EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK
TRANSNATIONAL WORKING GROUPS

ECRIN-TWG

FP6-2005-Life Sciences and Health LSH-2005-3-4
Contract # 037199

Deliverable 13 & 14

Development of a risk assessment tool, assessment of its reliability and definition of a common monitoring strategy and report

---

Date of preparation: 8 October 2008

Working Group 5: **Transnational Working Group on Monitoring**

Workpackage leader : Prof Geneviève Chêne
Institut de Santé Publique, Epidémiologie et Développement (ISPED)
Université Victor Segalen Bordeaux 2 - Case 11
146 rue Léo-Saignat
33076 Bordeaux cedex
Tel +33 (0)5 57 57 12 57
Fax +33 (0)5 57 57 11 72
email: Genevieve.Chene@isped.u-bordeaux2.fr

List the members of the working group

Alberti Corinne, France
Arnaiz Joan Albert, Spain
Becker Ursula, Switzerland
Blasko Georgy, Hungary
Brosteanu Oana, Germany
Carcas Antonio, Spain
Franzosi Maria Gracia, Italy
Friis Bach Karine, Denmark
Hansabut Robert, Austria
Joppi Roberta, Italy
Journot Valérie, France
McDonald Alison, UK
Scalise Andrea , Spain
Schlemmer Birgitte, Denmark
VanRiel Wilma, UK
Wennerholm Solveig, Sweden
Cevallos Myriam, Switzerland
Cooney Margaret, Ireland
Gaynor Siobhan, Ireland
Hernandez Raquel, Spain
Johansson Hanna, Sweden
Kardos Gabriella, Hungary
Kubiak Christine, France
Kuchinke Wolfgang, Germany
Pleiner Johannes, Austria
Robinson Wendy, Germany
Sanz Nuria, Spain
Sassun Alfonso, Italy
Souri Pegah, Sweden
Svetozar Mihaylov, UK
Whitfield Kate, Denmark
Winter Diana, Austria

Abbreviations

CRC	Clinical Research Centre
CTU	Clinical Trial Unit
CIC	Centre d'Investigation Clinique (Clinical Investigation Centre)
CPP	Comité de Protection des Personnes (French research ethics committee)
ECRIN	European Clinical Research Infrastructures Network
ECRIN-PPI	European Clinical Research Infrastructures Network and Biotherapy Facilities: Preparation Phase for the Infrastructure
ECRIN-RKP	European Clinical Research Infrastructure Network – Reciprocal Knowledge
ECRIN-TWG	European Clinical Research Infrastructures Network-Transnational Working Groups
EMEA	European Medicines Agency
EU	European Union
FP	Framework Programme
GMP	Good Manufacturing Practice
GCP	Good Clinical Practice
IMP	Investigational Medicinal Product
IR	Ireland
ICC	Intraclass Correlation Coefficient
ISS	Instituto Superiore della Sanita
It	Italy
KKS	Koordinierungszentrum für Klinische Studien (German national network)
PI	Principal Investigator
QA	Quality Assurance
QM	Quality Management
RAT	Risk Assessment tool
REC	Research Ethics committee
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale

Table of content

1. Introduction

ECRIN (European Clinical Research Infrastructures Network) is designed to bridge the fragmentation of clinical research in Europe through the interconnection of national networks of academic clinical research centres (CRC) and clinical trial units (CTU) and to develop services to provide support for multicentric clinical studies in Europe.

Study monitoring is a sponsor's task, and includes all activities aiming at overseeing the planning, initiation, conduct and data processing of clinical studies. Monitoring includes control of data integrity and validity both at the scientific and regulatory levels. The guideline for Good Clinical Practice[1] reminds that all trials must be monitored: "the sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and end-points of the trial. In general there is a need for on-site monitoring before, during and after the trial: however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with Good Clinical Practices. Statistically controlled sampling may be an acceptable method for selecting the data to be verified".

So, depending on the type of study, on sponsor, on countries, the use and intensity of monitoring (systematic and exhaustive, adapted to the benefit/risk ratio) is variable.

In a first FP6-funded step (ECRIN-RKP, 2004-2005), the monitoring practices of academic sponsors across Europe were evaluated and a comparative analysis between the different ECRIN countries was performed. This analysis demonstrated a lack of harmonisation of practice, an increasing use of monitoring, and contribution of systematic and exhaustive monitoring to the increase of clinical research cost.

Based on the outcome of this first project, the objective of the Working group 5 on Study Monitoring in step two (ECRIN TWG, 2006-2008) was designed to address these issues through the development and validation of a common set of criteria for

[1] Note for Guidance on Good Clinical Practice: ICH harmonised tripartite guidelines, CHMP/ICH/135/95. http://www.ich.org

gradual risk assessment, leading to the proposal of risk based procedures for monitoring.

2. Objectives

Academic clinical research studies require optimisation of limited financial resources. The knowledge of the study risk level of the study involving participant's safety and validity of study results would allow optimising monitoring, and thus resources distribution. In order to build a standardised risk assessment tool, a consensus was initiated by the Study Monitoring group of ECRIN.
The task of ECRIN Working Package 5 was:

- To identify a relevant common set of criteria for evaluation of the risk related to multinational clinical research
- To validate a risk assessment tool
- To define a common monitoring strategy based on risk

As ECRIN will cover different types of clinical research and not only clinical trials covered by the European Directive 2001/20/EC, the evaluation of the risk will not be restricted to clinical trials with medicinal products.

3. Methods

3.1. Identification of existing risk assessment tools

The literature was searched, and participants in the ECRIN Working Package 5 were asked to share the already existing tools they knew.

3.2. Identification of criteria for evaluation of risk

Existing risk assessment tools were analysed for risk covered and studies concerned. Possible criteria were identified through the identified tools.

The Delphi method was used to reach a consensus on a list of items:

- A first questionnaire was built (See appendix 1), and sent to clinical research experts from ECRIN countries. This questionnaire aimed at evaluating the acceptance of the principle of a risk-based approach, and at delimitating the desired fields for risk assessment. Responses were analysed according to their relative frequency. Additional suggestions from the experts were considered and discussed within the ECRIN Working Package 5.

- A second questionnaire was then built (See appendix 2), and sent to the experts. This questionnaire aimed at estimating their ability to increase or to reduce the risk. Items were selected on a frequency basis. Additional suggestions from the experts were considered and discussed within the ECRIN Working Package 5.
- The final list was designed after a meeting of the ECRIN Working Package 5 (see appendix 4: 19 items assessments).

3.3. Validation of the risk assessment tool

Protocols were assessed by assessors in terms of risks and items on visual analogue scales (VAS).

Risks: Different risks were defined:
- primary risks: risk for participants, risk for validity of study results
- secondary risks: risk for study organisation, risk for study governance, risk for target population and public health

Items: Items were those selected by the ECRIN Working Package 5 during the Delphi process. They were grouped into 5 topics:
- items about participants
- items about validation of study results
- items about study organisation
- items about study governance
- items about impact of study results on target population and public health

Assessors: Assessors volunteered in each ECRIN country. Assessors were:
– experts in clinical research (epidemiologist, statistician, pharmacologist, project leader, senior clinical research assistant, investigators ...);
– clinical experts in different medical fields.
Each assessor signed a confidentiality agreement concerning the protocols they had to assess.

Protocols: Since the aim of ECRIN is to conduct transnational trials, it was decided to focus on risk for clinical trials only. A standard protocol synopsis (See appendix 3) was designed to concisely describe the scientific and organisation aspects of the protocol, thus covering the 19 items, among other questions. Real protocols covering different types of clinical trials and different therapeutic areas were collected, and their scientific and organisation aspects were described by the person responsible for

the protocol (sponsor or CTU or CRC responsible of the management of the study) through the standard synopsis.

Experimental plan: Protocols and assessors were randomly distributed into small groups of protocols or assessors. Groups of protocols were randomly allocated to groups of assessors through an incomplete partially balanced block design.

Questionnaire: A single questionnaire for risks and items assessment was designed (See appendix 4). All risks and items were measured on a visual analogue scale (VAS). Risk and items values on VAS were corrected to get a 0-10 scale. Since the intended use of the risk assessment tool is to define a few levels of monitoring, VAS values for risks were also empirically divided into 3 levels of risk: low, medium, and high.

Internal validity: As internal validity, reproducibility of risks and items assessments on VAS was calculated through an intraclass correlation coefficient estimated from a random-protocol linear model. Reproducibility was also calculated through an intraclass correlation coefficient estimated from a random protocol proportional odds model.

Items selection: VAS risks were modelled through a random-protocol linear regression, with adjustment for VAS items. Risk levels were also modelled through a proportional odds model, with adjustment for VAS items, and robust variance estimation (repeated data by protocol). For both models, items were selected with backward selection at the 0.05 significance level. These two models were used to capture all relevant information in spite of variability between assessors.

Score building: If possible, a formal risk score was to be built and validated. This score would be directly used to choose monitoring intensity.

Sample size: We assumed that the intraclass correlation coefficient would be about 0.60, close to the one estimated in the Pre-Optimon study 0.62.[2] With 20 protocols, a two-sided 95% confidence interval computed using the large sample normal approximation for an intraclass correlation based on 15 assessors will extend to 0.165 from the observed intraclass correlation when the expected intraclass correlation is 0,60 (nQuery Advisor®, version 6.0). Adding 5 more protocols would improve precision to

[2] Journot V et al. Validité et reproductibilité d'une échelle de risque dans les études de recherche clinique institutionnelles. 1ère Conférence Francophone d'Epidémiologie Clinique 2007. Bordeaux, France

0.147, while adding 5 more assessors would improve it to 0.162 only. The main gain would come from an improved intraclass correlation coefficient.

4. Results

4.1. Identification of existing risk assessment tools

Different risk assessment tools have already been developed, and are used in common practice.

Several examples of tools came from United Kingdom. They combine the likelihood of risk and its impact, thus determining the appropriate risk management, either to approve the initiation of a study, or to adapt its management while it is already ongoing.

In France, The Paris hospital network Assistance Publique – Hôpitaux de Paris led the way in 2001 with a risk assessment tool for any type of clinical research study. The tool is based on risk for participant only. This risk assessment is used to define a monitoring strategy adapted to risk. The adaptation concerns the on-site monitoring mainly.

A French trial, Optimon, is presently running to formally assess a risk adapted approach. It is funded through the National Programme of Clinical Research (grant obtained in 2005). A German trial, Adamon, started more recently with the same aim. Both use their own risk assessment tool.

Altogether, identified tools differed in format and field delimitation. Some are specific to trials, other apply to any type of clinical research study. Some deals with risk for participants, others with any type of risk. They were usually adapted for national purpose, not for transnational studies.

4.2. Identification of criteria for evaluation of risk

The first questionnaire included 36 questions, grouped into 8 topics (See appendix 1):

- 1. principle of risk adapted monitoring (1 question)
- 2. types of clinical research studies covered by the risk assessment tool (5 questions)
- 3. types of risks included in the risk assessment tool (4 questions)
- 4. risk for participant (6 items questions)
- 5. risk for validity of study results (4 items questions)
- 6. risk for study organisation (8 items questions)
- 7. risk for target population (3 items questions)
- 8. proposals for the risk assessment tool (5 formats)

Experts had to choose between 4 possible answers: I totally disagree, I partly disagree, I partly agree, I totally agree. A final open question collected additional comments.

Fifty-one experts from 10 countries (Germany, Denmark, Spain, France, Hungary, Ireland, Italy, United Kingdom, as well as Canada and the USA) answered the questionnaire (See appendix 5).

The principle of risk assessment was largely accepted: 95% experts partly or totally agreed. This agreement hold for any domain of clinical research (any objectives, any designs): 90% agreed, as well as for any type of risk: 90 to 100% agreed depending on type of risk.

From the discussion about answers to items questions, it was decided to build a more detailed questionnaire on items.

There was no clear consensus on the format of the risk assessment tool (continuous or categorical). Yet, there was a large agreement (89%) that risk assessment should be done at start of study and while on-going, whenever large changes occur.

The second questionnaire included 36 items, grouped into 5 topics (See appendix 2):

- 1. study participants (8 items)
- 2. validity of study results (8 items)
- 3. study organisation (10 items)
- 4. study governance (7 items)
- 5. study impact on target population and public health (3 items)

Examples were added to each item to clarify its meaning.

Experts had to choose between 4 possible answers, depending on the influence of the item on risk: no influence, increase only, decrease only, both increase or decrease. A final open question collected additional comments.

Forty-nine experts from 11 countries (Germany, Denmark, Spain, France, Hungary, Ireland, Italy, United Kingdom, Switzerland, as well as Canada and the USA) answered the second questionnaire (See appendix 6).

In addition to raw data, the results were presented in three different ways:

- the items were sorted in order of decreasing maximal frequency (whatever the response is, i.e. increase, decrease, both or no impact on the risk), showing for which items the consensus was the most important
- the items were sorted in order of decreasing frequency of response "increase the risk", pointing items which increased the risk
- the items were sorted in order of decreasing frequency of response "decrease the risk", pointing items which decreased the risk

Most items were judged to have an impact on the risk, either increase or decrease, thus being relevant from the experts point of view. Only 8 items seemed to have no impact and were discussed.

Three items were judged as having no influence on the risk, and were removed:

- No study intervention
- Clarity of ownership of database intellectual property
- Expected events leading to major legal or financial aftermath

One item was reworded:

- Partnership with a private organisation

Twenty-four items were grouped into 10 items because of redundancy:

- Expected inherent hazards related to study interventions
- Expected inherent hazards related to study investigations
- Expected inherent hazards related to disease or impaired condition defining target population, whatever the interventions or investigations

- Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population
- Early stage /phase in the development of the study interventions
- Study interventions used outside authorised indication / product licence / state of the art
- Concealment of randomised study interventions allocation
- Blinding of study interventions
- Complexity of study recruitment
- Complexity of study design
- Complexity of study follow-up
- Education and experience of the sponsor to GCP procedures
- Education and experience of the sponsor to study procedures
- Education and experience of the investigator sites' staff to GCP procedures
- Education and experience of the investigator sites' staff to study procedures
- Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation
- Existence of quality assurance and quality control systems, implemented and maintained by the investigator sites
- Involvement of a Coordinating Centre
- Validation of major events by an Adjudication / Validation Committee
- Existence of a Steering Committee
- Existence of a Data Safety and Monitoring Board
- Key trial for registration purpose
- Major impact of study results on public health management
- Impossibility to reiterate the study

Altogether, 19 items covering 5 topics were retained:

- study participant
  - difficulties or incapacity to give informed consent
  - collection of indirectly identifying or sensitive characteristics
  - expected inherent hazards related to study interventions or investigations
  - combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population
  - study intervention used outside authorised indication/product licence/ state of the art or in early stage/ phase of development
- validity of study results

        - pre feasibility assessment of the study recruitment based on reliable sources
        - concealment of randomised study interventions, allocated or to be allocated, during allocation, follow-up and investigations
        - objective assessment of primary and secondary outcomes
        - complexity of study procedures
    - study organisation
        - education and experience of the sponsor or investigator sites' staff to GCP or study procedures
        - existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the coordinating centre in case of documented delegation, and by the investigator sites
        - Intervention management tracking system run by a qualified organisation
        - Quickness and security of data entry in the database
        - Full cleaning of database while study is still in progress
        - Availability of the appropriate resources at the start of the study
    - study governance
        - existence of management review organisations
        - existence of ethic and scientific review organisations
        - influence/interference of a private organisation upon study governance
    - target population and public health
        - major impact of study results on target population and public health

4.3. Validation of the risk assessment tool

<u>Assessment process</u>

Finally, 5 assessors refused to assess protocols by lack of time, and 24 clinical trial protocols were assessed by 15 assessors (See appendix 7):

- 7 from study management, quality assurance or regulatory affairs
- 4 methodologists
- 4 principal investigators

Some assessors declined assessment of protocols for conflict of interest. Each assessor assessed 7 to 12 protocols. Each protocol was assessed by 6 to 8 assessors.

The median duration of the assessment was 40 minutes (range: 15-130).

Risks

Table 1: Non missing (N) and missing (MISS) assessments per risk.

RISK FOR PARTICIPANTS		RISK FOR VALIDITY OF STUDY RESULTS		RISK FOR ORGANISATION		RISK FOR GOVERNANCE		RISK FOR TARGET POPULATION AND PUBLIC HEALTH	
N	MISS	N	MISS	N	MISS	N	MISS	N	MISS
170	0	169	1	165	5	167	3	157	13

Missing assessments mainly concerned secondary risks, and risk for target population and public health particularly.

Raw and median assessments were described for each risk (See Table 1).

Table 2: Raw and median assessments of risks.

	RAW ASSESSMENTS						MEDIAN ASSESSMENTS					
	N	MIN	Q1	MED	Q3	MAX	N	MIN	Q1	MED	Q3	MAX
RISK FOR PARTICIPANTS	170	0	1	2	5	10	24	0	2	3	4	7
RISK FOR VALIDITY OF STUDY RESULTS	169	0	1	2	4	9	24	1	1	2	3	5
RISK FOR ORGANISATION	165	0	1	2	3	7	24	0	1	2	3	5
RISK FOR GOVERNANCE	167	0	1	1	3	8	24	0	1	1	2	4
RISK FOR TARGET POPULATION AND PUBLIC HEALTH	157	0	0	1	3	8	24	0	1	1	2	4

Raw values were more dispersed than median values. Three levels of risk were defined with cut-off values broadly corresponding to interquartile range on median of the 5 risks:

- low risk: [0-1]
- medium risk:]1-4]
- high risk:]4-10]

Table 3: Median distribution of each risk in 3 levels.

	ALL	
	N	%
RISK FOR PARTICIPANTS		
low [0-1]	3	13
medium]1-4]	17	71
high]4-10]	4	17
RISK FOR VALIDITY OF STUDY RESULTS		
low [0-1]	3	13
medium]1-4]	19	79
high]4-10]	2	8
RISK FOR ORGANISATION		
low [0-1]	6	25
medium]1-4]	16	67
high]4-10]	2	8
RISK FOR GOVERNANCE		
low [0-1]	8	33
medium]1-4]	15	63
high]4-10]	1	4
RISK FOR TARGET POPULATION AND PUBLIC HEALTH		
low [0-1]	13	54
medium]1-4]	10	42
high]4-10]	1	4

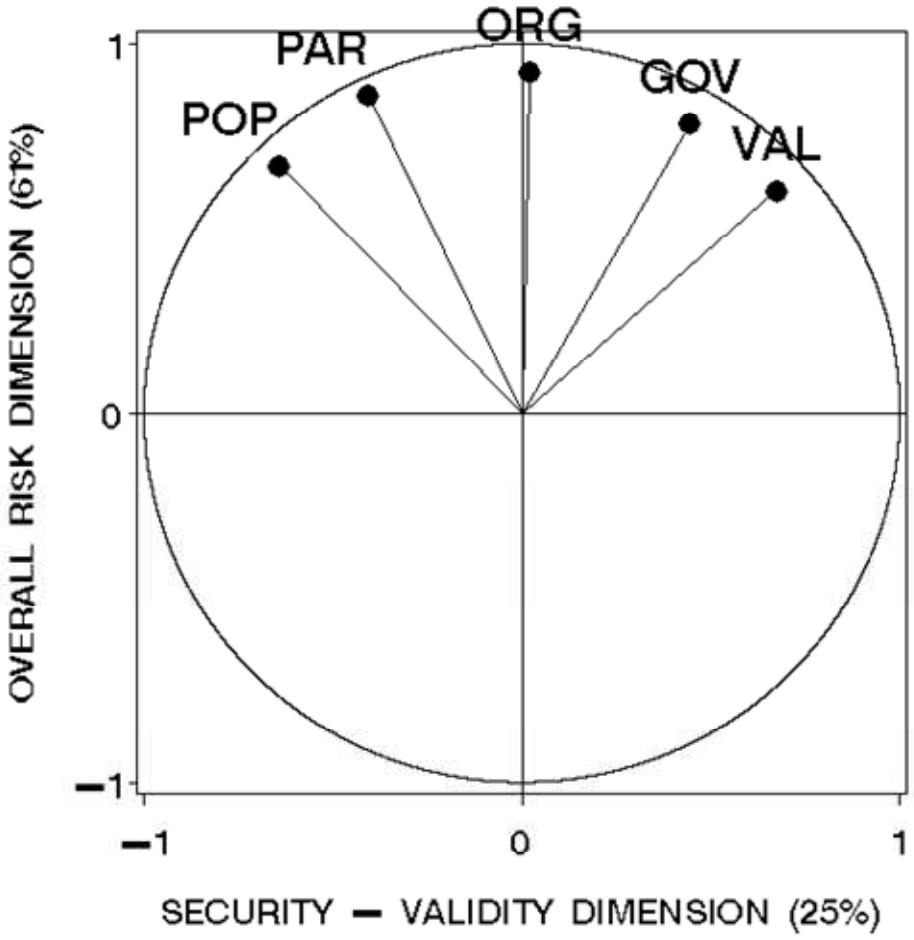
On average, risk for participant was considered higher, and risk for governance and for target population and public health lower than the other risks.

Pearson correlation coefficients between risks were calculated (See Table 3), and a principal component analysis was performed (See Figure 1).

Table 4: Pearson correlation coefficients between median risks (N=24 protocols)

	risk for participants	risk for validity of study results	risk for organisation	risk for governance	risk for target population and public health
risk for participants	1.00 -	0.23 0.29	0.78 <.0001	0.50 0.01	0.76 <.0001
risk for validity of study results		1.00 -	0.52 0.01	0.64 0.001	0.07 0.73
risk for study organisation			1.00 -	0.69 0.0002	0.53 0.01
risk for study governance				1.00 -	0.22 0.31
risk for target population and public health					1.00 -

Figure 1: Principal components analysis on median risks (PAR: risk for participant; VAL: risk for validity of study results; ORG: risk for study organisation; GOV: risk for study governance; POP: risk for target population and public health).



Risk for participants and for target population and public health were strongly correlated (0.76). Risk for validity of study results and risk for study governance were correlated (0.64). Risk for study organisation was correlated with all other risks.

Thus data may be best represented in a two-dimension space: overall risk on the first axis (61% of variability), and opposition between security and validity for the second (25% of variability).

The intraclass correlation coefficient of risk on VAS was estimated through a random-protocol linear model, for each risk.

Table 5: Intraclass correlation coefficient of risk, for each risk, estimated through a random-protocol linear model on VAS risks, and through a random-protocol proportional odds model on risk levels.

	intraclass correlation coefficient	
	linear model on VAS	proportional odds model on risk levels
risk for study participants	0.30	0.33
risk for validity of study results	0.07	0.07
risk for study organisation	0.05	0.12
risk for study governance	0.19	0.06
risk for target population and public health	0.11	non estimable

Reproducibility is very low for each risk, whatever the model used. This is due to a very high variability between assessors compared to variability between protocols.

Items

Table 6: Number of non missing (N) and missing (MISS) assessments per item.

	N	MISS
ITEMS ABOUT PARTICIPANTS		
Difficulties or incapacity to give informed consent	170	0
Collection of identifying or sensitive characteristics	161	9
Expected hazards related to interventions or investigations	169	1
Combination of interventions or investigations and condition	170	0
Interventions outside authorisation	166	4
ITEMS ABOUT VALIDITY OF STUDY RESULTS		
Pre feasibility assessment	161	9
Concealment of randomised interventions	153	17
Objective assessment of outcomes	170	0
Complexity of procedures	170	0
ITEMS ABOUT STUDY ORGANISATION		
Education and experience	156	14
Quality assurance and quality control systems	167	3
Intervention management tracking system	152	18
Quickness and security of data entry	170	0
Full cleaning of database	163	7
Availability of resources	157	13
ITEMS ABOUT STUDY GOVERNANCE		
Existence of management review organisations	167	3
Existence of ethic and scientific review organisations	164	6
Influence of a private organisation	160	10
ITEMS ABOUT TARGET POPULATION AND PUBLIC HEALTH		
Major impact on target population and public health	157	13

Most items have few missing data, except for some items: existence of a management tracking system for intervention, concealment of randomisation, education and experience of sponsor and site, availability of resources, and impact on target population and public health. These items were not likely to be described in the protocol. The aim of the synopsis was to collect all necessary data for assessment, but they were not always complete.

Table 7: Median assessments of items.

	N	MIN	Q1	MED	Q3	MAX
ITEMS ABOUT PARTICIPANTS						
Difficulties or incapacity to give informed consent	24	0	0	1	2	9
Collection of indirectly identifying or sensitive characteristics	24	0	1	1	2	3
Expected hazards related to interventions or investigations	24	0	1	2	3	6
Combination of interventions or investigations and condition	24	0	1	1	3	7
Interventions outside authorisation	24	0	1	2	4	9
ITEMS ABOUT VALIDITY OF STUDY RESULTS						
Pre feasibility assessment	24	0	2	4	5	9
Concealment of randomised interventions	24	0	2	5	9	9
Objective assessment of outcomes	24	2	5	7	9	9
Complexity of procedures	24	0	1	2	3	6
ITEMS ABOUT STUDY ORGANISATION						
Education and experience	24	3	4	5	6	7
Quality assurance and quality control systems	24	2	6	7	7	9
Intervention management tracking system	24	1	3	6	7	9
Quickness and security of data entry	24	2	3	5	9	9
Full cleaning of database	24	1	3	5	7	9
Availability of resources	24	3	7	9	9	9
ITEMS ABOUT STUDY GOVERNANCE						
Existence of management review organisations	24	1	6	7	9	9
Existence of ethic and scientific review organisations	24	0	5	7	9	9
Influence of a private organisation	24	0	1	1	2	6
ITEMS ABOUT TARGET POPULATION AND PUBLIC HEALTH						
Major impact on target population and public health	24	1	4	5	6	7

Table 8: Intraclass correlation coefficient of risk, for each risk, estimated through a random-protocol linear model on VAS risks, and through a random-protocol proportional odds on risk levels.

	intraclass correlation coefficient	
	linear model on VAS	proportional odds model on risk levels
ITEMS ABOUT PARTICIPANTS		
Difficulties or incapacity to give informed consent	0.73	0.5396
Collection of indirectly identifying or sensitive characteristics	0.02	non estimable
Expected hazards related to interventions or investigations	0.27	0.3021
Combination of interventions or investigations and condition	0.29	0.3081
Interventions outside authorisation	0.27	0.3534
ITEMS ABOUT VALIDITY OF STUDY RESULTS		
Pre feasibility assessment	0.01	non estimable
Concealment of randomised interventions	0.11	non estimable
Objective assessment of outcomes	0.05	non estimable
Complexity of procedures	0.19	0.09469
ITEMS ABOUT STUDY ORGANISATION		
Education and experience	0.00	non estimable
Quality assurance and quality control systems	0.00	non estimable
Intervention management tracking system	0.08	non estimable
Quickness and security of data entry	0.05	non estimable
Full cleaning of database	0.05	non estimable
Availability of resources	0.02	non estimable
ITEMS ABOUT STUDY GOVERNANCE		
Existence of management review organisations	0.02	non estimable
Existence of ethic and scientific review organisations	0.09	non estimable
Influence of a private organisation	0.22	0.2523
ITEMS ABOUT TARGET POPULATION AND PUBLIC HEALTH		
Major impact on target population and public health	0.16	non estimable

Reproducibility is very low also for each item, except for the first one. Inter-assessors variability is much larger than inter-protocols variability

Selection of items

Table 9: Selection of items for risk for participants through a linear regression and a proportional odds model (backward selection at the 0.05 significance level).

	linear regression			proportional odds model		
	order of removal	p level for removal	p level in final model	order of removal	p level for removal	p level in final model
ITEMS ABOUT PARTICIPANTS						
Difficulties or incapacity to give informed consent			<0.0001			0.006
Collection of indirectly identifying or sensitive characteristics	5	0.75		5	0.99	
Expected hazards related to interventions or investigations			<0.0001			<0.0001
Combination of interventions or investigations and condition	14	0.29		12	0.46	
Interventions outside authorisation			<0.0001			<0.0001
ITEMS ABOUT VALIDITY OF STUDY RESULTS						
Pre feasibility assessment	3	0.84		1	0.99	
Concealment of randomised interventions	7	0.04		9	0.99	
Objective assessment of outcomes	12	0.32		13	0.12	
Complexity of procedures	4	0.76		2	0.91	
ITEMS ABOUT STUDY ORGANISATION						
Education and experience	9	0.28		4	0.87	
Quality assurance and quality control systems	6	0.68				0.04
Intervention management tracking system	12	0.26		11	0.74	
Quickness and security of data entry	8	0.05		6	0.93	
Full cleaning of database	2	0.85				0.001
Availability of resources	10	0.33		8	0.99	
ITEMS ABOUT STUDY GOVERNANCE						
Existence of management review organisations	11	0.30		3	0.89	
Existence of ethic and scientific review organisations	13	0.17		14	0.18	
Influence of a private organisation	1	0.94		7	0.87	
ITEMS ABOUT TARGET POPULATION AND PUBLIC HEALTH						
Major impact on target population and public health	15	0.05		10	0.66	

Table 10: Selection of items for risk for validity of study results through a linear regression and a proportional odds model with repeated measures (backward selection at the 0.05 significance level).

	linear regression			proportional odds model		
	order of removal	p level for removal	p level in final model	order of removal	p level for removal	p level in final model
ITEMS ABOUT PARTICIPANTS						
Difficulties or incapacity to give informed consent	12	0.35		13	0.48	
Collection of indirectly identifying or sensitive characteristics			<0.0001			0.0003
Expected hazards related to interventions or investigations			0.0008			<0.0001
Combination of interventions or investigations and condition	11	0.24		5	0.62	
Interventions outside authorisation	7	0.62		12	0.63	
ITEMS ABOUT VALIDITY OF STUDY RESULTS						
Pre feasibility assessment	13	0.12		2	0.99	
Concealment of randomised interventions	2	0.72		1	0.95	
Objective assessment of outcomes			<0.0001			<0.0001
Complexity of procedures			0.007			0.0003
ITEMS ABOUT STUDY ORGANISATION						
Education and experience	9	0.38		10	0.33	
Quality assurance and quality control systems	14	0.07		14	0.15	
Intervention management tracking system	10	0.33		11	0.44	
Quickness and security of data entry	4	0.99		6	0.58	
Full cleaning of database	6	0.81		7	0.68	
Availability of resources	15	0.09		8	0.77	
ITEMS ABOUT STUDY GOVERNANCE						
Existence of management review organisations	5	0.99		4	0.85	
Existence of ethic and scientific review organisations	8	0.44		15	0.33	
Influence of a private organisation	1	0.75		3	0.87	
ITEMS ABOUT TARGET POPULATION AND PUBLIC HEALTH						
Major impact on target population and public health	3	0.88		9	0.28	

Some items are strongly related with risks, some others more lightly. Since inter-assessors variability is very high, the results of selection must be regarded with caution. Yet, it is probable that some items may be dropped out.

This selection leaves 16 items in the list. Yet, when considering primary risks only, the list is reduced to 8 items only:

- study participant
  - difficulties or incapacity to give informed consent
  - collection of indirectly identifying or sensitive characteristics
  - expected inherent hazards related to study interventions or investigations
  - study intervention used outside authorised indication/product licence/ state of the art or in early stage/ phase of development
- validity of study results
  - objective assessment of primary and secondary outcomes
  - complexity of study procedures
- study organisation
  - existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the coordinating centre in case of documented delegation, and by the investigator sites
  - Full cleaning of database while study is still in progress

4.4. Monitoring strategy

Adherence with the regulations (EU CT Directive 2001/20/EC) must be taken into consideration, when designing a monitoring strategy for clinical trials with medicinal products. This requires compliance with the international standard of ICH GCP.

Different criteria can be used to adapt the monitoring of clinical research.

One approach can be the gradual approach taking into account the level of risk associated with the research and with the intervention, and designed to guarantee the safety aspects of the clinical research, while at the same time taking into account all the resources available. This approach is used by the Paris Public Assistance and Hospital[3] and UKCRN[4].

Another approach can be the centralised monitoring defined by the systematic organisation of feedback to the central monitor of predefined data essential to the trial, but this is not sufficient for IMP trials.

A sampling approach can also be used; data sampling, case sampling or centre sampling.

[3] http://www.drrc.aphp.fr
[4] http://www.ct-toolkit.ac.uk

Adaptation of monitoring can also be based on results from these three different approaches.

For the monitoring of the ECRIN studies, working group 5 developed an standard operating procedure (SOP) (See appendix 8) to provide guidance to the ECRIN team (and their cooperation with the sponsor) for the development of a optimised monitoring plan including the minimum levels of monitoring required for all studies performed within the ECRIN network.

The extent and nature of monitoring will be based upon the risk involved as assessed by the risk assessment tool (RAT) developed by the group.

Every protocol will be graded as high, medium or low risk and this will determine the minimum level of monitoring required. Irrespective of the minimum monitoring guidelines where there is any question over participant safety and/or data quality consideration, a site visit must be made.

The frequency and duration of visits is scheduled on a trial-specific basis and is dependent on the complexity of the trial, rate of recruitment at a site, and trial duration. The frequency of visits, suggested for each trial is to be understood as minimal and can be increased at the sponsors discretion.

5. Conclusion

At the European level, clinical trials with medicinal products are conducted within a strict regulatory framework[5]. The Directive 2001/20/EC sets out requirements for clinical trials on medicinal products, and these requirements are the same for all such trials, regardless of risk. This means that the same requirements are applied to 'low risk' trials as well as 'high risk' trials. There is a need for appropriate risk assessment of clinical trials with accompanying risk-adapted monitoring strategies. What is more, risk assessment and risk-adapted monitoring should apply to all categories of clinical research, not only to medicinal products.

[5] Directive 2001/20/EC dated 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use.Official Journal of the European Communities L121/34

Academic clinical research studies that are necessary to develop knowledge into new diagnostic, preventive and therapeutic intervention require optimisation of limited financial resources.

The knowledge of the study risk level involving participant's safety and validity of study results would allow for optimised monitoring, and optimised use of resources.

The ECRIN working group 5 on study monitoring has identified a relevant common set of criteria for evaluation of the risk related to multinational clinical research. This set of criteria contains 19 items and covers 5 types of risk; the risk for the study participant, the risk for the validity of the study results, the risk for the study organisation, the risk for the study governance and the risk for the impact of study results on target population and public health.

A validation study was set up. Data contained a high inter-assessor variability, which prevented to go as far as expected. There was no attempt to build a score of risk from the identified items. Only a selection of items was performed, to reduce the number of items.

This high variability was probably due to the fact that assessors had various functions and prior histories. Besides, though generally highly interested by the approach, they had received no training concerning risk assessment in general, and on this tool in particular.

The ECRIN Working Package 5, or its continuing entity, should probably work on standardising conditions of use, that could consist for instance in:

- synthesising experiences among other organisations
- setting-up an assessment committee within ECRIN
- training of the committee members through risk assessment of study projects within or outside ECRIN
- switching the approach from risk score from items, to straight risk assessment after items assessment to ensure that all relevant information was taken into account

Anyway, ECRIN has now a procedure for risk adapted monitoring.

In order to share this knowledge across Europe, the WP5 is working in the preparation of paper with the final objective of being published.

6. Appendices

Appendix 1:Questionnaire 1-V4

ECRIN (European Clinical Research Infrastructures Network) is based on the connection of national networks of clinical research infrastructures. Its main objective consists in developing an integrated EU infrastructure for clinical studies, providing one-stop shop services to investigators and sponsors in EU multinational studies.
The current project (ECRIN-TWG) aims at preparing this integrated infrastructure through the activity of transnational working groups in charge of defining guidelines and procedures for multinational studies on how to interact with ethics committees, with competent authorities and regulatory affairs, how to report adverse event, how to perform data management and monitoring and how to use the resulting material for educational programmes.
The Working Group 5 (study monitoring) will review the existing sets of criteria for gradual risk evaluation, will evaluate their reliability and assess cost-effective methods to monitor the studies.

A Questionnaire to Establish Consensus on Quality Risk Assessment for Monitoring of Clinical Research Studies

Study Monitoring includes all activities aiming at overseeing the planning initiation, conduct and data processing of clinical studies. Monitoring includes control of patient's safety and data integrity. All trials have to be monitored with diligence and attention to detail.

Though it is a major role of the sponsor to ensure that the principles of monitoring according to ICH-GCP (1.38) are respected, the extent and the nature of monitoring can be determined by the sponsor (ICH-GCP 5.18.3). Prioritisation of monitoring tasks can be based on the risks involved and effectiveness of monitoring can be improved by focusing resources on studies of highest risk.

There have been several initiatives in Europe to develop monitoring plans based on an *a priori* quality risk assessment but their purpose or content vary widely, at least apparently. Harmonisation within ECRIN will be necessary for developing common approaches used by/for sponsors and for transparency towards our users.

With the present questionnaire, we hope to be able to define a consensus within ECRIN on:

i. the principle of quality risk assessment;

ii. the concerned fields (clinical trial/other clinical research areas);

iii. the list of items to be documented to assess risk.

However, this questionnaire does not deal with a precise content (to be defined through a further questionnaire) or with the format to be used for presentation of the risk assessment (left to the sponsor's choice).

Thank you for accepting to answer this questionnaire. For each question or sub-question, please tick the answer closer to your feeling towards the proposition.

Name and First name .....

Affiliation .....

Professionnal role in clinical research studies (i.e. PI, CRA, sponsor,...) .....

Country .....

	I totally disagree	I partly disagree	I partly agree	I totally agree
Question 1. Sponsors of institutional clinical research should always adapt the monitoring plan based on the level of different components of risk	❑	❑	❑	❑
Question 2. Clinical research domains covered by quality risk assessment should include				
2a. clinical trials (among other domains).	❑	❑	❑	❑
2b. diagnostic studies.	❑	❑	❑	❑
2c. prognostic studies.	❑	❑	❑	❑
2d. all types of clinical research with the same risk-assessment scale.	❑	❑	❑	❑
2e. all types of clinical research but with different risk-assessment scales developed for clinical trials and other studies.	❑	❑	❑	❑

	I totally disagree	I partly disagree	I partly agree	I totally agree
Question 3. Types of risk/hazard included in the risk assessment				
3a. Potential risk/hazard for the participants (e.g. participants' rights, safety, specific populations)	❑	❑	❑	❑
3b. Potential risk/hazard for the validity of results (e.g. data completion, reliability of the results, complexity of the design)	❑	❑	❑	❑
3c. Organisation of the trial (e.g. previous experience of clinical studies, commitment to GCP, trained personnel, coordinating centre, experience, appropriate budget)	❑	❑	❑	❑
3d. Potential risk/hazard for the target population (e.g. potential impact of the results, financial impact, difficulty to reiterate such a study)	❑	❑	❑	❑
Question 4. Items to be considered in the risk/hazard for the participants				
Risk assessment should include item(s) regarding:				
4a. informed consent	❑	❑	❑	❑
4b. potential deviations and withdrawals	❑	❑	❑	❑
4c. protection of the privacy of participants	❑	❑	❑	❑
4d. inherent hazards to the study intervention (e.g. drug, medical device, other procedures)	❑	❑	❑	❑
4e. inherent hazards to assessment methods	❑	❑	❑	❑
4f. inherent hazards to specific populations	❑	❑	❑	❑

	I totally disagree	I partly disagree	I partly agree	I totally agree
Question 5. Items to be considered in the risk/hazard for the validity of results Risk assessment should include item(s) regarding:				
5a. the necessity for randomisation	❑	❑	❑	❑
5b. the necessity for blinding	❑	❑	❑	❑
5c. the complexity for data collection	❑	❑	❑	❑
5d. the complexity of protocol design	❑	❑	❑	❑
Question 6. Items to be considered regarding the organisation of the study Risk assessment should include item(s) regarding:				
6a. sites' experience of clinical studies	❑	❑	❑	❑
6b. sites' commitment to GCP	❑	❑	❑	❑
6c. availability of resources on sites	❑	❑	❑	❑
6d. training of personnel on sites	❑	❑	❑	❑
6e. support for study management (coordinating centre/data centre/clinical trials unit)	❑	❑	❑	❑
6f. trial governance ?	❑	❑	❑	❑
6g. the ability to achieve target recruitment	❑	❑	❑	❑
6h. the availability of trial budget	❑	❑	❑	❑

	I totally disagree	I partly disagree	I partly agree	I totally agree
Question 7. Items to be considered in the risk/hazard for the target population Risk assessment should include item(s) regarding:				
7a. the potential impact of the results on health management for the target population.....	❑	❑	❑	❑
7b. the potential economic impact of the results.....	❑	❑	❑	❑
7c. the need for results and the difficulty to reiterate such a study if necessary.....	❑	❑	❑	❑
Question 8. Presentation of the risk assessment				
8a. The risk assessment is better described by a continuum (quantitative continuous variable)	❑	❑	❑	❑
8b. This risk assessment is better described by a scale graded with 4 categories.....	❑	❑	❑	❑
8c. This risk assessment is better described by a scale graded with 5 categories.....	❑	❑	❑	❑
8d. Risk-assessment is a continuous process from start to finish (to be revisited whenever large changes are made to trial).....	❑	❑	❑	❑
8e. Risk-assessment is a one-off assessment done at start of trial.....	❑	❑	❑	❑

Question 9. Are there any other fields/items related with risk assessment that should be added?

Many thanks for your participation.

Please send this completed questionnaire to

christine.kubiak@tolbiac.inserm.fr

before March 26th, 2007.

Appendix 2: Questionnaire 2-V5

ECRIN (European Clinical Research Infrastructures Network) is based on the connection of national networks of clinical research infrastructures. Its main objective consists of developing an integrated EU infrastructure for clinical studies, providing one-stop shop services to investigators and sponsors in EU multinational studies.
The current project (ECRIN-TWG) aims at preparing this integrated infrastructure through the activity of transnational working groups in charge of defining guidelines and procedures for multinational studies on how to interact with ethics committees, with competent authorities and regulatory affairs, how to report adverse event, how to perform data management and monitoring and how to use the resulting material for educational programmes.
The Working Group 5 (study monitoring) will review the existing sets of criteria for gradual risk evaluation, will evaluate their reliability and assess cost-effective methods to monitor the studies.

A Questionnaire to Establish Consensus on Quality Risk Assessment for Monitoring of Clinical Research Studies

Study Monitoring includes all activities aiming at overseeing the planning initiation, conduct and data processing of clinical studies. Monitoring includes control of patient's safety and data integrity. All trials have to be monitored with diligence and attention to detail.

Though it is a major role of the sponsor to ensure that the principles of monitoring according to ICH-GCP (1.38) are respected, the extent and the nature of monitoring can be determined by the sponsor (ICH-GCP 5.18.3). Prioritisation of monitoring tasks can be based on the risks involved and effectiveness of monitoring can be improved by focusing resources on studies of highest risk.

There have been several initiatives in Europe to develop monitoring plans based on an *a priori* quality risk assessment but their purpose or content vary widely, at least apparently. Harmonisation within ECRIN is necessary for developing common approaches used by/for sponsors and for transparency towards our users.

A **first questionnaire** allowed us to validate the principle of quality risk assessment and to define a list of themes to be documented to assess risk.

With this **second questionnaire**, we aim at fixing the list of items that influence risk. Some items are useful for risk assessment only, whilst others may lead to modulation of monitoring intensity.

We would like to ask your feedback on the individual items listed below. Please indicate (using the pop-down menu) which of the items you feel increases, decreases, both increases and decreases risk or has no influence on risk. **The most frequently selected items will be considered for the final list**.

Please, note this questionnaire does not deal with the format to be used for presentation of the risk assessment as this is left to the sponsor's choice.

AMONG THE FOLLOWING ITEMS, WHICH ONES DO YOU CONSIDER AS INFLUENCING RISK, AND IN WHICH DIRECTION?

ABOUT STUDY PARTICIPANTS	
Difficulties or incapacity to give informed consent *e.g., language, emergency condition, age, legal incapacity, cognitive impairment...*	
Collection of indirectly identifying or sensitive characteristics *e.g., social security number, phone number... or ethnic origins, sexual, religious, politic preferences...*	
Expected inherent hazards related to study interventions *e.g., drug, surgical procedure...*	
Expected inherent hazards related to study investigations *e.g., blood sample, radiography, biopsy...*	
Expected inherent hazards related to disease or impaired condition defining target population, whatever the interventions or investigations *e.g., infants, elderly people, advanced stage cancer population...* **and/or** Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population *e.g., open-heart surgical intervention on infants...* *counterexample: blood sample in advanced stage cancer population...*	
Early stage / phase in the development of the study interventions *e.g., first studies on human being...*	
Study interventions used outside authorised indication / product licence / state of the art *e.g., new target population, drug combination, dose, timing, procedure...*	
ABOUT THE VALIDITY OF STUDY RESULTS	
Pre feasibility assessment of the study based on reliable sources	
Concealment of randomised study intervention allocation	
No study intervention	
Blinding of study intervention	
Objective assessment of primary and the main secondary outcomes *e.g., blood pressure, laboratory assessment on blood sample, scanner...*	
Complexity of study recruitment *e.g., number of investigator sites, number of participants...*	
Complexity of study design *e.g., crossover, dose escalation, structured therapeutic interruption...*	
Complexity of study follow-up *e.g., long duration of follow-up, different types of visit, complex investigations schedule, uncommon investigation as compared with standard of care...*	

AMONG THE FOLLOWING ITEMS, WHICH ONES DO YOU CONSIDER AS INFLUENCING RISK, AND IN WHICH DIRECTION?

ABOUT STUDY ORGANISATION	
Education and experience of the sponsor with regards to GCP procedures *e.g., informed consent, anonymisation, SAE reporting, queries management...*	
Education and experience of the sponsor to trial procedures *e.g., trial interventions, trial investigations...*	
Existence of quality assurance and quality control systems, implemented and maintained by the Sponsor and/or by the Coordinating Centre in case of documented delegation	
Education and experience of the investigator sites' staff with regards to GCP procedures *e.g., informed consent, anonymisation, SAE reporting, queries management...*	
Education and experience of the investigator sites' staff with regards to trial procedures *e.g., trial interventions, trial investigations...*	
Existence of quality assurance and quality control systems, implemented and maintained by the investigator sites	
Intervention management tracking system run by a qualified organisation *e.g., drug packaging and tracking system...*	
Quickness and security of data entry in the database *e.g., through e-CRF, FTPS site...*	
Full cleaning of database while the study is still in progress	
Availability of the appropriate resources at the start of the study *e.g., budget, staff, premises, equipment...*	
ABOUT STUDY GOVERNANCE	
Involvement of a Coordinating Centre *e.g. Clinical Trial Unit, GCP Unit, Clinical Research Centre...*	
Existence of a Study Steering Committee	
Validation of major events by an Adjudication / Validation Committee *e.g., severe / related adverse events, primary outcome...*	
Existence of a Data Monitoring Committee	
Partnership with a private and established organisation *e.g., drug supply by a pharmaceutical firm...*	
Clarity of ownership of intellectual property	
Expected events leading to major legal or financial aftermath *e.g., legal proceedings, financial compensation...*	
ABOUT STUDY IMPACT ON TARGET POPULATION AND PUBLIC HEALTH	
Key trial for registration purpose	
Major impact of study results on public health management *e.g., modification of standard of care in target population, economic impact...*	
Impossibility to reiterate the study	

ARE THERE ANY OTHER ITEMS HAVING INFLUENCE ON RISK THAT SHOULD BE ADDED?

Many thanks for your participation.

Please send this completed questionnaire to

christine.kubiak@tolbiac.inserm.fr

before September 21st, 2007.

Appendix 3: Protocol synopsis

FILL-IN INSTRUCTIONS

OBJECTIVE

This synopsis is designed to summarise both scientific and organisation aspects of any clinical research protocol. In its expected future use, this synopsis will be filled-in and sent to sponsor for assessment of risk and definition of a risk-adapted monitoring plan.

INSTRUCTIONS

Items relevant for risk assessment are blended in with others. Some may seem useless from a scientific point of view, but are crucial for risk assessment. Therefore:

> **COMPLETE ALL QUESTIONS**

Though most of scientific information is already present in the protocol, some required in the synopsis within the same section may not. Besides, the synopsis should be evaluated as it will be used in the future. Therefore:

> **COMPLETE QUESTIONS IF INFORMATION ALREADY PRESENT IN THE PROTOCOL**

The synopsis was designed mainly thinking about a 2-group comparison trial. This may not be relevant for the protocol in question. Therefore:

> **ADD NEW LINES WHEN NECESSARY**

It was impossible to anticipate all specific cases. But a full information is required. Therefore:

> **ALWAYS SPECIFY A GENERAL ANSWER SUCH AS "OTHER"**

> **MULTIPLE ANSWERS ARE ACCEPTED**

> **ANSWER "NA - NOT APPLICABLE" IS ACCEPTED**

PROTOCOL IDENTIFICATION

Full title

ACRONYME

SPONSOR

Name

Affiliation

City

Type Funding Agency / Hospital / Clinical Trials Unit / Clinical Research Centre / Clinical Department / other

COORDINATING CENTRE

Name

Affiliation

City

Type Clinical Trials Unit / Clinical Research Centre / Clinical Department / other

SCIENTIFIC ASPECTS

RESEARCH QUESTION

Research question defined in one sentence

STUDY OBJECTIVES

Primary objective

Main secondary objectives /

STUDY DESIGN

Phase I / II / III / IV / other

Comparison comparative / non comparative

Number of groups

Design parallel groups / cross-over / cluster / factorial plan / other

Reference group active group / placebo

Randomisation randomised / non randomised

Blinding double blinding / simple blinding / open label

Stratification stratified / non stratified

Stratification variable(s)

Strata /

Number of sites

STUDY POPULATION

Main inclusion criteria

Socio-demographic characteristics

Diagnostic and/or symptoms

Laboratory characteristics

Therapeutic characteristics

Other

Main exclusion criteria

Socio-demographic characteristics

Diagnostic and/or symptoms

Laboratory characteristics

Therapeutic characteristics

Other

Informed consent

Expected difficulties to receive information from age / emergency condition / cognitive impairment / other

Expected incapacity to give consent from age / emergency condition / legal incapacity / cognitive impairment / other

INTERVENTIONS

Trial intervention(s)

Nature intervention drug / surgery procedure / radiotherapy procedure / medical device / other

Administration scheme dose escalation / structured therapeutic interruption / other

Existing use authorisation none / drug licencing / medical device markage / other

Foreseen use in authorised indication / outside authorised indication / consistenly with state of the art / unconsistently with state of the art / other

Expected risks none / adverse reactions / constraints / other

Expected risk increase due to study population none / adverse reactions / constraints / other

Control intervention

Nature intervention drug / surgery procedure / radiotherapy procedure / medical device / other

Administration scheme one administration / few administrations / continuous / dose escalation / structured therapeutic interruption / other

Existing use authorisation none / drug licencing / medical device markage / other

Foreseen use in authorised indication / outside authorised indication / consistenly with state of the art / unconsistently with state of the art / other

Expected risks none / adverse reactions / constraints / other

Expected risk increase due to study population none / adverse reactions / constraints / other

OUTCOMES

Main outcome

Target target phenomenon

Measurement variable(s) / technique(s) / time schedule

Assessment centralised / local / blinded / open label / validation by a committee / no validation

Outcome definition must be a mathematical formula combining collected data and leading to 1 value per group

Main secondary outcomes

Target target phenomenon

Measurement variable(s) / technique(s) / time schedule

Assessment centralised / local / blinded / open label / validation by a committee / no validation

Outcome definition must be a mathematical formula combining some/all collected data and leading to 1 value per group

INVESTIGATIONS

Socio-demographic characteristics

Demographics characteristics gender / age

Social characteristics occupation

Indirectly identifying characteristics social insurance number / phone number / other

Sensitive characteristics ethnic origins / sexual preferences / religion / politic preferences / other other

Clinical investigations

History clinical / laboratory

Status at recruitment clinical / laboratory

Clinical events all / specific

Laboratories abnormalities all / specific

Specific events related to disease defining study population / interventions / investigations / other

Other investigations

Laboratory investigation(s)

Radiological investigations

Other investigations

Risk related to investigations

Nature

Expected risks none / adverse reactions / constraints / other

Expected risk increase due to study population none / adverse reactions / constraints / other

SAMPLE SIZE

Total number of participants

Ratio between groups e.g. 1:1

EXPECTED IMPACT OF STUDY RESULTS

Nature of impact on target population knowledge of pathophysiology / standard of care improvement / intervention licencing / other

Importance of impact on target population none / minor / major

Public health management major economic impact on public health management / other

Importance of impact on public health management none / minor / major

ORGANISATION ASPECTS

GOVERNANCE

Existence of management review organisations none / Coordinating Centre / Validation Committee

Existence of ethics and scientific review organisations none / Steering Committee / Data Safety and Monitoring Board

Influence or interference of a private organisation none / drug supply / frozen database transfer / interference in publication policy / other

STUDY STAFF'S EXPERIENCE

Sponsor

Training in GCP not trained / practical experience / specific training

Number of past multicenter studies

Investigator sites

	description of 1 to 3 different site types		
	type 1	type 2	type 3
Training in Good Clinical Practices: informed consent, anonymisation, Serious Adverse Events reporting, queries management,...	not trained / practical experience / specific training	not trained / practical experience / specific training	not trained / practical experience / specific training
Number of past participation in multicentric studies			
Number of past participation in studies managed by the Coordinating Centre	none / 1 study / several studies	none / 1 study / several studies	none / 1 study / several studies
Experience in study procedures: trial interventions, trial investigations,...	none / practical experience / specific training	none / practical experience / specific training	none / practical experience / specific training

STUDY MANAGEMENT

Feasibility evaluation

Based on none / clinical department activity / documented pre screening registry / investigator's declaration / other

Accrual scheme

Accrual clustered by Network / Hospitals / Clinical Departments / surgery office / other

Number of sites

Number of sites with foreseen accrual below participants

Number of sites with foreseen accrual between and participants

Number of sites with foreseen accrual over participants

Follow-up scheme

Follow-up content as compare to standard of care no additional investigation / additional investigations

Follow-up visits content one type / several types / other

Intervention allocation

Allocation centralised / local

Exchanges by website / phone / fax / envelope

Managed by computer / person

Intervention management

Existence of a management tracking system for intervention none / by sites and sponsor / by a qualified organisation

Data management

Questionnaire type e-CRF / paper CRF

Questionnaire administration self questionnaire / questionnaire administered by physician / questionnaire administered by other site staff / other

Data entry at end of sudy / on a regular basis

Data entry system e-CRF / double entry / single entry

Files transfer by none / post-mail / messenger / File Transfert Protocol site / File Transfer Protocol/Secure Scket Layer site

Database access security different passwords / different access rights / traced access

Computer check frequency none / at end of study / on a regular basis

Computer check intensity missing data / coding values / data limits / inter-variables consistency

Query reminders none / at end of study / on a regular basis

Data corrections at end of study / on a regular basis / real-time

Cleaning of database at end of study / on a regular basis / real-time

Quality assurance system / quality control system

Implementation and maintenance none / by the sponsor / by the Coordinating Centre / by the investigation sites

RESSOURCES

Type and timing of funding

Funding sources public / private / both public and private

Public funding exclusively by the Sponsor / various public funding / other

Private funding with intervention licencing expected from the study / without licencing expected / other

Funding available obtained before study beginneng / during study implementation / after end of study

Timing of recruitment of study staff at the sponsor's or at the Coordinating Centre's

Project management staff during study implementation / during participants' recruitment / during study follow-up

Monitoring staff during study implementation / during participants' recruitment / during study follow-up

Data management staff during study implementation / during participants' recruitment / during study follow-up / at end of study

Statistical staff during study implementation / during participants' recruitment / during study follow-up / at end of study

Timing of recruitment of study staff at the investigation sites'

Project management staff during study implementation / during participants' recruitment / during study follow-up

Name

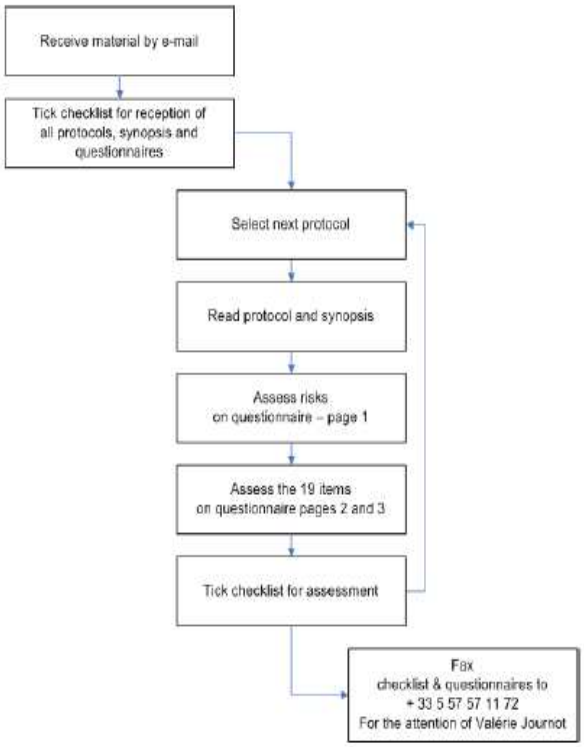
Affiliation .....

Professional role in clinical research studies (i.e. PI, CRA, sponsor,...) .....

Country

PROTOCOL	RECEPTION		ASSESSMENT		COMMENTS
	❑ OK	❑ problem	❑ done	❑ problem	
	❑ OK	❑ problem	❑ done	❑ problem	
	❑ OK	❑ problem	❑ done	❑ problem	
	❑ OK	❑ problem	❑ done	❑ problem	
	❑ OK	❑ problem	❑ done	❑ problem	
	❑ OK	❑ problem	❑ done	❑ problem	
	❑ OK	❑ problem	❑ done	❑ problem	
	❑ OK	❑ problem	❑ done	❑ problem	

Appendix 4: Validation questionnaire



☞ *READ SYNOPSIS AND PROTOCOL.*

☞ *COMPLETE RISK ASSESSMENT QUESTIONNAIRE BELOW.*

RISK ASSESSMENT

ASSESSOR PROTOCOL	Please quantify each risk by ticking the corresponding line at the appropriate place. *no risk at all* — *extreme risk*	CODING
RISK FOR PARTICIPANTS	————————————————	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
RISK FOR VALIDITY OF STUDY RESULTS	————————————————	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
RISK FOR ORGANISATION	————————————————	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
RISK FOR GOVERNANCE	————————————————	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
RISK FOR TARGET POPULATION AND PUBLIC HEALTH	————————————————	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋

☞ *COMPLETE THE 19 ITEMS QUESTIONNAIRE ON PAGES 2 AND 3.*

ASSESSOR PROTOCOL		Please quantify each item by ticking the corresponding line at the appropriate place. *not at all* — *extremely*	CODING
STUDY PARTICIPANTS			
1	Difficulties or incapacity to give informed consent *- from language, emergency condition, age, legal incapacity, cognitive impairment,...*		
2	Collection of indirectly identifying or sensitive characteristics *- indirectly identifying characteristics: social insurance number, phone number,...* *- sensitive characteristics: ethnic origins, sexual, religious, politic preferences,...*		
3	Expected inherent hazards related to study interventions or investigations study interventions: *drug, procedure,...* *- study investigations: outcome assessments,...*		
4	Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population *- target population: babies, elderly people, at risk of mortality or severe morbidity,...* *- risk carrying interventions or investigations: open-heart surgical intervention on babies,...*		
5	Study interventions used outside authorised indication / product licence / state of the art or in early stage / phase of development *- outside authorised indication / product licence / state of the art: new target population, new drug combination, dose or timing, new procedure,...* *- early stage / phase of development: first studies on human being, exploratory trial,...*		
VALIDITY OF STUDY RESULTS			
6	Pre feasibility assessment of the study recruitment based on reliable sources *- pre feasibility assessment: estimation based on clinical department activity, documented pre-screening registry,...*		
7	Concealment of randomised study interventions, allocated or to be allocated, during allocation, follow-up and investigations *- concealment during allocation: centralised allocation,...* *- concealment during follow-up: placebo,...* *- concealment during investigations: blinded outcome assessment,...*		
8	Objective assessment of primary and the main secondary outcomes *- objective assessment: blinded biological measurement, Adjudication / Validation Committee,...*		
9	Complexity of study procedures *- study procedures: recruitment, design, follow-up* *- complex recruitment: cluster accrual,...* *- complex designs: crossover design, dose escalation, structured therapeutic interruption,...* *- complex follow-up: different types of follow-up visit, additional investigations as compared to standard of care,...*		

ASSESSOR PROTOCOL		Please quantify each item by ticking the corresponding line at the appropriate place. *not at all* — *extremely*	CODING
STUDY ORGANISATION			
10	Education and experience of the sponsor or investigator sites' staff to GCP or study procedures *- GCP procedures: informed consent, anonymisation, SAE reporting, queries management,...* *- study procedures: trial interventions, trial investigations,...*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
11	Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation, and by the investigator sites		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
12	Intervention management tracking system run by a qualified organisation *- for drugs: packaging, labelling, distribution, restocking, dispensation, accountability, expiry date, re-labelling, storage conditions,...*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
13	Quickness and security of data entry in the database *- quick data entry: e-CRF,...* *- secure data entry: secured websites (FTP/SSL), passwords,...*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
14	Full cleaning of database while study is still in progress *- frequent computer data checking, frequent query reminders, real-time data corrections,....*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
15	Availability of the appropriate resources at the start of the study		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
STUDY GOVERNANCE			
16	Existence of management review organisations *- management review organisations: Coordinating Centre, Adjudication/Validation Committee*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
17	Existence of ethic and scientific review organisations *- ethic and scientific control organisations: Steering Committee, DSMB*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
18	Influence / interference of a private organisation upon study governance *- influence / interference: drug supply by a pharmaceutical firm, agreement to transfer the database to the organisation, publication policy...*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
IMPACT OF STUDY RESULTS ON TARGET POPULATION AND PUBLIC HEALTH			
19	Major impact of study results on target population and public health *- on target population: modification of standard of care,...* *- on public health: major economic impact on public health management,...*		⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋

DURATION OF ASSESSMENT ⌊_⌋⌊_⌋ minutes

☞ *TICK THE CHECKLIST.*

Appendix 5: Analysis of answers to Questionnaire 1- V4

SEARCH FOR A CONSENSUS ON A RISK-ASSESSMENT TOOL

questionnaire 1 - V4

analysis of answers

	TOTAL	
	N	%
TOTAL	51	100
COUNTRY		
Canada	1	2
Denmark	3	6
France	6	12
Germany	17	33
Hungary	4	8
Ireland	4	8
Italy	5	10
Spain	3	6
USA	1	2
United Kingdom	7	14

SEARCH FOR A CONSENSUS ON A RISK-ASSESSMENT TOOL
questionnaire 1 - V4
analysis of answers

	TOTAL	
	N	%
TOTAL	51	100
ROLE		
	1	2
(earlier medical director of Sanofi-Aventis - Budapest)	1	2
CRA	3	6
CRO	2	4
Cancer Research Network Manager	1	2
Clinical Investigator	1	2
Clinical Research Associate (sponsor)	1	2
Clinical Research Coordinator, Consultant, General Practitioner	1	2
Compliance & Training Manager	1	2
Compliance and Training Manager	1	2
Director of Clinical Research Centre	1	2
Ethics Committee Member	3	6
GCRU Clinical Research Coordinator	1	2
Good Clinical Practice Inspector	1	2
Head	3	6
Head of CRAs	1	2
Head of Clinical Operations in a unit that designs and sponsors trials	1	2
Head of Clinical Research Unit	1	2
Head of the CTOGHS	1	2
Head of the unit	1	2
Investigator	6	12
Monitor	1	2
PI, consultat	1	2
PI, head	1	2
PI; medical director; professionnal overseer of monitoring activities	1	2
QA/Head of monitoring	1	2
R & D Manager	1	2
Regulatory authority	2	4
Senior Project Manager	1	2
Trial Director	1	2
attending physician, clinical investigator	1	2
coordinating physician	1	2
director US RMN	1	2
none	1	2
professional of clinical research	1	2
project leader	1	2
sponsor	1	2
study coordinator	1	2

SEARCH FOR A CONSENSUS ON A RISK-ASSESSMENT TOOL
questionnaire 1 - V4
analysis of answers

	TOTAL	
	N	%
Sponsors of institutional clinical research should always adapt the monitoring plan based on the level of different components of risk.		
.	1	2
I partly disagree	2	4
I partly agree	11	22
I totally agree	37	73

	TOTAL	
	N	%
Clinical research domains covered by quality risk assessment should include clinical trials (among other domains).		
.	4	8
I partly agree	4	8
I totally agree	43	84
Clinical research domains covered by quality risk assessment should include diagnostic studies.		
.	4	8
I partly agree	13	25
I totally agree	34	67
Clinical research domains covered by quality risk assessment should include prognostic studies.		
.	5	10
I totally disagree	1	2
I partly disagree	2	4
I partly agree	18	35
I totally agree	25	49
Clinical research domains covered by quality risk assessment should include all types of clinical research with the same risk-assessment scale.		
.	5	10
I totally disagree	10	20
I partly disagree	13	25
I partly agree	12	24
I totally agree	11	22
Clinical research domains covered by quality risk assessment should include all types of clinical research but with different risk-assessment scales developed for clinical trials and other studies.		
.	1	2
I totally disagree	1	2
I partly disagree	3	6
I partly agree	19	37
I totally agree	27	53

SEARCH FOR A CONSENSUS ON A RISK-ASSESSMENT TOOL
questionnaire 1 - V4
analysis of answers

	TOTAL	
	N	%
Types of risk/hazard included in the risk assessment potential risk/hazard for the participants (e.g. participants' rights, safety, specific populations).		
I partly disagree	1	2
I partly agree	1	2
I totally agree	49	96
Types of risk/hazard included in the risk assessment potential risk/hazard for the validity of results (e.g. data completion, reliability of the results, complexity of the design).		
I partly agree	6	12
I totally agree	45	88
Types of risk/hazard included in the risk assessment organisation of the trial (e.g. previous experience of clinical studies, commitment to GCP, trained personnel, coordinating centre, experience, appropriate budget).		
I partly agree	19	37
I totally agree	32	63
Types of risk/hazard included in the risk assessment potential risk/hazard for the target population (e.g. potential impact of the results, financial impact, difficulty to reiterate such a study).		
I partly disagree	5	10
I partly agree	15	29
I totally agree	31	61

	TOTAL	
	N	%
Items to be considered in the risk/hazard for the participants - Risk assessment should include item(s) regarding informed consent.		
.	1	2
I totally disagree	1	2
I partly disagree	1	2
I partly agree	3	6
I totally agree	45	88
Items to be considered in the risk/hazard for the participants - Risk assessment should include item(s) regarding potential deviations and withdrawals.		
.	1	2
I partly disagree	3	6
I partly agree	13	25
I totally agree	34	67
Items to be considered in the risk/hazard for the participants - Risk assessment should include item(s) regarding protection of the privacy of participants.		
.	1	2
I totally disagree	4	8
I partly disagree	4	8
I partly agree	10	20
I totally agree	32	63
Items to be considered in the risk/hazard for the participants - Risk assessment should include item(s) regarding inherent hazards to the study intervention (e.g. drug, medical device, other procedures).		
I partly agree	4	8
I totally agree	47	92
Items to be considered in the risk/hazard for the participants - Risk assessment should include item(s) regarding inherent hazards to assessment methods.		
I partly agree	14	27
I totally agree	37	73
Items to be considered in the risk/hazard for the participants - Risk assessment should include item(s) regarding inherent hazards to specific populations.		
I partly disagree	3	6
I partly agree	14	27
I totally agree	34	67

	TOTAL	
	N	%
Items to be considered in the risk/hazard for the validity of results - Risk assessment should include item(s) regarding the necessity for randomisation.		
.	1	2
I totally disagree	2	4
I partly disagree	2	4
I partly agree	13	25
I totally agree	33	65
Items to be considered in the risk/hazard for the validity of results - Risk assessment should include item(s) regarding the necessity for blinding.		
.	1	2
I totally disagree	2	4
I partly disagree	3	6
I partly agree	14	27
I totally agree	31	61
Items to be considered in the risk/hazard for the validity of results - Risk assessment should include item(s) regarding the complexity for data collection.		
I partly disagree	2	4
I partly agree	14	27
I totally agree	35	69
Items to be considered in the risk/hazard for the validity of results - Risk assessment should include item(s) regarding the complexity of protocol design.		
I totally disagree	1	2
I partly disagree	1	2
I partly agree	12	24
I totally agree	37	73

	TOTAL	
	N	%
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding sites' experience of clinical studies.		
I partly agree	18	35
I totally agree	33	65
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding sites' commitment to GCP.		
.	1	2
I totally disagree	2	4
I partly disagree	4	8
I partly agree	15	29
I totally agree	29	57
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding availability of resources on sites.		
I partly disagree	1	2
I partly agree	21	41
I totally agree	29	57
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding training of personnel on sites.		
I partly disagree	1	2
I partly agree	20	39
I totally agree	30	59
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding support for study management (coordinating centre/data centre/clinical trials unit).		
I partly disagree	3	6
I partly agree	22	43
I totally agree	26	51
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding trial governance.		
.	5	10
I totally disagree	2	4
I partly disagree	3	6
I partly agree	23	45
I totally agree	18	35
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding the ability to achieve target recruitment.		
.	1	2
I totally disagree	3	6
I partly disagree	8	16
I partly agree	24	47
I totally agree	15	29
Items to be considered regarding the organisation of the study - Risk assessment should include item(s) regarding the availability of trial budget.		
.	3	6
I totally disagree	3	6
I partly disagree	11	22
I partly agree	24	47
I totally agree	10	20

	TOTAL	
	N	%
Items to be considered in the risk/hazard for the target population - Risk assessment should include item(s) regarding the potential impact of the results on health management for the target population.		
I totally disagree	4	8
I partly disagree	7	14
I partly agree	20	39
I totally agree	20	39
Items to be considered in the risk/hazard for the target population - Risk assessment should include item(s) regarding the potential economic impact of the results.		
I totally disagree	7	14
I partly disagree	15	29
I partly agree	20	39
I totally agree	9	18
Items to be considered in the risk/hazard for the target population - Risk assessment should include item(s) regarding the need for results and the difficulty to reiterate such a study if necessary.		
.	1	2
I totally disagree	5	10
I partly disagree	9	18
I partly agree	17	33
I totally agree	19	37

	TOTAL	
	N	%
Presentation of the risk assessment - The risk assessment is better described by a continuum (quantitative continuous variable).		
.	3	6
I totally disagree	8	16
I partly disagree	16	31
I partly agree	11	22
I totally agree	13	25
Presentation of the risk assessment - This risk assessment is better described by a scale graded with 4 categories.		
.	5	10
I totally disagree	3	6
I partly disagree	14	27
I partly agree	22	43
I totally agree	7	14
Presentation of the risk assessment - This risk assessment is better described by a scale graded with 5 categories.		
.	8	16
I totally disagree	6	12
I partly disagree	13	25
I partly agree	16	31
I totally agree	8	16
Presentation of the risk assessment - Risk-assessment is a continuous process from start to finish (to be revisited whenever large changes are made to trial).		
.	1	2
I totally disagree	3	6
I partly disagree	2	4
I partly agree	11	22
I totally agree	34	67
Presentation of the risk assessment - Risk-assessment is a one-off assessment done at start of trial.		
.	3	6
I totally disagree	27	53
I partly disagree	11	22
I partly agree	6	12
I totally agree	4	8

	TOTAL	
	N	%
Are there any other fields/items related with risk assessment that should be added?	35	69
- 8d : to be revisited in case of safety issues or other new events related to the conduct of the trial.	1	2
- Duration of follow-up. Other comments : - Level of monitoring must take into account patient's safety but not only. The other aim of monitoring is to obtain data of quality such that an answer can be given to the clinical question and this point must not be omitted. - Sometimes, the level of monitoring is increased, just because patients to be included are from specific populations (such as children or patients with a cancer). I disagree with such an approach to be generalized. As an example genotype-phenotype study in patients with a cancer is of no risk for the patients (just a blood sample) and it is not sensible to be more stringent regarding monitoring only because those patients have a cancer.	1	2
- Experience of Sponsor. Lack of experience on the part of the Sponsor is causing delay to the start of trials which is a risk.	1	2
- For this clarification, only "risk/hazard" is taken into account to establish this classification but other elements should be considered. Question 2: If the study classification is A or B (in accordance to "Optimon" classification), some data shouldn't be checked: what about missing or incoherent data? What is the stratgey concerning these data? Should they be completed by queries by data manager (time to be passed and possibility to collect them without monitoring help)? If not collected, should these data be considered as "lost data" and so, what about the data quality of such studies with A or B monitoring level? Question 3d: Variable depending on study type for certain studies: if research procedures are very light (eg: only one blood sample), the criteria linked to target population seem to be less important (eg: genetic study in population with cancer: this population has potential risk but research procedure and follow-up duration is very light). Question 6: These elements should be taken into account for risk evaluation but, very often, this evaluation is performed before the information is available: risk evaluation is necessary for financial evaluation (i.e. CRA implication). Question 7: From our point of view, these	1	2
- I like to make a few comments on the following questions: - Question 2: the quality risk assessment should include clinical research with drugs or medical devices. - Question 5: items 5a and 5b are not clear to me. - Question 6: items 6f and 6h are not clear to me.	1	2
- I'd put more emphasis on the importance of appropriate protocol design (structure, determination of endpoints, assessment methods selected, statistical planning, etc.).	1	2
- Monitoring experience in TA.	1	2
- No mention of safety reporting as part of the assessment - this should be included. No mention of IMP management - inadequate storage and accountability could impact the quality of data, espacially in th EU where the competent authorities are very focused on the importance of Annex 13.	1	2
- None.	1	2
- Risk assessment should be related to the risk of standard therapy (e.g. therapy in oncology is always toxic).	1	2
- Stage of IMP development (early vs late). Possible class issues with IMP. Use of multiple vendors in study management / involvment of non-commercial organisations.	1	2
- Supplement to Question 6: The number of investigators/nurses involved. There is a large risk for non-compliance to the protocol if there is a large number of persons involved compared to a single PhD trial.	1	2
- The method of randomisation is very important - i.e. the potential for recruiters to the trial to predict the next allocation. This is the issue rather thand the need for randomisation. Similarly the quality of the blinding and the objectivity of the outcome and safety assessments should be considered. Rather than a single overall assessment, I believe that the various aspects of the trial should be considered in the risk assessment and systems put in place to control the key risks.	1	2
- There is no mention of Serious Adverse Events, this could be included.	1	2
- Use of drugs or devices off licence and safety issues of treatment.	1	2
- Which phase (I-IV)? - Known profile of IMP. - Indication of trial.	1	2

Appendix 6: Analysis of answers to Questionnaire v2.5

ECRIN – WP5 Study Monitoring
Search for a consensus on a risk assessment tool
analysis of responses to questionnaire 2

1. Data collected

Answers to questionnaire 2 were received from 45 participants. Information regarding participants' country, affiliation, and professional role in clinical research studies is currently collected. Responses are described as follows in several tables.

- Table 2 - pages 5-10: Raw results, items sorted by topic
- Table 3 - pages 11-12: Items sorted by decreasing maximal frequency(in bold) – any modality of response
- Table 4 - pages 13-14: Items sorted by decreasing maximal frequency (in bold) of total "increase" – "increase" modalities only
- Table 5 - pages 15-16: Items sorted by decreasing maximal frequency (in bold) of total "decrease" – "decrease" modalities only

2. Summary of the results

There were very few missing answers: 1 to 3 responders (2% to 7%) per item. Only 8 items were concerned: none out of 8 for topic "Study Participants", 2 out of 8 for topic "Validity of Study Results", 1 out of 10 for topic "Study Organisation", 2 out of 7 for topic "Study Governance", and 3 out of 3 for "Study Impact on Target Population and Public Health".

TABLE 1. AVERAGE PERCENTAGE OF ANSWERS PER TOPIC.

	INFLUENCE ON RISK			
TOPIC	no influence	increase	decrease	both
Study Participants	15%	68%	2%	16%
Validity of Study Results	18%	31%	33%	18%
Study Organisation	6%	2%	80%	11%
Study Governance	23%	5%	58%	13%
Study Impact on Target Population and Public Health	19%	41%	13%	26%

For the 8 items concerning Study Participants, a majority of responders (49% to 91%) considered it as increasing risk.

For 3 items concerning Validity of Study Results, a majority of responders (53% to 76%) considered it as increasing risk. For 4 items, a majority of responders (38% to 71%) considered it as decreasing risk. For the item "No study intervention", 42% considered it as having no influence on risk, and 42% as decreasing risk.

For the 10 items concerning Study Organisation, a large majority of responders (64% to 93%) considered it as decreasing risk.

For 4 items concerning Study Governance, a large majority of responders (76% to 96%) considered it as decreasing risk. For the item "Clarity of ownership of database intellectual property", 58% of responders considered it as having no influence on risk. For the item "Partnership with a private organisation", 47% considered it as both increasing and decreasing risk, and 42% considered it as having no influence on risk. For the item "Expected events leading to major legal or financial aftermath", 37% of responders considered it as having no influence on risk.

For 2 items concerning Study Impact on Target Population and Public Health, a majority of responders (40% to 49%) considered it as increasing risk. For the item "Major impact of study results on public health management", 36% of responders considered it as both increasing and decreasing risk, and 34% considered it as increasing risk.

3. Discussion

Results presented in Table 3 were particularly discussed at the WP5 teleconference of December 13th, 2007, and proposals for items modifications were done.

Most items seem to be rather clearly considered as influencing risk by responders, so that they should be maintained in the risk assessment tool.

Yet, some items should be removed because they are considered as having no impact on the risk:

- topic "Validity of Study Results"
  - . No study intervention
- topic "Study Governance"
  - . Clarity of ownership of database intellectual property
  - . Expected events leading to major legal or financial aftermath

Some items should also be clarified because they seem ambiguous:

- topic "Validity of Study Results"
  - . Concealment of randomised study intervention allocation
  - . Blinding of study intervention
  - → *combined into one item*
- topic "Study Governance"
  - . Partnership with a private organisation
  - → Influence / interference of a private organisation upon study governance
- topic "Study Impact on Target Population and Public Health"
  - . Major impact of study results on public health management
  - → *combined with other items*

Finally, some items should be combined because they seem to be redundant, both in meaning and in responses:

- topic "Study Participants"
  - . Expected inherent hazards related to study interventions
  - . Expected inherent hazards related to study investigations
  - → Expected inherent hazards related to study interventions or investigations
  - . Expected inherent hazards related to disease or impaired condition defining target population, whatever the interventions or investigations
  - . Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population
  - → Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population
  - . Early stage /phase in the development of the study interventions
  - . Study interventions used outside authorised indication / product licence / state of the art
  - → Study interventions used outside authorised indication / product licence / state of the art or in early stage / phase of development

- topic "Validity of Study Results"
  - . Concealment of randomised study interventions allocation
  - . Blinding of study interventions
  - → Concealment of randomised interventions, allocated or to be allocated, during allocation, follow-up and investigations (centralised allocation, blinding for participants, investigator sites' staff, and outcome evaluators)
  - . Complexity of study recruitment
  - . Complexity of study design
  - . Complexity of study follow-up
  - → Complexity of study procedures (recruitment, design, follow-up)
- topic "Study Organisation"
  - . Education and experience of the sponsor to GCP procedures
  - . Education and experience of the sponsor to study procedures
  - . Education and experience of the investigator sites' staff to GCP procedures
  - . Education and experience of the investigator sites' staff to study procedures
  - → Education and experience of the sponsor or investigator sites' staff to GCP or study procedures
  - . Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation
  - . Existence of quality assurance and quality control systems, implemented and maintained by the investigator sites
  - → Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation, and by the investigator sites
- topic "Study Governance"
  - . Involvement of a Coordinating Centre
  - . Validation of major events by an Adjudication / Validation Committee
  - → Existence of quality control structures (Coordinating Centre, Adjudication / Validation Committee)
  - . Existence of a Steering Committee
  - . Existence of a Data Safety and Monitoring Board
  - → Existence of ethic and scientific control structures (Steering Committee, Data Safety and Monitoring Board)
- topic "Impact of Study Results on Target Population and Public Health"
  - . Key trial for registration purpose
  - . Major impact of study results on public health management
  - . Impossibility to reiterate the study
  - → Major impact of study results on target population and public health

4. Reduced list

The final list of items could have 19 items:

- topic "Study Participants" (5 items)
  - . Difficulties or incapacity to give informed consent
  - . Collection of indirectly identifying or sensitive characteristics
  - . Expected inherent hazards related to study interventions or investigations
  - . Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population
  - . Study interventions used outside authorised indication / product licence / state of the art or in early stage / phase of development
- topic "Validity of Study Results" (4 items)
  - . Pre feasibility assessment of the study based on reliable sources
  - . Concealment of randomised study interventions, allocated or to be allocated, during allocation, follow-up and investigations (centralised allocation, blinding for participants, investigator sites' staff, and outcome evaluators)
  - . Objective assessment of primary and the main secondary outcomes
  - . Complexity of study procedures (recruitment, design, follow-up)
- topic "Study Organisation" (6 items)
  - . Education and experience of the sponsor or investigator sites' staff to GCP or study procedures
  - . Existence of quality assurance and quality control systems, implemented and maintained by the sponsor, or eventually by the Coordinating Centre in case of documented delegation, and by the investigator sites
  - . Intervention management tracking system run by a qualified organisation
  - . Quickness and security of data entry in the database
  - . Full cleaning of database while study is still in progress
  - . Availability of the appropriate resources at the stat of the study
- topic "Study Governance" (3 items)
  - . Existence of quality control structures (Coordinating Centre, Adjudication / Validation Committee)
  - . Existence of ethic and scientific control structures (Steering Committee, Data Safety and Monitoring Board)
  - . Influence / interference of a private organisation upon study governance
- topic "Impact of Study Results on Target Population and Public Health" (1 items)
  - . Major impact of study results on target population and public health

5. Validation

A protocol to validate the tool (validity and reproducibility) should be discussed at the next teleconference.

TABLE 2. RAW RESULTS – ITEMS SORTED BY TOPIC

RESPONSES ABOUT STUDY PARTICIPANTS

	ALL	
	N	%
ALL	45	100
Difficulties or incapacity to give informed consent		
no influence	4	9
increase only	41	91
Collection of indirectly identifying or sensitive characteristics		
no influence	20	44
increase only	22	49
both increase and decrease	3	7
Expected inherent hazards related to study interventions		
no influence	4	9
increase only	29	64
decrease only	2	4
both increase and decrease	10	22
Expected inherent hazards related to study investigations		
no influence	4	9
increase only	27	60
decrease only	2	4
both increase and decrease	12	27
Expected inherent hazards related to disease or impaired condition defining target population, whatever the interventions or investigations		
no influence	8	18
increase only	25	56
decrease only	2	4
both increase and decrease	10	22
Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population		
no influence	1	2
increase only	29	64
decrease only	1	2
both increase and decrease	14	31
Early stage / phase in the development of the study interventions		
no influence	2	4
increase only	40	89
both increase and decrease	3	7
Study interventions used outside authorised indication / product licence / state of the art		
no influence	4	9
increase only	32	71
both increase and decrease	9	20

RESPONSES ABOUT THE VALIDITY OF STUDY RESULTS

	ALL	
	N	%
ALL	45	100
Pre feasibility assessment of the study based on reliable sources		
no influence	10	22
decrease only	30	67
both increase and decrease	5	11
Concealment of randomised study intervention allocation		
.	1	2
no influence	12	27
increase only	8	18
decrease only	19	42
both increase and decrease	5	11
No study intervention		
.	2	4
no influence	18	40
increase only	2	4
decrease only	18	40
both increase and decrease	5	11
Blinding of study intervention		
no influence	10	22
increase only	8	18
decrease only	17	38
both increase and decrease	10	22
Objective assessment of primary and the main secondary outcomes		
no influence	6	13
increase only	3	7
decrease only	32	71
both increase and decrease	4	9
Complexity of study recruitment		
no influence	4	9
increase only	24	53
decrease only	2	4
both increase and decrease	15	33
Complexity of study design		
increase only	34	76
both increase and decrease	11	24
Complexity of study follow-up		
no influence	3	7
increase only	30	67
decrease only	1	2
both increase and decrease	11	24

RESPONSES ABOUT STUDY ORGANISATION

	ALL	
	N	%
ALL	45	100
Education and experience of the sponsor to GCP procedures		
no influence	5	11
increase only	2	4
decrease only	30	67
both increase and decrease	8	18
Education and experience of the sponsor to trial procedures		
no influence	3	7
increase only	1	2
decrease only	35	78
both increase and decrease	6	13
Existence of quality assurance and quality control systems, implemented and maintained by the Sponsor, or eventually by the Coordinating Centre in case of documented delegation		
no influence	1	2
decrease only	41	91
both increase and decrease	3	7
Education and experience of the investigator sites' staff to GCP procedures		
increase only	1	2
decrease only	38	84
both increase and decrease	6	13
Education and experience of the investigator sites' staff to trial procedures		
increase only	1	2
decrease only	38	84
both increase and decrease	6	13
Existence of quality assurance and quality control systems, implemented and maintained by the investigator sites		
decrease only	42	93
both increase and decrease	3	7
Intervention management tracking system run by a qualified organisation		
no influence	3	7
decrease only	39	87
both increase and decrease	3	7
Quickness and security of data entry in the database		
no influence	5	11
increase only	1	2
decrease only	29	64
both increase and decrease	10	22
Full cleaning of database while the study is still in progress		
.	1	2
no influence	9	20
increase only	1	2
decrease only	30	67
both increase and decrease	4	9
Availability of the appropriate resources at the start of the study		
no influence	5	11
increase only	2	4
decrease only	36	80
both increase and decrease	2	4

RESPONSES ABOUT STUDY GOVERNANCE

	ALL	
	N	%
ALL	45	100
Involvement of a Coordinating Centre		
no influence	3	7
decrease only	36	80
both increase and decrease	6	13
Existence of a Steering Committee		
no influence	8	18
increase only	1	2
decrease only	34	76
both increase and decrease	2	4
Validation of major events by an Adjudication / Validation Committee		
no influence	1	2
decrease only	43	96
both increase and decrease	1	2
Existence of a Data Safety and Monitoring Board		
no influence	3	7
decrease only	40	89
both increase and decrease	2	4
Partnership with a private organisation		
no influence	19	42
increase only	1	2
decrease only	4	9
both increase and decrease	21	47
Clarity of ownership of database intellectual property		
.	2	4
no influence	25	56
decrease only	16	36
both increase and decrease	2	4
Expected events leading to major legal or financial aftermath		
.	2	4
no influence	16	36
increase only	13	29
decrease only	7	16
both increase and decrease	7	16

RESPONSES ABOUT STUDY IMPACT ON TARGET POPULATION AND PUBLIC HEALTH

	ALL	
	N	%
ALL	45	100
Key trial for registration purpose		
.	3	7
no influence	3	7
increase only	17	38
decrease only	11	24
both increase and decrease	11	24
Major impact of study results on public health management		
.	1	2
no influence	11	24
increase only	15	33
decrease only	2	4
both increase and decrease	16	36
Impossibility to reiterate the study		
.	2	4
no influence	11	24
increase only	21	47
decrease only	4	9
both increase and decrease	7	16

TABLE 3. ITEMS SORTED BY DECREASING MAXIMAL FREQUENCY (bold) – ANY MODALITY OF RESPONSE

	Items	No impact	Increase	Decrease	Both
Study Governance	Validation of major events by an Adjudication / Validation Committee	2	0	**96**	2
Study Organisation	Existence of quality assurance and quality control systems, implemented and maintained by the investigator sites	0	0	**93**	7
Study Participants	Difficulties or incapacity to give informed consent	9	**91**	0	0
Study Organisation	Existence of quality assurance and quality control systems, implemented and maintained by the Sponsor, or eventually by the Coordinating Centre in case of documented delegation	2	0	**91**	7
Study Participants	Early stage / phase in the development of the study interventions	4	**89**	0	7
Study Governance	Existence of a Data Safety and Monitoring Board	7	0	**89**	4
Study Organisation	Intervention management tracking system run by a qualified organisation	7	0	**87**	7
Study Organisation	Education and experience of the investigator sites' staff to GCP procedures	0	2	**84**	13
Study Organisation	Education and experience of the investigator sites' staff to trial procedures	0	2	**84**	13
Study Organisation	Availability of the appropriate resources at the start of the study	11	4	**80**	4
Study Governance	Involvement of a Coordinating Centre	7	0	**80**	13
Study Organisation	Education and experience of the sponsor to trial procedures	7	2	**78**	13
Validity of Study Results	Complexity of study design	0	**76**	0	24
Study Governance	Existence of a Steering Committee	18	2	**76**	4
Study Participants	Study interventions used outside authorised indication / product licence / state of the art	9	**71**	0	20
Validity of Study Results	Objective assessment of primary and the main secondary outcomes	13	7	**71**	9
Validity of Study Results	Pre feasibility assessment of the study based on reliable sources	22	0	**67**	11
Validity of Study Results	Complexity of study follow-up	7	**67**	2	24
Study Organisation	Education and experience of the sponsor to GCP procedures	11	4	**67**	18
Study Organisation	Full cleaning of database while the study is still in progress	20	2	**67**	9

	Items	No impact	Increase	Decrease	Both
Study Participants	Expected inherent hazards related to study interventions	9	64	4	22
Study Participants	Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population	2	64	2	31
Study Organisation	Quickness and security of data entry in the database	11	2	64	22
Study Participants	Expected inherent hazards related to study investigations	9	60	4	27
Study Participants	Expected inherent hazards related to disease or impaired condition defining target population, whatever the interventions or investigations	18	56	4	22
Study Governance	Clarity of ownership of database intellectual property	56	0	36	4
Validity of Study Results	Complexity of study recruitment	9	53	4	33
Study Participants	Collection of indirectly identifying or sensitive characteristics	44	49	0	7
Study Governance	Partnership with a private organisation	42	2	9	47
Study Impact on Target Population and Public Health	Impossibility to reiterate the study	24	47	9	16
Validity of Study Results	Concealment of randomised study intervention allocation	27	18	42	11
Validity of Study Results	No study intervention	40	4	40	11
Validity of Study Results	Blinding of study intervention	22	18	38	22
Study Impact on Target Population and Public Health	Key trial for registration purpose	7	38	24	24
Study Governance	Expected events leading to major legal or financial aftermath	36	29	16	16
Study Impact on Target Population and Public Health	Major impact of study results on public health management	24	33	4	36

TABLE 4. ITEMS SORTED BY DECREASING FREQUENCY OF TOTAL "INCREASE" (bold) – "INCREASE" MODALITIES ONLY

	Items	Increase	Both	Total
Validity of Study Results	Complexity of study design	76	24	**100**
Study Participants	Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population	64	31	**96**
Study Participants	Early stage / phase in the development of the study interventions	89	7	**96**
Study Participants	Difficulties or incapacity to give informed consent	91	0	**91**
Study Participants	Study interventions used outside authorised indication / product licence / state of the art	71	20	**91**
Validity of Study Results	Complexity of study follow-up	67	24	**91**
Study Participants	Expected inherent hazards related to study interventions	64	22	**87**
Study Participants	Expected inherent hazards related to study investigations	60	27	**87**
Validity of Study Results	Complexity of study recruitment	53	33	**87**
Study Participants	Expected inherent hazards related to disease or impaired condition defining target population, whatever the interventions or investigations	56	22	**78**
Study Impact on Target Population and Public Health	Major impact of study results on public health management	33	36	**69**
Study Impact on Target Population and Public Health	Key trial for registration purpose	38	24	**62**
Study Impact on Target Population and Public Health	Impossibility to reiterate the study	47	16	**62**
Study Participants	Collection of indirectly identifying or sensitive characteristics	49	7	**56**
Study Governance	Partnership with a private organisation	2	47	**49**
Study Governance	Expected events leading to major legal or financial aftermath	29	16	**44**
Validity of Study Results	Blinding of study intervention	18	22	**40**
Validity of Study Results	Concealment of randomised study intervention allocation	18	11	**29**
Study Organisation	Quickness and security of data entry in the database	2	22	**24**
Study Organisation	Education and experience of the sponsor to GCP procedures	4	18	**22**
Validity of Study Results	No study intervention	4	11	**16**
Validity of Study Results	Objective assessment of primary and the main secondary outcomes	7	9	**16**

	Items	Increase	Both	Total
Study Organisation	Education and experience of the sponsor to trial procedures	2	13	**16**
Study Organisation	Education and experience of the investigator sites' staff to GCP procedures	2	13	**16**
Study Organisation	Education and experience of the investigator sites' staff to trial procedures	2	13	**16**
Study Governance	Involvement of a Coordinating Centre	0	13	**13**
Validity of Study Results	Pre feasibility assessment of the study based on reliable sources	0	11	**11**
Study Organisation	Full cleaning of database while the study is still in progress	2	9	**11**
Study Organisation	Availability of the appropriate resources at the start of the study	4	4	9
Study Organisation	Existence of quality assurance and quality control systems, implemented and maintained by the Sponsor, or eventually by the Coordinating Centre in case of documented delegation	0	7	7
Study Organisation	Existence of quality assurance and quality control systems, implemented and maintained by the investigator sites	0	7	7
Study Organisation	Intervention management tracking system run by a qualified organisation	0	7	7
Study Governance	Existence of a Steering Committee	2	4	7
Study Governance	Existence of a Data Safety and Monitoring Board	0	4	4
Study Governance	Clarity of ownership of database intellectual property	0	4	4
Study Governance	Validation of major events by an Adjudication / Validation Committee	0	2	2

TABLE 5. ITEMS SORTED BY DECREASING FREQUENCY OF TOTAL "DECREASE" (bold) – "DECREASE" MODALITIES OF RESPONSE ONLY

	Items	Decrease	Both	Total
Study Organisation	Existence of quality assurance and quality control systems, implemented and maintained by the investigator sites	93	7	**100**
Study Organisation	Existence of quality assurance and quality control systems, implemented and maintained by the Sponsor, or eventually by the Coordinating Centre in case of documented delegation	91	7	**98**
Study Organisation	Education and experience of the investigator sites' staff to GCP procedures	84	13	**98**
Study Organisation	Education and experience of the investigator sites' staff to trial procedures	84	13	**98**
Study Governance	Validation of major events by an Adjudication / Validation Committee	96	2	**98**
Study Organisation	Intervention management tracking system run by a qualified organisation	87	7	**93**
Study Governance	Involvement of a Coordinating Centre	80	13	**93**
Study Governance	Existence of a Data Safety and Monitoring Board	89	4	**93**
Study Organisation	Education and experience of the sponsor to trial procedures	78	13	**91**
Study Organisation	Quickness and security of data entry in the database	64	22	**87**
Study Organisation	Education and experience of the sponsor to GCP procedures	67	18	**84**
Study Organisation	Availability of the appropriate resources at the start of the study	80	4	**84**
Validity of Study Results	Objective assessment of primary and the main secondary outcomes	71	9	**80**
Study Governance	Existence of a Steering Committee	76	4	**80**
Validity of Study Results	Pre feasibility assessment of the study based on reliable sources	67	11	**78**
Study Organisation	Full cleaning of database while the study is still in progress	67	9	**76**
Validity of Study Results	Blinding of study intervention	38	22	**60**
Study Governance	Partnership with a private organisation	9	47	**56**
Validity of Study Results	Concealment of randomised study intervention allocation	42	11	**53**
Study Impact on Target Population and Public Health	Key trial for registration purpose	24	24	**49**
Validity of Study Results	No study intervention	40	11	**51**
Study Governance	Clarity of ownership of database intellectual property	36	4	**40**
Study Impact on Target	Major impact of study results on public health management	4	36	**40**

	Items	Decrease	Both	Total
Population and Public Health				
Validity of Study Results	Complexity of study recruitment	4	33	38
Study Participants	Combination of risk carrying interventions or investigations, and population with disease or impaired condition defining target population	2	31	33
Study Participants	Expected inherent hazards related to study investigations	4	27	31
Study Governance	Expected events leading to major legal or financial aftermath	16	16	31
Study Participants	Expected inherent hazards related to study interventions	4	22	27
Study Participants	Expected inherent hazards related to disease or impaired condition defining target population, whatever the interventions or investigations	4	22	27
Validity of Study Results	Complexity of study follow-up	2	24	27
Validity of Study Results	Complexity of study design	0	24	24
Study Impact on Target Population and Public Health	Impossibility to reiterate the study	9	16	24
Study Participants	Study interventions used outside authorised indication / product licence / state of the art	0	20	20
Study Participants	Collection of indirectly identifying or sensitive characteristics	0	7	7
Study Participants	Early stage / phase in the development of the study interventions	0	7	7
Study Participants	Difficulties or incapacity to give informed consent	0	0	0

Appendix 7: List of protocols evaluated

Austria: BOPSAC, HEMAHS
Denmark: CLARICOR, DIPOM
France: AUBIER, BINGO, EPICURE, PREMILOC
Germany: ALDO-DHF, CASP-MTD, ETHIG-II, EURONET-PHL, GAHB, HYPRESS, IDANAT2, MOOD-HF, SPIRR-CAD
Hungary: ZOLPIDEM
Ireland: HIV-CMP
Spain: RISVAC, SPIRAL
Sweden: DIP
United Kingdom: IMOP, MAPS

Other protocols were collected but could not be used because of missing information, and especially of missing completed synopsis.

Appendix 8: ECRIN-MO-SOPØØ1 “Monitoring ECRIN studies”

Monitoring ECRIN studies
Reference: ECRIN-MO-SOPØØ1-VØ.1
Version number: draft VØ.1

APPROVAL	
Author: Siobhan Gaynor	
Validated by Chair of Working Group 5 : Date:	Signature:
Validated by QA representative: Date:	Signature:
Effective Date:	
Supersedes version number (*if applicable*):	
REVISION	
Version number: Not applicable	
Date: Not applicable	
Reason for change: Not applicable	
Main modifications: Not applicable	
COUNTRIES	
Valid in: Austria, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Spain, Sweden, United Kingdom	

1. PURPOSE

This SOP is intended to provide guidance to the sponsor and ECRIN team for the development of a monitoring plan and to describe the minimum levels of monitoring required for all ECRIN studies.

2. SCOPE

All clinical trials selected by the ECRIN scientific board will require assessment using the risk assessment tool and a monitoring plan developed dependent on the risk level established
Monitoring requirements for studies that fall outside of EU Directives governing clinical trials and medical devices including 2001/20/EC, 2005/28/EC, 90/385/EEC, 93/42/EEC and 98/79/EC, shall be considered on a case by case basis in line with country specific requirements.
This procedure will cover all clinical trials selected by the ECRIN scientific board and that will be performed within the ECRIN network

This procedure will cover all clinical trials selected by the ECRIN scientific board and that will be performed within the ECRIN network.

3. DEFINITIONS AND ABBREVIATIONS

CRF Case report/record form: A printed, optical, or electronic document designed to record all the protocol required information to be reported to the sponsor on each trial subject (ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6)

ECRIN_ European Clinical Research Infrastructures Network
Based on the interconnection of national networks of academic clinical research infrastructures, the European Clinical Research Infrastructures Network (ECRIN) is designed to bridge the fragmented organisation of European clinical research and to develop an integrated EU-wide clinical research infrastructure

European Correspondent: *is the contact point and the local support to the sponsor in his/her country.*

ICF_ Informed Consent Form: decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation. (*Directive 2001/20/EC*)

Investigator: a doctor or a person following a profession agreed in the Member State for investigations because of the scientific background and the experience in patient care it requires. The investigator is responsible for the conduct of a clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the leader responsible for the team and may be called the principal investigator. (*Directive 2001/20/EC*)

Risk: ***In this paper, the term 'risk' refers exclusively to the risk of non-compliance with GCP objectives:***

1. ***Protection of the safety, rights, well-being and confidentiality of identity of trial subjects;***
2. ***Credibility of data and results.***

Risk may be divided in two primary components:- risk for study participants;
- risk for the validity of study results.

All other components of risk for studies follow from these primary risks:

- risk for sponsor or other study managing organisation;
- risk for study governance;
- risk for target population and public health.

Risk assessment tool:

Risk-assessment tool will be used to adapt monitoring intensity, but should be strongly related to primary risks. Therefore, validity of the risk-assessment tool should be assessed relatively to primary risks, not to monitoring intensity.
A good risk-assessment tool must respect the usual qualities of any good outcome: relevance, validity, and reliability.

SAE_ Serious adverse event: Definition to be assigned on a per protocol basis, as depends on intervention being studied.

SOP_ Standard Operating Procedure: Detailed, written instructions to achieve uniformity of the performance of a specific function. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*).

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. (*Directive 2001/20/EC*)

Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*).
Source data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Study participant: an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control (*Directive 2001/20/EC*) In addition individuals who participate in a clinical trial involving other interventions, can also be described as study participants.

4. RESPONSIBILITY

Common elements	Country specific elements
The sponsor (or delegated entity or person) is responsible for the development of the monitoring plan for each ECRIN study. They are also responsible for ensuring that adequate resource is assigned to the study as required to comply with the study specific monitoring plan and any additional requirements for national monitoring specific procedures	
Evaluation of risk by assessment tool and determination of whether study is low, medium or high risk must be done by the sponsor and a relevant monitoring plan will be developed according to the template provided in appendix 1.	
The sponsor is responsible for providing each ECRIN Member State, participating in the trial, with the validated version of the monitoring plan.	
The European Correspondent is the local contact point and is responsible for adding any additional national specific requirements to the ECRIN monitoring plan, for validating this document with the sponsor and then providing the	

national monitoring plan to all relevant parties	

5. DESCRIPTION

The extent and nature of monitoring will be based upon the risk involved as assessed by the risk assessment tool (RAT). The frequency and duration of visits is scheduled on a trial-specific basis and is dependent on the complexity of the trial, rate of recruitment at a site, and trial duration. The frequency of visits, suggested for each trial is to be understood as minimal and can be increased at the sponsors discretion.

Every protocol will be graded as high, medium or low risk and this will determine the minimum level of monitoring required. Irrespective of the minimum monitoring guidelines where there is any question over participant safety and/or data quality consideration to making a site visit must be made . It is the responsibility of the study sponsor to ensure all national requirements in relation to monitoring are also being observed.

All activities described can be conducted by an on-site visit or by remote central/monitoring by the sponsor.

5.1 Low risk

The minimum requirements for all ECRIN monitoring plans include:

A minimum of one on-site monitoring visit.

Verification of a proportion of SAE's, data query resolution, confirmation of consent and other monitoring procedures, can be conducted remotely, providing the study participants identity is not revealed.

Before study

Verify that appropriate ethical and regulatory approvals are in place prior to study commencement.
Ensure that investigators and their staff have received protocol specific training.

During study

Verify that all participants have properly conducted the process of informed consent and recorded it;
Verify eligibility of a sample of participants enrolled onto trial
Verify that a proportion of SAEs are reported within correct time frame (per protocol and national legislation)
Study end points: As part of the key data a percentage of the CRF's will be reviewed with respect to study end points. This will be specified in the study monitoring plan.

After study

Verify that all requirements with ethics and regulatory notification have been completed;
Verify that appropriate archiving of all essential documents has been completed by asking investigators to confirm this has been done.

All monitoring activities must be completed in writing with follow-up actions highlighted and tracked to completion

5.2 Medium risk

If the study is identified as medium risk the following must be monitored in addition to requirements above. This can be achieved through a combination of on-site and remote data monitoring, but a minimum of 2 on-site monitoring visits over the duration of the study must be performed.

During study

Key data as defined prospectively in the monitoring plan, to be reviewed for 50% of the participants at that trial site;
Drug/device and clinical supply accountability;
Ongoing acceptability and adequacy of staff and facilities.

5.3 High risk

If the study is classified as high risk the following must be monitored in addition to the requirements outlined for low and medium risk above.
This can be achieved through a combination of on-site and remote data monitoring, but a minimum of 3 on-site monitoring visits over the duration of the study must be performed.

During study

Key data as defined prospectively in the monitoring plan, to be reviewed for 75% of the participants at that trial site.

5.4 Monitoring Resource

It is the responsibility of the sponsor to ensure there is sufficient monitoring resource for each study.

6. Specific References

Risk-adapted monitoring in non-commercial clinical trials" draft paper supplied by the Adamon project group in Germany- Monitoring in IIT's project group (reference http://www.tmf-ev.de/site/DE/int/AG/MKS/Projekte/IIT-Monitoring/c_Monitoring.php)

7. ECRIN References

ECRIN-EC-SOP002 Interaction with Ethics Committees before the conduct of a multinational clinical trial on multinational products
ECRIN-EC-SOP003 Interaction with ethics committees duing the conduct of a multinational clinical trial on medicinal products
ECRIN-EC-SOP 004 Interaction with Ethics committees after the conduct of a multinational clinical trial on medicinal products
ECRIN-AE-SOP001 How to support adverse event reporting in multinational clinical studies

8. Appendices

Appendix 1: Monitoring template
Appendix 2: Overview of the proposed monitoring strategies

8 Appendix 1

Monitoring template, including mandatory elements. To be used as basis for monitoring plan to be developed for each protocol.

This must be generated by the sponsor for all ECRIN studies

Principles

- The monitoring activities focus on those trial data and information that are essential for an assessment of participant safety, well-being and rights, and to achieve the primary and secondary trial objectives (referred to in the following as 'key data')
- Each protocol should specify which montoring activities must be done by on-site monitoring and which can be achieved by remote/central monitoring.
- The extent of monitoring and the minimum frequency of site visits depends primarily on the level of risk established by the risk assessment tool and should also take other issues, including recruitment, visit schedule and trial duration into consideration..
- Timely central monitoring of the clinical trial's progress (by data management and other appropriate means) is warranted, with the option to trigger additional site visits if irregularities are noticed (referred to in the following as 'for-cause monitoring')
- In order to warrant an efficient supervision of the clinical trial's progress, CRFs have to be swiftly available at the data centres and have to be processed in a timely manner. This holds for trials using paper based documentation as well as for trials using remote data entry systems.
- The monitors are trained on all relevant aspects identified by the clinical trial risk analysis

Irrespective of the type of basic monitoring, an unscheduled visit should be made to the trial site if problems or irregularities are noticed by the central monitoring or if fraud is suspected. This for-cause monitoring is described in more detail below

Definition of the key data

The key data comprise the trial data and information that are essential to assess patient safety, well-being and rights, and to achieve the primary and secondary trial objectives.

Key data always include:

- **Existence** of the trial participant

A check is made to establish whether the trial participant is included in the patient identification list and whether a patient file exists in connection with any list entry.

- **Informed consent**

A check is made to establish whether a written inform consent form exists, and whether it was filled in correctly, completely and on time.

- **Serious adverse events (SAE)**

A check is made to establish whether all serious adverse events mentioned in the participant's file are correctly and completely documented and whether they correspond to the trial protocol specifications.

The following are also key data, though they have to be specified in the monitoring plan as per the trial protocol:

- **Inclusion and exclusion criteria**

In general, eligibility criteria in clinical trials should have been chosen due to their relevance for either safety or efficacy of the trial intervention or due to their relevance for the statistical power of the trial. Thus, all eligibility criteria should be considered as key data. In exceptional cases, it may happen that some inclusion and exclusion criteria do not match the description above – these criteria may be excluded from the key data.

- **Application and dosage** of the experimental intervention.
- **Primary endpoint**

The primary endpoint(s) for the clinical trial is/are subjected to a source data verification process. This applies if the parameter(s) was/were assessed at the trial site. If the assessment is done on a centralised basis by a reference panel or institution, the monitoring activity on site referring to the primary endpoint will consist in checking whether the necessary material or the necessary information has been passed on.

Further trial-specific data and information can be included in the key data. These are derived from the trial-specific risk analysis and include, for instance

- **Adverse events** (AEs): In clinical trials with **medicinal products** whose **safety profile (in the range of indications being investigated) is little known**, **AEs** should always be classified as key data.
- Essential **secondary endpoints** (if assessed locally in the trial sites)
- Possibly other aspects ensuing from the risk analysis of **patient-related indicators**

Planning monitoring activities

The planning phase involves the following:

- Clinical trial risk assessment as previously described
- Specification of the trial-specific key data
- Design of the monitoring plans specifying visit frequencies and durations. The following aspects have to be taken into consideration when estimating the duration of monitoring activities:
  - Parameters that can influence the duration of monitoring activities for an individual patient (e.g. extent of key data, number and type of inclusion and exclusion criteria and adverse events due to the underlying disease or co-morbidity)
  - Further tasks to be implemented at the trial site; these ensue from the analysis of trial site-related indicators
  - The type of data collection (data collection with remote data entry may simplify on-site monitoring).
- Definition of standard procedures for the reaction to and the follow-up of problems which are detected by the monitors during their on site visits and are described in the monitoring reports
- Trial-specific training for the assigned monitors

Low risk study monitoring

Pre-study visit	**Not made**
Initiation visit	**Can be replaced by an investigators' meeting (either face to face and/or teleconference)** and detailed written instructions, e.g. - in trials designed similarly to standard treatment and involving an established trial population if similar trials for the same range of indications have already been implemented in the trial sites - in trials with a very simple design
Visits	Each site is visited at least once during the duration of the trial. The order in which the trials are visited is randomly assigned by the central study office.
Verification of key data	- **Existence and informed consent for 100% of participants** - **Further key data** (if it is available at the time of the visit) **for at least 20% of the participants at the trial site**. (i.e. if there are 1-5 participants at the centre, 1 participant is selected. If there are 6-10 participants, 2 participants are selected etc.) The selection of participants to be monitored is made by the central study office.
Further contacts	Additional telephone and/or e-mail contacts **as required**.

Close-out visit	**Not made**

For-cause monitoring

It is necessary to ensure prompt intervention if problems become evident or are suspected at certain trial sites. This is only possible if the implementation and documentation of the trial are centrally monitored, which involves additional data management and central monitoring measures. The methods used to analyse possible problems or irregularities should, if possible, be statistical monitoring methods (e.g. multivariate analysis of possible outlier candidates, conspicuous data patterns, preferred numerical sequences, accumulation of values close to defined limits etc. Please refer to Al-Marzouki et al BMJ 2005, Buyse et al Stat Med 1999 in this connection). In clinical trials which use paper-based documentation, it is necessary to ensure that the CRFs are posted to the central study office in good time, and to operate a reminder system for outstanding documentation.

A structured interview in regular telephone calls can also be a source of information about potential problems at the site. The following questions are feasible:

- Investigator team member: Have any changes of personnel or task allocation taken place since the trial started? Do you have any training requirements? (Contact other trial team members if necessary)
- Current site status: participants who are taking part / have dropped out of the trial/ have concluded the trial
- Planned participants: get the centre to send screening lists if necessary and discuss them (including reasons for rejection)
- Problems: enquiry about current site-specific problems; specific questions about problems at other sites or general problems encountered in the course of the trial.
- Specific trial-related questions: requirements or questions about trial materials, incidence of (S)AEs, questions on trial documentation.

When problems or irregularities that exceed a trial-specific ???? are ascertained at a trial site a prompt unscheduled monitoring visit to the trial site is made. It is necessary to ensure that the criteria for a monitoring visit are quite specifically formulated so that not too many unscheduled visits are necessary.

Problems or irregularities can include:

- Relevant deviations from the scheduled intervention according to the trial protocol and/or diagnostic procedures without CRF-documented medical necessity, observed in several participants (e.g. dose too low / too high, therapy duration too short, unauthorised concomitant intervention, necessary diagnostic procedures not performed, components of the intervention omitted; criteria and number of participants to be defined in advance on a trial-specific basis)
- Conspicuously higher/lower incidence of SAEs compared with other trial sites, SAEs regularly reported too late or in too little detail
- Suspected fraud
- Suspected gross irregularities that cannot be clarified on the phone

monitoring visits are not made regularly to all trial sites, only on a random basis. That is why further criteria for an unscheduled monitoring visit should be considered, e.g.:

- Outstanding trial-specific documentation (>50% of documentation due) despite two reminders
- A high incidence of inconsistencies and/or implausible data compared with other trial sites
- If the inclusion/exclusion criteria define limits for certain laboratory values, and the trial site's values are often up to the limit at the time of inclusion
- Lack of response to data management queries

In for-cause monitoring visits, unresolved problems are clarified, up to 100% source document verification of all relevant trial-specific data for all participants (the proportion has to be specified in the monitoring manual) and personnel are trained in the use of the trial protocol and implementation methods.

Appendix 2

Overview of the proposed monitoring strategies

The following table provides an overview of the basic monitoring in each of the 3 risk assessment categories.

	High Risk	Medium risk		Low risk
Pre-study visit	Recommended	Recommended Can be substituted by telephone contact + request for qualification documents		Not made
Initiation	Recommended	Recommended (Exception: rare diseases – in this case, the initiation can take place when the first participant is recruited)		Can be replaced by an investigators' meeting and detailed written instructions
First visit	After inclusion of the first participant	After the recruitment of 1-2 participants		Not made
Further visits	The frequency and duration of visits is scheduled on a trial-specific basis. It depends on the list of tasks to be performed during the monitoring visits and takes the trial site's recruitment rate into account. The frequency of visits stated in the following is to be understood as minimal.			
		Trial site with noticeable problems	**Trial site without noticeable problems**	
Frequency	Depending on the site's recruitment and the catalogue of monitoring tasks (in general at least 6x year)	Depending on the site's recruitment and the catalogue of monitoring tasks (in general at least 3x year) Annual re-evaluation and, if applicable, change of status to 'without noticeable problems'	Depending on the site's recruitment and the catalogue of monitoring tasks (in general at least 1x year) Annual re-evaluation and, if necessary, change of status to 'with noticeable problems'	At least one visit at each trial site
Verification of key data	Existence, informed consent, SAE and all further key data for 100% of participants at the trial site	- Existence and informed consent for 100% of participants - SAE data for 100% participants - Further key data for at least 50% of the participants at the trial site	- Existence and informed consent for 100% of participants - SAE data for 100% participants - - Further key data for at least 20% of the participants at the trial site	Only at the trial sites visited: - Existence and informed consent for 100% of participants - SAE data for 100% participants - Further key data for at least 20% of the participants at the trial site

Verification of further data	Generally 10% of the trial site's participants, but at least one participant with 100% source data verification	A 100% SDV is made for one participant in the random sampled trial site (to ascertain any systematic errors)	None
Further contacts	As required	At least every 8 weeks, as a structured interview	As required
Close-out visit	Recommended	Only if there are still monitoring tasks to be performed or queries to be clarified	Not made