Medical research supporting facilities

Started as IT coordination facility of the Competence Network on Parkinson’s Disease the Central Information Office (CIO) has focused on the development of IT systems and solutions to support clinical research for many years. Due to successful third-party funds in the field of competence networks (e.g. Parkinson, Multiple Sclerosis, Child and Youth Psychiatry, Lung Fibrosis) and by sponsored clinical trials comprehensive communication and infrastructure concepts were developed. The CIO focuses on the standardization of technical concepts and solutions for building horizontal and vertical networks. Offered support services are based on already implemented IT solutions in the division of human medicine including remote data entry system for medical data, images and biomaterials, pseudonymisation, interfaces to statistical programs, content management system for internet websites and groupware tools to support project management.

With its long lasting experience in supporting medical research with IT technologies and scientific research methods, the CIO can implement and maintain today needed IT-technical infrastructures for all medical research activities, accompanied by state-of-the-art standards for data set definitions, data processing, IT process specifications, workflow definitions, nomenclature and ontology specifications and standard operation procedures according to national and international (AMG, GCP, FDA 21 CFR 11) requirements for single clinical trials as well as for widespread research networks.
The CIO develops SOPs for quality management and IT-technical processes to guarantee highest methodological standards for data collection including data safety and data protection according to ICH and GCP regulations.

**State of the art and previous work**

The management of clinical research data is permanently under strict observation from several national boards (e.g. FDA in USA). Demands of these institutions for efficient and secure IT methods in managing medical data become more detailed from year to year. The German Ministry of Education and Research has funded several national platforms which address such issues; e.g. the Technology and Methods Platform for Medical Research Networks (TMF) and the Clinical Trial Network (KKS-Network). Specially the TMF tries to import American and European standards and has set up several projects in this field.

The Central Information Office Marburg (CIO) has been a driving force in these developments since 2000. Started as IT coordination for one of the oldest medical competence networks in Germany (Competence Network on Parkinson’s Disease) the CIO has gone through all these development phases. Today the CIO with its valid and audited IT infrastructure methods and tools is partner for several medical research consortia and companies, dealing with e.g. Parkinson, Multiple Sclerosis, Epilepsy, Child and Youth Psychiatry, Lung Fibrosis, guideline and therapy evaluation, health care economy and pharmacovigilance. For these research networks and groups a full set of data management skills and programs have been acquired, adapted and maintained. The CIO is collaborating with several academic institutions and industrial companies for further development of the software and tools needed in modern high end medical research.

Furthermore the CIO offers support in contract and agreement affairs conform to data protection regulations, in planning and realization of data protection concepts, in composition of questionnaires, scales, items and plausibility rules, in statistic-cordial build-ups of medical databases, development of operating manuals and training material, user administration and training, data administration and processing for statistical analysis, regularly data quality measurements and feedback.

Having long lasting experience in the field of medical research, the CIO is integrated in a wide resource network, co-operating with the TMF (workgroups for IT infrastructure and data quality management, data safety, biobanking), GMDS (medical informatics department), KKS Marburg (monitoring, data management), IMBEI Mainz (central pseudonymisation services), IMBS Lübeck (biometry, statistics), iAS (software development), I-Motion (secure hosting), German Parkinson Study Group Office (CRO services), MH Hannover (feasibility calculations, statistics), University Würzburg (central laboratory services), CTCC Rochester, USA, (CRO services), spm² (safety company), e.g. Each of these partners can be involved to add additional special resources for special research and network demands.

Due to permanent standard progression and changing requirements from legal and statistical sides the CIO is permanently involved in several IT research and development projects.
As a matter of principle participation of the CIO in each medical research project consists of two components:

1. consultation, service and coordination
2. continuous research to optimize the methodological tool set.

**CIO Publications (sample):**


**CIO’s medical research database system**

Since 1999 the medical database system secuTrial® was originally developed exclusively for the Competence Network on Parkinson’s disease (CNP) by the Interactive Systems (iAS, Berlin). The development of the secuTrial® system was funded with more than 2 Mio € by the Competence Network on Parkinson’s Disease.

Within the last years secuTrial® was adapted for several competence networks, patient registers, biomaterial banks, national and international multi- and monocenter clinical trials and post marketing studies.

The continuous conceptual design of secuTrial® based on existing generic concepts of the Technology and Methods Platform for networked medical research (TMF). Additional concepts were acquired in cooperation with the Clinical Trial Coordination Network (KKS network) and several biostatistical researchers and biometry work groups. Legally demanded quality control, such as remote monitoring support, source data verification functions, adverse and serious adverse event messaging functions or electronic signature, were integrated with state-of-the-art technology.

secuTrial® is strictly internet based and operation system independent. It can be deployed on Windows, Unix or Mac servers. It can be handled by administrators and users via web browser without any client add-ons necessary.
The secuTrial® program development is regularly audited by the ABB Eutech. Program updates are regularly audited against all requirements of FDA (21 CFR Part 11) and GCP. Last audit was in May 2013.

(For more information about the secuTrial® medical research database system see the attached short description.)

Remote data entry system

Multicenter studies require a solution for electronic data capture (EDC system) that covers pseudonymization and secure access. Using the generic solutions already in use in other CIO’s projects, for every new project blocks of the generic infrastructure are customized focusing on the EDC system. Customization uses blocks of the generic infrastructure and is done in close collaboration with the project’s research staff.

All basic software licenses, secure hosted hardware and security infrastructure are provided by the CIO. All staff working with the EDC system will be trained, optional via web conference technology.

The CIO accompanies the project from first planning period until the close of the database. The double database strategy of the secuTrial® system allows changes and enhancements during the runtime of a project, GCP conform logged in audit trails.

Pseudonymisation

Pseudonymisation is offered as included feature of the EDC system or in co-operation with a central patient list. In no way identifying patient data (IDAT) are stored with medical data (MDAT) in the same database.

Using the internal pseudonymisation feature the identifying data are printed together with the created pseudonym and held in the patient’s or study’s dossier. This concept can be enhanced by engaging a data trustee to held paper copies. Using the external pseudonymisation service (central patient list), the identifying data are stored in a separate database, located and hosted at the University Mainz*.

Biomaterial management

The CIO staff has long lasting experience in studies using human biomaterial, collecting samples from different institutions or allocations, and central administration. Sample management follows a predefined algorithm according to the regulations of data protection authorities and GCP. Details of sample procurement (types, volumes) for blood draws, subsequent processing and allocation are prespecified. Blood draws per patient can range between once and several times. Standardized SOPs are customized for sample acquisition, processing, transport and storage. All biomaterial shipments are locked in the tracking database enabling tracking of shipment and receipt of all material. Involved principal investigators and co-operating clinical centers can be provided with ethical approvals, standard operation procedures for sample processing and access to the internet-based material management.

This concept can be enhanced by establishing additional databases for material administration in the participating central biobank(s).
Image storage (incl. DICOM)

The correct unification of image data (incl. DICOM images) is offered by the integrated image administration of the secuTrial® system. According to data protection regulations the software removes identifying parts of image headers before image storage and stores images using the patient’s pseudonym.

Adverse and serious adverse event reporting

According to patient and quality security requirements predefined forms for reporting adverse events (AE) and serious adverse events (SAE) are included. After signed with the principal investigator’s electronic signature the event describing data can be send from the secuTrial® system automatically to the institutions, which have to be informed (e.g. principal investigator, monitor, security authorities), per email and/or fax. Forms and message workflow can be customized for each single project.

Remote monitoring features

Remote monitoring is supported by the integrated query system and optional features for data entry complete, review settings, form freezing, source data verification, discrepancy management, completeness and query details reports. The workflow for a special project is always customized in co-operation with the project’s monitor staff.

Data management and export

Due to well defined interfaces and structured export possibilities of the secuTrial® system and its monitoring concepts, any external biometry can participate. The separation of IT and biometry benefits a clean journalized confirmation of quality achievements. Data stored with secuTrial® data capture can be exported to external files in various data formats (SAS, CSV/Text, CDISC ODM), optional optimized for SPSS or EXCEL. Audit trail, comments and eSignatures may be included in the export data. Special data analysis schemes are supported with numerous filter options. The data export history function facilitates regular data reporting (e.g. for benchmarking purposes).

Roles and rights

In the secuTrial® system roles and rights are administrated in a high scalable user administration tool. Each clinical or administrative center can have users with several different roles (e.g. clinical investigator, principal investigator, monitor, data manager). Each role can be given different rights for accessing single eCRF forms, downloadable documents, reports, statistics and messages.

Clinical investigators have by default only access to medical data of their own center’s patients. Strictly controlled by written participation contracts central roles can be established, which allow to see, but not change, the pseudonymized medical data of several centers.

Furthermore the visibility of patient’s pseudonyms can be deactivated to enable access to overview reports and statistics (recruitment statistics for example) strongly according to data safety and security regulations.

The user administration tool is companied with an own audit trail. It logs any establishment or change of roles and rights during the whole runtime of a project.
Patient Self Report

Patient Self Report is another included module of the secuTrial® system family. Patients can be given access rights to their own data – and patients can give other physicians the right to access their medical data. For this patient self report functionality comprehensive enhancements of the user management and roles and right system were programmed. In a first evaluation patients voted the secuTrial® system as user friendly, easy to understand and handle.

Special expertise

The Central Information Office staff of the Competence Network on Parkinson’s disease has long lasting experience and expertise in the field of managing and supervising national and international medical research networks and multicenter clinical trials, and in establishing network IT infrastructures according to all requirements of GCP, AMG, EMEA and FDA (21 CFR Part 11) and legal authorities, inclusive standard operation procedures for data safety and security and data quality management.

Since 2002 Gisela Antony (diploma in psychology and acknowledged as computer scientist) is the leading Central Information Officer. Working since 2003 in the workgroups for IT Infrastructure and Data Quality Management and for Biobanking of the German Technology and Methods Platform for Medical Research Networks (TMF e.V.), since 2010 she is deputy speaker of the TMF's Data Safety and Security workgroup.
REFERENCES

**Competence Network on Parkinson’s Disease:**
- Register of patients with Parkinson’s Disease (BMBF funded, 44 centers, active)
- Gene bank GEPARD register for patients with Parkinson’s Disease (BMBF funded, DPV funded, 28 centers, active)
- European register EuroPA of patients with PD (EU funded, 11 European centers, closed)
- Register of patients with Restless Legs syndrome (BMBF funded, 7 centers, closed)
- Evaluation of the guideline for PD diagnosis and therapy study (BMBF funded, 40 centers, closed)

**German Parkinson Study Group (GPS):**
- Potential of transdermal nicotine in early PD study (MJFF funded, randomized, placebo-controlled double-blind study, 26 centers in Germany and USA, active)
- Cardiac valve fibrosis in PD patients treated with Neupro study (sponsored, drug monitoring study, 12 centers, active)
- PPPMI study: Evaluation of sleep behavior imaging (MJFF funded, 11 centers in USA and Germany, active)
- ACR325 study (sponsored, clinical trial phase Ib, 16 centers, closed)
- Dementia in patients with PD study (sponsored, prospective cohort, 16 centers, active)
- Mental effects in PD patients treated with Deep Brain Stimulation (DPV funded, prospective cohort, 1 center, closed)
- TASMAR post marketing study (sponsored, drug monitoring study, 72 European centers, closed)

**Competence Network Multiple Sclerosis:**
- Register of patients with Multiple Sclerosis (BMBF funded, 22 centers, active)
- Prospective cohort of patients with KIS and early RRMS (BMBF-funded, 19 centers, active)
- Prospective validation of ABC-transporter gene polymorphisms for prediction of therapy response/side study (BMBF-funded, 9 centers, active)
- PBMC in patients with KIS, early RRMS and PPMS study (BMBF-funded, 12 centers, active)
- Prospective validation of biomarkers for clinical response to early IFN- β therapy (BMBF-funded, 7 centers, active)
Biomaterial management in the central TU biobank of the CNMS (BMBF-funded, active)
Mitoxantrone and Dexrazoxane in Multiple Sclerosis study (sponsored, drug monitoring study, 1 center, active)
Pharmacovigilance register for treatments with immunosuppressive medication in MS (BMBF funded, 40 centers, in development)
Evaluation of the influence of special information training in MS for the decision making of MS patients in immunosuppressive treatments (BMBF-funded, 6 centers, in development)

Cambridge Centre for Brain Repair
An observational study to assess longitudinal changes in clinical abnormalities in patients with Parkinson's Disease (EU-funded, 7 European centers, active)
An observational study to assess longitudinal changes in clinical abnormalities in patients with Parkinson's Disease with Deep Brain Stimulation (EU-funded, 7 European centers, in development)

Competence Network on Therapeutic Drug Monitoring in Child and Youth Psychiatry:
Pharmacovigilance in Child and Youth Psychiatry study (BMBF funded, prospective cohort, 11 European centers, active)
Eating disorders study (sponsored, prospective cohort, 5 centers, active)
Pharmacovigilance study in Antidepressiva and Neuroleptica treatment in the child and youth psychiatry (BfArM-sponsored, prospective cohort, 11 centers, active)
Pharmacovigilance study in Psychostimulantia treatment in hypokinetic diseases in the child and youth psychiatry (BfArM-sponsored, prospective cohort, 11 centers, active)

European Idiopathic Pulmonary Fibrosis Network:
Register of patients with lung fibrosis (EU funded, prospective cohort, 11 European centers, active)
Register of patients with diffuse parenchymatous lung diseases (EU funded, 9 European centers, active)

European Epilepsy Presurgical Research (EPICURE)
Patient register of the European Epilepsy Presurgical Research EPICURE (prospective cohort, 7 European centers, in pilot state)
Tuberous sclerosis complex study (in pilot state)
Deep Brain Stimulation study (in pilot state)

Further:
Scientific data pool of the International Workgroup on REM sleep behavior disorder (patient register, 9 centers in Europe, USA and Canada, active)
Biomaterial management for the University Münster Neurology clinic (active)
Available medication for Parkinson’s Disease in Europe (EFNS funded, medication register, 42 European centers, in pilot state)
Register for patients with recidivated malignant glioma (sponsored, cohort, 7 European centers, in pilot state)
Register for patients with anorexia (Universities Aachen and Essen, in pilot state)

MARBURG, JULY 2013
## List of Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>Ajax</td>
<td>Asynchronous JavaScript and XML</td>
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<td>AMG</td>
<td>Arzneimittelgesetz; German Pharmaceuticals Act</td>
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<tr>
<td>BfArM</td>
<td>Bundesinstitut für Arzneimittel und Medizinprodukte</td>
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<tr>
<td>CDISC</td>
<td>Clinical Data Interchange Standards Consortium</td>
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<td>CFR</td>
<td>Code of Federal Regulations</td>
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<tr>
<td>CIO</td>
<td>Central Information Office</td>
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<tr>
<td>CMS</td>
<td>Content Management System</td>
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<td>CNP</td>
<td>Competence Network on Parkinson's Disease</td>
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<tr>
<td>CRO</td>
<td>Clinical Research Organization</td>
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<tr>
<td>CSS</td>
<td>Cascading Style Sheets</td>
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<tr>
<td>CSV</td>
<td>Comma separated values file format</td>
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<tr>
<td>CTCC</td>
<td>Clinical Trial Coordination Center</td>
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<td>DGN</td>
<td>German Neurological Society</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communication in Medicine</td>
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<tr>
<td>eCRF</td>
<td>electronic case report form</td>
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<td>EDC</td>
<td>electronic data capture system</td>
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<td>EMEA</td>
<td>European Medicines Agency</td>
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<td>FDA</td>
<td>Food and Drug Agency</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GMDS</td>
<td>German Society for Medical Informatics, Biometry and Epidemiology</td>
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<tr>
<td>ICH</td>
<td>Guideline for Industry: Structure and Content of Clinical Study Reports</td>
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<tr>
<td>IDAT</td>
<td>Identifying data</td>
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<tr>
<td>IMBEI</td>
<td>Institute of Medical Biostatistics, Epidemiology and Informatics</td>
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<tr>
<td>IMBS</td>
<td>Institute of Medical Biometry and Statistics</td>
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<tr>
<td>IT</td>
<td>Information technology</td>
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<tr>
<td>KKS</td>
<td>Coordination Center for Clinical Trials</td>
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<td>MDAT</td>
<td>Medical data</td>
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<td>MJFF</td>
<td>Michael J. Fox Foundation USA</td>
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<td>ODM</td>
<td>Observation Data Model</td>
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<td>RDE</td>
<td>Remote data entry system</td>
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<td>SAE</td>
<td>Serious adverse event</td>
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<td>SAS</td>
<td>Statistical Analysis System</td>
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<td>SOP</td>
<td>Standard operating procedure</td>
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<td>SPSS</td>
<td>Statistical Package of the Social Sciences</td>
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<td>TMF</td>
<td>Technology and Methods Platform for Medical Research Networks</td>
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</table>
Since 1999 the EDC-system secuTrial® was originally developed exclusively for the Competence Network on Parkinson’s disease (CNP) by the Interactive Systems (iAS, Berlin), and adapted within the last years (samples):

For academic research:
- Competence Network Dementia
- Competence Network Congenital Heart Defects
- Competence Network Creutzfeldt Jakob Disease
- BrainNet Germany
- European Network-of-excellence EuroPa
- European Network-of-excellence BrainNet
- Coordination Center for clinical trials, Charitè Berlin
- Competence Network Therapeutic Drug Monitoring in Child and Adolescent Psychiatry
- European Idiopathic Pulmonary Fibrosis network
- Central Information Office of the University Erlangen
- Central Information Office of the Medical University Hannover
- Competence Network on Multiple Sclerosis
- International Gliom Register
- National Clinical Trial Coordination Switzerland

for multicenter clinical trials of pharmaceutical companies and international foundations (samples):
- Amgen, Cyberonics, Kuros, Meda, Michael J. Fox Foundation, Ortho Biotech, Roche Pharma, Teraklin, Valeant

**SYSTEM DESCRIPTION**

secuTrial® is an internet based EDC-system with connection to a rational ORACLE® data base. The software serves as remote data entry system for pseudonymized medical data. It includes functions for data entry in electronic forms, for data view, analysis and export.
The clinical data are organised in groups of forms, which builds the complete data set. Medical data can be collected with these forms over a time line of different visits. The succession of entries per patient is represented in a history (=audit trail). For authorized persons a user, right and roll concept is defined. All entries of authorized persons are logged in a history.

Currently secuTrial® consists of six modules, each with an own URL address and an own access authorisation:

**Task Daemon** (only development)
  Function: generation of statistics, bundled message transmission

**Customer Admin Tool** (only development)
  Function: customer and administrator management, construction of database areas

**Form Builder** (only development)
  Function: construction and configuration of projects and registers, form generating, internal database adaptation

**Admin Tool** (development and productive)
  Function: user management, management of rights and roles

**Data Capture** (development and productive)
  Function: creation of medical data sets for new patients, data entry, data change

**Export Search Tool** (development and productive)
  Function: search for patients, data export

For reason of data protection and security patients and authorized persons are assigned to the different research centers (hospitals, medical practices, research groups). Authorized persons only have access to data of patients assigned to the same center. Visible for them are only the data forms of these patients. Monitors can get the right to view all patients of all centers. Several monitor supporting features are available.

**ARCHITECTURE**

The application is programmed in Java 2 SE and implemented for the WebObjects® (WO) Application Server. Two different frameworks of the WO Server are used: the WO Components framework for server side generation of web pages and the Enterprise Object Framework, which represents the object-relational model of the tables in the database and controls the data access.

The application logic is related to a web-session, which is represented by a class derived from WOSession. The GUI consists of classes derived from WOComponent, each representing HTML-pages with dynamic data bindings (respectively parts of framesets).

One central component is the form builder, based on the WOComponents framework. This form builder generates the application specific forms from data base queries. Structure and look of the forms are parameterized and defined within the data base as well as the content shown.

The definitions are organized in a separate framework, the IASComponents framework.

The data model is combined within a separate framework (SRTEnterpriseObjects), which contains JAVA-representations of data base tables. The user management is abstracted in the framework IASUsermanagement. The underlying database is implemented in SQL with ORACLE®-specific extensions. On the data base level it contains an ORACLE®-specific primary key generator.
DATA PROTECTION

In all parts the internet-based EDC-system secuTrial® of the CNP conforms to the strictest security requirements. Since 2002 the Central Information Office (CIO) of the CNP is active member of the Workgroup for Data Safety and Security of the Technology and Methods Platform for Medical Research Networks (TMF e.V.). If required the projects partner’s data protection concepts can be presented in this workgroup and supervised.

SECURE HOSTING

The server system of the CNP is always on the newest technical state (last upgraded in November 2012). The server system is housed in a cage-in-cage-room in the High Security Data Center Itenos of the T-Systems AG, Nürnberg (20000-1 and ITIL certified). For the secure system administration the I-Motion GmbH, Fürth, is responsible (ISO-9001 and KV-Safenet certified). Server support is provided exclusively by high qualified and experienced personal.

The secure hosting concept includes the conception and implementation of the safety and security standard operating procedures, the professional audit of all formal processes of data security and the continuous support by competent personal.

The whole network traffic between the internet and the firewall systems, between the firewall systems and the application servers and between the application and the database servers is controlled by network based intrusion detection systems. All warnings and errors are logged in a separated database, located in the seperated IT-center of the I-Motion GmbH, Fürth, permanently controlled and watched by internal implemented analysis tools.

The high availability of the medical research data is guaranteed by redundant hard disk systems (RAID) and a generation based data backup strategy.

All medical data on the database servers and all log files of the firewall systems are back-uped daily. Exchange of the backup-tapes of the individual generations is weekly with a three-week rotation. Tapes of the last generation are stored in a banque safe-deposit box. All systems are secured from power failures by a redundant uninterruptable emergency power supply system (USV, NEA).

The ASP-hosting and server connections (ISP-Connectivity) of the CNP server farm, located in the T-Systems Data Center Itenos, Nürnberg, and their system administration by the I-Motion GmbH, Fürth, is audited regularly by the CIO of the CNP.

Audit is based on
- German National Institute of Security in Information Technology (BSI): Safeguard catalogues
- ISO 27000 (Management systems for Information Security)
- ISO 27001 (Information security management systems requirements specifications)
- ISO 27005 (Information security risk management)
- FDA Guidance for industry: Computerized Systems used in Clinical Trials (CSUCT)
- Good Clinical Data Management practices, ver. 4

The last audit was in June 2012; audit report is attached.
SYSTEM VALIDATION

The software development of secuTrial® is strictly proceeded in accordance to a standardized procedural model, meeting all ISPE GAMP4 requirements of software validation. secuTrial® is permanently audited to meet all requirements according to GCP, AMG, EMEA and FDA (21 CFR Part 11). Last audit was in May 2013.

REMOTE ADMINISTRATION

In the secuTrial® EDC-system not only data input and data evaluation systems are internet-optimized: all database management systems are internet-optimized as well. The administrator of the data system, who is provided with particular authorisations, is able to work worldwide at any computer with an internet access. He may establish new group files, user and user locations, set back passwords, assign authorisations and functions, shift patients between centers, and so on.
MODULAR STRUCTURE

secuTrial® has a modular structure. For data security and research project safety reasons all main modules are accessed by an own internet address. Among others the following features are available:

Customer administration tool:

- administration of separate research project areas
- activation of users with administration rights and project schemes
- configuration of fundamental application functions

Project administration tool:

- configurable, scalable role and right system for data forms, messages, documents, reports and statistics
- user management (rights, roles, projects, centers, locations)
- determination of the preferred user interface language for each user (English / German / French)
- determination of a preferred report for each user
- possibility of limitation of patient recruitment for each center
- import of external used patient pseudonyms
- layout management for each project
- complete audit trail for all changes in the right and roll administration system

Form builder:

The form building tool is the kernel of the secuTrial® module family, a powerful tool to create datasets and data tables in the database, forms, data input rules, report and statistic definitions etc. It is only used by the form building staff for the development of a new or changes of an existing eCRF. Some project partners like to build their forms themselves. In this case the Central Information Office CNP offers training sessions in form building.

- browser based establishment of study designs, incl. eCRF and data base
- generation of data capture forms
- generation of online checks and plausibility controls (formats, logic checks, completeness checks, cross value checks, value limits, value transfer, score calculation, follow-up-actions like form locks and message forwarding)
- import of catalogues (e.g. ICD10-tables, predefined CSV-tables)
- construction and configuration of individual visit plans
- configuration of treatment arms
- configuration of typical study workflows (electronic signature, randomization, source data verification, message forwarding, monitoring, etc.)
- construction of online statistics (e.g. completeness status of medical forms, status of patient recruitment per center / time) and individual online reports (e.g. overview of medical scores in follow-up visits)
- separate test area for each project (user training, continuous project enhancements)
- change management with versioning of all form setups and configurations
- automatic documentation of the project setup with all annotated eCRFs
• construction and configuration of picture forms and overviews (per patient / visit)
• construction and configuration of the download area for each project (e.g. assessment documents, manuals, patient information and agreement print forms)

Data capture:
• strictly internet based data capture of patient data with eCRF
• no client installation at all, only internet access necessary
• electronic signature (scalable)
• capture of patients with automatic pseudonymization
• separate center ID and laboratory ID available (double pseudonymization) due to data safety and security requirements of different countries
• scalable audit trail for all medical data (complete or change audit trail)
• online monitoring with query management (internal messaging system and/or external email messages)
• online patient overviews and statistics (with possibility of direct Excel export)
• included adverse and serious adverse event workflow (optional fax and/or email messages)
• integrated messaging system (e.g. for the internal communication between project centers, with the principal investigator, with the data management, with central laboratory or gene bank services)
• form import of data from medical devices
• generic catalogues (e.g. diagnoses, pharmaceuticals)
• source data verification function
• patient files (selectable from one form of one visit of one patient to all forms of all visits of all patients of a center)
• randomisation functions
• unlimited scalable help function for each question of a form (e.g. percentile tables)
• reintegration function for external generated discrepancies into the query management
• download area for printouts (e.g. study protocols, assessment manuals)
• integrated image management (usable image formats and DICOM pictures, up- und downloads) per patient / visit with thumbnail overview
• integrated patient self reporting tool

Data export and search:
• scalable export of medical data (optional with comments, queries)
• scalable export of audit trail data
• export formats: CDISC-ODM, CSV (Excel- and SPSS-optimized), SAS, TXT
• possible combination of search and filter functions for feasibility studies
• search and export history function for regular exports

DATA CAPTURE BASIS FUNCTIONS

secuTrial® is a strictly internet-based system in connection to a relational Oracle database, made for collecting pseudonymized medical data. It contains functions for data input about forms, reports, statistics, inspection and data evaluation. The collected data are organised in form families; together they form the complete dataset:
- master data
- medical data
- biomaterial bank data
- standard scales (e.g. UPDRS, MMST, CGI)
- pictures (incl. DICOM)
- patient self reports forms

With these forms it is possible to collect medical data from as many examinations as wanted. The follow-ups are presented as case history.

**PSEUDONYMISATION FUNCTION**

A pseudonymisation function is integrated. During the process of collecting data of a new patient, the system generates a new pseudonym. The system checks if the pseudonym is already existing and generates a new database set. At no time the personal data are stored (neither on the local client, nor on the central system). The personal data and the corresponding patient pseudonym are created as printout to be kept in the patient’s file. Alternatively a connection to and data exchange with a special patient list server can be constituted.

**RIGHT AND ROLL SYSTEM**

Persons authorized for data input are part of a sophisticated user, privilege and roll system. This system defines and authenticates the user. Each single data input or change of authorized persons is saved in a history (logged as “audit trail”). Patients as well as authorized persons are relocated to the enclosed centers (hospitals, medical practices, study groups in connection to treatment) due to data protection law and protection of data privacy. This right and roll system enables secuTrial® to be used for all kind of patient registers and clinical trials.

The allocation of rights to single rolls or single centers can be defined due to the user’s intention how to apply the system. The system is able to administrate as many centers with as many investigators as wanted; all investigators to only one center or several investigators to different centers. Moreover it is possible to give authorized user access to single, some or all forms, single, some or all reports and statistics. E.g. the head of the gene bank may look at and alter gene bank forms of all centers – but may not see or alter clinical data forms. The role “monitor” has other rights than the role “clinical investigator”.

The different forms of the database system react interactive with these rights and rolls: a user with a role, not authorized for a certain form, will not see this form on his screen.
For the purpose of patient self report forms special authentication features are implemented. A patient can authorize one or more physicians to access his medical data.

AUDIT TRAIL

According to requirements of GCP and FDA (21 CFR Part 11) each data change is noted together with user name, date and time in the audit trail. It includes not only the data input, but also the database queries (generated with the patient recruiting tool and data export and import tools). Therefore it is always possible to reconstruct who was responsible for creating, changing or deleting any single data or database query. Moreover, secuTrial® contains two more audit trails, one for the right and roll system in the user management, and one in the form builder for the versioning of data capture forms.

MESSAGING SYSTEM

With help of the integrated messaging system the centers may exchange messages (for example in case of a patient is changing to another center) or send messages to the administration centers (IT coordination, monitors) for example, if a patient withdraw his consent.

If the status of a patient is turned to “deceased”, the system automatically sends a message to the administrator, so that he may delete the pseudonym and all corresponding data.

Furthermore the messaging system can be used to send filled adverse event forms automatically to the principal investigator and/or monitors and/or regulation authorities.

All messages can be sent as email and/or fax and/or internal database message.

MONITORING - THE QUERY SYSTEM

The query system was developed for monitoring purposes, but may also be used for the internal communication between investigators working with the same patient data set. The “monitor” may attach his question directly at each single item. The investigator may answer the question immediately, when he accesses the system next time.

COMMENTS

It is possible to attach comments at each item. As well as each other data of a form comments can be changed or completed. They are audit trailed as well.

HELP FUNCTION

Questions or items can be enhanced by exploring help texts. This function is especially helpful in case of difficult medical circumstances or technical expressions. In case of data recording by people without medical background and lack of technical terms, it is possible to deposit more or less extensive explanations. The “Help”-function is very reasonable at European or worldwide multi center studies: for each item translations can be deposited in the according help text.
secuTrial® works with many different graphic symbols and accentuations which make it easier to identify the status of a form at first sight. Is there a comment or a query at a question, it can be immediately identified by a graphic symbol at the input form. A form which is not completely recorded has another color than one already completed, etc.

<table>
<thead>
<tr>
<th>Icon</th>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>without data, tab to</td>
<td>These forms will not be stored in the database.</td>
</tr>
<tr>
<td></td>
<td>not stored</td>
<td>No data has been entered yet.</td>
</tr>
<tr>
<td></td>
<td>empty</td>
<td>The form has been saved empty. In the form family at least one form has been stored empty.</td>
</tr>
<tr>
<td></td>
<td>partially filled</td>
<td>At least some data has been entered but not all mandatory fields have been filled.</td>
</tr>
<tr>
<td></td>
<td>completely filled</td>
<td>All mandatory fields have been filled.</td>
</tr>
<tr>
<td></td>
<td>data entry complete</td>
<td>The data entry is finished. This status does not display the underlying completion status.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Color</th>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>standard form</td>
<td>Used for the capture of normal data.</td>
</tr>
<tr>
<td></td>
<td>Adverse Event form</td>
<td>For capturing data during the workflow of Adverse Events.</td>
</tr>
<tr>
<td></td>
<td>Serious Adverse Event form</td>
<td>For capturing data during the handling of Serious Adverse Events.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>validation</td>
<td>The rule validation of this form finished with problems (warning, error).</td>
</tr>
<tr>
<td></td>
<td>comment</td>
<td>At least one comment has been posted.</td>
</tr>
<tr>
<td></td>
<td>open query</td>
<td>At least one query is open.</td>
</tr>
<tr>
<td></td>
<td>answered query</td>
<td>All queries in this form have been answered.</td>
</tr>
<tr>
<td></td>
<td>resolved query</td>
<td>All queries have been resolved.</td>
</tr>
<tr>
<td></td>
<td>reviewed data</td>
<td>The form has been reviewed, all queries are answered (review A, review B, both).</td>
</tr>
<tr>
<td></td>
<td>partly review</td>
<td>In a form family some forms have been given the status review A (upper flag) or B (lower flag). If all included forms have been reviewed, the flag turns green (last example, upper flag).</td>
</tr>
<tr>
<td></td>
<td>manually frozen</td>
<td>The form has been edited and examined completely, no further processing is allowed.</td>
</tr>
<tr>
<td></td>
<td>frozen</td>
<td>The form is not longer editable (frozen by system).</td>
</tr>
<tr>
<td></td>
<td>patient un-editable</td>
<td>The patient is not longer editable (frozen, deceased). In deceased patients new adverse events can still be created and edited.</td>
</tr>
<tr>
<td></td>
<td>opened form family</td>
<td>If the form family has been opened the included forms are shown at the bottom of the page.</td>
</tr>
</tbody>
</table>
Besides the medical data in visit forms information about the status of a patient can be stored in case forms. These case forms may collect information about exit (decease, withdrawal of the consent, or others), change of the center, participation in other clinical trials etc. In some cases the stored status of the patient leads to a different view of the input mask. If a patient deceased, the forms for medical data input are crisscrossed – in order to prevent further accidentally data input.

In case of using the system for clinical trials the visit and case forms are supplemented by forms for adverse events (AE) and serious adverse events (SAE). The system allows to send the content of AE or SAE forms directly per email and/or fax transmission to the principal investigator and/or regulation authorities.

STATISTICS AND REPORTS

secuTrial® allows a limitless number of statistics and reports. Reports and statistics may be defined before the start of a clinical trial or register as well as during the runtime. Reports are always calculated for the data of a single center and available in real time. Statistics are calculated with the data of the whole database and updated each night. Reports and statistics can be defined for all kind of data: medical data, case data, patient status data, event data or to show the progress of patient recruitment for billing and control purposes.
While reports are always in list form, statistics are pictured in graphics at the screen (pie chart or bar chart), but it is possible to open, work with and save the underlying data in Excel sheets as well.

Furthermore the report function is often used as reminder: e.g. as list of patients who need to be invited for the next follow-up examination.

In general the purpose and content of these statistics and reports is absolutely frank and free eligible – depending of the data of the database. Moreover, the availability of the statistics and reports may be linked to the different rights of the different user roles. Different access to different statistics or reports can be given to an investigator, a monitor, the principal investigator, etc.

PATIENT RECRUITMENT TOOL

The module for the recruitment of patients was especially created for patient registers. It enables the user to carry out feasibility studies within shortest time. It supports the selection of inclusion and exclusion criteria and immediately provides a list with pseudonyms of patients to be considered for the study in question. This module allows the immediate estimation (if the patient register contains enough patients for a study ...).

DATA EXPORT TOOL

With this tool all data or any data combinations of the database may be exported for analysis reasons.
The selection possibilities are sophisticated: single or all forms may be chosen, all questions of a form or single ones, all centers or single ones – and within the single questions it can be chosen between different answer categories. With this, queries are available like: “I need the Hoehn & Yahr status and list of comorbidities of all female patients between 40 and 60 years with diagnosis "multi system atrophy" = "possible" or “probably” registered in the centers in Belgium, the Netherlands, Germany and Suisse.”

All requested data are elective in XML, SAS, CSV for Excel or CSV-format. They may be transferred directly in excel-scales or a statistic analysis programs (e.g. SPSS, SAS). The data export tool is collecting the defined queries in a history for regularly repetitions (for example: process research) without need to repeat the export definition.

DATA IMPORT TOOL

secuTrial® includes a function for single or mass data importation (laboratory values for example). In connection with the form builder, the importation tool allows the storage of external data in list or CSV format via defined parsers into the database. Lists or parsers and mapping rules only have to be defined once. For the importation of external data with different data models in one and the same database table several parsers and mapping lists can be defined. During the importation process the adequate import rule for the specific data can be chosen. Several import safety checks secure the data consistency of the database.

PRODUCTIVE AND TRAINING SYSTEM

secuTrial® creates always two versions of the database for a clinical trial or a patient register - a productive system and a training version. The productive version is working with the "real" database of all medical data. The training system is working with a dummy database. It has the same functions as the productive system. It can be used to organize training sessions or presentations without use of real patient data according to data safety requirements on the one hand.
On the other hand, the training system is an effective part of the change management. All planned changes (data recording forms; database scales, additional reports and statistics) during the runtime of a clinical trial or register can be tested extensively without disturbing the data input progress or the risk to endanger the data of the "real" medical database. Should the test of the training system be successful, the change of the productive system may proceed.