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Survey on data management,
tools and procedures within ECRIN

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Work package 4: **Transnational working group on data management**

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Content

		Page
Summary		3
1.	Background	4
2.	Aim of the survey	5
3.	Methods and instruments	5
4.	Results	6
4.1	General information	6
4.2	DM-technology	8
4.3	Human resources for DM	13
4.4	QM of DM	15
4.5	Support of multinational trials within ECRIN	16
4.6	Country profiles	18
5.	Discussion	23
6.	References	26
7.	Appendix	27
7.1	Abbreviations	27
7.2	Questionnaire	28
7.3	Glossary	34
7.4	Description of ECRIN national networks	35

Summary

Data management in multinational clinical trials is a major challenge for academic research and most clinical trial units or clinical research centers have no professional tools adapted to these studies. In an EU-funded project (ECRIN-RKP) missing harmonization of procedures and quality management related to data management was identified as one of the major problem areas. In a second EU-funded project (ECRIN-TWG), a survey was performed to assess the structure, resources and activities related to data management in clinical trial units and clinical research centers belonging to ECRIN. The survey was performed in March/April 2007, 78 centers/units participated. ECRIN units/centers cover a wide range of differerent sizes. All types of trials are support with a focus on phase 2- (73%) and phase 3- (85%) trials. Data management is performed in 82% of centers/units participating in the survey. In 61 center/units (78%), a clinical data management system is in routine use. Approximately half of the clinical data management systems used are commercial systems (48%) and 38% proprietary solutions. Only one commercial product is used by a larger number of centers/units. From those centers/units using a clinical data management system, 75% have their own computing center and 79% use their own installation. Remote monitoring, remote eCRF design, remote query management and remote reporting is supported by approximately half of the installations. 45% of the centers/units are providing support to ongoing multinational trials with remote data entry, however, only a minority are involved in at least 5 ongoing trials (13%). Approximately 42% of the units performing data management are rather small and employ only up to 4 persons. A quality management system for data management is in place in 91% of the centers/units. Internal data management audits have been performed in 31% of the centers/units, an internal system validation in 42% and an external data management system audit in 41%. Overall, 60% of the participants reported to have experience with data management of multinational trials and 45% to have a clinical data management system available for multinational trials, however, only in 9 centers (12%) the system has been validated for this type of use. 82% of the centers/units declared themselves to be able to provide infrastructures and human resources to support multinational trials. The participants expressed overwhelming interest to support data management in multinational trials (86%) and are interested in being involved as a potential partner in ECRIN data centers to be established (68%). For Germany, Denmark, United Kingdom, France and Italy short individual country profiles are provided in the report. The survey identified software heterogeneity as one of the main critical issues for data management in ECRIN centers/units with the problem to buy, implement, validate and use all these different systems. The majority of centers/units have their own local computing center with their own installation. Alternative software tools (e.g. open source) and cost- efficient solutions (e.g. application service providing) are not widespread so far. A considerable number of centers/units have deficits with respect to quality management (e.g. missing system validation, audit). There is the necessity to harmonize and improve quality management of data management within ECRIN. Standards with respect to data management, such as CDISC and MedDRA, should be promoted within ECRIN. There is a high interest of ECRIN centers/units to be involved in data management of multinational trials, but major experience and professional infrastructures, a prerequisite for the ECRIN data centers to be established, are only available in a limited number of centers/units.

1. Background

Data management (DM) in multinational clinical trials is a major challenge for academic and Small Medium Enterprises (SME) research, and most national networks currently lack professional tools adapted to such studies. Based on national and international rules and regulations, compliance to Good Clinical Practice (GCP), Food and Drug Administration (FDA)-rules and other standards is required (1-6). Quality management (QM) systems have to be implemented to achieve these targets. Software platforms should provide extensive flexibility to support a huge range of different scenarios, covering different phases and types of clinical trials. Professional software tools are needed, implemented and validated according to standard procedures. In multinational trials, a lot more aspects, such as multilingualism, different working times, different medical cultures and inhomogeneous research infrastructures, have to be taken into consideration. Therefore major requirements have to be fulfilled in order to be able to provide GCP-compliant and user-friendly DM-services for multinational clinical trials.

In a first (ECRIN-RKP) FP6-funded step the status of DM in clinical trials was assessed in each country participating in the ECRIN-project and a comparative analysis between the countries was performed. The analysis demonstrated that there is a major diversity in national rules and regulations related to DM (e.g. archiving, data protection). Procedures and tools used for DM differ widely between ECRIN members (e.g. SOPs, software). In the majority of centers no professional commercial software is routinely used except for data-analysis. Only exceptionally DM audits are performed. Experience is available in individual centers/networks of ECRIN for the systematic evaluation of software, use of professional commercial software and DM audits.

Several problems areas were identified. The major problem in the ECRIN network is the missing harmonization of procedures and QM related to DM. The situation is complicated by limited financial resources, high prices for commercial software and uncertainty in the software marketplace. So far validated software is not used on a regular basis. Standards such as CDISC and MedDRA are rarely implemented. Integration between study software tools and clinical information systems has not been performed.

From the results of the analysis it was concluded that a primary task is to improve and harmonize QM in DM (e.g. harmonized SOPs). The suitability of software products for academic research should be evaluated (e.g. open source software). Interfacing and integration should be based on standards. DM audits should be supported. A further task for the future would be the implementation of centralized data bases for research.

In the ongoing second FP6 project (ECRIN-TWG) transnational working groups are in charge of defining procedures and guidelines for multinational trials in the EU. The focus of the Working Group on DM is on assessing DM tools and procedures within ECRIN, providing recommendations for GCP-compliant DM in multinational trials and identifying, evaluating and priorizing GCP-compliant DM tools. The working group has started working on current practices and existing resources in terms of GCP-

compliant DM systems, on possible specifications for ECRIN data centers implemented in the next step of the ECRIN project, and on the needs of both the academic community and the EU biotechnology SME.

The next step is the preparatory phase for the construction and operation of an infrastructure for EU-wide clinical trials and biotherapy (ECRIN-PPI), based on the integration of competence centers coupled to data centers and biotherapy facilities. The ECRIN preparatory phase will be in charge of implementing a strategy for the development of data centers, taking advantages of existing resources and competencies within the network. Existing or emerging data centers, alone or as network, will be qualified to become ECRIN data centers providing services and consulting for multinational trials. In order to develop a strategy for ECRIN data centers the full picture of existing DM structures and procedures in ECRIN centers has to be assessed and explored. For that reason a comprehensive survey was performed among ECRIN members, the results are presented in this deliverable.

2. Aim of the survey

The aim of the survey was to assess the DM structure, resources and activities of ECRIN members and to measure the interest to support multinational clinical trials within ECRIN. Typical and representative patterns of DM should be identified for countries having joined ECRIN. The survey should give substantial input into the conception of ECRIN data centers within ECRIN-PPI, taken into consideration that such centers should be based on existing experiences, competencies and resources.

3. Methods and questionnaire

The draft version of the questionnaire was designed by the chairman of Working Group 4. Based on written comments, and the discussion during telephone conferences of Working Group 4, the questionnaire was revised and finally agreed on.

The questionnaire (see 7.2) covers 6 sections:

- General Information
- DM-Technology
- Human-resources for DM
- QM of DM
- Support of multinational trials within ECRIN
- Comments

The questionnaire was sent out on 1 March 2007 to the European Correspondents, respectively to the Network Committee members in case no European Correspondant was available, for further distribution to the clinical trial centers and units within their national network. Initial deadline was 15 March 2007, which was prolonged to 29 March 2007. On 27 April 2007 a reminder was sent to the European Correspondants/Network Committee members. Altogether, the survey was sent to 167 centers/units within ECRIN (Table 1).

No.	Country	Questionnaire	
		send out	filled in
1	Denmark	12	10
2	EORTC	1	1
3	France	66	18
4	Germany	12	10
5	Ireland	8	4
6	Italy	23	19
7	Spain	8	5
8	Sweden	18	2
9	UK	19	9
total		167	78

Table 1: Distribution of questionnaires per country

4. Results

4.1 General information

From 167 questionnaires sent out, 78 were filled in and transmitted to the chairman of the working group (response rate: 47%). For Denmark, France, Germany and Italy at least 10 questionnaires were available for analysis (Table 1).

The majority of responders classified themselves as pure Clinical Trial Units (42%) or Clinical Research Centers (21%) (Figure 1).

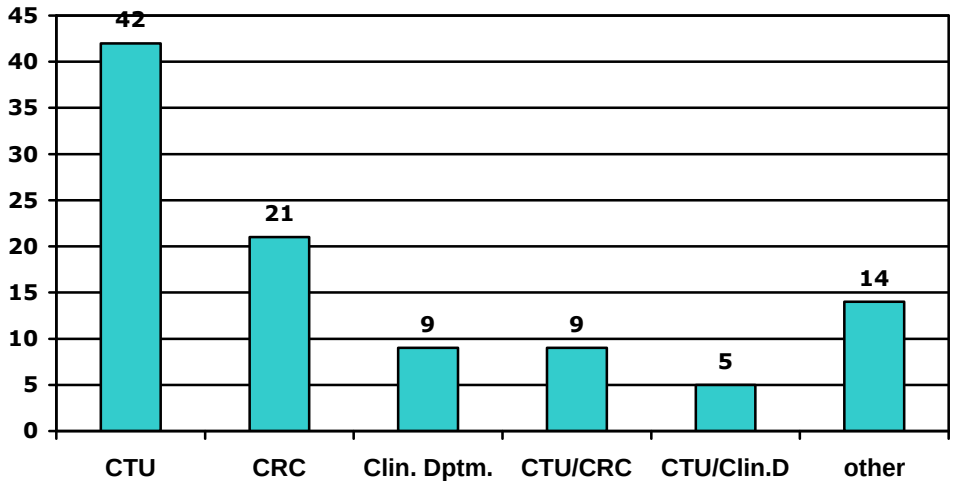

Figure 1: Type of center/ unit
CTU = Clinical Trial Unit
CRC = Clinical Research Center
Clin. D (ptm) = Clinical Department

The size and activity of the centers/units was assessed by the number of ongoing trials supported and the number of persons employed (Table 2, 3).

Number of ongoing trials supported	Centers/units	
	N	%
< 10	24	(30.8)
10-19	15	(19.2)
20-29	14	(17.9)
30-49	12	(15.4)
≥ 50	12	(15.4)
unknown	1	(1.3)
total	**78**	**(100)**

Table 2: Number of ongoing trials supported

Number of persons employed in the unit	Centers/units	
	N	%
< 10	23	(29.5)
10-19	17	(21.8)
20-29	17	(21.8)
30-49	9	(11.5)
≥ 50	11	(14.1)
unknown	1	(1.3)
total	**78**	**(100)**

Table 3: Persons employed in the center/unit

The ECRIN consortium spans a wide range of different sizes of centers/units with a concentration on smaller centers/units. All types of trials are supported by the consortium partners, with a clear cut focus on phase 3-trials (85%) and phase 2 (73%) trials (Figure 2).

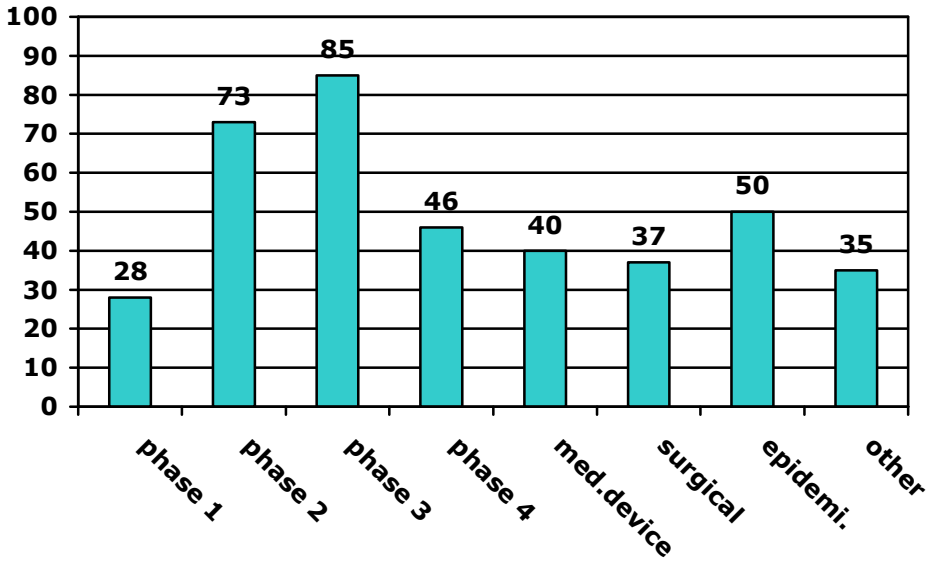

Figure 2: Type of trials supported

In addition, 40% of the partners are supporting trials with medical devices, 37% surgical trials and 28% phase 1-trials.

4.2. DM-technology

The majority of centers/units participating in the survey perform DM for clinical trials (82%, Table 4).

DM performed within center/unit	Centers/units	
	N	%
yes	64	(82.1)
no		
- another unit	6	(7.7)
- outsourced to external DM center	5	(6.4)
- not involved in DM	3	(3.8)
total	**78**	**(100)**

Table 4: Performance of DM in center/unit

Outsourcing to external DM centers or to other units of the organization/university is minimal. Only three centers/units reported not to be involved in DM. In 61 centers/units (78%) a Clinical Data Management system (CDMS) is in routine use (Table 5).

Clinical Data Management System (CDMS) in routine use	Centers/units	
	N	%
Type of CDMS*		
- commercial	**29**	**(47.5)**
- open source	6	(9.8)
- proprietary, developed by software company	6	(9.8)
- proprietary, developed by your own	15	(24.6)
- proprietary, developed by other institution	2	(3.3)
- unknown	3	(4.9)
total	**61***	**(100)**

Table 5: CDMS in routine use
*centers/units with CDMS in routine use

57 centers have their own CDMS, two reported to have access to a CDMS in another unit, and two outsourced DM to an external center with a CDMS (Table 6).

		CDMS in routine use			total
		+	-	missing	
DM performed within center/ unit	+	57	7*	-	64
	-	4**	9	1	14
total		**61**	**16**	**1**	**78**

Table 6: DM performed and CDMS in routine use
*3 centers using DM- services (university: 2, commercial: 1) but not a dedicated CDMS
**2 centers having access to a CDMS in another unit (1 proprietary system, 1 Epidata™) and 2 outsourced DM to an external center with CDMS (1 software company, 1 Phosco™)

The following analysis (table 7 to 10) refers to the 61 centers/units with a CDMS in routine use.

Approximately half of the CDMS used are commercial systems (48%) and 38% proprietary solutions. Open source systems are used by 6 partners (10%). There are several different commercial software tools in use from different providers. Apart from Macro™ (14 users), no other product is used by more than three centers/units (Table 7).

Product name*	
Commercial	**Open Source**
• Macro™ (n=12+2)[1]	• GCP base™ (3)
• eResearchNetwork™ (3)	• PhosCo™ (1+1)
• SAS™-based (3)	• Psy Grid™ (1)
• Capture System™ (2)	• Epidata™ (1)[2]
• ECTrial™ (2)	
• CliniInfo™ (1)	
• SecuTria™l (1)	
• Clin Trial™ (1)	
• Epidata™ (1)[2]	
• Unknown (3)	

Table 7: CDMS in routine use
*centers/units with CDMS in routine use
[1]2 centers with Macro™ classified as proprietary, developed by software company
[2]1 center/unit with Epidata™ classified as commercial

From those using a CDMS 75% have a computing center within their unit and 79% use their own CDMS-installation (Table 8).

CDMS for clinical trials in routine use	Centers/units	
	N	(%)
Type of use of CDMS		
– own installation	**48/61**	**(78.7)**
– application service providing	9/61	(14.8)
– other	3/61	(4.9)
– unknown	1/61	(1.6)
Location of installation of CDMS		
– own computing center of unit	**46/61**	**(75.4)**
– computing center of university	12/61	(19.7)
– other institution	3/61	(4.9)
Type of clinical trials supported by CDMS		
– academic trials	**57/61**	**(93.4)**
– industry sponsored trials	31/61	(50.8)
– other	7/61	(11.5)
total	**61***	**(100)**

Table 8: Type of CDMS used
*centers/units with CDMS in routine use

The CDMS implemented are used mainly for academic trials (93%), but also for industry-sponsored trials (51%). Main features of the CDMS are data collection (94%), query management (89%) and reporting (74%) (Table 9).

Implemented functionality of CDMS	Centers/units	
	N	%
data collection	**57/61**	**(94.4)**
double data entry	30/61	(49.2)
coding	31/61	(50.8)
safety management	31/61	(50.8)
reporting	45/61	(73.8)
query management	**54/61**	**(88.5)**
study management	34/61	(55.7)
other	4/61	(6.6)
total	**61***	**(100)**

Table 9: Functionality of CMDS
*centers/units with CDMS in routine use

Double data entry, safety management and study management are supported in approximately 50% of the centers/units. Approximately 80% of the installations provide remote functionality with a clear focus on remote data entry (online: 69%, offline: 33%) (Table 10).

Remote functionality of CMDS	Centers/units	
	N	%
none	10/61	(16.4)
yes		
- remote data entry, online	**42/61**	**(68.9)**
- remote data entry, offline	20/61	(32.8)
- remote monitoring	28/61	(45.9)
- remote query management	28/61	(45.9)
- eCRF-Design	29/61	(47.5)
- remote reporting	26/61	(42.6)
- remote study management	16/61	(26.2)
- other	3/61	(4.9)
total	**61***	**(100)**

Table 10: Remote functionality of CDMS
*centers/units with CDMS in routine use

Remote monitoring, remote eCRF-design, remote query management and remote reporting is supported by approximately half of the installations. 89% of the centers/units provide DM-support for ongoing trials, 69% for ongoing trials with remote data entry and 45% for ongoing multinational trials with remote data entry (Table 11).

Number of ongoing trials	DM Support N (%)	External remote data entry N (%)	Ongoing multinational trials with external RDE N (%)
none	0 (0)	11 (17.2)	27 (42.2)
1-2	7 (10.8)	23 (35.9)	16 (25.0)
3-4	7 (10.8)	9 (14.1)	5 (7.8)
5-9	16 (25.0)	6 (9.4)	7 (10.9)
10-19	14 (21.9)	4 (6.3)	1 (1.6)
≥ 20	13 (20.3)	2 (3.1)	-
unknown	7 (10.9)	9 (14.1)	8 (12.5)
total	64* (100)	64* (100)	64* (100)

Table 11: Number of ongoing trials with DM-support
*only centers/units performing DM

Only a minority of centers/units provide remote services for at least 5 ongoing multi-national trials (13%).

There is widespread use of other software tools to support clinical trials. 80% of the partners use statistical analysis software, 60% a sample size calculation tool and 53% a randomization tool (Table 12).

Other software products used	Centers/units N (%)
software	
- statistical analysis	**62/78 (79.5)**
- randomization tool	41/78 (52.6)
- study management	18/78 (23.1)
- sample size calculation tool	47/78 (60.3)
- project management	18/78 (23.1)
- safety management tool	16/78 (20.5)
- document management system	15/78 (19.2)
- other tools	12/78 (15.4
total	**78 (100)**

Table 12: Other software tools/products used

In Table 13 software tools used by at least 5 centers/units are presented.

Statistical analysis - SAS™ (n = 17) - Stata™ (13) - SPSS™ (10)
Randomization tool - SAS™ (8)
Sample size calculation tool - nQuery™ (21)
Project management software - MS project™ (6) - Projectile™ (6)
Safety management tool - Vigilance I™ (5)

Table 13: Other software products used by at least 5 centers/units

4.3. Human resources for DM

Approximately 42% of the units performing DM are rather small and employ only up to 4 persons (Table 14).

Number of persons employed for DM	**Centers/units**	
	N	**(%)**
≤ 1	**5**	**(7.8)**
2 – 4	**22**	**(34.4)**
5 – 9	14	(21.9)
10 – 14	7	(10.9)
15 – 19	2	(3.1)
≥ 20	**2**	**(3.1)**
unknown	12	(18.8)
total	**64***	**(100)**

Table 14: Persons employed for DM
*only centers/units performing DM

A trend but no significant correlation between the number of persons employed for DM and the number of ongoing trials with DM support was observed (Figure 3).

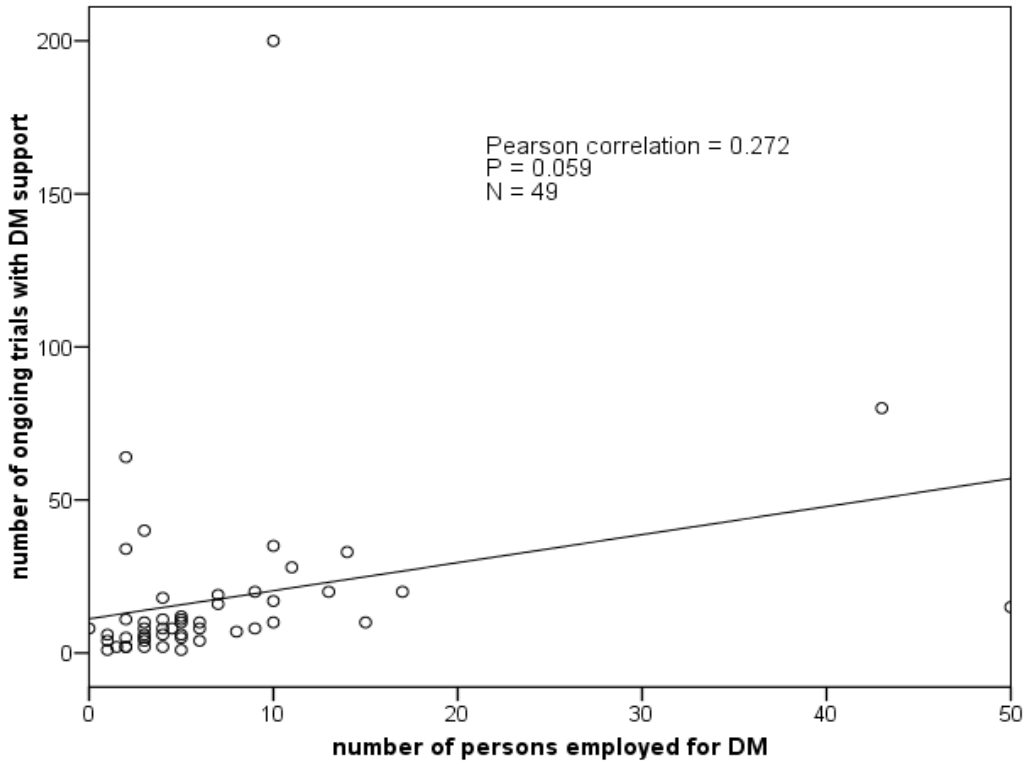

Figure 3: Association between the number of persons employed for DM and the number of ongoing trials with DM support

There are several large DM-units with at least 15 employees (4 centers/units). 83% of the units/centers have data managers, 66% data entry staff and 63% database administrators (Figure 4).

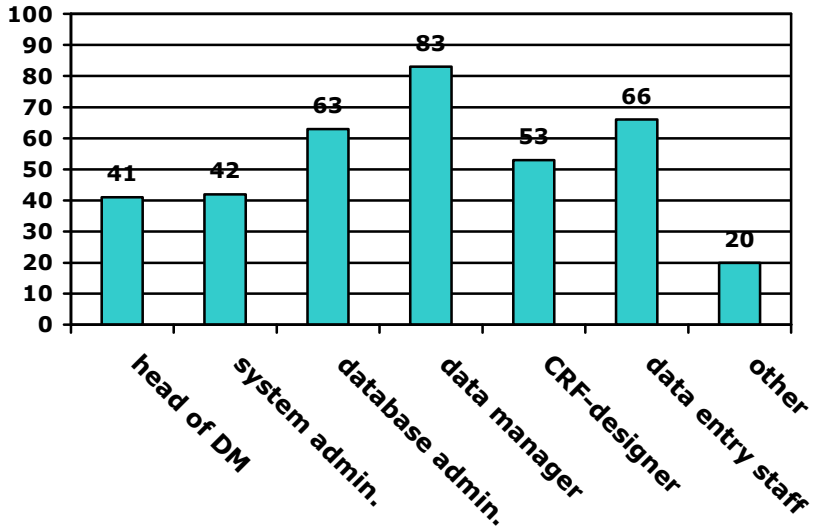

Figure 4: Type of DM staff
*only centers/units performing DM

A dedicated head of DM is appointed in 24 (41%) of the centers/units.

4.4. QM of DM

A QM system for DM is in place in 91% of the centers/units performing DM. This covers SOPs (78%) and internal DM-Audits (31%). Certified quality management systems have been implemented only in 3 centers/units (Table 15).

Quality of management of DM	**Centers/units N**	**(%)**
QM-system in place for DM		
- no	6/64	(9.4)
- yes		
- SOPs für DM	**50/64**	**(78.1)**
- internal DM–audits	20/64	(31.3)
- certified QM-system	**3/64**	**(4.7)**
- other	6/64	(9.4)
total	**64***	**(100)**

Table 15: Quality management of DM
*only centers/units performing DM

An internal DM-system validation was performed in 42% of the centers/units, in 39% according to GCP and in 11% according to FDA (Table 16).

Quality of management of DM	**Centers/units N**	**(%)**
Internal DM-system validation		
- no	35	(54.7)
- yes, according to GCP	**18**	**(28.1)**
- yes, according to GCP/FDA	**3**	**(4.7)**
- yes, according to GCP/GAMP	**2**	**(3.1)**
- yes, according to GCP/GAMP/FDA	**2**	**(3.1)**
- yes, according to GAMP/FDA	**2**	**(3.1)**
unknown	2	(3.1)
external DM-system audit		
- no	35	(54.7)
- yes	**26**	**(40.6)**
- unknown	3	(4.7)
total	**64***	**(100)**

Table 16: Quality management of DM
*only centers/units performing DM

An external DM-system audit was reported by 41% of centers/units involved in DM.

An association between the size of the center/unit and QM- activities was observed. SOPs are in place in 70% of the centers with less than 5 persons employed for DM compared to 88% in centers/units with 5 or more employees. Similar trends are observed for internal DM audits performed (19% versus 44%), internal system validation performed (27% versus 52%) and external DM audits performed (40% versus 48%). No clear association is observed if QM is related to the number of ongoing trials with DM support. From the centers/units with 10 or more ongoing trials with DM support 91% have SOPs compared to 79 % of the centers/units with less than 10 ongoing trials. Internal DM audits have been performed in 33 % versus 30% of the centers/units, internal DM system validation in 44% versus 47% and external DM system audits in 54% versus 37%.

4.5. Support of multinational trials within ECRIN

There are experiences with DM in multinational trials in 60% of the centers/units and 56% reported to have a CDMS available and appropriate for use in multinational clinical trials (Table 17).

Support of multinational trials	**Centers/units N**	**(%)**
Experience with DM of multinational trials		
- no	27	(34.6)
- yes	47	(60.3)
- unknown	4	(5.1)
CDMS for multinational trials available		
- no	29	(37.2)
- yes, GCP-/FDA-compliant	35	(44.9)
- yes, validated	**9**	**(11.5)**
- unknown	5	(6.4)
total	**78**	**(100)**

Table 17: Support of multinational trials

However, only in 9 centers (12%) the system has been validated for this use. 82% of the center/units declared themselves able to provide infrastructures and human resources to support multinational trials (Table 18).

Support of multinational trials	Centers/units N (%)
Infrastructures and human resources to support multinational trials	
- no	11 (14.1)
- yes	**64 (82.1)**
- unknown	3 (3.8)
Interest to support DM of multinational trials	
- no	7 (9.0)
- yes	**67 (85.9)**
- unknown	4 (5.1)
total	**78 (100)**

Table 18: Support of multinational trials

There is overwhelming interest to support DM in multinational trials (86%). Several limitations for remote use of a CMDS in multinational clinical trials were reported, covering firewall, browser restrictions, license modeling, VPN connection and software/network dependence (Table 19).

Limitations
– firewall
– browser restrictions
– license model
– VPN connection
– software/network dependence

Table 19: Limitations for remote use of CDMS

Finally, 68% of the centers/units participating in this survey are interested to be involved as a partner providing remote services to multinational clinical trials for the ECRIN data centers to be built up (Table 20).

Interest to be involved in ECRIN data centers	Centers/units N (%)
Assuming that audited and certified ECRIN data centers will be built up, would you be interested to be involved as a partner providing remote services to multinational clinical trials?	
- no	11 (14.1)
- yes	**53 (67.9)**
- unknown	14 (17.9)
total	**78 (100)**

Table 20: Interest to be involved in ECRIN data centers

4.6. Country profiles

Germany

From 10 centers participating in the survey all have a CDMS in routine use. In all these centers commercial software tools are implemented (Macro™: 6, eResearchNetwork™: 3, SecuTrial™: 1). 7 Centers work with their own installation, 3 centers use commercial software via an Application Service Providing (APS) model provided by another center or sharing a terminal server installation. In all centers remote data entry is supported by the software. A quality management system covering SOPs is in place in all centers. An external DM audit has been performed in the majority of centers (n = 7), but not an internal system validation (n = 3). Experience with remote data entry in ongoing multinational trials is limited throughout the KKS-Network.

Nevertheless all 10 centers are interested to support DM in multinational trials, have a CDMS appropriate for use in multinational trials and have from their viewpoint the ability to provide infrastructures and human resources. Experiences with DM of multinational trials are available in 9 centers, 8 centers would be interested to be involved in ECRIN data centers as a partner providing services to multinational clinical trials.

DM for clinical trials has been systematically developed in the German KKS-network. The majority of centers is prepared to provide GCP-compliant services for multinational trials, however, more experience with RDE in multinational trials is needed.

Denmark

From 10 centers in Denmark responding in the survey 7 reported to perform DM. Only in four centers a CDMS is in routine use, one open software tool (PhoSCo™) and three proprietary tools covering an own development (CITDAS™), a tool developed by a software company and a tool development by another academic institution. The four centers work with their own installation and in three centers remote data entry is supported. From the three centers performing DM without a CDMS in routine use, one had outsourced DM to an external center, one use a CDMS via application service providing and there was no information in one center. A quality management system for DM has been implemented in 6 out of 7 centers performing DM, of which the majority (n = 5) had an external DM system audit. An internal system validation has been performed in three centers.

All 7 centers are interested to support DM in multinational trials and would be interested to be involved as a partner in providing services for multinational trials. The majority of them have experience with multinational trials and are able to provide infrastructures and resources (n = 6). 6 centers reported to have a CDMS available for use in multinational trials despite the fact that only four centers have such a system in routine use.

In the Danish network professional software tools have not been implemented systematically. Nevertheless, the centers performing DM have major interest to support multinational trials and are able to provide tools, infrastructures and resources. Necessary prerequisites are a policy to introduce professional software and to perform an adequate system validation.

United Kingdom

Data from 9 responding centers/units in UK are available for analysis. All these centers perform DM and have a CDMS in routine use. The majority uses one commercial system (Macro™: 6, one unknown commercial product). In addition, one open source product (PsyGrid™) and one proprietary tool with own development is in use. 6 centers work with their own installation. Online remote data entry is supported in 6 centers/units. A quality management system based on SOPs has been implemented in 7 centers/units. An internal system validation has been performed in five and an external DM system audit in three centers.

All 9 centers/units have experience with DM for multinational trials and 8 would be interested to support DM in multinational trials. 6 centers have a CDMS appropriate for use in multinational trials and reported the ability to provide infrastructures and resources. Finally, 7 centers would be interested to be involved in the implementation of ECRIN data centers.

Due to the fact that the analysis is based on a sample of 9 responders out of 19 centers/units addressed (47%), representativeness may be limited. Nevertheless, 5 out of 8 centers (1 missing) responders declared their DM procedure to be typical and representative for the country. The majority of centers uses a commercial software system and is able to provide GCP-compliant services for multinational trials, however, only a few (n = 3) have had an external DM system audit so far.

France

From 18 centers/units participating in the survey 15 reported to perform DM and to have a CDMS in routine use. The majority uses one of several commercial software tools (SAS™: 3, Capture System™: 2, Macro™: 2, ClinInfo™: 1, Epidata™ (also classified as open source): 1). In three centers/units DM is performed with a proprietary system™), one proprietary tool developed by a software company (Cleanweb™) and one proprietary tool developed by another institution (GenEpi™) are in use. Nearly all centers (n = 14) work with their own installation. Online remote data entry is supported in 9 centers. A quality management system covering SOPs has been implemented in 11 centers. An external DM system audit has been reported by 5 and an internal system validation by 3 centers/units.

All 15 centers/units are interested to support DM in multinational trials. From these centers/units 14 would be interested to be involved in the implementation of ECRIN data centers and 13 declared the ability to provide infrastructures and resources. So far 7 centers have experience with DM in multinational trials and 8 have a CDMS available and appropriate for use in multinational clinical trials.

With a response rate of 27% (18 out of 66 centers/units) representativeness of the sample is questionable, despite the fact that 8 out of 12 centers/units (6 missing) reported that their DM procedure is typical and representative for the country. From the centers/units taking part in the survey, the majority is able to provide commercial software systems with remote data entry features. QM systems have been widely implemented, however, there are deficits in the majority of centers/units with respect to internal system validation and external DM system audits.

Italy

19 centers/units from Italy participated in the survey. The majority of them perform DM (n = 15) and have a CDMS in routine use (n = 16). Commercial systems are rarely used (ClinTrial™: 1, unknown: 2). Software system used cover proprietary tools based on an own development (n = 5), open source software (GCP-base™: 3, Phosco™: 1) and proprietary tools developed by a software company (Echolab™: 1, unknown: 1). For two products no classification is available. 11 centers/units have their own installation and 10 are able to support remote data entry. A QM system has been implement in 11 centers/units. External DM system audit and internal system validation were performed in three centers.

16 from the 19 responders are interested to support DM in multinational trials and are able to provide infrastructures/resources. In 10 centers/units there is experience available with DM and 8 have a CDMS available for use in multinational trials. 7 centers would be interested to be involved in the implementation of ECRIN data centers.

Representativeness of the Italian centers/units in the survey is high. 7 of 11 the Italian centers/units (8 missing) reported that the DM procedure applied is typical and representative for their country. There is no widespread use of commercial systems. QM should be strengthened by introducing internal system validations and external DM system audits.

5. Discussion

The survey gives an overview on DM tools and procedures within ECRIN based on a sample of 78 responders. There is major variation with respect to the response rate between countries. In the majority of countries the survey was restricted to ECRIN centers/units, however, in some countries (e.g. UK) the questionnaire was distributed to a larger audience. Response rates in some countries were lower, may be due to the fact, that only centers involved in DM responded (e.g. France, Sweden, UK). In other countries (e.g. Germany, Denmark), where only ECRIN centers were included in the survey, the response rate was high, indicating good representativeness. Approximately two thirds of centers/units participating in the survey reported that their DM procedure is representative for their country. Interestingly, 82% of the responders perform DM within their unit. Whether this is due to the selection of centers or is a general characteristic of CTU/CRCs linked to ECRIN, this cannot be definitely answered for some of the countries (e.g. France, Sweden, UK).

ECRIN covers a wide spectrum of CTUs and CRCs. The consortium includes very large centers with many employees and performing many trials (e.g. EORTC), but also a substantial portion of small units with less than 10 ongoing trials and less than 10 employees. Importantly, all types of clinical trials with medicinal products, but also trials with medical devices and surgical trials, are supported by a substantial number of ECRIN centers with a focus on Phase 3- and Phase 4- trials. Bearing in mind that ECRIN will provide services and consulting for multinational clinical trials in the next phase (ECRIN-PPI), the broad coverage of different clinical trial types is of major importance.

Those centers/units, who are involved in DM normally have a CDMS in routine use. Interestingly, approximately half report to use commercial systems. Approximately 38% of the centers/units use proprietary software, often developed in- house. Open source may be an alternative but has not been introduced on a large scale so far (10%). From the commercial systems only one system is used by several center/units (Macro™), mainly influenced by the fact that in Germany and UK this software product has been introduced into several Clinical Trial Units. From the other commercial systems, which could be identified to be a CDMS, no single system is used in more than three centers. The survey identifies software heterogeneity as one of the issues for DM harmonization in ECRIN centers. Most of the issues are around resources to buy, implement, validate and use all these systems. Some of the variability may be due to the necessity of specific CDMS for disease- specific networks (e.g. cancer, paediatrics). Today, however, generic software packages are available, which are able to support different trial types and different disease- specific conditions. In addition, approximately three quarters of the centers/units using a CDMS have their own local computing center with their own installation. Application Service Provision, a more cost-efficient solution to DM in clinical trials, is not widespread so far (15%, see Table 8).

An alternative to commercial systems could be open source software. Despite many advantages, this approach is followed only by a minority of the centers/units participating in the survey. Open source is characterized by the possibility of the user to access the source code and his right to modify and distribute the software. Open

source supports knowledge sharing and open standards. Primarily, it is a software development model based on distributed, cooperative development structures. For academia, commercial software may be disadvantageous, mainly because of costs, and their requirements may be better suited by the philosophy of open source. In order to be applicable, the risk regarding delivery and future maintenance should be under control and the license should not restrict integration with other systems, the scaling up of the infrastructure and the creation of specific extensions or modifications. In addition, development, quality control and software support is the responsibility of the open source community or dedicated partners. Critical is the business model of open source, covering all costs including those born by the network. So far, only a few open source systems are in routine use within ECRIN (e.g. GCP base™, Phosco™, Epidata™). It will be necessary to evaluate these software packages for a potential use in the ECRIN data centers to be established.

Most of the CDMS systems in use support data collection and query management. More sophisticated functionalities, available in some software packages, such as double-date entry, coding, safety management and reporting, are only supported in half of the centers/units. Surprinsingly, there is a high degree of support for remote data entry, which seems to be a standard feature in the software products applied. Again, other remote functionality, such as remote monitoring, remote query management or remote eCRF-design has been implemented only in about 50% of the centers/unit. The survey demonstrates, that full electronic and remote support of DM has not been achieved so far and that there is substantial room for improvement. Whereas a CDMS is used on a trial level, study management tools may act at an institutional level. So far only one quarter of the centers/units have software products in place to support project management.

It is remarkable that more than 91% of the centers/units performing DM have a quality management system in place, with the majority of them using SOPs. However, only 42% performed an internal DM-system validation and 31% performed internal DM-audits. From the survey it can be concluded that between two thirds and half of the centers/units have deficits with respect to quality management. Quality management is directly related to the number of persons employed for DM and (to a lesser degree) to the number of ongoing trials with DM. On average SOPs are more widespread than internal DM system validations/ external DM audits. These are performed more often in clinical trial centers with larger DM- units. Because comprehensive quality management is of utmost importance for the ECRIN data centers, available resources and workload should be a critical factor that has to be taken into consideration in the conception. There is the necessity to harmonize and improve quality management in DM. Standards with respect to DM should be promoted in the national networks. Due to the fact that national regulations (e.g. data protection, archiving) may be a problem for international standardization, activities to harmonize rules and regulations within the EU should be supported by the ECRIN consortium.

Several points that are of major importance have not been tackled in the survey. In order to reduce time effort and resources, integration of CDMS with clinical information systems, registers, cohort studies and genomic databases would be essential. Pilots have been performed and prototypes are available, but interoperability has not been achieved so far on a larger scale. This aspect has to be taken into considera-

tion in the conception of the ECRIN data centers to be developed. Another aspect not covered is related to the financing of DM, especially for academic trials. Major resources, covering hardware, software and personnel are needed. Cost models need to be developed as a prerequisite for providing services and consulting by ECRIN.

There is overwhelming interest for support of multinational trials within ECRIN (86%). More than 80% would be willing to provide infrastructures and human resources. The interest is only partly backed-up by profound experience with DM in multinational trials. 60% of the centers/units report to have experience, however, only about 13% are involved in at least 5 ongoing multinational trials with external remote data entry and only 12% are able to provide a validated CDMS system for multinational trials. The survey reveals that the majority of centers would be interested to be involved in DM of multinational trials, but major experience and professional infrastructures are only available in a limited number of centers/units.

6. References

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3. ICH Topic E6, Guide for Good Clinical Practice
Consilidated Guideline vom 1.5.1966, EMEA CPMP/ICH/135/95, date for coming into operation January 1997

4. FDA 21 CFR Part 11 (Electronic Records, Electronic Signatures, Final Rule; Electronic Submission, Notice
vom 20.3.1997, Federal Register, Vol, 62, No. 54, FDA

5. FDA Guidance for Industry: Computerized Systems Used in Clinical Trials
FDA, April 1999

6. GAMP
The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture, Version 4, International Society for Pharmaceutical Engineering, 2003, electronic version

GAMP was founded in 1991 by a core of pharmaceutical experts in the UK who were interested in meeting evolving FDA expectations for GMP compliance of manufacturing and related systems. In 1994, GAMP partnered with ISPE to publish the first GAMP guidelines and to run training seminars. GAMP quickly became influential throughout Europe as the quality of its work was recognized internationally, and in 2000 GAMP Americas was founded. Also in 2000, GAMP became formally affiliated with the International Society for Pharmaceutical Engineering (ISPE) as a technical sub-committee within the organization. Partnering with ISPE, GAMP has become the acknowledged expert body when it comes to computer system validation issues. As the organization matured the scope of its interest and expertise has expanded to include the preclinical and clinical arenas. (www.ispe.org)

7. Appendix

7.1 Abbreviations

CRC	- Clinical Research Center
CTU	- Clinical Trial Unit
CDISC	- Clinical Data Interchange Standards Consortium
CDMS	- Clinical Data Management System
DM	- Data Management
eCRF	- electronic Case Report Form
ECRIN	- European Clinical Research Network
ECRIN-PPI	- European Clinical Research Infrastructures Network and Biotherapy Facilities: Preparation Phase for the Infrastructure
ECRIN-RKP	- European Clinical Research Infrastructures Network-Reciprocal Knowledge Programme
ECRIN-TWG	- European Clinical Research Infrastructures Network-Transnational Working Groups
EU	- European Union
FDA	- Food and Drug Administration
GAMP	- Good Automated Manufacturing Practice
GCP	- Good Clinical Practice
MedDRA	- Medical Dictionary for Regulatory Activities
QM	- Quality Management
SME	- Small Medium Enterprises
SOP	- Standard Operating Procedure
VPN	- Virtual Private Network

7.2 Questionnaire

Survey on data management (DM) tools and procedures within

ECRIN

(Final version)

Aim of the survey is to assess the status of data management structures, resources and activities of ECRIN members and to elucidate the interest to support multinational clinical trials within ECRIN

(Please tick appropriate boxes or fill in text and fax the completed forms until ***15 March 2007*** to:
Prof. Dr. C. Ohmann, Koordinierungszentrum für Klinische Studien, Heinrich- Heine-Universität, Moorenstr. 5, 40225 Düsseldorf, Germany, Fax: ***+0049-211-81-19702***)

I. General information		
1.	**Name of unit/center/department**	
2.	**Location**	
3.	**Country**	
4.	**Head of unit/center/department**	
5.	**Type of unit/ center/ department**	☐ Clinical Trial Unit (CTU) ☐ Clinical Research Center (CRC) ☐ Clinical Department ☐ other, _____
6.	**Number of *ongoing* trials supported**	
7.	**Number of persons *employed* in the unit/ center/department**	

8.	**Type of trials supported predominantly** *(several answers possible)*	☐ drug trial, phase 1 ☐ drug trial, phase 2 ☐ drug trial, phase 3 ☐ drug trial, phase 4 ☐ trial with medical device ☐ surgical trial ☐ epidemiological/cohort ☐ other, _____

II. DM - technology		
9.	**Data management for clinical trials performed at your unit/center/ department**	☐ yes ☐ no, performed by another unit of our organization/university ☐ no, outsourced to external DM center ☐ no, not involved in DM *In case DM is performed inside your organization by another unit or outside your organization, please take care that the following information is coordinated with the responsible persons*
10.	**Clinical data management system (CDMS) for clinical trials in *routine use* at your unit**	☐ no ☐ yes
If yes:		
11.	**Type of clinical data management system**	☐ commercial (*off the shelf*) ☐ open source ☐ proprietary, developed by software company ☐ proprietary, developed by your own ☐ proprietary, developed by another academic institution ☐ other, _____
12.	**Product name and version of Clinical Data Management System**	product: version:
13.	**Type of use of Clinical Data Management System:**	☐ own installation ☐ used by application service providing (ASP) ☐ other, _____

2

14.	**Location of installation of Clinical Data management System**	☐ own computing centre of unit/center/department ☐ computing center of university/organization ☐ other, _____
15.	**Type of clinical trials supported by Clinical Data Management System** *(several answers possible)*	☐ academic trials (IITs) ☐ industry sponsored trials (drug approval trials) ☐ other, _____
16.	**Implemented functionality of Clinical Data Management System** *(several answers possible)*	☐ data collection ☐ double data entry ☐ coding *(e.g. MedDRA)* ☐ safety management ☐ reporting ☐ query management ☐ study management ☐ other, _____
17.	**Implemented remote functionality of Clinical Data Management System** *(several answers possible)*	☐ none ☐ remote data entry, online ☐ remote data entry, offline ☐ remote monitoring ☐ remote query management ☐ eCRF-Design ☐ remote reporting ☐ remote study management ☐ other, _____
18.	**Number of *ongoing* trials with DM-support**	
19.	**Number of *ongoing* trials performed with external *remote data entry***	
20.	**Number of *ongoing multinational trials* performed with external remote data entry**	

21.	**Other software tools/ products used in your unit/ center/ department to support clinical trials** *(several answers possible)*	☐ statistical software, which _____ ☐ randomization tool, which _____ ☐ study management software, which _____ ☐ sample size calculation tool, which _____ ☐ project management software, which _____ ☐ safety management tool, which _____ ☐ document management system, which _____ ☐ other tools _____

III. Human resources for DM

22.	**Number of persons employed for DM:**	
23.	**Type of DM-staff** *(several answers possible)*	☐ dedicated head of DM ☐ system administrator ☐ database administrator ☐ data manager ☐ electronic CRF- Designer ☐ data entry staff ☐ other, _____

IV. Quality management of DM

24.	**Quality management system in place for DM** *(several answers possible)*	☐ no ☐ yes, Standard Operating Procedures (SOPs) for DM ☐ yes, internal DM- audits ☐ yes, certified quality management system according to _____ ☐ yes, other, _____
25.	**Internal DM- system validation performed in your unit/ center/ department** *(within last 3 years)*	☐ no ☐ yes, according to GCP ☐ yes, according to GAMP ☐ yes, according to FDA
26.	**External DM- system audit performed in your unit/ center/ department** *(within last 3 years)*	☐ no ☐ yes

V. Support of multinational trials within ECRIN

27.	**Experience available with DM of multinational trials at your unit/center/department**	☐ no ☐ yes
28.	**Clinical Data Management System available and appropriate for use in multinational clinical trials**	☐ no ☐ yes, GCP-/FDA- compliant ☐ yes, validated
29.	**Abilitity to provide infrastructures and human resources to support multinational trials**	☐ no ☐ yes
30.	**Is there an interest to support DM in multinational trials by your unit/center/organization ?**	☐ no ☐ yes
31	**Which infrastructures, resources and services would you be willing to offer for multinational clinical trials?**	
32	**Are there limitations for remote use of your Clinical Data Management System in multinational clinical trials (e,g, firewall)**	

33	**Assuming that audited and certified ECRIN data centers will be built up, would you be interested to be involved as a partner providing remote services to multinational clinical trials ?**	☐ no ☐ yes, comments:
33	**Is your data management procedure typical and representative for your country ?**	☐ no ☐ yes

VI. Comments

Date	Name + Function at your unit/ center/department	Signature

7.3 Glossary

Audit A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). [ICH E6 Glossary] www.cdisc.org

Clinical Data Management System A Clinical Data Management System or CDMS is used in clinical research to manage the data of a clinical trial. www.wikipedia.org

Clinical Research Centers (CRC) are non-profit, public-funded, and hospital- based infrastructures devoted to clinical research, with specific beds, equipment, medical and study- nurse staff, allowing enrolment and investigation of patients or volunteers both in early phases of drug trials and in non- therapeutic studies. www.ecrin.org

Clinical Safety Data Management The management of safety relevant data in clinical trials including the reporting of Adverse Events.

Clinical Trial Management System A CTMS is used to manage the planning, preparation, performance, and reporting of clinical trials, with emphasis on keeping up-to-date contact information for participants and tracking deadlines and milestones. (www.wikipedia.org)

Clinical Trial Unit (CTU) manage clinical trials (mainly randomised clinical trials – phase II/phase III, prognostic, diagnostic studies, and meta- analyses), dealing with the design of the study, its organisation, logistics, centre selection, data management, monitoring, data analysis, and reporting. www.ecrin.org

Computer System Validation Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes. (Source: FDA Guidelines on General Principles of Process Validation, 1987). Applies to all GxP critical systems.

Data Management (DM) Tasks associated with the entry, transfer, and/or preparation of source data and derived items for entry into a clinical trial database.
NOTE: Data management could include database creation, data entry, review, coding, data editing, data QC, locking, or archiving; it typically does not include source data capture. www.cdisc.org

Data Manager Role of a person in the context of a clinical trial responsible for managing the clinical data, from data base design to data collection, validation, and data base audits and finally the data base lock.

Document Management System A computer system (or set of computer programs) used to track and store electronic documents and/or images of paper documents. www.wikipedia.org

eCRF 1. Auditable electronic record designed to capture information required by the clinical trial protocol to be reported to the sponsor on each trial subject. 2. A CRF in which related data items and their associated comments, notes, and signatures are linked electronically.
NOTE: eCRFs may include special display elements, electronic edit checks, and other special properties or functions and are used for both capture and display of the linked data. [FDA CSUCT] www.cdisc.org

Electronic Data Capture (EDC) The process of collecting clinical trial data into a permanent electronic form.
NOTE: "Permanent" in the context of these definitions implies that any changes made to the electronic data are recorded via an audit trail. www.cdisc.org

Open-source software Software which permits the use and modification of its source code by the users of the software. Refers to a development methodology as well as to a business concept and a licence model.

Project management software is a term covering many types of software, including scheduling, resource allocation, collaboration software, communication and documentation systems, which are used to deal with the complexity of large projects. www.wikipedia.org

Query Management Ongoing process of data review, discrepancy, generation, and resolving errors and inconsistencies that arise in the entry and transcription of clinical trial data. www.cdisc.org

Remote Data Entry (RDE) Collection of data in clinical trials in electronic format at trial sites, using electronic Case Report Forms. A special form is Electronic Data Capture.

Standard Operating Procedures (SOPs) Detailed, written instructions to achieve uniformity of the performance of a specific function. [ICH] www.cdisc.org

7.4 Description of ECRIN national networks

In order to enable readers to get an overview on the ECRIN consortium, a short description of the national networks, that participated in the survey, is presented. The description was taken from the official proposal of the EU- funded project "European Clinical Research Infrastructures Network – Transnational Working Groups (ECRIN-TWG)" (Specific Support Action 037199, FP6-2005-LIFESCIHEALTH-I) and may not be up to date. For each country there is one national network, except for Italy and France contributing two national networks to the ECRIN project. In addition, EORTC participated in the survey.

French network of 21 Clinical Investigation Centres (CIC) (Lille, Rouen, Nancy, Strasbourg, Rennes, Tours, Lyon, Grenoble, Marseille, Montpellier, Nantes, Toulouse, Bordeaux, and 8 in Paris)

Steered by INSERM (Institut National de la Santé et de la Recherche Médicale) and University Hospitals

Between 1992 and 2001, 21 Clinical Investigation Centres (CIC) were created in France after competitive calls. They undergo, every 4th year, a scientific peer evaluation and a systematic GCP audit. Steered by INSERM and University Hospitals, these hospital-based facilities form a bidirectional link between experimental and clinical research, especially in genotype/phenotype or pathophysiological studies. They also participate in the therapeutic evaluation, with a special emphasis on the early phases of drug registration, or in the development of innovative strategies including biotherapy. CIC are equipped with investigation tools and specific beds, and the staff includes doctors, study nurses, and research assistants, and provide the users with an access to scientific and technological resources. Research projects conducted within the CIC observe quality standards and Good Clinical Practice, and follow ethical rules regarding investigation of human subjects. Individual centres may focus on specific medical fields, whereas other are facilities acting in a wider panel of diseases. Methodology and data management may be performed either by the CIC team, or through the support of a Clinical Trial Unit. Operated by a co-ordinator, and with a central office at INSERM headquarters, the French CIC network promotes harmonisation of practice, and scientific activity within these structures through thematic sub-networks (currently cardiology, neurosciences, paediatrics). Working groups designed to harmonise practice within the network cover quality management and SOPs, shared information systems, cost evaluation, and collaborative website. Half of the studies carried out within the network are industry- or public-sponsored diagnostic and therapeutic studies (drug trials, surgery, biotherapy), and the second half are academic, non-therapeutic studies (mainly genotype/phenotype or pathophysiology). With 95 beds, the network currently conducts 500 clinical studies.

Network of 12 Coordination Centres for Clinical Trials in Germany (Marburg, Heidelberg, Freiburg, Leipzig, Tübingen, Mainz, Berlin, Halle, Dresden, Münster, Köln, Düsseldorf)

With the help of the German Ministry of Education and Research 12 Coordination Centres for Clinical Trials were established in Germany (Berlin, Dresden, Düsseldorf,

Freiburg, Halle, Heidelberg, Köln, Leipzig, Mainz, Marburg, Münster, Tübingen). It is the aim of the initiative to establish structures to improve the quality of clinical trials and further develop competence in the area of clinical trials in Germany. Specific aims include initiating, planning and performing innovative and competitive international trials, supporting drug regulatory and scientific-driven trials, harmonising quality management to establish international standards (e.g. GCP), improving education related to scientific and organisational aspects of trials and long-term establishment of the centres with university and pharmaceutical industry support. The centres are involved in all aspects of planning, performing and analysing clinical trials. In general, the co-ordination centres are central units of the medical faculty with an approximate turnover of 1,000,000 € per annum, with approximately 20 employees (including statisticians, study nurses, data managers, system administrators) and they support in average 10 to 30 ongoing clinical trials in different fields. The German Coordination Centres for Clinical Trials are organised in a permanent network with established working teams. The working team “Education” deals with the concept and implementation of education programs, the working team “Quality Management” with the concept and implementation of quality management and SOPs and the “Data Management” working team with computer support of clinical trials. One of their additional activities is related to public relation. The Coordination Centres for Clinical Trials have been successfully audited externally and reviewed by international experts. Recently a central co-ordination body of these centres has been set up for Germany.

Italian network of 7 IRCCS (Genova, Pavia, Bologna, Trieste, and 3 in Milano) and 12 Cancer Centres, and IPASVI, the Italian Association of Nurses, Consorzio Italiano per la Ricerca in Medicina (C.I.R.M.), Milan, Italy.

The Consorzio Italiano per la Ricerca in Medicina is a growing organisation including 8 Research Hospitals, the majority of which belonging to IRCCS (Istituti di Ricovero e Cura a Carattere Scientifico, which are reference centres for the Health Ministry), and 12 Oncologic University Institutions, for more than 12.000 beds. More than 100 Clinical Divisions are performing randomised trials; the majority are large and high quality national or transnational trials. Their tasks include design, randomisation, data collection, and management. Some of them also work on Phase I, II trials, diagnostic evaluation, prognostic studies and quality of life. Biometry Centres are present in all IRCCS elaborating methodological research, epidemiology, meta-analysis, cost evaluation and possess many clinical data banks. All IRCCS are yearly organising courses on methodology for clinical trial. Most of them work on several fields, covering a very large spectrum of disease: from child to maturity and ageing.
Specific areas are: Cardiovascular, Neurology, Orthopaedics, Respiratory and allergic diseases, Infectious diseases, Oncology. Clinical and Research activity include: Preventative Medicine (Genetic/Congenital Diseases, Diabetes, Atherosclerosis, Reproduction Pathology, Menopause/Andropause Pathology, Degenerative Diseases), Innovative Diagnostic (Molecular/Genetic Markers, Histopathological Markers, Electromedical Profiles, Imaging, Psychometry), Innovative Therapeutics (Biological Response Modifiers, Synthetic Drugs, Enteral/Parenteral Nutrition, Critical Care Medicine, Endoscopic Surgery), Organ Transplant/Artificial Organs (Heart, Heart/Lung, Intestine/Liver, Kidney, Bone-Marrow, Bone, Prothesis/Endoprothesis), Rehabilitation: (Psychological, Neuromotor, Cardiovascular, Pulmonary, Geriatric, Occupational

Ergonomy). The network is organising task forces on Standard Operating Procedure, training and teaching, quality procedures (accreditation, peer-review, data quality control). The IPASVI, the Italian Association of Nurses, has joined the network, given support for all the requirements needed in the study nurse sector.

Network of 38 French Clinical Trial Units (ISPED)

(Angers, Bordeaux - 2 units-, Caen, Dijon, Lille, Limoges, Lyon- 3 units -, Marseille, Montpellier, Nancy, 2 units, Paris - 17 units-, Rennes, Rouen, St Etienne, Toulouse, Tours, Villejuif - 2 units)

Set up in 2002, the French Clinical Trial Unit Network is a growing organisation including more than 30 Clinical Trial Units able to design, plan, and conduct randomised clinical trials. Their tasks include methodological support for the design, randomisation, data processing, analysis, interpretation and reporting of randomised clinical trials. Their activities also cover Phases I, II, III and IV trials, systematic reviews and meta-analysis, evaluation of diagnostic tools or screening programs, prognostic studies, genomic studies, quality of life and cost evaluation. Some are mostly working on cancer, cardiovascular diseases, or infectious diseases (AIDS, hepatitis, tropical diseases), but the network is covering a wide spectrum of diseases. Moreover, these units are involved in development of innovative trial methodology and training of investigators and researchers in the field. Five are INSERM units, 10 cancer institute units, and the remaining are university-hospital units. Their staff includes more than 50 project managers, 60 methodologists, and 70 data managers. The network is currently conducting more than 200 randomized trials ongoing, including around 40 international trials. The trials have included more than 15,000 patients. The network is aiming to perform large and high quality national or transnational trials. Working groups are designed to harmonise practice within the network concerning 1) GCP, quality assurance and SOPs, 2) training and teaching, 3) definition and services of a typical CTU. Further working groups on the use of software and trial planning and implementation are being organised. Collaboration with research institution, industry, scientific associations, consumers and other networks are planned or ongoing.

Network of 8 Danish Clinical Research Centres / Clinical Trial Units - DCRIN

The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital; Clinic of Haematology, Copenhagen University Hospital; Clinical Research Unit 136, Copenhagen University Hospital; Danish Epidemiology Science Centre, Statens Serum Institut, Copenhagen; Clinic of Oncology 5073, Copenhagen University Hospital; The Clinical Research Unit, Hvidovre Hospital, Copenhagen University Hospital; The GCP Units of Aarhus, Odense, and Copenhagen University Hospitals.

The Danish Clinical Research Centres/Clinical Trial Units Network (DCRIN) is a growing national network presently including 8 non-profit institutions/centres involved in clinical research and clinical trials (phase I to phase IV). Their tasks include methodological support for the design of clinical research, randomisation, data management, analysis, and reporting as well as providing expertise in good clinical research practice (GCP). They also work with diagnostic evaluation, pathophysiological

evaluation, prognostic studies, quality of life and cost evaluation, methodological research, epidemiology, meta-analyses, and systematic reviewing both within and outside The Cochrane Collaboration. The staff conducts national and international courses on research methodology, design of clinical studies, and GCP. The network is covering a large spectrum of diseases: from child and mother diseases over diseases within all specialities to gerontology. Its personnel include more than 30 methodologists, project managers, and data managers. The network has more than 100 trials ongoing in 2005, including a number of international trials. The network aims at performing high-quality multi-centre national or transnational trials. The network has task forces on Standard Operating Procedure, training and teaching, quality procedures (accreditation, peer-review, data quality control), collaboration on software, and trial realisation. Collaboration with research institutions, industry, scientific associations, consumers' and patients' organisations are planned or ongoing.

Mario Negri Institute, Italy

The Mario Negri Institute for Pharmacological Research is as a non-profit foundation established in 1963 devoted to the study human diseases, with particular emphasis on the mechanism of actions of drugs. The Institute has developed centres in three locations: Milan, Bergamo, and S. Maria Imbaro. The scientific staff is composed of more than 900 researchers, with a wide range of professional backgrounds. While the initial emphasis of the research programs was concentrated on basic research, during the last 20 years the Mario Negri Institute has become increasingly involved in clinical research and clinical trials, and has gained international recognition in several fields, including cardiovascular disease, renal disease and transplantation, neurology diseases, ageing, pharmacovigilance, paediatrics, and rare diseases.

A Clinical Research Centre provided with inpatients and outpatients facilities was open in 1992 to run clinical research protocols and clinical trials, including facilities to perform phase I, II and III clinical trials and classical pharmacokinetics studies. During the past ten years, clinical trials and clinical research projects have been carried out including the GISSI studies focused on the therapy of acute myocardial infarction; the REIN studies aimed to the prevention of end stage renal disease in chronic nephropathies; the ICAI study on critical leg ischaemia, the PPP study in patients with cardiovascular risk factors recruited in a large network of general practices. All the scientists involved in the present proposal are either promoter or partner in several national and international networks of clinical researchers for implementation of multicentre clinical studies.

The Institute was the first institution in Italy and one of the first in Europe to establish an information service for patients with rare disease that has been instrumental in creating a database which has been used for clinical studies in rare diseases such as haemolytic uraemic syndrome, Takayasu's arteritis, systemic lupus, etc. The Mario Negri Institute is also actively contributing to the circulation of ideas in Europe concerning issues such as the promotion of high standard Good Clinical Practice (GCP), and it participates in the discussion on critical issues concerning biomedical research and health, independent clinical research, education, transfer of knowledge from clinical research to medical practice.

Network of 7 Spanish Clinical Research Centres / Clinical Trial Units - SCReN

The Spanish Clinical Research Network (SCReN) is currently composed by 7 different units located in High Technology University hospitals. The sites show complementary expertise in different clinical research activities which include the following three main tasks:

1) Design, support, development, conduction, monitoring and analysis of phase I to phase IV clinical trials. The studies include from pharmacological evaluation in healthy human volunteers and patients in restricted experimental situations (tolerability, drug-drug and food-drug interactions, pharmacokinetics-pharmacodinamics (PK-PD), drug metabolic genotyping, evaluation of gender differences in disposition of drugs), to the multicentre randomised comparisons with broad enrolment criteria for the assessment of efficacy and effectiveness of drugs and therapeutic approaches in different clinical conditions.

2) Research in pharmacoepidemiology (cohort and case-control studies, relationship between specific diseases and the use of drugs, drug utilization studies, systematic reviews and meta-analyses of drug effectiveness and safety); and

3) Teaching activities (training in clinical trial methodology, GCP, monitoring, etc) as well as methodological support to the investigators in the conduct of independent clinical research activities.

Network of 10 Swedish Clinical Research Centres/Clinical Trial Units – SweCRIN

Vastmanland County centre for clinical research, Uppsala cardiovascular clinical research centre, Karolinska oncology clinical research department, Linköping academic research group, Örebro general clinical research centre, Malmö/Lund clinical research unit, Uppsala department of public health and caring sciences, Karolinska clinical research centre.

The Swedish network for clinical research (SweCRIN) has only recently been organised. The network consists of ten clinical research centres distributed over the country. They deal with clinical research from phase 1 to phase IV, in a variety of therapeutic areas; oncology, endocrinology, cardiology, neurology, psychiatry.

The main driving force is implementation of new rules governing clinical research (EU legislation transformed into national requirements), setting standards for establishing SOPs at level of hospital ward and acting as sponsor in an academic investigator-driven environment. The work is done according to ICH-GCP and related documents. The staff conducts and participates in national and international courses on design and biostatistics, informed consent, protocol writing, CRF construction and more. Advice to neighbour researchers are part of daily missions. The network aims at developing competence for its members, but also to be a partner in national or inter-national high-standard multi-centre trials.

Irish Clinical Research Infrastructures Network (ICRIN)

The five Irish Universities with medical schools have negotiated a Memorandum of Understanding for the formation of ICRIN. This is currently being finalised and will be signed by the end of July 06.

The creation of the Irish network stems from the well established and proven collaborative model of Dublin Molecular Medicine Centre (DMMC) which for the past 4 years has been building important translational and clinical research capabilities within the three Dublin universities and their 5 affiliated teaching hospitals (+ the children's hospital).

The success of the DMMC model has been made possible due to specific government investments of €80 million over the past 5 years. The current tranche of this investment is the €45 M Programme for Human Genomics which has allowed networked technologies, education programmes and dedicated facilities on hospital sites to be developed. Clinical studies are undertaken in several disease areas covering cardiovascular, oncology, inflammation and neuropsychiatric diseases. The expansion of the DMMC network to create a truly national initiative has resulted in Galway and Cork joining with the Dublin universities in the formation of ICRIN.

Through the creation of ICRIN we will develop a situation analysis following the ten point plan laid down by ECRIN and organise workshops on Education and Training, Ethics and Informed Consent, Information Systems, Data Management and the Monitoring of Clinical trials.

The participant medical schools in ICRIN are: Trinity College Dublin, University College Dublin, the Royal College of Surgeons in Ireland, National University of Ireland Galway, and University College Cork together with their respective affiliated teaching hospitals.
ICRIN is recognised by the Health Research Board and the Health Service Executive in Ireland.

UK Clinical Research Network (UKCRN)

The UK Clinical Research Network (UKCRN) was established in February 2005 with funding from the Department of Health in England to provide a world-class health service infrastructure to support clinical research in the UK. It consists of a managed set of Clinical Research Networks, initially covering six priority topic areas – cancer, mental health, medicines for children, diabetes, stroke and dementias and neurodegenerative diseases. A Primary Care Research Network is also being established. From April 2007, a Comprehensive Research Network will be established that will include these Topic-Specific Research Networks and that will also provide infrastructure support for all other disease areas, enabling research to be conducted across the full spectrum of disease and clinical need. A UKCRN Coordinating Centre has been established, based in Leeds, to oversee and manage the development of the Comprehensive Research Network.

UKCRN also recognises the need for expertise in the design, conduct and analysis of clinical trials and other well designed studies is vital in order to ensure high quality, timely study conduct and to meet regulatory and governance requirements. Within the Cancer Research Network, a Clinical Trials Unit accreditation process has been established which assesses key competencies of units able to provide high quality and expert input into trial design, conduct and analysis. UKCRN provides a coordination role to network the accredited Clinical Trials Units and the Directors of the Units are working together to address issues on a national level, such as implementation of the EU Directive for Clinical Trials and IT issues. UKCRN will expand this work to include Clinical Trials Units working on other disease areas.

European Organisation for Research and treatment of Cancer (EORTC) (data centre)

Created in 1962, the European Organisation for Research and Treatment of Cancer (EORTC, www.eortc.be) is a non-profit international cancer research organisation under Belgian Law. The EORTC mission is to improve the standard of cancer treatment in Europe through the development of new drugs and to test more effective therapeutic strategies, using drugs which are already commercially available, surgery or radiotherapy. The EORTC has the aim to facilitate the passage of experimental discoveries into state-of-the-art treatment by keeping to a minimum the time lapse between the discovery of new anti-cancer agents and the implementation of their therapeutic benefit for patients with cancer. The EORTC research takes place in a network of over 300 participating institutions located in 32 countries. More than 2,000 clinicians are collaborating on a voluntary basis in 15 Disease/ Treatment Oriented Groups. More than 5,000 cancer patients are entered into EORTC multidisciplinary trials each year. The EORTC is the cooperative cancer clinical research group that detains the biggest publication record worldwide. The activities of the EORTC are peer reviewed by the US National Cancer Institute and the EORTC Drugs Master File is registered with the US Federal Drugs Agency.

The EORTC Data Centre is a unique facility in Europe located in Brussels that provide scientific, legal, logistic and administrative support to EORTC clinical and translational research activities (protocol development, data management, statistical analysis, new drugs development, translational research, virtual biobanking, quality of life, regulatory and ethical affairs management, Pharmacovigilance and Quality Assurance). The Data Centre staff is constituted by highly experienced and trained professionals who have developed so far 42 Working Procedures and 16 Policies on the basis of the ISO 9000 concept. The EORTC has already been involved in European Commission funded projects.