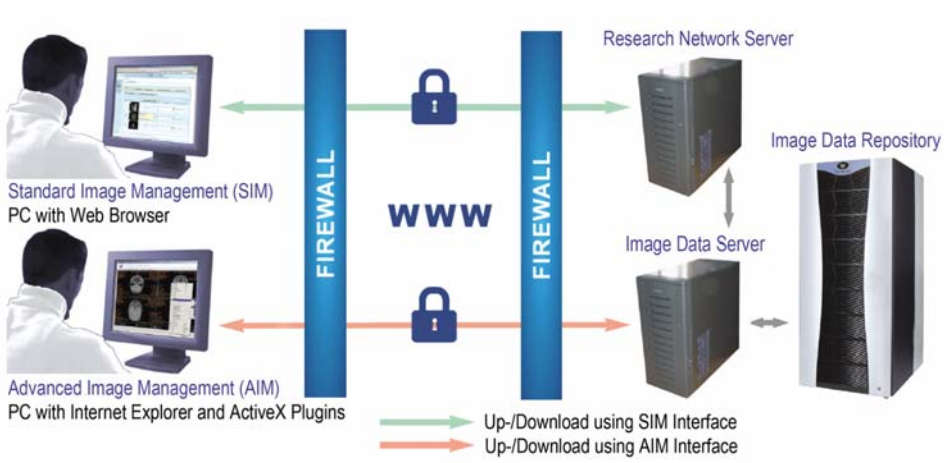

Figure 5. Standard (SIM) and advanced (AIM) image management allowing users to upload and download images stored in the system. The SIM module communicates with the research network server, which again communicates with the image server. The image server finally communicates with the image repository. The AIM module directly communicates with the image server.

server (Figure 5). The image server finally communicates with the image repository. The AIM module directly communicates with the image server.

4.3. Patient and user statistics

There is no personal identification data for patients within the SIOPEN-R-NET (such as real patient names). This was achieved by assigning a unique ID to each individual upon entry. Cross-reference tables identifying the patient for clinical care are not available within the SIOPEN-R-NET but are within the responsibility of institutes entering patients.

The electronic activities within the SIOPEN-R-NET as of April 30, 2008, are shown in Table 1. Currently the system is already used by 345 active users from 240 institutions in 18 countries. More than 960.000 item entries and 7962 images from 1260 patients were stored. Figure 6 depicts the continuous increase of registered patients over time as well as the increase of stored images.

Within the SIOPEN-R-NET 54 different roles, 301 groups and 100 access control definitions were implemented, reflecting the diverse requirements of the medical research community with respect to different kinds of access to data. Figure 7 indicates that the majority of institutions (144 out of 171) have registered less than 13 patients. However, 54 % of all patients were registered by those institutions.

4.4. Recent research results

The SIOPEN-R-NET has facilitated research activities in many ways. As a result first publications based on these efforts are now available, mainly focusing on standardizing common European efforts.

The LNESG1 study of the SIOPEN group defined surgical risk factors (SRFs) based on the imaging characteristics. A total of 905 patients with suspected localized neuroblastoma were registered by 10 European countries. The adoption of SRFs as predictors of adverse surgical outcome was validated and they will be part of the new international consensus of revised risk grouping in neuroblastoma (16). The prognostic value of the revised International Neuroblastoma Pathology Classification (INPC) was investigated by the European SIOP neuroblastoma pathology panel. The study showed for the first time that the INPC prognostic categorization has a significant impact on outcome prediction in INSS stage 2 localized peripheral neuroblastic tumours (17). For monitoring of minimal residual disease, techniques offering a considerably higher sensitivity have been developed. The potential clinical application of these techniques had to be preceded by thorough standardisation and validation in multi-centre studies (18).The SIOPEN Neuroblastoma Bone Marrow Committee developed a sensitive and reproducible anti-GD2 immunocytochemical assay and introduced morphological and immunocytological criteria for the interpretation of results (19). Reference laboratories across Europe have established SOPs for the detection of neuroblastoma cells by quantitative reverse transcriptase polymerase chain reaction (QRT-PCR). As a result the sensitivity of QRT-PCR increased from 58% to 90% following the development of SOPs (20).

5. DISCUSSION

A web-based platform for interdisciplinary biomedical research has been developed and used to support a large-scale medical research community dedicated to the treatment of Neuroblastoma. Particular aspects such as integrated image management and collaboration between various medical specialties make this solution unique.

Clinical research in oncology is very complex. This is related to the fact that many different medical disciplines are involved. Any IT solution must also deal with this complexity. This is even more pronounced within the frame of childhood cancer reflecting rare disease entities. For this reason research in this field necessitates large scale trials referring to the number of investigational

Table 1. Electronic activities within the SIOPEN-R-NET as of April 30, 2008

Electronic activity	Number
Participating countries	18
Participating institutions registered	240
Participating institutions with patients	171
Clinical trials	3
Scientific studies online	8
Patients registered	1260
Users registered	506
Users logged in	361
Users with data entry	345
Item entries	> 960 000
Images stored	7962
User management: roles	54
User management: groups	301
User management: access control definitions	100

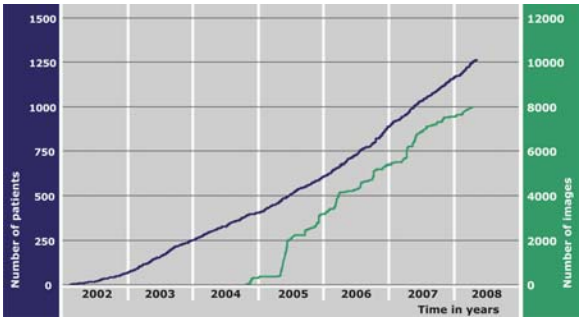

Figure 6. Accrual of patients and images during the SIOPEN-R-NET from 2002 to 2008.

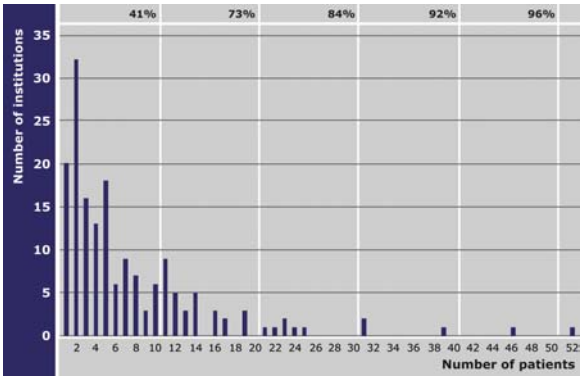

Figure 7. Bar chart of the number of institutions in relation to the number of patients registered by them during the SIOPEN-R-NET. Additionally, percentage of patients registered by institutions with less than 11, 21, 31, 41 and 51 patients is also displayed.

sites, study physicians, countries, duration of trials, etc. Many clinical trial groups do not have the skills or resources to establish and use software systems required to manage trial data in compliance with the International Conference on Harmonisation's guidelines (11). The SIOPEN-R-NET IT platform addresses daunting challenges of capturing, cleaning, extracting, and storing trial data.

Successful treatment of stage 4 neuroblastoma remains a major challenge in paediatric oncology. The SIOPEN-R-NET IT platform resources allow now and in the future to support further drug developments and clinical trials from Phase 0 to Phase III. As an example, the SIOPEN Group has investigated passive immunotherapy using human-mouse chimeric monoclonal anti-disialoganglioside GD2 antibody ch14.18 in an early phase II clinical trials with promising results in progressing stage 4 neuroblastoma patients (21).

The large scale high risk study HR-NBL-1/SIOPEN has benefited from the IT platform allowing online randomization in 17 European countries independent of working hours. It investigated the prophylactic use of granulocyte colony-stimulating factor (g-CSG/filgrastim) during the chemotherapy induction phase using a rapid dosing schedule. Through randomisation it was possible to demonstrate that the use of G-CSF (Filgrastim) is indeed a beneficial adjunct to Rapid Cojec induction and hence its use is recommended for the HR-NBL-1/ESIOP study on the basis of these results.

The system must have a high degree of intuitiveness, because many users logged in quite rarely. It also poses particular challenges with respect to training and management of these users. Figure 7 indicates that most of the centres have dealt with only a small number of patients during the last five years – only 16 % of the centres had more than 2 patients per year (corresponding to more than 12 patients overall). This challenge has been addressed by:

1. Providing an intuitive user interface
2. Supporting various hierarchical roles with different levels of responsibilities and “needs to know”
3. Keeping the system simple – the majority of users must and can use only very few features
4. Providing sufficient support to the users by highly experienced personnel (primarily by data managers and secondarily by an IT helpdesk)

Another area of concern is interdisciplinary research. Interdisciplinary not only means that various researchers deal with different data sources and formats but also that they have different workflows and organizational structures. IT must recognize this and must provide some flexibility and customized solutions which are tailored to the requirements of the various groups. As a consequence, there are no off-the-shelf solutions to facilitate this. The willingness to provide individual solutions, however, must be carefully balanced through a strategic development plan. Otherwise, over time, systems evolve which are ultimately difficult to maintain.

Future IT development activities will focus on:

1. Horizontal expansion, i.e. to add further clinical trials and incorporate additional countries and investigational sites

2. Vertical expansion, i.e. to provide upcoming additional

scientific disciplines with tailored tools, in particular to account for the increasing importance of biomolecular aspects in cancer by adding bioinformatics links.

A crucial factor for the success of SIOPEN-R-NET was a high level of communication and organizational efforts accompanying and supporting the establishment of the IT system. IT experts attended many of the groups' meetings to better understand the requirements and expectations of clients.

A number of further publications on the basis of this network are to be expected in the near future, including major randomised, multinational trials. Combining European research and medical efforts with a modern IT platform start just now to show its major benefits not only on the daily routine level of relevant data capture in ongoing clinical trials for diagnosis, review purposes and adverse event management but also from the perspectives of research output.

Information is a crucial asset in researching and treating cancer. A powerful IT infrastructure is of significant importance because it increases the productivity of physicians and scientists by allowing rapid assessment of relevant new diagnostic and therapeutic options with the ultimate goal to improve the survival of children suffering from cancer.

6. ACKNOWLEDGMENT

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Abbreviations: AIM: Advanced Image Management; AMED: Agreed Minimum Essential Data; BM: Bone Marrow; eCRFs: electronic case report forms; EDC: Electronic Data Capture; ICH: International Conference on Harmonization; INPC: International Neuroblastoma Pathology Classification; PACS: Picture Archiving and Communication System; QRT-PCR: Quantitative Reverse Transcriptase Polymerase Chain Reaction; SAE: Serious Adverse Event; SC: scientific committees; SIM: Standard Image Management; SIOP: International Society of Paediatric Oncology; SIOPEN: European Neuroblastoma Group of the International Society for Paediatric Oncology; SIOPEN-R-NET: International Society of Paediatric Oncology European Neuroblastoma Research Network; SOPs: Standard Operating Procedures; SRFs: Surgical Risk Factors

Key Words: Neuroblastoma; Medical Research Network; Electronic Data Capture; Clinical Trials; Biomedical Informatics

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