secuTrial®

the medical electronic data capture system (EDC) of the Competence Network on Parkinson’s disease

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, Charité 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
- European Management Platform for Childhood Interstitial Lung Diseases

for multicenter clinical trials of pharmaceutical companies and international foundations (samples):
- Amgen, Cyberonics, Kuros, Meda, Michael J. Fox Foundation, Ortho Biotech, Roche Pharma, Teraklin, UCB, 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 database tables. The user management is abstracted in the framework IASUsermanagement. The underlying database is implemented in SQL with ORACLE®-specific extensions. On the database 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 Itonos 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 backed-up 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 Itonos, 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 October 2013; last audit report can be provided on request.

**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 October 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.
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
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 generate 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 central 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.

### Help - Form overview

<table>
<thead>
<tr>
<th>Icon</th>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Icon" /></td>
<td><strong>without doc-table</strong></td>
<td>These forms will not be stored in the database.</td>
</tr>
<tr>
<td><img src="image2" alt="Icon" /></td>
<td><strong>not stored</strong></td>
<td>No data has been entered yet.</td>
</tr>
<tr>
<td><img src="image3" alt="Icon" /></td>
<td><strong>empty</strong></td>
<td>The form has been saved empty. In the form family at least one form has been stored empty.</td>
</tr>
<tr>
<td><img src="image4" alt="Icon" /></td>
<td><strong>partially filled</strong></td>
<td>At least some data has been entered but not all mandatory fields have been filled.</td>
</tr>
<tr>
<td><img src="image5" alt="Icon" /></td>
<td><strong>completely filled</strong></td>
<td>All mandatory fields have been filled.</td>
</tr>
<tr>
<td><img src="image6" alt="Icon" /></td>
<td><strong>data entry complete</strong></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><img src="image7" alt="Icon" /></td>
<td><strong>standard form</strong></td>
<td>Used for the capture of normal data.</td>
</tr>
<tr>
<td><img src="image8" alt="Icon" /></td>
<td><strong>Adverse Event form</strong></td>
<td>For capturing data during the workflow of Adverse Events.</td>
</tr>
<tr>
<td><img src="image9" alt="Icon" /></td>
<td><strong>Serious Adverse Event form</strong></td>
<td>For capturing data during the handling of Serious Adverse Events.</td>
</tr>
</tbody>
</table>

### Symbol - Status

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image10" alt="Icon" /></td>
<td><strong>validation</strong></td>
<td>The rule validation of this form finished with problems (warning, error).</td>
</tr>
<tr>
<td><img src="image11" alt="Icon" /></td>
<td><strong>comment</strong></td>
<td>At least one comment has been posted.</td>
</tr>
<tr>
<td><img src="image12" alt="Icon" /></td>
<td><strong>open query</strong></td>
<td>At least one query is open.</td>
</tr>
<tr>
<td><img src="image13" alt="Icon" /></td>
<td><strong>answered query</strong></td>
<td>All queries in this form have been answered.</td>
</tr>
<tr>
<td><img src="image14" alt="Icon" /></td>
<td><strong>resolved query</strong></td>
<td>All queries have been resolved.</td>
</tr>
<tr>
<td><img src="image15" alt="Icon" /></td>
<td><strong>reviewed data</strong></td>
<td>The form has been reviewed, all queries are answered (review A, review B, both).</td>
</tr>
<tr>
<td><img src="image16" alt="Icon" /></td>
<td><strong>partly review</strong></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 (best example, upper flag).</td>
</tr>
<tr>
<td><img src="image17" alt="Icon" /></td>
<td><strong>manually frozen</strong></td>
<td>The form has been edited and examined completely, no further processing is allowed.</td>
</tr>
<tr>
<td><img src="image18" alt="Icon" /></td>
<td><strong>frozen</strong></td>
<td>The form is not longer editible (frozen by system).</td>
</tr>
<tr>
<td><img src="image19" alt="Icon" /></td>
<td><strong>patient uneditable</strong></td>
<td>The patient is not longer editible (frozen, deceased). In deceased patients new adverse events can still be created and edited.</td>
</tr>
<tr>
<td><img src="image20" alt="Icon" /></td>
<td><strong>opened form family</strong></td>
<td>If the form family has been opened the included forms are shown at the bottom of the page.</td>
</tr>
</tbody>
</table>
STATUS OF PATIENTS AND ADVERSE EVENTS

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.
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

securTrial® 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 rules for the specific data can be chosen. Several import safety checks and the included log file system secure the data consistency of the database.
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.