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Identification, evaluation and prioritization of possible common or compatible GCP-compliant data management tools for multinational trials

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Work package leader: Christian Ohmann
Coordination Centre for Clinical Trials
Medicine Faculty
Heinrich-Heine-University
Moorenstr. 5
40225 Düsseldorf
+49 (0211) 81-19701
+49 (0211) 81-19702
email: Christian.Ohmann@uni-duesseldorf.de

Working group members and authors:

Wolfgang Kuchinke, Coordination Centre for Clinical Trials, Heinrich- Heine- University, Düsseldorf, Germany

Nader Salas, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Jens Lauritsen, Orthopedic Department, Odense University, Hospital and Institute of Public Health, Dept. of biostatistics, Southern Denmark University. Odense, Denmark

Francois Gueyffier, Centre d'Investigation Clinique, Hôpital Cardiologique Louis Pradel, Lyon Cedex 03, France

Alan Leizorovicz, Faculté RTH Laennec, Service de Pharmacologie Clinique, Lyon Cedex 8, France

Carmen Schade-Brittinger, Maik Hahmann, Koordinierungszentrum für Klinische, Studien, Philipps- Universität Marburg, Germany, supported by data managers of the KKS-Network, Germany

Zoltán Voko, Division of Epidemiology and Biostatistics, Department of Preventive Medicine, Debrecen University, Hungary

Siobhan Gaynor, Margerete Cooney, Molecular Medicine Ireland

Peter Doran, General Clinical Research Unit, Mater, Misericordia University Hospital, Dublin, Ireland

Aldo Maggioni, Andrea Lorimer, Centro Studi ANMCO, Firenze, Italy

Ferràn Torres, Hosptital Clinic i Provincial, Barcelona, Spain

Joseph M Castel, Hospital Universitari de la Vall d'Hebrón, Barcelona, Spain

Gladys McPherson, Health Services Research Unit, University of Aberdeen, UK

Jim Charwill, UK Clinical Research Network Coordinating Centre, Leeds, UK

Stuart W. Cummings, PSI Pharma support International, Brussels, Belgium

Mats Hellström, Department of Oncology, Karolinska University Hospital Sweden

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1 Background

A Clinical Data Management System (CDMS) is used to manage the data of a clinical trial. The clinical trial data are collected at the investigator site in special forms, so-called Case Report Forms and are stored in the database of the CDMS. To reduce the possibility of errors during entry, the systems employ different means to verify the entry. After the input has been screened for typographical errors, the data can be validated to check for logical errors. An example is a check of the subject's age to ensure that it is within the inclusion criteria for the study. Another function of the CDMS can be to code the data. Currently, the coding is generally centred around two areas: adverse events and medication names. In the early phases of clinical trials, when the number of patients is small, most managers use an in-house or home-grown program to handle their data. As the amount of data and the number and size of phase II and III trials grows, organizations increasingly look to replace their own systems with more feature-rich software provided by software vendors. Despite major differences in the requirements of CDMS between CROs, pharma industry and academic sponsors, several requirements are pervasive, including online data entry, data validation, query management, reporting, project management, compliance with GCP and FDA regulations, and compatibility with adverse event reporting systems. An Electronic Data Capture (EDC) system is a front-end part of the CDMS and designed for the collection of clinical data in electronic format for use mainly in human clinical trials. Typically, EDC systems provide: a graphical user interface for data entry, a validation component to check user data, a reporting tool for analysis of the collected data. EDC systems are particularly beneficial for late-phase (phase III-IV) studies. EDC can increase the data accuracy and decrease the time to collect data for studies of drugs and medical devices.

It is now generally accepted, that clinical trial data management software can improve and accelerate clinical trial conduct. A CDMS is able to assist with all aspects of a trial, from enrolment to study submission. Early on the importance to move from remote data capture, which still needs paper CRFs, to electronic data capture and direct data capture was recognized and models to support collaboration, interdependency and interactive sharing of information among the various parties in clinical trials were recognized [1, 2]. It was noted that with using the internet for clinical trials, processes for performing clinical research changed in several fundamental ways. Nonetheless, the implementation of electronic data collection systems in clinical trials was lagging behind other industry sectors (e.g. banking, biotechnology). One reason for this may be a difficult product and vendor landscape, risk-averse pharma culture and organizational protectionism [3]. A relatively large market of software tools for data management support of clinical trials has meanwhile developed. This makes any selection and evaluation of a suitable CDMS an expensive undertaking. The selection of a CDMS is a major effort and done often by a group of consultants. In addition, because most CDMS products are relatively expensive and aimed at pharmaceutical industry as clients, they are not suited for the academic area.

In the planning phase of ECRIN-2 it was thought necessary to have a process of prioritising and selecting suitable GCP-compliant data management tools to be used by ECRIN data centres. Due to the conception of data centres for ECRIN worked out within the working group, this strategy has been changed. Because ECRIN data centres will be based on existing resources, centres applying to become an ECRIN data centre will probably use their own clinical data management software. Requirements for these software tools will be formulated by the IT coordination group. Centres which will apply to become an ECRIN data centre will be audited whether their software tools are able to fulfil

the requirements specified by the IT coordination group and the working group. This strategy is regarded as more successful than trying to select software tools which have to be purchased by data management centres already using an own solution. This procedure does not exclude the possibility that a centre will buy or rent a new CDMS to become an effective ECRIN data management centre. Therefore, it is important to know the market, pay attention to trends in CDMS development and gather information about new solutions. The working group will collect and update information on potential software tools to be used for data management in clinical trials. For this reason, a survey has been performed in 2007 and updated in 2008. In addition, information on software tools including evaluations is collected by the IT coordination group and will be distributed to the ECRIN scientific user community. This document is part of the dissemination of information; it gives an overview of the CDMS market and describes trends and assessments of several consultant groups about developments in the area of CDMS software. It should be read in view of the definitions and clarifications made by the work group in deliverable 10 [4] which defines GCP in terms of ambition and level of implementation.

2 Identification and evaluation of software tools

ECRIN centres are already using software tools for data management. Therefore, any analysis of the CDMS market has to be preceded by establishing an inventory of software solutions in ECRIN itself. Therefore, at first it was analysed what software solutions for clinical trial data management are being used in ECRIN clinical centres. Using a survey the data management tools in routine use at ECRIN centres were recorded and specified.

2.1 CDMS used in ECRIN centres

The questionnaire was sent out on March 1, 2007 to the ECRIN European Correspondents, for further distribution to the different national clinical trial centres and trial units within their national networks [3]. Altogether, the questionnaire was sent to 167 centres or units within ECRIN.

		Questionnaire		
No.	**Country**	**Sent out**	**completed**	**% of total completed**
1	Denmark	12	10	13
2	EORTC	1	1	1
3	France	66	18	23
4	Germany	12	10	13
5	Ireland	8	4	5
6	Italy	23	19	24
7	Spain	8	5	6
8	Sweden	18	2	3
9	UK	19	9	12
	sum	**167**	**78**	**100**

***Table 1**: Distribution of questionnaires per country*

Eight ECRIN countries and EORTC participated in the survey. Most responses were received from France and Italy, with nearly 20 responses, followed by UK and Germany with about 10 answers.

	Centres / Units	
DM performed in centre or unit	**N**	**%**
DM is performed	64	82
DM is not performed in the centre, but:		
By another unit	6	8
External centre (outsourcing)	5	6
No DM	3	4
total	78	100

***Table 2**: Performance of DM in ECRIN*

It was confirmed, that the majority of centres / units are conducting data management: 82% of centres are doing their own DM. Outsourcing of DM processes to an external unit of the organisation or university is minimal. Only 3 centres reported not to be involved in DM. In 61 centres, that is 78 %, a CDMS is in routine use. This means that nearly all ECRIN centres are conducting data management and using software support for this task.

The next question addressed the type of software solutions used. Only centres performing DM were included.

	Centres / Units	
Type of CDMS in routine use	**N**	**%**
Commercial	29	48
Open source	6	10
Proprietary, developed by software company	6	10
Proprietary, developed by yourself	15	25
Proprietary, developed by	2	3
unknown	3	5
total	61	100

***Table 3**: CDMS in routine use at ECRIN centres*

Approximately half of the centres that have CDMS in routine use, are using commercial systems (48%) and 38% proprietary solutions. Open source systems are used by only 6 centres (10%). There are several commercial software systems in use; but apart from MACRO™ with 14 users no other product is used by more than three centres.

Commercial product		Open source product*	
Product	**N**	**Product**	**N**
Macro™	14	GCP base™	3
eResearch Network™	3	PhOSCo™	2
SAS-based	3	Psy Grid™	1
Capture System™	2	EpiData™	1
ECTrial™	2		
ClinInfo™	1		
SecuTrial™	1		
ClinTrial™	1		
EpiData™**	1		
Unknown	3		

***Table 4**: CDMS products in routine use at ECRIN centres*

** one tool was reclassified, ** EpiData™ is an open source product, though one centre classified it as commercial*

In general, it was found that there are many different CDMS in use at ECRIN centres. With the exception of eResearch Network and MACRO no major commercial solution is used. Both products are used in the pharma industry too. Obviously, solutions disseminated widely in the pharmaceutical industry, like Oracle Clinical, PhaseForward, Medidata, are too expensive for academic centres. A heterogeneous CDMS environment in ECRIN will impede data sharing and cooperation between ECRIN data centres.

Some centres have outsourced data management operations to a CRO. For example, the Centre in Lyon uses Clininfo SA facilities through ad hoc contracts, with a budget established specifically by project. Clininfo SA is a French company specializing in the data management of clinical studies. It was created in 1998, originally as technical support centre for the Clinical Pharmacology Service at University Claude Bernard—Lyon 1 to enable the conduct of large-scale, multi-centre clinical studies. The data management system of Clininfo is scalable and can be adapted to small or large studies. Experience exists with multilingual electronic case report forms (eCRF) and with integrated procedures in production, development, test and maintenance in compliance with 21CFR Part 11. The CDMS developed by Clininfo uses an Oracle™ database. It is known, that at least 11 clinical investigation centres in France are using or have used Clininfo data management services (centres for example in Lyon, Saint Etienne, Bordeaux, Grenoble, Clermont Ferrand and Paris), as well as one centre in Denmark, Sweden and Norway. To use data management services by an external provider has the important advantage that the clinical centre is not involved in the computer technical work, software development and maintenance, but only in developing the clinical trial specifications that have to be implemented in the CDMS. This is also the case for SaaS (software as a service) solutions (see later). Clininfo SA offers two types of contracts for data management: (1) a proportional fee, for an individual study (by the number of characters entered, by the number of controlled variables, or by the number of edits and corrections, by the number of randomised patients, etc.) and (2) a base cost fee, with the same types of invoicing as above and a monthly minimum use.

Another special case is the Copenhagen Trial Unit that is using a groupware platform for clinical trial data management. The unit employs Lotus Notes/Domino from IBM imple-

mented in a way that the solution is FDA compliant. It is a rich Client / Server and web based CDMS solution with workflow support and it is platform independent. In addition, it offers many open development facilities. Lotus Notes/Domino is a cross-platform, distributed document-oriented database and messaging framework which allows rapid application development and which includes applications like email, browser, calendar, etc. A key feature of Lotus Notes is that many replicas of the same database can exist at the same time on different servers and clients. In addition to being a groupware system (e-mail, calendar, shared documents and discussion boards), Lotus Notes/Domino is also a platform for developing customized client-server and web applications. Since version 7, Lotus Notes provides a web services interface. From IBM and Winchester Business Systems a trial management system based on Lotus Notes was developed, the Protocol Manager Solution™. It is able to manage the workflow in large-scale global trials.

	Centres / Units	
Functionality:	**N**	**%**
No remote functionality in CDMS	10	16
remote functionality in CDMS available, with:	51	84
- online RDE	42	69
- offline RDE	20	33

***Table 4**: Remote functionality of CDMS used at ECRIN data centres. RDE = remote data entry.*

About 80% of the installations provide remote functionality with a clear focus on RDE (online RDE 69%). Online RDE is a major prerequisite for the efficient conduct of multi-centre trials, because it allows for a centralized data collection.

An important question is: are the CDMS employed at ECRIN centres able to support international multi-lingual trials? This is the case for MACRO and eResearch Network, commercial solutions used in the pharma industry for this purpose. Both products provide a web based user interface for EDC or RDE. eResearch Network even offers a global layer for designing und reuse of CRF templates in data management. There may be other candidates for ECRIN:

PsyGrid was developed for data management of large trials of complex interventions in mental health. It is able to support multi-centre remote electronic data collection, configurable online randomisation and project management reporting including generation of reports for recruitment. The PsyGrid System has been renamed openCDMS (since Sep. 2008). This move was done because the PsyGrid system was growing continuously and it has been adopted across many health domains. As part of this move, the Informatics team announced that the openCDMS software is now available under a free licence (LGPLv3). openCDMS provides purpose built visual tools enabling clinical researchers to design, develop, implement, and manage large scale, multi-centre studies and trials quickly and easily. openCDMS is a mature and stable system used by the UK Mental Health Research Network, the UK Diabetes Research Network and the National Institute of Health Research. It has many features that are comparable with high-end commercial systems but it is available under a free software license. The system is actively developed and maintained by a team of developers at the University of Manchester.

GCP BASE is a web-based tool for remote data capture in a clinical trial developed at the Mario Negri Institute for Pharmacological Research in Italy. It was developed with a user-

friendly interface for investigators respecting a strict compliance with the requirements of current national and international laws concerning data protection, ethical and regulatory issues. All developed software is released as free software under the General Public Licence.

EpiData Entry can be used for simple or programmed data entry and data documentation. It handles simple forms with optimised documentation and error detection features (e.g. double entry verification, list of ID numbers in several files, codebook overview of data, date added to backup and encryption procedures). Data conversion can be done to CSV, SAS, SPSS, Stata, dBASE, Excel and imported from dBASE, CSV and Stata. A prototype has GCP compliance according to deliverable 10. Basic level compliance is in test by Oct. 2008 with the expected general release in spring 2009. EpiData Analysis performs basic statistical analysis, graphs, and comprehensive data management. All developed software is released as free software under a General Public License and conversion is ongoing for release as open source by mid 2009.

2.2 List of products and tools

2.2.1 Result of the evaluation of the German Coordination Centres for Clinical Trials (KKS Network)

Based on an extensive user profile for academic clinical centres 14 CDMS solutions were evaluated by the KKS Network in 2002/2003 for use at KKS centres. The initial selection process included 40 solutions; 14 candidate solutions were determined and at the end the systems MACRO and eResearch Network were chosen. As can be seen in the table several solutions are not anymore in the market.

Software Provider	**solution**	**comment**
Araccel Corp.	Araccel Solution Platform™	has been acquired
CB Technology	Metatrial™	has been acquired
Clinarium	e-Trials™	
Clinsoft	Clintrial™	has been acquired
ClinSource	TrialXS™	
eResearch Technology	eResearch Network™	
Eskuell	Butterfly™	
Guillemot Design	PhOSCo™	Open source
iAS	secuTrial™	
InferMed	MACRO™	
Oracle	Oracle Clinical™	
PhaseForward	InForm™	
SAS Institute	SAS/IntrNet, AppDev Studio™	Development tool
TEAMworks	TRIALink™	

Table 5: *Candidate solutions in the software evaluation process of the KKS Network*

2.2.2 CDMS which were demonstrated at the Coordination Centre for Clinical Trials Duesseldorf

The market for CDMS and other study tools is highly mobile. The instability has been lamented by many sponsors searching for a solution. Often newcomers as well as established software providers are taken over by other software providers (e.g. Clintrial) or a CRO (e.g. Araccel).

Software Provider	solution	comment
Medidata	RAVE™-Platform	Integrated solution including EDC, data management, reporting. Supports CDISC, full sharing of CDISC files, used CDASH compliant eCRFs. Supports IITs outcome studies. Used by the National Cancer Research Network in the UK. Multiple language support in a single system. Recently with Medidata Vision.
DataTRAK	Eclinical™ Suite	Integrated solution with StudyTRAK, patient recruitment, trial management. ASP model.
Formedix Ltd.	Origin™, Transform™, Express™	EDC system uses CDISC ODM to create entire study.
Entimo AG	DARE™, ePRO™	DARE is an integrated solution for management, analysis and reporting of clinical information. It supports CDISC. Its basis consists of a data repository. Connection to mobile solutions for ePRO data capture is possible.
Adept Scientific GmbH	StudyBuilder™	Different versions of StudyBuilder are available, also bargain versions for academic research. Professional edition already for 1500€. Supports multilingual CRFs, and integrated with data collection by PDAs.
SAS	eClinStar™	A special EDC user interface developed by SAS and therefore integrated optimally with SAS platform
ARC Seibersdorf Research GmbH	Forschungsnetzwerk	Web-based research network covering EDC, patient register, second-opinion system, data analysis, monitoring, etc. Is able to be integrated into HIS. Mobile data collection by handy or mobile phone or telemedical applications is possible and already in use (e.g. blood pressure). Used in large cancer trials in Austria.
COMMEDIA-Group GmbH & Co.KG	Profiler-RES™	Integrated solution for EDC and for study management, patient management, monitoring. Connection with mobile data collection possible.

IOMEDICO AG	IOstudy™ office	IOstudy office allows the collection, surveillance and verification of clinical data, as well as the study management. Added are archiving of documents with versioning, reporting, administration of patients, centres, essential documents, SAEs. Project controlling with IoPilot. Supports electronic signature with chip card. Interface with Oracle Clinical and SAS, SDTM, ODM export and import possible.
trialogic GmbH	Trialogic™ Manager	Main focus is the optimisation of clinical trial processes. Integration of tables, e-mail system, calendar and project management. Budget controlling, planning of resources, surveillance of study conduct and study sites. Reporting.
AMEDON GmbH	ProzessManager™, eCRF	ECRF is the EDC component of the process manager which allows project control of clinical studies and the management of study processes. Project management and reporting is integrated.
Infermed	MACRO™	A relatively inexpensive EDC solution. Can be used together with AREZZO, a decision support system. Is used by several academic institutions in the UK and in Germany (Medical Research Council, Institute of Cancer Research, College London, National Blood Service, etc.)
eResearch Technology	eResearch Network™	Is used by 3 KKS for clinical trials and patient registries. Extensive software suite including EDC, data management, study management, SAE management and eDictionary. Integrated study portal.
University Leiden	PROMISE™	Data and project management solution
DataTRAK International	DataTRAK™	Data management suite
SecuTrial	iAS™	Web-based data collection with extensive security infrastructure.
CAP Network	CAP-Net™	Data management with EDC solution of CAP network
NovaXon BV	XClin™	EDC solution, Tablet-PC
Ladanyi	Congruens	Data management based on a new and slim data model
XClinical GmbH	MARVIN™	Web-based and CDISC compatible EDC solution. Is based on a CDISC-ODM database. Integrated are CDM and CTM.

Table 6: *CDMS that have been demonstrated at the KKS Duesseldorf in 2002/2003 and later*

Not a single CDMS has a dominating market penetration, as is the case for SAS in the field of biometrics. In addition, new software providers enter the market with new concepts or solutions with added functionalities and make a potential buyer insecure. For several years the KKS Duesseldorf is observing the market, and has received many CDMS product demonstrations by the corresponding software providers (table 6).

2.2.3 Open source CDMS

Open source solutions for the support of the data management in clinical studies are of special interest for academic centres.

Software Provider	solution	Comment
Penguin Trials Ltd	PhOSCo	Extensive Open Source EDC solution, with many modules. Inexpensive for academic trials. Full functional evaluation CD based on KOPPIX, or online access are available. Self-validation tool.
Akaza Research	OpenClinica	Open source web-based software platform. Enables electronic data capture, and study and data management. Streamlined eCRF creation process. In use for example at the General Clinical Research Centre (GCRC) at the University of Connecticut.
Granite Health Systems Inc.	Visitrial	Web-based Electronic Data Capture (EDC) software for clinical trials. Uses XML- based data store based on CDISC ODM standard for clinical data interchange.

Table 7: *Examples of open source CDMS*

2.2.4 Current CDMS

Following CDMS are part of the actual market and are discussed in the consultation literature.

Software Provider	solution	Comment
Majoro Infosystems	ClinAccess™	SAS based clinical data management tool. ClinAccess links images of CRFs to the underlying trial data.
DataLabs	DataLabs Clinical™	Includes modules for study design, data capture, data management. Browser based application, but allows for functionality of a thick client application. Exports in CDISC standard.
DM	DMSys™	CDMS with record keeping and electronic signatures
ClinPhone	DataLabs™	a hybrid system incorporating EDC and paper data management

ClinicalTrialNet Inc.	ClinicalTrialNet™	Data management and project management for web-based studies as well as paper studies. Fully browser based.
Clinipace	TEMPO™	On demand clinical research platform for data capture and study management in a single solution. Especially suited for post-approval studies. Imports and exports CDISC files.
EclinForce	SmartStudy™	Comprehensive functionalities in a single web platform.
Nexttrials	Prism™	Comprehensive EDC solution
Quadratek Data Solutions	Clincase™	Complete EDC and CDM solution, inclusive error tracking, monitoring, CDISC import and export, supply management.
SyMetric Science	SyMetric™	Comprehensive CDM solution
TranSenda	Clinical Trial Manager™	Comprehensive solution, especially for CROs and Biotech
TrialStat	Clinical Analytics™	Solution for the collection and management of trial data.
Logical Progression	Clinical Ink™	Data entry, validation and review. Enables eSource for clinical trials.
ClickTrials	ClickFind™	ClickTrials provides EDC and data. management solutions for CROs,. pharmaceutical, medical device companies. Was acquired by Datatrak.
ClinSource NV	TrialXS™	TrialXS™ is an integrated, web-based clinical research environment for: Electronic Data Capture and Clinical Trial Management
DataTrial Inc.	NowEDC™	Innovative provider of clinical data services and electronic data capture through its Electronic Data Capture (EDC) suite.
Ascon Health Inc.	EDC solutions™	EDC solution for easy and efficient completion of CRFs, work flow at the site for PI and site coordinator and easy training for PIs and site coordinators
invivo data, Inc.	DiaryPRO™	Simple-to-use patient eDiary that allows for automatic data transfers. DiaryPRO patient diary automatically connects and transfers secure patient data on any schedule. Integration with EPX ePRO Management System.
MedChannels	TrialPro™, OrderPro™ and netSDTM™	MedChannels offers the TrialPro™ products, a comprehensive, regulatory compliant, clinical data management system used to collect, manage and review clinical data. CDISC support

Edgewater Technologies	integrated clinical trials solution™	A Framework for Integrating Clinical Trials Data, Documents and Decisions that promotes data and document standards in all aspects of protocol design, data collection, document management (embedded electronic signatures and audit trails) and systems operations
Quintera	clinical data management system	Centralized clinical data management and analysis system. Web-based and platform-independent, framework includes Microsoft .NET, IBM WebSphere and Object-relational Bridge (OJB)
Innovative Clinical Research Solutions	Acquire™	Easily-customisable Electronic Data Capture system. Acquire features an extensive library of standard Case Report Forms and reports
PercipEnz	OnCore®	Informatics infrastructure for managing clinical and translational research operations. Customizable electronic Case Report Forms (eCRFs), Subject safety monitoring, Electronic Data Capture and Data Management
mdlogix	CRMS (Clinical Research Management System)	Enterprise-scale solution. At the core is a repository for data. It is a process management tool. CRMS is designed to facilitate data exchange with electronic medical records; laboratories; regulatory systems, finance/billing systems; authentication/user account management systems; and document libraries. CRMS: SOAP, HTTPS, FTP, REST, LDAP, API, SQL and HL7. The informatics core of the CRMS comprises the CDISC (Clinical Data Interchange Standards Consortium), HL7 (Health Level 7) and caBIG (cancer Biomedical Informatics Grid) object models. mdlogix CRMS is Bronze Certified by the National Cancer Institute's Centre for Biomedical Informatics and Informational Technology.
IBM	Lotus/Notes™	Cross-platform, distributed document-oriented database and messaging framework, including email, browser, calendar, etc. Allows for rapid application development
ClinInfo SA	ClinInfo™	Oracle database based clinical data management tool. Includes eCRF, IVRS and is able to support paper based data management, multilingual eCRFs and is 21CFR Part 11 compliant. Browser based access.
MedScienceNet AB	Clinical Trial Framework	Clinical trial management solution with an internet-based architecture, supports global

		trials, with real-time reporting and integrated data management system, functions for monitoring, query generation and alerting, ASP hosting is available by the company

Table 8: *List of the main commercial software providers for CDMS in 2007*

2.3 Analysis and development trends for the CDMS market

The ECRIN working party agreed that if possible a CDMS already in use in ECRIN should be used for ECRIN international trials. Therefore, the evaluation of potential software solutions of CDMS must begin with an inventory of the ECRIN data centres. These software solutions are already in use for many trials and ECRIN members have gathered experience using them. But it must be considered, that these solutions might not be optimal solutions for the support of international trials which will have to be GCP-compliant as well as multilingual. For this reason an evaluation must consider the actual market and future trends of CDMS solutions, identifying for example the „best of breed“ solutions. In addition this document will consider analyses and recommendations of consultants in the field.

Especially multicentre trials require hardware and software systems which are normally provided by the sponsor to the different sites. Thus, to participate in a clinical trial investigators and their staff always have to learn new software systems. Often physicians who participate in different trials have to use a separate system with a different user interface for each trial. New CDMS use the internet (browser based CDMS) and thus no proprietary hardware or software is needed at the site. The common interface here is the internet browser. This development has changed the market for CDMS, which is now offering mainly web-based solutions available.

Anot
her possibility is to use a software on demand EDC platform. This solution is offered for example by Trialstat with Clinical Analytics™. It is a suite of clinical data management and security features, including user configurable reporting across base and aggregated data sets, Double Data Entry, integrated data entry validation and correction form generation, standard and custom data dictionary automation and On Demand Encryption for sensitive data elements (e.g. health card data).

To get an overview what is the state-of-the-art of CDMS and to be able to select a suitable solution for ECRIN centres it is necessary to take into consideration the different ideas of market specialists and consultants. It follows a list with several of the major insights in this area.

2.3.1 Life Science Insights

In a paper by Life Science Insight [5] it was found, that “trial sponsors are increasingly looking to replace home-grown systems” to be able to add much-needed functionality to their drug development IT systems. An inspection of the competitive landscape of the CTMS market yielded following findings:

No	Life Science Insights findings
1	Companies placed in the leadership portion include: Phase Forward, Oracle Clinical, Nextrials, and Medidata, followed by Siebel and SAS
2	Technology buyers should determine the functionality that will give them the best results while carefully watching the financial and operational viability of chosen vendors
3	Current technology leaders must assess their position and identify weaknesses
4	System integrators and partners need to forge key alliances that will help them implement and customize solutions efficiently while meeting the business needs and budgets of a diverse group of pharma and biotech companies.

Table 9: *Directions for the CDMS market (from [5])*

More and more EDC providers have extended their systems of core functions of clinical data management with clinical trial management functionalities. Clinical trial management systems (CTMS) encompass trial data such as documentation (protocols, case report forms, etc.), patient recruitment and enrolment, investigator relationship management (IRM), monitoring, reporting, site management, medication management and cost tracking. CTMS products might deliver a part or a full set of these functions as additional software modules, including recruitment and study documentation preparation, financial management including tracking study costs, reimbursing investigators, clinical supply management including supply tracking, storage, and shipment, clinical data archiving, data analysis, adverse event reporting, tracking, and documentation.

To determine a company's ability to gain share it was recommended to analyse the following factors:

No	factors
1	Current market share
2	Breadth of product offering
3	General appeal of the vendor's functionality set

No	scoring list
1	EDC functionality
2	Project management, supply, and financial management functionality
3	Ease of interfacing
4	Nature of product architecture
5	Product positioning
6	Flexibility and configurability

Table 10: *Factors to consider during CDMS provider selection (from [5])*

For research sites at academic and government institutions Hanover and Julian [5] have discovered that these institutions constitute only a secondary market for clinical trial

software providers. These institutions are faced with conducting trials with multiple sponsors and subsequently, using multiple systems. Thus, they often try to find a single system with which to consolidate the research operations of the institution. In addition, “these systems are used to support research projects at the institutional level, particularly in the teaching hospital setting. While these projects may be subsidized or otherwise sponsored by pharma and biotech companies, they are directed by academic professionals. “

No	functions of clinical trial systems
1	Enable the efficient management of multiple trials at different stages, with different sponsors and multiple researchers
2	Build protocols and construct budgets at the site level
3	Coordinate patient visits and procedures
4	Monitor revenue, profitability, and contract milestones
5	Track reimbursement of professionals by commercial clinical trial sponsors
6	Follow recruitment activities and conduct analysis of their effectiveness
7	Facilitate activities of the institutional review board

Table 11: *Functions of clinical trial systems at academic sites (from [5])*

In research sites and academic institutions in large multicenter trials often different systems for data capture are used. “trial participants are likely required to use the EDC systems put in place by sponsors or CROs. However, this is expected to change as standard communication protocols for the conduction of trials, particularly CDISC, emerge and interfacing between EDC and trial management becomes simpler.” Using standard data exchange protocols, academic research sites are able to centralize EDC for multiple trials while transferring data to the sponsor or CRO's trial database or EDC system. Using standards, more academic clinical research facilities are able to use their own data management systems yet share data with external systems. An example of a vendor that specializes in serving this academic and biotech market is Advanced Clinical Software. PhOSCo provides EDC capabilities to European academic researchers in an open source system. “While many large CTMS vendors such as Siebel, Oracle, and SAS provide this market with applications, they typically do not offer specialized functionality or are priced too high for any but the largest clinical research centres.”

No	Recommended requirements
1	Growing price pressure is expected to cause erosion in application pricing as sponsors look to licensing arrangements such as hosting and ASPs to lower the entry cost for applications, creating additional competition
2	A highly competitive market will force all vendors to refine their products and services
3	An increasing level of customization is expected to become available in off-the-shelf products, and a growing number of vendors will develop the functionality needed to enter the market
4	Many of these new entrants will come from the EDC space as the market for CTMSs matures and EDC vendors add additional CTMS functionality

5	Trial sponsors will move from custom and home-grown systems to vendor-supplied systems as the available applications become more competitive and sponsors seek the stability and support of commercially developed applications
6	Identify challenges in multiple areas of the market as newly available technology strives to meet the needs of stakeholders
7	Supporting group sequential and multi-arm trial designs
8	Accommodate to growing numbers of trials using clinical genomic data
9	Intensifying efforts by sponsors and regulators to extend adverse event reporting into full-spectrum pharmacovigilance
10	Adding CDISC data interchange format compatibility to facilitate interoperability between applications
11	Complying of the system with regulatory requirements
12	Improving the value equation for applications as cost containment pressure continues to intensify

Table 12: *Factors buyers of CTMS systems should take into account (from [5])*

Many clinical trial sponsors have looked at different systems in the past but have often been disappointed by vendor offerings or made the decision to develop internally as a result of the need for a very specialized functionality. “While this market is still not at full maturity in terms of functionality offerings for trial sponsors, it is worth re-examining frequently as the opportunity to adopt a system that can save in trial data management costs but that comes with a lower total cost of ownership than home-grown or custom systems may exist for clinical trial sponsors.” Even the spectrum of the main CDMS providers differs greatly; there are companies with 600 employees and some with as few as only 4 employees.

Product	Revenues	Employees	comments
Phoenix data systems: EDC	6,3 Mio $	74	EDC and IVR, reporting
OmniComm Systems: Trialmaster	1,3 Mio $	25	Web-based data capture, CDISC
Datatrial Ltd.: LogiXML	7 Mio $	40	User-friendly, scalable EDC solution
PhaseForward: InForm	134 Mio. $	467	comprehensive EDC and data management system
Medidata Solutions Inc.: RAVE	61 Mio $	603	Internet-driven technology
Datatrak International, Inc.: Datatrak EDC	11 Mio. $	122	Platform of applications, ASP
ClinPhone Inc.	50 Mio. $	175	Perceptive Informatics
DSG Inc.: CaseLink	6,7 Mio. $	62	
Planet Data	4 Mio.$	22	Data management platform

Solutions Inc.			
Acumen Healthcare Solutions LLC	1 Mio $	4	TracIt2k
Logos Technologies Ltd.			ALPHADAS, mobile phase I EDC
Ninaza	2 Mio $	20	

Table 13: *List of the main software providers for CDMS in 2007 (from [5])*

2.3.2 Open source CDMS as an alternative to commercial solutions

Fegan and Lang [6] noted that „clinical trials-related software can be prohibitively expensive, especially for individual researchers or groups based in developing countries. The two most commonly used packages, Oracle Corp's Oracle Clinical and Phase Forward's Clintrial, are both designed for use with commercial database systems. Investing in such systems would cost in the range of hundreds of thousands of dollars, depending on the size of the trial and number of licenses needed. Such costs would take up a disproportionate amount of a typical non-commercial trial budget, which is generally in the same order of magnitude as the cost of these systems, and must cover everything required by the trial."

„We propose a commitment by the major international donor and implementing groups to encourage efforts to develop a free and open-source data-management system for clinical trials that adheres to evolving standards such as those set by CDISC." [6] In this spirit the National Cancer Institute in the US has begun a wide-ranging development project based an open-source concept called caBIG (Cancer Biomedical Informatics Grid), which includes also the development of clinical trials management systems. In the context of caBIG the OpenClinica is an open-source clinical trials data management system. This software is built entirely using open and free systems and programming languages. An open source CDMS could be the core of a shared platform that would bring wider benefits such as electronic submission, automated sharing of data and export to important public databases such as drug-monitoring registries. „We believe that an open-source approach to a truly designed-for-purpose data-management system for clinical trials is attractive. Such a system would save money by eliminating the reliance on the use of expensive database software systems and their administrators. This would empower and enable a wider variety of people to conduct trials, as the question of capturing, cleaning, and extracting data would not be overly daunting or expensive." [6]

2.3.3 Distinction between "basic level" and "comprehensive level" CDMS

In deliverable 10 [4] the distinction between "basic level" and "comprehensive level" requirements of GCP compliant data management was made. This distinction can also be conveyed to CDMS solutions. The basic services of a clinical centre offering data management cover the development of a data management plan, CRF design and CRF management, creation of a study data base, programming of validation rules and edit checks, randomisation, query management, coding and reporting. To cover these processes one needs in principle a data entry tool and a data management tool. The data entry tool is often a web based EDC system, allowing online collection of clinical data entered by the

investigator or an assistant into electronic CRFs in addition to data validation and the display of the status and completeness of CRFs. Additional processes, like the design of CRFs, creation of selection lists, query management and comprehensive study reporting, require a data management tool. A data management system allows entering paper case report forms by using Double Data Entry and subsequent data cleaning. The EDC system, the data management tool and the clinical trials data base constitute the minimal basic level for a CDMS. Added to this basic level of features are often additional tools, like the statistical analysis features of EpiData™.

A comprehensive level would cover additional trial management and site management features. During the conduct of a trial often questions emerge, like how is the patient recruitment progressing, what is with investigator recruitment, how is the medication distributed? A CTMS can answer these questions because it includes features, like budgeting, contract management, investigator payment, recruitment monitoring, contact management for investigators and patients, monitoring of visit schedules, export of reports in XPT, XML, PDF and RTF formats (see above).

On the software level, these functionalities are offered as additional modules. For example the eResearch Network™ possesses modules for EDC (eData Entry), data management (eData management), clinical trial management (eStudy Conduct) and safety surveillance (eSafety Net). Other systems like InForm™ or Medidata™ offer a similar comprehensive range of trial management capabilities. But most software solutions on the market limit themselves to a basic level and offer data capture and data management functions.

A complete system, a so-called e-Clinical System, would cover modules dedicated to (EDC, ePRO, online randomization, clinical drug labelling, safety surveillance / SAE reporting, site management and offer on-time reporting of important operational study metrics, like CRF status by site, CRF site performance by site, query status by site and subject, query volume by month by site, subject enrolment status, subject dropout by reason and SDV item listing. However, offering trial management features as additional modules alone is not sufficient, the degree of integration of the EDC / data management units with the CTMS is important. In case of low level integration staff has to enter operational data as an additional step into the CTMS by hand. Recently, web-based EDC systems are an alternative for obtaining trial operational metrics and integrating them into clinical trials management accelerating the visibility of clinical data and parameters.

2.3.4 Are distributed clinical trials information management tools a solution?

Oliveira and Salgado [7] have analysed the area of clinical trials informatics from an academic point of view and have found that „a number of commercial software applications for clinical trials management have been introduced and are being used mainly by the pharmaceutical industry. Almost all large pharmaceutical companies in the United States use a Clinical Trials Information System (CTIS).” [7] ... The primary functionality of commercial applications is mainly concerned with delivering valid and accurate data in conformity with Good Clinical Practice. In a number of cases, commercial systems provide additional features in addition to data entry and data validation. A few systems support clinical trial management (budgeting, scheduling, patient tracking and study site management). More advanced features, like patient recruitment, eligibility checking, treatment allocation and adverse events reporting, can be found only in one or two commercial systems. Within the academic community, earlier publications consisted mostly of reports

of successful experiments with the utilization of relational database technology for clinical trial data management. Later reports have focused on the utilization of Web technologies for the development and implementation of data-entry systems for clinical trials. While earlier systems were typically used by a single institution and designed to manage just one study, Web-based systems have been successfully used for data-entry in distributed, multicentre national and international clinical trials, although usually restricted to a single therapeutic area. “Therefore, both commercial and academic systems show little design focus on end to end processes, user interface, and interoperability. They have adopted an approach to the development of CTIS that could be called a data-centric approach where the types of variables found in clinical trials drive the modelling, resulting in some common data structures.” [7]

No	Drawbacks of data-centric approach
1	little design focus on processes, user interface or interoperability
2	absence of a common data model
3	proliferation of clinical trial databases, and to an inability to create repositories of clinical trials or to easily integrate the data from different clinical trials
4	Absence of development of powerful reporting and analysis tools, able to create complex reports that are not restricted to simple descriptive data tabulations
5	For each new clinical trial, it is necessary to recreate a new data access module, and extensive data integrity and data consistency checks
6	complex and lengthy process of database set-up
7	flat-file design which is not adequate for data that are naturally relational
8	high acquisition and maintenance costs
9	because of their complexity, commercial systems usually require specialised personnel, comprehensive training programmes and a good support network

Table 14: *List of drawbacks associated with the data centric approach found in common CDMS (from [7])*

Another important limitation of commercial systems is that because they are a proprietary system, data cannot be freely distributed within the research community. A solution to the data centric problem of incompatibility of data among different commercial products, or even within the same product, is provided by the CDISC consortium. CDISC is developing data structures to represent the three major information components relating to a clinical trial (administrative data, study metadata and study data). The main objective of this ODM standard is to enable data interchange between different applications used in collecting clinical trials data.

“As opposed to the data-centric approach, we sustain that the commonality across clinical trials goes far beyond the data structures that they use. For example, since study designs must obey a set of identifiable methodological principles to be valid, clinical trials must share a common basic study design. A large number of data entities are also shared across studies, like concomitant medication, previous illnesses, adverse events and several others. Most of the workflow model is also common and, actually, most of it is specified in the GCP guidelines. The recognition of a significant commonality among clinical trials leads inevitably to the search for a generic data model that would be able to capture the relevant details of each experimental design and study plan, and most or all of the data used in clinical trials. Therefore, we suggest a paradigm shift toward a study-

centric approach. A CTIS based on this general data model would be process-oriented and generic, in the sense that it could accommodate the data management and data flow required by any clinical trial.

Our approach has common aspects with ontology-based approaches to information integration from heterogeneous sources [8]. Ontology-based approaches are based on the notion that interoperability between distributed computer systems has to be provided not only at the technical, but at the informational level as well. In other words, interoperability in a heterogeneous information system can be achieved only if the meaning of the information that is interchanged can be understood across the systems.

Another issue is the possibility of using common, and sometimes competing, terminologies across multiple clinical trials. CTIS, like other clinical applications, must make extensive use of existing ontologies applicable to clinical trials. These include well-known ontologies for adverse events (e.g., MedDRA, WHOART), cancer trials toxicity (e.g., NCI's CTC, WHO nomenclature), disease classification (e.g., ICD-9-CM, SNOMED), procedures (e.g., CPT), drugs (e.g., ATC, MMX), as well as generic ontologies (e.g., UMLS). Consistent coding and description of study variables is an essential feature for semantic data interchange, and methods and tools that help us maintain the consistency of concepts across studies need to be developed." [7]

2.3.5 Recommendations based on CDMS market analysis

It is generally argued that the best technology available for clinical trials is the Internet-based clinical trial system. The use of paper based studies have become insufficient to meet the data needs of companies and academic institutions due to the enormous disadvantages accompanied with the generation of large amounts of paper, redundant and inefficient processes, and major delays during the conduct of a study. In international clinical trials, updated software applications must be implemented to support the data management activities. "A sophisticated data management system is required to help streamline the clinical trial from the beginning to the end. (…) For data efficiency to occur, first management must identify the need for an integrated database system, the type of software required, and what information should be loaded into the system so that the design and support of the database can be effective. (…) Software used for the research database should include the availability of training and technical support, statistical software packages, sophisticated query features, the ability to update, efficient data entry features, an e-link, and the ability to import external files. (…) Through an in-house data management system, users and external Contract Research Organization (CRO) can access information (administrative data, trial monitoring and budget data, drug information and supplies, warehouse shipping, and other relevant information including screening data, randomization document images, lab data, etc.) by using a single web-based log on that accesses a variety of tools and databases through one interface."[8].

For data management systems that will support all aspects of an electronic clinical trial, there should be real-time reporting, document tracking, automated data and notification of tasks. The software must have the ability to identify and respond to data key points and archive documents. A comprehensive solution should offer statistical analysis data, data entry reporting, training modules, and on-line access to sponsor and investigator information [8]. Because based on reporting and documentation decisions about the conduct of a clinical trials and therefore can influence patient safety, all features of the data and trial management solution must be validated according to GCP compliance. An integrated

system would allow data capture from electronic health records and electronic data capture from patient care and clinical research databases. This could improve the workflow and efficiency at clinical research sites, reduce errors from data transcription, and reduce the costly and time-consuming process of source data verification. By having a centralized system it is easy to collect and extract data for statistical information, prospective observational studies, chart mining, and more. Employees must be trained quickly and efficiently in electronic data management processes and manuals / SOPs must be available to teach GCP compliance.

Ramos [9] analysed the market for CDMS and developed a set of predictions and recommendations. It was predicted that demand for simplified integration and collaboration would drive electronic data capture (EDC) vendors to develop broader trial (eCT) suites to give sponsors shorter, less costly trials. Until now several factors were found to limit the implementation of a widespread electronic study support as well as different market interests.

No	Technology limitation
1	Integration headaches continue.
2	Suppliers don't leverage common software infrastructure and middleware
3	Disjointed, nonstandard user experiences dominate.
4	eSource and patient-reported data give regulators heartburn.

Table 15: *Technical limitations of the CDMS market (from [9])*

No	Divergent market interests
1	CROs fight to maintain services revenues
2	Ingrained industry practices protect status quo
3	US EHR progress lags behind
4	Running trials is not a core competency

Table 16: *Differences in market interests (from [9])*

No	Advantages of using eClinical solutions
1	eClinical trial suites will march forward
2	Web-based applications show solid payoffs
3	Cost savings make eTrial management more attractive
4	eClinical software lets sponsors shift to higher-performing sites
5	Real-time metrics and site visibility streamline studies
6	Cleaner data improves efficacy and safety monitoring

Table 17: *Advantages of eClinical (from [9])*

No	Software providers: who are the strong performers
1	Phase Forward — product integration and collaboration tools
2	Oracle — expect a clinical product makeover

No	Software providers: who are the strong performers
3	Medidata — shift from data capture to data mart
4	DATATRAK acquired ClickFind
5	DataLabs acquired Broadpeak
6	OmniComm builds on Microsoft platform
7	Nextrials in biotech community

Table 18: *Characteristics of the main software providers (from [9])*

Recommendations which were developed include to make the commitment to EDC and to run all trials as “electronic only”, to use trial portals to manage service partners, to shift from clinical risk absorption to mitigation and to think about EHR and clinical data integration.

2.4 Diversity of CDMS - conclusions

EDC solutions for academic centres: the leading commercial product costs about 200000 – 400000 Euro for the basic installation and 20% annual maintenance costs, resulting in additional 40000 Euro. However, one should consider, that maintenance by a provider means development of the products, offerings of regular updates and offering a help desk for problems. The provider will install the software at the centre and will conduct the first steps in system validation, including installation qualification and operational qualification. Nonetheless, commercial products are focused on the needs of pharma industry. Academic centres try to use clinical trials as a means to increase income and to build a steady portfolio of trials, but have to do this with small resources and with as little interruption in health care and research as possible. For academic centres, the priority must be the conduct of the trial and not to maintain a computer centre. Hosted solutions and the ASP concept might be a solution. Compared to what is available in industry, data centres of ECRIN members are often small and with a small number of IT staff. In addition, academic staff will change employment, often the person knowledgeable of the database or the CDMS will leave the centre, jeopardising the entire infrastructure. This can only be absorbed by an academic user community offering mutual support and able to set up a common knowledge base. Such a user community should be built around the CDMS solutions in use. Another point is, that most processes are similar in industrial and academic GCP-compliant trials. However, academic trials may be more complex than industry trials, requiring tight cooperation between investigators and data management. Several types of implementation of CDMS should be considered and some of them may solve some of the data management problems at academic centres.

No	Different sorts of CDMS solutions
1	In house development of a new system
2	Commercial Off-the-shelf software (COTS)
3	COTS accompanied by extensive customization (adaption to the requirements of the user)
4	Open Source Solution
5	Application Service Providing (ASP)

No	Different sorts of CDMS solutions
6	Software as a Service (SaaS)
7	Commission a CRO with data management and software services

Table 19: *Flexibility in the kind of deployment of CDMS*

Historically the main decision of an institution in need of a CDMS solution was to decide between self-built (In-house development) or propriety. Especially academic institutions have the tendency to commission one or two students with the development of system. This can be relatively simple if common web technology is used for an online EDC system. A COTS solution on the other hand is mainly directed to clients in the pharmaceutical industry, because here the necessary resources for these heavily priced products of the software providers are available. Pharmaceutical industry owns the resources to instruct software providers with the time consuming task of customizing the COTS solution to the special needs of the client company. Several open source CDMS are available for the conduct of clinical trials. Owning the source code and supported by an user community it is possible to develop a open source solution further and share it within the community.

Recently software deployment has developed several alternatives. Because these new ways to use software may be important for ECRIN, they will be discussed here. The Application Service Providing concept allows to offer the use of a CDMS system installation to a third party. This is a form of renting the access to a software application and thereby offering an alternative to buying the services of a CRO for data management.

In this way one ECRIN centre may rent its CDMS to another ECRIN centre, supporting the new user with maintenance and training. But only a small number of software solutions are able to provide secure ASP. Recently, another concept is gaining importance. The internet enabled the “software as a service” (SaaS) concept, whereby software can be deployed from a central server, most often by allowing for individual instances for each user. Software is typically offered on a subscription basis. The deployment of SaaS solution does not need a large IT and data management staff to manage the software and its users. In conclusion, the market is very heterogeneous, there are many newcomers and it is difficult to decide which providers will exist in several years.

Before establishing a suggested solution or decided solution at any centre or specific study it is important to go over all of the aspects of GCP compliance which are covered in detail in deliverable 10 [4]. It might well be, that the optimal solution for one study and collaborating centres is not the same as the optimal solution for another study and set of centres or single centre.

3 Abbreviations

API	application program interface
ASP	application service providing
ATC	Anatomical Therapeutic Chemical groups
caBIG	cancer bioinformatics grid
CDASH	Clinical Data Acquisitions Standards Harmonization
CDISC	clinical data interchange consortium
CDM	clinical data management
CDMS	clinical data management system
COTS	commercial of the shelf
CPT	Current Procedural Terminology
CRF	case report form
CRMS	clinical research management system
CROs	clinical research organisation
CSV	comma separated values
CTIS	clinical trials information system
CTM	clinical trial management
CTMS	clinical trial management system
DM	data management
ECRF	electronic case report form
EDC	electronic data capture
ECRIN	European Clinical Research Infrastructures Network
EORTC	European organisation for research and treatment of cancer
EPRO	electronic patient reported outcome
FDA	Federal Drug Administration
FTP	File Transfer Protocol
GCP	good clinical practice
HIS	hospital information system
ICD-9-CM	International Classification of Diseases 9th Revision Clinical Modification
HL7	Health Level 7
HTTPS	Hypertext Transfer Protocol over Secure Socket
KKS	Coordination Centre for Clinical Studies
LDAP	Lightweight Directory Access Protocol
MedDRA	Medical Dictionary for Regulatory Activities Terminology (latest V 11.0)
MMX	Multimedia Extensions
NCI CTC	National Cancer Institute Common Terminology Criteria
ODM	operational data model
PDA	personal digital assistant
RDE	remote data entry
REST	Representational State Transfer
SaaS	Software as a Service
SAEs	severe adverse events
SAS	Statistical Analysis System
SDTM	study data tabulation model
SDV	Source data validation
SNOMED	Systematized Nomenclature of Medicine
SOAP	Simple Object Access Protocol
SPSS	Statistical Package for the Social Sciences
SQL	Structured Query Language
UMLS	Unified Medical Language System

UK	United Kingdom
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Terminology

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