Medical research supporting facilities

Started 1999 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, work flow 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.
Example: Integrated IT infrastructure for the Competence Network on Multiple Sclerosis

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, Multi-
ple Sclerosis, Epilepsy, Child and Youth Psychiatry, Lung Fibrosis, Eating disorders, 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 October 2013.

(For more information about the secuTrial® medical research database system see the attached short secuTrial® 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 SAS, 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 administered 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 accompanied 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 rights 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, 10 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 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, prospective cohort, 11 European centers, active)
Evaluation of the influence of special information training in MS for the decision making of MS patients in immunosuppressive treatments (BMBF-funded, 8 centers, active)

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 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)

Management Platform for Childhood Interstitial Lung Disease (chiLDEU):
- Register of patients with interstitial lung disease (EU funded, cohort, centers in 5 European countries, active)
- Central biobank database for the chiLDEU (EU funded, centers in 5 European countries, active)
- EAA Stop exogenous allergic alveolitis study (EU funded, double-blind placebo-controlled parallel group study, centers in 5 European countries, in development)
- HCQ Hydroxychloroquine in pediatric ILD study (EU funded, double-blind placebo-controlled study, centers in 5 European countries, in development)

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)
Sonderforschungsbereich Translationale Neurologie der Universität Mainz (FTN)

- Patient register of the FTN (cohort, monocenter Mainz, active)
- Central biobank database for the FTN (monocenter Mainz, active)
- prg-1: Studie zu sensorischen Filterprozessen Aufmerksamkeit (monocenter Mainz, active)
- MuSCLE: Übernahme einer bereits bestehenden Datenbank zu MRT-Bildern und Biomaterialien (monocenter Mainz, in development)

Further:

- Scientific data pool of the International Workgroup on REM sleep behavior disorder (patient register, 9 centers in Europe and USA, 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, active)
- Register for clinics for and patients with anorexia (Universities Aachen and Essen, in active)

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<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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<td>BfArM</td>
<td>Bundesinstitut für Arzneimittel und Medizinprodukte</td>
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<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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<td>CIO</td>
<td>Central Information Office</td>
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<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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<td>CRO</td>
<td>Clinical Research Organization</td>
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<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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<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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<td>DICOM</td>
<td>Digital Imaging and Communication in Medicine</td>
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<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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<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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<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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<td>IMBEI</td>
<td>Institute of Medical Biostatistics, Epidemiology and Informatics</td>
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<td>IMBS</td>
<td>Institute of Medical Biometry and Statistics</td>
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<td>IT</td>
<td>Information technology</td>
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<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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<tr>
<td>TMF</td>
<td>Technology and Methods Platform for Medical Research Networks</td>
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