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ECRIN-TWG



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DELIVERABLE N° 6

REGULATORY REQUIREMENTS FOR ADVERSE REPORTING IN ECRIN COUNTRIES

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Working Group 3

Transnational Working Group on Adverse Events reporting

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Summary

Abbreviations	4
Definitions	6
Background	9
Preliminary consideration.....	9
Premises	9
WP3 Activity	10
Objectives	10
The survey	12
Activity on regulatory requirements	12
Presentation of the websurvey	13
How was filled out the questionnaire.....	14
Who filled out the questionnaire	15
Considerations on the analysis on results	15
Introduction	15
Data model.....	16
Countries who participated in the survey	17
Data representation	17
Item N°1	18
Item 1 bis.....	19
Item N°2	20
Item N°3	21
Item N°4	22
Item N°5	23
Item N°6	24
Item N°7	25
Item N°8	26
Item N°9	27
Conclusions	28
Appendix	31
Notes	31
Questionnaire Sections	31
Possible Flow Diagram Elements.....	34

Abbreviations

AEMPS	Spanish Agency for Medicines and Medical Devices
AIFA	Agenzia Italiana del Farmaco (Italian National Drug Agency)
AMG	Arzneimittelgesetz (German Federal Drug Act)
AFSSAPS	Agence française de Sécurité Sanitaire des Produits de Santé (french competent authority)
ATU	Temporary Authorisation for Use
CEIC	Clinical Research Ethics Committees
CRC	Clinical Research Centre
CTU	Clinical Trial Unit
CIC	Centre d'Investigation Clinique (French Clinical Investigation Centre)
CNIL	Commission Nationale de l'Informatique et des Libertés
CCTIRS	Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé
CPP	Comite de Protection des Personnes (french research ethics committee)
CTA	Clinical Trial Authorisation
DMA	Danish Medicine Agency
DGS	Direction Générale de la Santé (french General Direction of Health)
DIMDI	Medical Documentation and Information
DK	Denmark
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
EMA	European Medicines Agency

EU	European Union
EFCGP	European Forum for Good Clinical Practice
FP	Framework Programme
FR	France
GMP	Good Manufacturing Practice
GTAC	Gene Therapy Advisory Committee
Ger	Germany
GCP	Good Clinical Practice
HU	Hungary
IMP	Investigational Medicinal Product
IR	Ireland
ISS	Instituto Superiore della Sanita
It	Italy
KKS	Koordinierungszentrum für Klinische Studien (German national network)
MPA	Swedish Medical Products Agency
NHS	National Health System
PEI	Paul- Ehrlich-Institute (German competent authority)
PI	Principal Investigator
PIAG	Patient Information Advisory Group
QA	Quality Assurance
QM	Quality Management
REC	Research Ethics committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Sp	Spain
Sw	Sweden

Definitions

CA: Competent authority

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities. *(ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6).*

Multicentre CT: Multicenter Clinical trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single Member State, in a number of Member States and/or in Member States and third countries. *(Directive 2001/20/EC)*

CTA: Clinical trial authorisation

An authorisation of a clinical trial by the competent authority of a Member State will be a Clinical Trial Authorisation (CTA) and will only be valid for a clinical trial conducted in that EU Member State. This authorisation does not imply approval of the development programme of the tested IMP. *(EU Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial)*

CTAA: Clinical trial authorisation application (often shortened to CTA)

According to Article 9(2) of the Directive the applicant must submit a valid request for authorisation to the competent authority. *(EU Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial)*

EC: Ethics committee

An independent body in a Member State, consisting of healthcare professionals and nonmedical members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent. *(Directive 2001/20/EC)*

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.

EudraCT: Clinical trial data base for the Regulatory Authorities in EU

GMO: Genetically modified organism

Means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination; (*Directive on the Deliberate Release into the Environment of Genetically Modified Organisms 2001/18/EG*).

IMP: Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form. (*Directive 2001/20/EC*)

However, as the transposition of this definition differs from one country to other, ECRIN SOPs use the term "Medicinal Product". Please see the document "*Deliverable 4: Clinical Research in Europe: national differences in legislative and regulatory framework*" for further information.

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*)

MS: Member State

Country involved in ECRIN.

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*).

Subinvestigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator. (*ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6*)

Subject: an individual who participates in a clinical trial as either a recipient of the investigational medicinal product or a control (*Directive 2001/20/EC*)

Within ECRIN framework, the term *participant* seems more adequate because includes both patients (clinical trial subjects) and healthy volunteers

Background

Preliminary consideration

In order to collect data from partner Countries an on-line questionnaire has been designed. Since the deliverables N° 6 & (in part) 7 and 8 required also to collect data from the same partners, a unique questionnaire has been designed to avoid duplication and risk of drop-outs.

The survey designed for regulatory requirements for vigilance systems in ECRIN countries is therefore comprehensive of the questions related to:

Deliverable N° 6 & (in part) 7 and 8

- Survey of implementation practice of adverse event reporting in Europe for drugs
- Survey of adverse event reporting practice for non drug intervention

Deliverable 7 - Establishment of networks for the development of EU-wide postmarketing surveillance studies,

Deliverable 8 - A report on the computerization of adverse event reporting

Premises

Clinical research is the basis of a well functioning, evidence-based health care system. In the 2001 the release of the European Directive 2001/20/EC aimed to promote harmonisation within European clinical research.

The comparative analysis on clinical research education presented in the ECRIN-RKP project showed a major diversity in national education programmes for investigators, study nurses and all the staff involved in clinical research. The definition of clinical research jobs and related tasks differed from one country to another.

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

In order to achieve this goal some Working Party groups were built up within ECRIN.

In particular WP 3 is responsible for mapping out adverse event reporting procedures within the ECRIN network.

In fact one essential piece of information which is missing is an inventory of adverse event reporting obligations under the law and/or under any normative procedures in the countries participating in the ECRIN TWG and PPI Projects.

WP3 Activity

Objectives

a) Adverse event reporting in interventional clinical research

Although its principles are now harmonised at the EU level for medicines trials through the Eudravigilance system, **adverse event reporting** requires in-depth examination of national implementation and practice, as this complex process involves many actors, including the national competent authorities and ethics committee. Therefore there is a need to define guidelines and procedures for adverse event reporting in medicines trials. This is even more critical in clinical research not covered by the 2001/20/EC Directive : medical device and biotherapy trials, surgery trials, radiotherapy trials, pathophysiology and genotype-phenotype studies. Some countries have extended the procedure used for medicines trials to other interventional studies (definition of expected adverse reactions, and notification of SUSARs by the sponsor to national competent authorities), but other countries use very different procedures. Similarly the field of implementation of the annual report, or of the notification of new facts to RECs and competent authority is another source of discrepancy.

b) Safety and risk assessment in observational, post-marketing studies

In addition, the working group will also consider the national differences in the post-marketing safety reporting, also relevant for observational post-marketing studies (pharmacoepidemiology). Once a drug is marketed, the number of patients who are exposed is unknown, as is the indication that the drug was used to treat and the dose used by each patient. When a new drug is marketed, the treated population is not restricted by a protocol, and there is an exponential increase in the number of patients exposed (which can only be estimated from sales volumes). New adverse events are reported that were not seen in the trials conducted before the marketing authorisation. We will investigate if Postmarketing safety reporting of adverse event information is

performed voluntarily ¹. No statistical analyses can be performed on postmarketing data because of the number of patients treated being unknown as well as the true number of occurrences of each adverse event. New adverse events can be added in the safety section of the package labelling from postmarketing use; however, no incidence for these new adverse events can be listed.

According to several analysts pharmacovigilance risk management will be one of the fastest-growing application areas in the drug development arena in the next future. Driven by growing interest among regulators, consumers, and the medical community, drug safety is rising in both importance and visibility to drug manufacturers. The ability to predict and thereby prevent catastrophic drug safety failures is the goal of all adverse event reporting and pharmacovigilance risk management activities. In this perspective, predictive toxicology at the preclinical step, and risk assessment during and after the clinical development are key bottlenecks to the development of new medicines as identified by the strategic research agenda of the FP7 Innovative Medicines Initiative project, and safety is one on the four pillars of this programme.

Adverse event reporting across the borders is a major issues addressed by the ECRIN programme – and in this perspective the EMEA has recently asked ECRIN to appoint a representative at the EudraVigilance Steering Committee. The co-chair of this working group (Nicola Fabris) was nominated by the ECRIN Network Committee to play this role on behalf of ECRIN.

c) Description of work

The work is based on a transnational working group including two members of each CRC-CTU network, plus a representative of EFGCP. The working group has invited also national experts, to collaborate in order to fill the survey questionnaire.

¹ In Spain Postmarketing safety reporting of adverse event information is performed mandatory by law; in France, it is performed voluntarily and also mandatory by law.

The survey

Activity on regulatory requirements

WP3 has designed a questionnaire to collect information from the different countries participating in the ECRIN TWG project. It's an inventory of adverse event reporting obligations under the law and/or under any normative procedures in the ECRIN countries.

The questionnaire has been designed by three of the members of WP3 (Jean Pierre Tassignon from EFCGP and Nicola Fabris and Francesca Savarese (European Correspondent from CIRM).

The questionnaire on "Regulatory requirements for Vigilance Systems in ECRIN Countries" is online. Every country has given the names of the compilers, who had a good knowledge of the detailed regulatory requirements at national, regional and local level, as appropriate.

The questionnaire is structured in 4 mains items, and each item has around 10 questions that give a general and detailed overview of each country organisation system (see Appendix for more details).

1 - PhV System Organisation

How the law and/or normative procedures define the organisation of PhV reporting.

2 - PhV Stakeholders

What responsibilities the law and/or normative procedures give to the various stakeholders concerned.

3 - Adverse Event Reporting Regulation by medical research type

How PhV observations have to be handled across the spectrum of diagnostic, therapeutic and preventive research methods. The different categories of research used were defined in the survey performed by the ECRIN WP2 on regulation.

4 - Adverse Event Reporting Regulation by product category

How PhV requirements differ depending on the product class on the market. The categories are from the French legislation.

Presentation of the websurvey

As WP3 of ECRIN TWG is responsible for mapping out Pharmacovigilance procedures within the ECRIN network. One essential piece of information which is missing is an inventory of Pharmacovigilance obligations under the law and/or under any normative procedures in the countries participating in the ECRIN TWG and PPI Projects.

This was anticipated, and therefore, WP3 planned – as part of its remit (deliverables 6-7-8) – to design a questionnaire to collect the missing information.

An outline of the questionnaire was proposed by the Chairman of WP3 at the plenary meeting of the ECRIN NW Committee in Dusseldorf in September 2007 and approved for distribution to the representatives on WP3.

Web connection and Personal Profile (username and password) were required in order to be able to fill the online questionnaire.

Every question/item listed in the category, requires to insert a document. This mean a national legislation document which is related to the current question/item and consequently give some information on the national organization. In this way, we should take a picture on the actual normative and legislative structure within every country about Vigilance System.

A web based survey was designed.

How was filled out the questionnaire

The Pharmacovigilance questionnaire is an Excel spreadsheet, which allows free text to be entered in each cell.

Normative Pharmacovigilance was considered in the four different angles indicated above.

All answers regarding each line in the questionnaire have to be considered along two levels of regulatory control:

a) the laws (parliamentary control) and decrees (ministerial control), and

b) the normative procedures defined under various instruments such as circular orders, guidelines, official recommendations, etc.
Laws and decrees are usually giving a broad picture of the responsibilities, whereas the normative procedures are detailed and more specific.

Given the federal nature of certain countries, laws (to a lesser extent) and decrees may vary in the same country. In this case, each region/province/federal entity should be considered for its own merit and separate answers should be provided.

Who filled out the questionnaire

The representatives of the working group 3 appointed by their national network coordination for their competences and expertise in pharmacovigilance were responsible for the completion of the questionnaire. Each representative can be supported by the European Correspondent and if appropriate by external resources (such as expert in the field at the Ministry of Health or Drug Agency or the National/Regional Ethics Committee

Considerations on the analysis on results

Introduction

In relation to the specific data required by the deliverable n°6 the sections of the questionnaire selected were:

Sections 3A (Adverse Event Reporting Regulation - By medical research type) and in particular:

Question 3.A.01

Clinical Trials on Medicinal Products.

Question 3.A.01.1

Phase I, II, III, IV.

Section 3B(Adverse Event Reporting Regulation - By product category)

Question 3.B.01

Biovigilance.

Question 3.B.02

Cosmetovigilance.

Question 3.B.03

Haemovigilance.

Question 3.B.04

Pharmacovigilance.

Question 3.B.05

Medical Devices Vigilance.

Question 3.B.06

Toxicovigilance (add specification about subject: drug abuse or therapeutical use).

Same questions of the section 3A were considered redundant since answered by the questions on 3B. In fact, the laws/decrees of adverse event reporting by medical research type, in ECRIN Countries were strictly related to the laws/decrees of adverse event reporting by product category, as reported in section 3B.

A relevant consideration has to be done as regarding to the Phases of clinical trial and in particular to Phase IV, that according to same data may fit in deliverable 6 as well as in deliverable 7.

Data model

Knowledge capacity represents one of the most important resources of the modern society. In fact, a lot of problems that we have to deal with depends on the way we do the important activities of 'problem finding', 'problem setting' and 'problem solving'.

Also if we know very well the difficulties and the complexity of what we described above, today the focus is on the 'human resource' and its capacity of relationship with other people. This gives an 'human' dimension to the entire problem.

Only in this context we could consider some important items as emergency management, cooperation - between people, organisations, nations - performance evaluation of the organisations, new cultural models creation, new rules setting on, etc.

Data Models are consequently an essential tool in order to analyze and study, from an analytic point of view, the issues we summarize above. During the last years data model development gives us two different approaches: 1) the *realistic* approach (its goal is to give substance and reliability to the elements we observe from the reality); 2) the *axiomatic* approach (its goal is to build up a set of coherent axioms and references).

Recently also a third approach has been adopted: the *constructive* approach (its goal isn't to discover the truth, but to discover new ways in order to better define and analyze a problem).

This approach is particularly used when we have questions regarding more general transformation processes as such those concerning the field of new communication and information technologies and changes in cultural context (more in general everything related to important questions regarding territorial and socio-economic systems). Consequently we have a various set of tools in data modelling that combines traditional and non traditional characteristics.

Generally we build up a system that is constituted by a central nucleus that describes the functioning of the system (for example an organisation, an urban system, etc.), another module in order to built up some significant indicators so that you can monitor the system, and a third module that help you in representing the data (graphical, maps, etc.).

This system could give us important information about the impact of our actions, or the activities required achieving the final goal, etc. as in our case.

Countries who participated in the survey

Austria
Denmark
Ireland
Italy
France
Germany
Hungary
Spain
Sweden
UK

Legends

For each question, we consider the answers if give a “yes” (independently for the specific data, eg law/decree – recommendation, guideline, etc) or “no” when no significant data are given and than distinguish the second level (law/decree/recommendation, etc).

Data representation

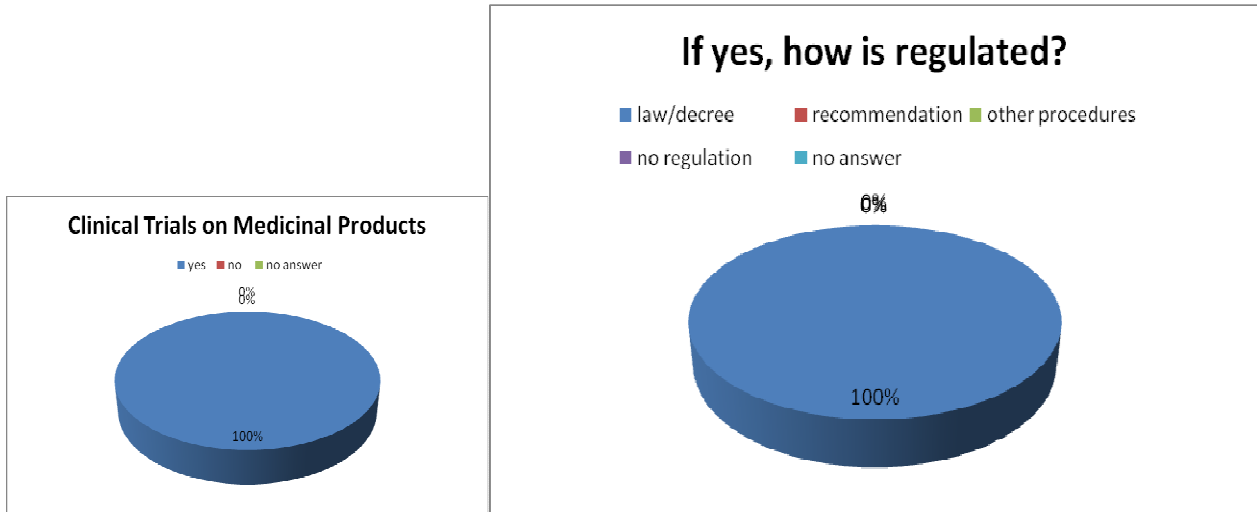
In order to achieve WP3 goals related to deliverable N° 6 here we report the data from the sections and the specific items selected.

The results were presented below:

Item N°1

Survey Question 3.A.01

Clinical Trials on Medicinal Products



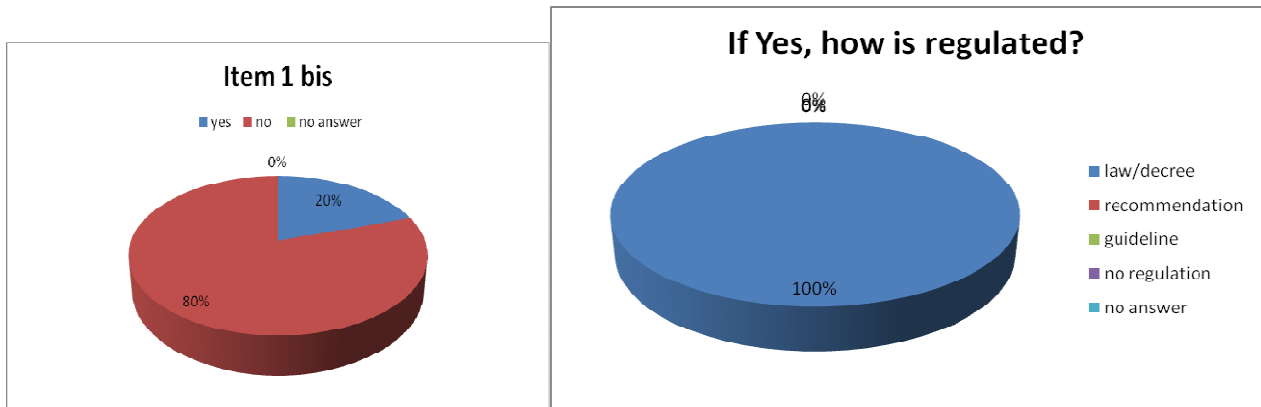
For adverse event reporting in clinical trials on medicinal products, all ECRIN countries implemented a law that complies with the European Directive 2001/20/EC.

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	yes	yes	yes	yes	-
Denmark	yes	yes	yes	yes	-
France	yes	yes	yes	yes	-
Germany	yes	yes	yes	yes	-
Hungary	yes	yes	yes	yes	-
Ireland	yes	yes	yes	yes	-
Italy	yes	yes	yes	yes	-
Spain	yes	yes	yes	yes	-
Sweden	yes	yes	yes	yes	-
United K	yes	yes	yes	yes	-

Item 1 bis

A specific consideration has to be made about the distinction in term of signalling of adverse reaction according to the fact that the signalling occurs during Phase IV or as general post-marketing.

Pre- e post marketing differences



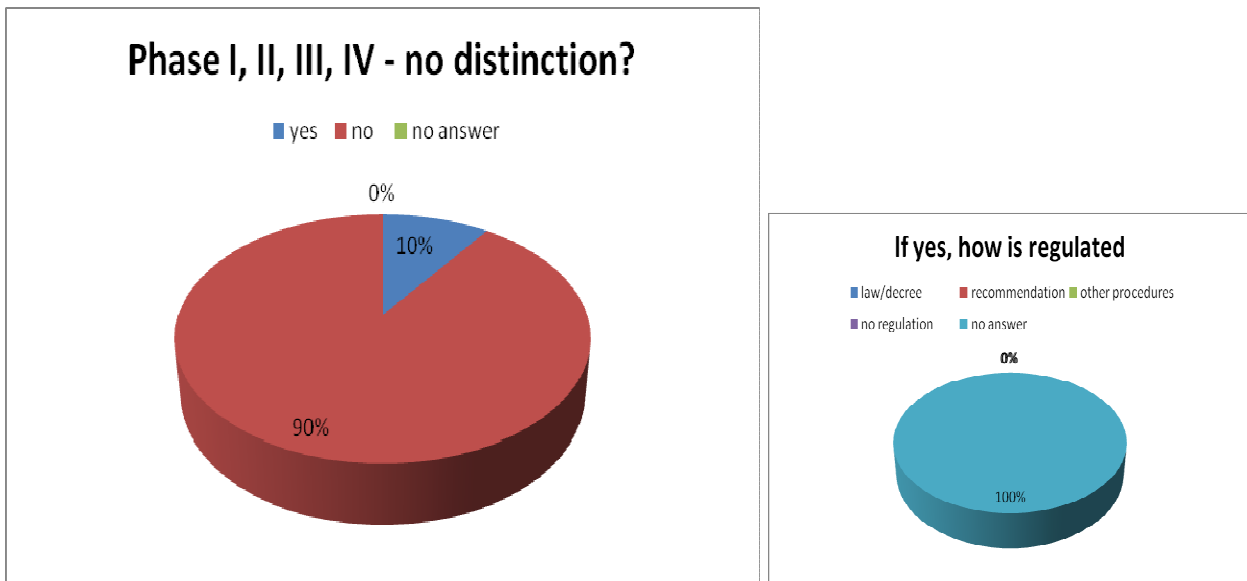
The analysis showed that only France and Germany make a distinction between pre- and post-marketing and this choice is supported by distinct governmental laws.

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	no	-	-	-	-
Denmark	no	-	-	-	-
France	yes	yes	yes	-	-
Germany	yes	yes	yes	-	-
Hungary	no	-	-	-	-
Ireland	no	-	-	-	-
Italy	no	-	-	-	-
Spain	no	-	-	-	-
Sweden	no	-	-	-	-
United K	no	-	-	-	-

Item N2

Survey Question 3.A.01.1

Phase I, II, III, IV.- see previous - no distinction?



We have a very important percentage of the participating ECRIN countries (90%) that answered “no” to the question. The further analysis shows us that in the remaining 10% of countries (Italy) we haven’t any more specification about how the issue is regulated.

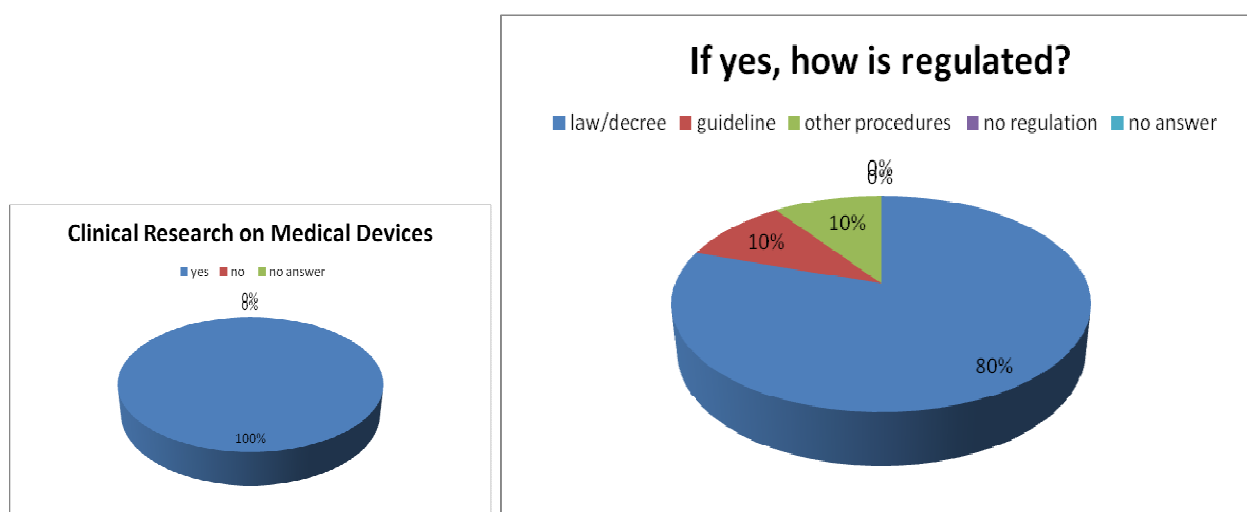
This point require further analysis.

		<i>law/decrece</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	no	-	-	-	-
Denmark	no	-	-	-	-
France	no	-	-	-	-
Germany	no	-	-	-	-
Hungary	no	-	-	-	-
Ireland	no	-	-	-	-
Italy	yes	-	-	-	-
Spain	no	-	-	-	-
Sweden	no	-	-	-	-
United K	no	-	-	-	-

Item N°3

Survey Question 3.A.02

Clinical Research on Medical Devices



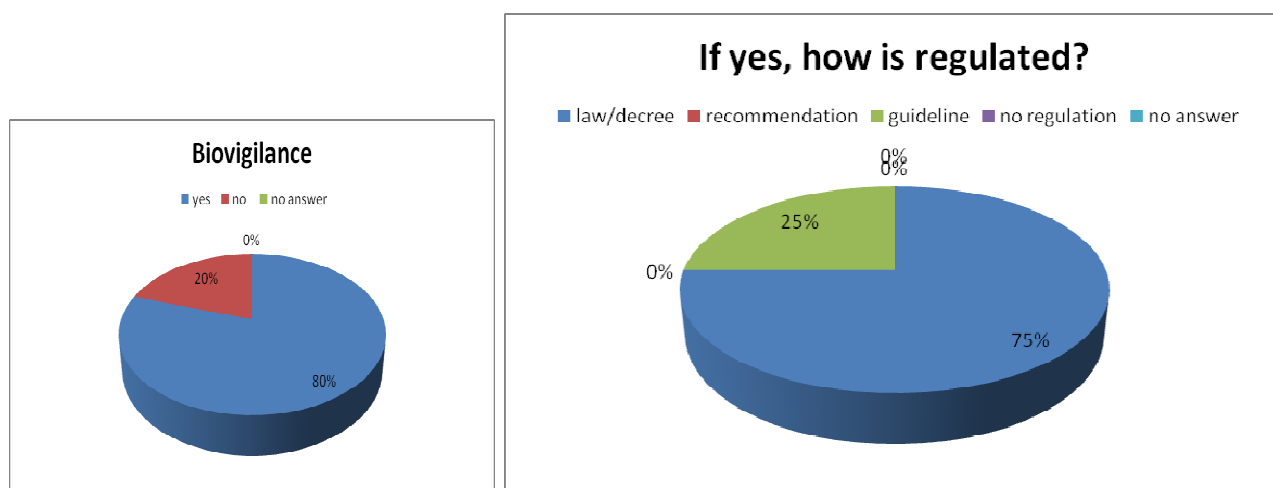
In all ECRIN countries that answered the survey, the adverse event reporting in clinical research on Medical devices is regulated. In 80% it is regulated by law, in 10% by guideline and in 10% by another procedure (to be specified)

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	yes	yes	yes	yes	-
Denmark	yes	yes	yes	yes	-
France	yes	yes	yes	yes	-
Germany	yes	yes	yes	yes	-
Hungary	yes	-	-	-	Other procedure
Ireland	yes	yes	yes	yes	-
Italy	yes	yes	yes	yes	-
Spain	yes	yes	yes	yes	-
Sweden	yes	-	yes	yes	guideline
United K	yes	yes	yes	yes	-

Item N°4

Survey Question 3.B.01

Biovigilance



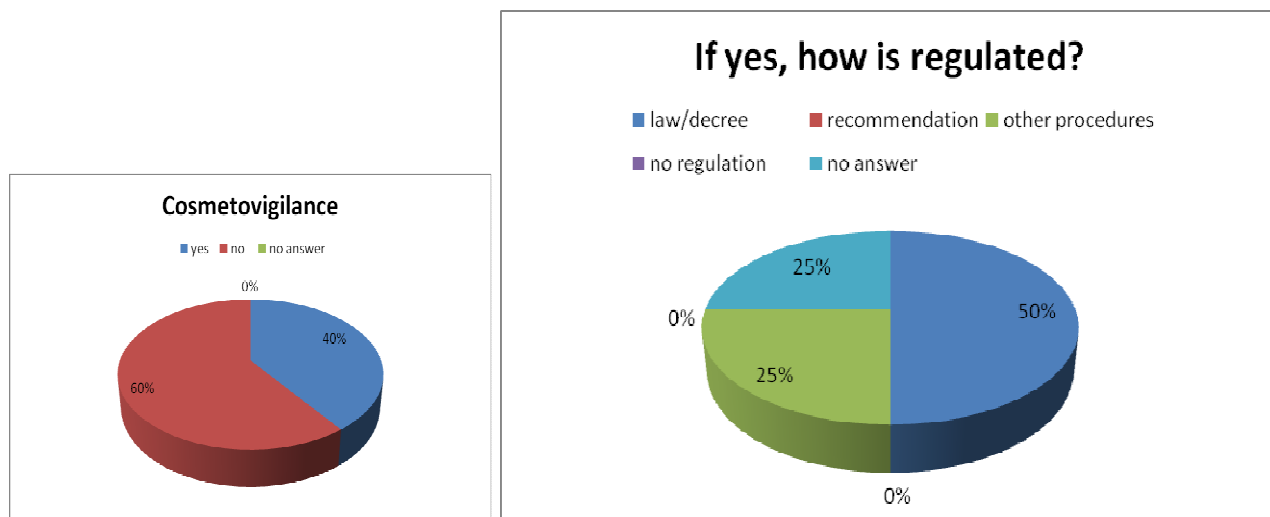
The result of the survey is that the 80% of the countries answered “yes” to the main question also if with different approaches (law/decree – 75%, guideline – 56%). We have also to notice that Austria answered “no” to main question but declared that they have other procedures/guideline, so we considered that Austria answer “yes” to main question.

		law/decree	article	EU compliance	Other procedures/guidelines
Austria	no	-	-	-	Other procedures/guidelines
Denmark	yes		yes	yes	Other procedures/guidelines
France	yes	yes	yes	yes	
Germany	no	-	-	-	-
Hungary	no	-	-	-	-
Ireland	yes	yes	yes	yes	-
Italy	yes	yes	yes	yes	-
Spain	yes	yes	yes	unknown	-
Sweden	yes	yes	yes	yes	-
United K	yes	yes	yes	yes	-

Item N°5

Survey Question 3.B.02

Cosmetovigilance



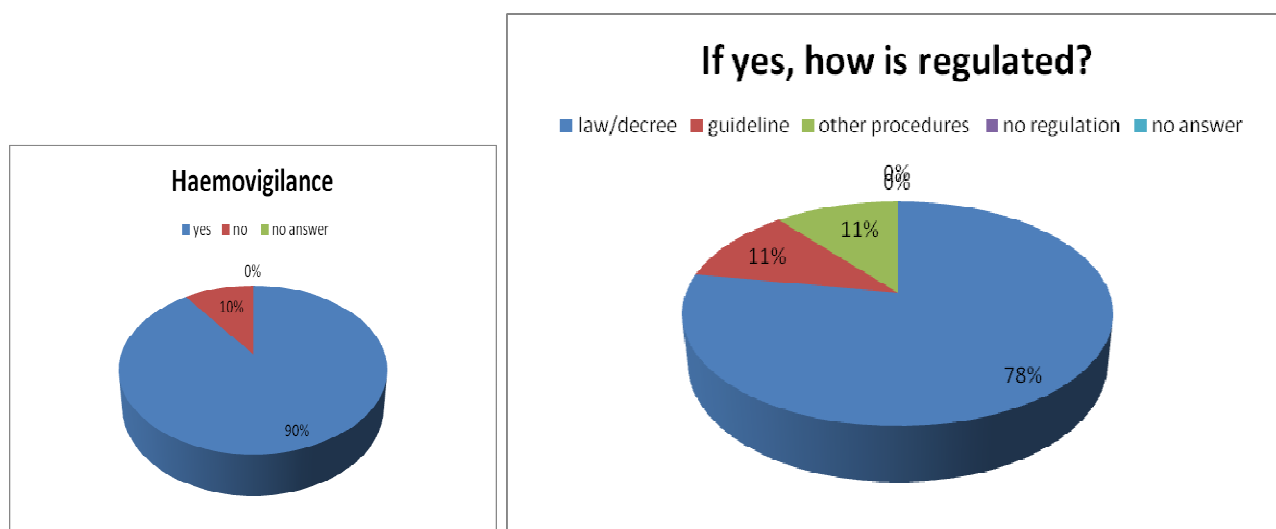
We have a very significant percentage of countries (60%) that answered “no” to the question. The further analysis shows us that the regulation, in the remaining 40% of countries, is regulated by different approaches (law/decree – 50%, other procedures 25%). We have also a 25% of countries that didn't give any more specification about how the issue is regulated.

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	no	-	-	-	-
Denmark	no	-	-	-	-
France	yes	yes	yes	yes	
Germany	no	-	-	-	-
Hungary	no	-	-	-	-
Ireland	yes	-	yes	yes	other procedure
Italy	yes	yes	yes	yes	-
Spain	no	-	-	-	-
Sweden	yes	-	-	-	-
United K	no	-	-	-	-

Item N°6

Survey Question 3.B.03

Haemovigilance

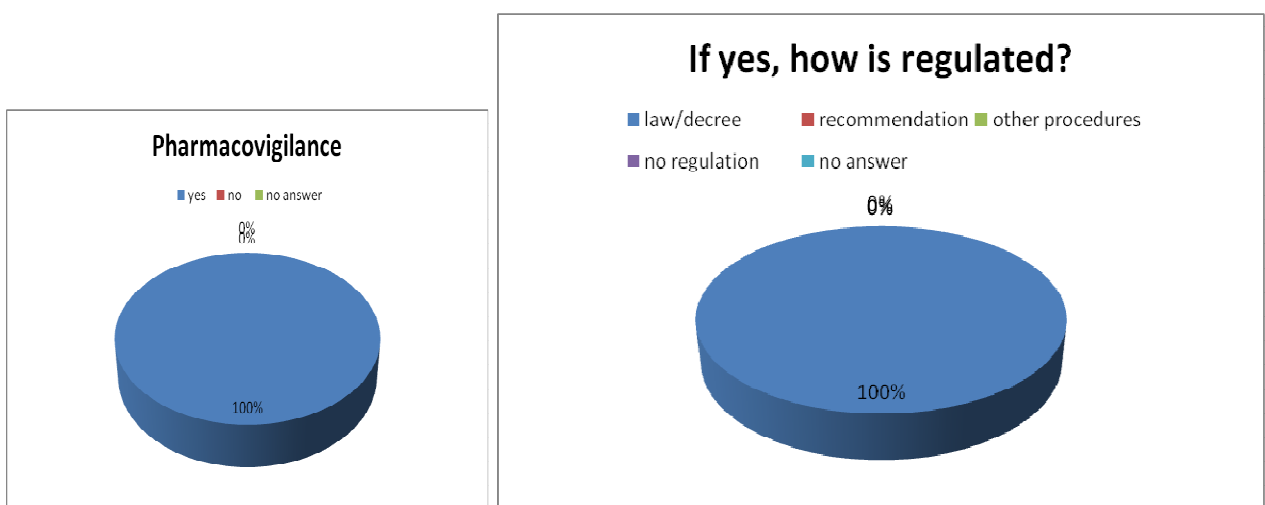


The result of the survey is that the 90% of the ECRIN countries answered “yes” to the main question also if with different approaches (law/decree – 78%, other procedures – 11%, guideline – 11%).

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	yes	yes	yes	yes	-
Denmark	yes	-	yes	yes	guideline
France	yes	yes	yes	yes	-
Germany	no	-	-	-	-
Hungary	yes	-	yes	unknown	Other procedure
Ireland	yes	yes	yes	yes	-
Italy	yes	yes	yes	yes	-
Spain	yes	yes	yes	yes	-
Sweden	yes	yes	yes	yes	-
United K	yes	yes	yes	yes	-

Item N7

Survey Question 3.B.04 Pharmacovigilance



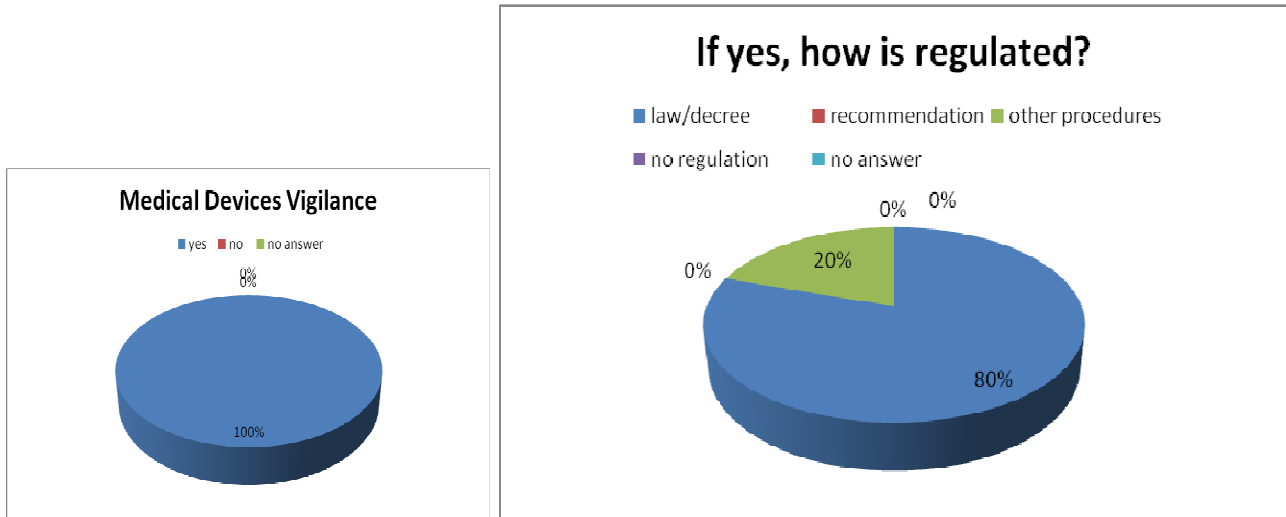
The result of the survey is that the 100% of the ECRIN countries answered “yes” to the main question and the issue is always regulated by law/decree (100%).

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	yes	yes	yes	yes	-
Denmark	yes	yes	yes	yes	-
France	yes	yes	yes	yes	-
Germany	yes	yes	yes	yes	-
Hungary	yes	yes	yes	yes	-
Ireland	yes	yes	yes	yes	-
Italy	yes	yes	yes	yes	-
Spain	yes	yes	yes	yes	-
Sweden	yes	yes	yes	yes	-
United K	yes	yes	yes	yes	-

Item N°8

Survey Question 3.B.05

Medical Devices Vigilance



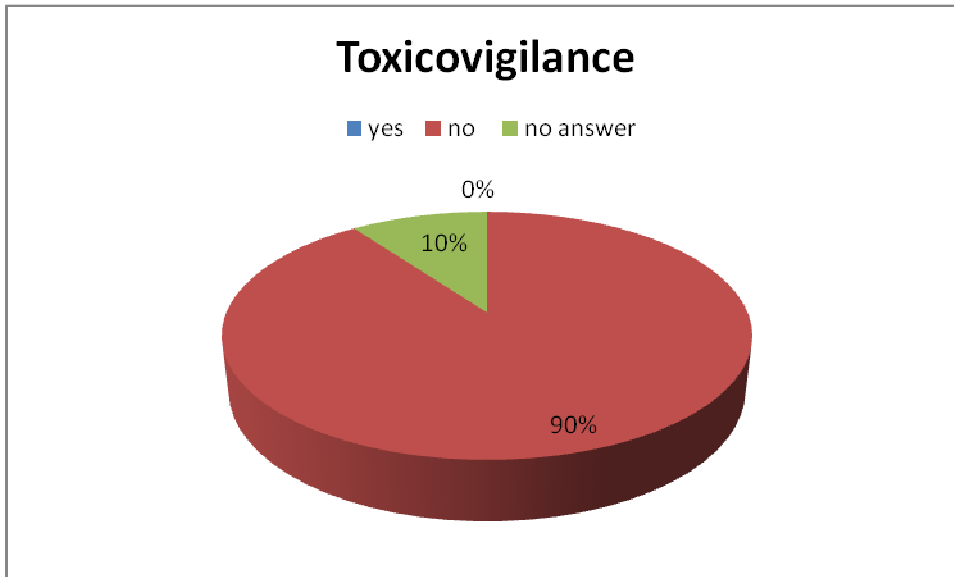
The result of the survey is that the 100% of the countries answered “yes” to the main question also if with different approaches (law/decree – 80%, other procedures – 20%).

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	yes	yes	yes	yes	-
Denmark	yes	yes	yes	yes	-
France	yes	yes	yes	yes	-
Germany	yes	yes	yes	yes	-
Hungary	yes	-	yes	yes	Other procedure
Ireland	yes	yes	yes	yes	-
Italy	yes	-	yes	yes	Other procedure
Spain	yes	yes	yes	yes	-
Sweden	yes	yes	yes	yes	-
United K	yes	yes	yes	yes	-

Item N°9

Survey Question 3.B.06

Toxicovigilance



We have a very important percentage of countries (90%) that answered “no” to the question.

		<i>law/decree</i>	<i>article</i>	<i>EU compliance</i>	<i>Other procedures/guidelines</i>
Austria	no	-	-	-	-
Denmark	no	-	-	-	-
France	yes	yes	yes	yes	
Germany	no	-	-	-	-
Hungary	no	-	-	-	-
Ireland	no	-	-	-	-
Italy	no	-	-	-	-
Spain	no	-	-	-	-
Sweden	unclear	-	-	unknown	-
United K	no	-	-	-	-

Conclusions

Deliverable 6: Guidelines

- Survey of implementation practice of adverse event reporting in Europe for drugs
- Survey of adverse event reporting practice for non drug intervention like medical device and surgical procedure
- Identification of possible pathways to implementation of common practices in adverse drug reporting.

The directive 2001/20/EC, has provided a definition of investigational medicinal products and non-investigational medicinal products as agreed between the Member States and the Commission, giving the following definition for an IMP: "a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form."

If the study is not intended to discover or verify: (a) its clinical, pharmacological and/or other pharmacodynamic effects or (b) to identify any adverse reactions associated with its use or (c) to study its absorption, distribution, metabolism and excretion; with the objective of ascertaining its safety or efficacy, it would not be classified as an IMP.

Another consequence of the definition of a medicinal product as an IMP is that it must be recorded in the EudraCT database, as stated in the Commission guidance on applications to the competent authority (CT-04-EN)4.

The WP3 was directed to analyze either the normative aspects of the procedures to investigate adverse events occurring both in drug or the non-drug products used in human diagnostic or therapeutic activities.

The adverse reporting is analysed particularly during experimentation of drug and non-drug products, i.e. during clinical studies adopted according the rules given by EMEA. This choice represents a limitation since, at present, the monitoring by EMEA is restricted to the pharmaceutical companies, and, consequently also the majority of EU Member States are monitoring, specifically per possible adverse event, the pharmaceutical products.

In this sector the adverse reporting is harmonised, in principles, at the EU level for clinical trials on medicinal products through the Eudravigilance system. Differences are however present in some particular aspects and require fostering for the harmonisation as follows:

- A. For the Phase I trials it has to be defined whether a different procedure or a subgroup of the actual procedure has to be adopted. This aspect may be relevant for

trials related to biotherapy and in particular for trials with new biological drugs, that have had already problems for first-in-man experimentation. How to use the proposed guide-line by EMEA, taking into account the different norms used by EU MSs is a main point to be assessed in the future

- B. The disharmony in the Phase IV trials in some countries is an other point to be addressed in the future. Here it is required to analyze in-depth the different norms present in EU MSs and try to interpret the reasons for disharmony, whether due really to a problem of different laws or decree, or simply a different interpretation of the norms, suitable of a modification through a circular by the Drug Agency that all MSs have. This point has also to be discussed with the EudraVigilance of EMEA, since adverse events are included by EudraVigilance in different ways according to the kind of reporting coming from the National Competent Authorities. A communication regarding this particular point should also be addressed to the Directorate of Enterprise who is responsible for the procedure to be adopted by EudraVigilance.

About the non-drug products the differences among EU Member States of ECRIN are quite consistent.

Only France, among ECRIN partners, consider globally the nature of the health product (medicinal product, medical device, blood product...), and consequently the adverse effects that are governed by specific categories of vigilance systems, whose implementation is ensured by the French Agency for the Safety of Health Products (Agence française de sécurité sanitaire des produits de santé- Afssaps).

They are :

- the pharmacovigilance (medicinal products and blood derived medicinal products),
- the haemovigilance (labile blood-derived products)
- the materiovigilance (medical devices), example: prostheses of hip,
- the reactovigilance (medical devices of in vitro diagnosis), example: tests of pregnancy
- the dependency on medication (psychoactive substances),
- the biovigilance (organs, tissues, cells and ancillary therapeutic products),
- the cosmetovigilance (cosmetics).

All vigilances have the same objectives: to identify and to reduce the risks related to the health products, by collecting, recording, identifying, analysing and evaluating adverse events or incidents contributes to the aim of optimising the safety of use of these products.

In the majority, if not all, MSs the non-drug products are in general taken in consideration for the approval of the product but not for the adverse event that may cause , this irrespective on whether the product come from EU MSs or out of EU.

The implementation is required for all these MSs; the activity should be addressed to define the procedure that an adverse event of non-drug product has to follow, taking into account the different procedure already existing for drug adverse event.

In fact it is not convenient to design new Institutions or agencies to charge of such a control. It has also to be defined whether it has been taken into consideration the simple spontaneous reporting of the adverse event or to consider also to have trials on a new non-drug product, in spite of being already authorized, at least by the Ethical Committee .

These considerations should be addressed particularly for the medical devices, both "materio" and "reacto" and for cosmetics, that show the most disharmony in EU, while haemovigilance is well controlled in all ECRIN Member states, this being probably due to the required monitoring for AIDS contaminated blood or haemo-derivatives infused in the past.

Biotherapy in consideration to the different actions available (organs, tissues, cells and ancillary therapeutic products) is such a broader area, that requires, first of all, a categorization, at present not available, to define the level of efficacy and level of risk that should be acceptable, since these patients are generally extremely fragile. The efficacy and the risk should be defined for each category as well as the kinds of possible adverse event in relation to the patients to whom these therapies have to be applied. The definition of specific protocol design and inclusive or exclusive criteria are compulsory.

The implementation needed to overcome the disharmony requires a specific intervention of the Commission; it is hoped that the new Directive in course of consultation might include some of the issues highlighted in the present survey.

The software program, that allows managing the survey and the questionnaire, was built up as an open system in order to manage in the future other and new ECRIN countries data and information or as well other different surveys and investigations.

Appendix

Notes

The documents are available on the questionnaire online at the address of the European Correspondent (and expert) of the single Country and on the ~~my~~ address:

<http://www.cirm.net/wp3/login.php>

Username: fsavarese

Password: admin

The questionnaire allows to consultation data for each Country, the answers for single question and the data for the partners for each Country.

Questionnaire Sections

We report below the 4 sections forecasted by the survey.

Section 1 PhV System Organisation

Question 1.01

Is there a Central Reporting Facility for SUSARs?

Question 1.02

Is Electronic Reporting available? How is it regulated? Is the purchase of MedDRA publicly restricted? How MedDRA training is delivered (free/other fees)? Other coding system are used?

Question 1.03

Is coding with MedDRA required/recommended? Is the purchase of MedDRA publicly subsidised? How MedDRA training is delivered (free/other fees)? Other coding system are used?

Question 1.04

Is EudraVigilance Reporting mandatory? Who must report?

Question 1.05

Is Education and Training in Vigilance required/recommended? For whom? How much? Is certificate required for certain stakeholders?

Question 1.05.1

Are the EMEA London Eudravigilance courses mentioned? Is attendance subsidised by the public sector?

Question 1.05.2

Are there national courses about Vigilance reporting? Please specify (academic, private, government, with website or reference).

Question 1.06

Is a standard reporting form imposed?

Question 1.07

Is casualty algorithm imposed

Section 2 PhV Stakeholders

Question 2.01

Subject; Patient; Volunteer; Consumer

Question 2.02

Doctors and Health Professionals (observing physician; observing healthcare professional; observing caregiver; family physician; healthcare institution; investigator).

Question 2.03

Specific Vigilance center.

Question 2.04

Local Health Authorities.

Question 2.05

National/regional Health Authorities (Ministry of Health, Product Agency).

Question 2.06

Supranational Health Authorities (e.g. WHO, EMEA).

Question 2.07

Ethical Committee (local and national/regional). Are Disease Oriented Ethical Committees present?

Question 2.08

Sponsor or Market Authorisation Holders.

Question 2.09

Manufacturer.

Question 2.10

Pharmacist/Distributor.

Section 3A Adverse Event Reporting Regulation - By medical research type

Question 3.A.01

Clinical Trials on Medicinal Products.

Question 3.A.01.1

Phase I, II, III, IV.

Question 3.A.01.2

Specific Interventions.

Question 3.A.02

Clinical Research on Medical Devices.

Question 3.A.03

Other Therapeutic Trials.

Question 3.A.04

Diagnostic studies.

Question 3.A.05

Clinical Research on Nutrition.

Question 3.A.06

Other CLinical Research.

Question 3.A.07

Epidemiology/observational studies

Section 3B Adverse Event Reporting Regulation - By product category

Question 3.B.01

Biovigilance.

Question 3.B.02

Cosmetovigilance.

Question 3.B.03

Haemovigilance.

Question 3.B.04

Pharmacovigilance.

Question 3.B.05

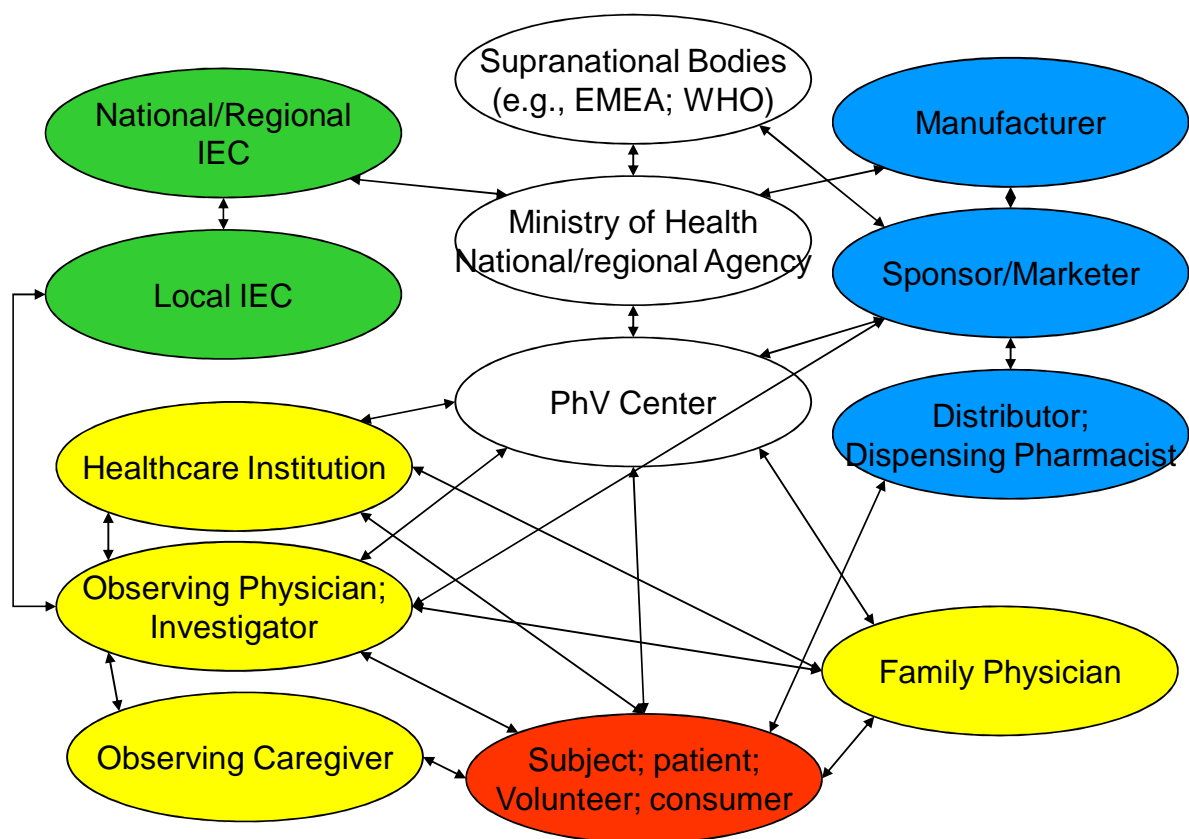
Medical Devices Vigilance.

Question 3.B.06

Toxicovigilance (add specification about subject: drug abuse or therapeutical use).

Possible Flow Diagram Elements

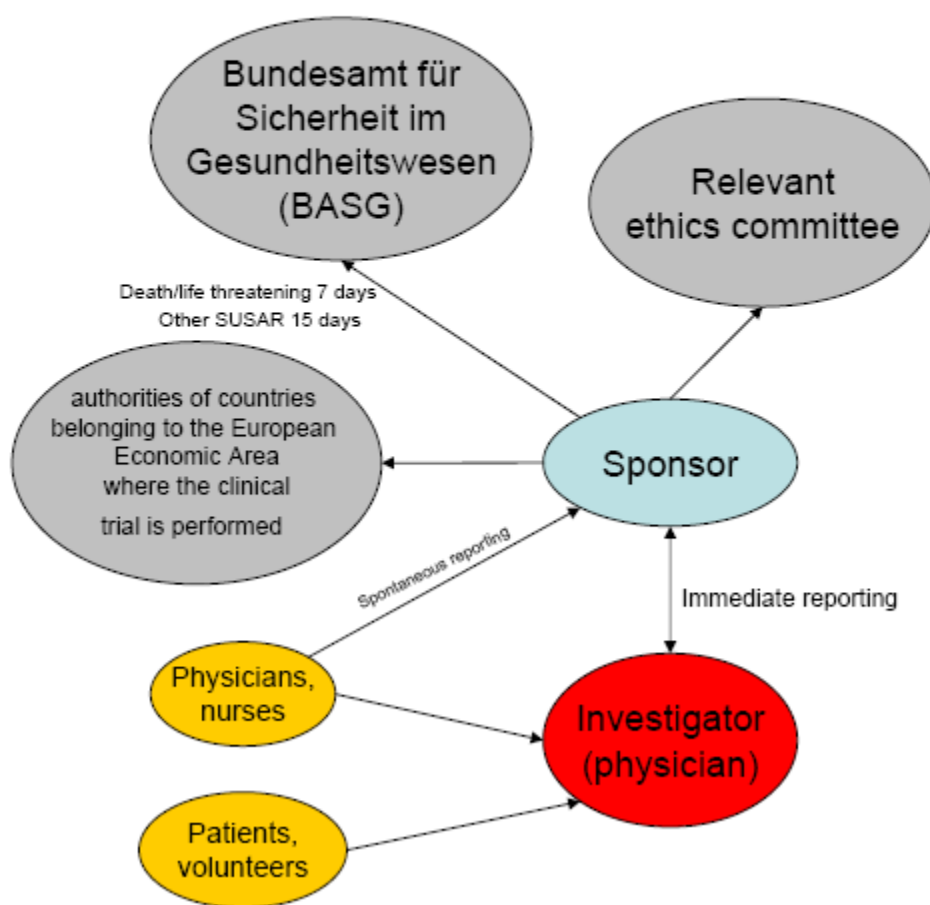
This is a general sort of diagram which represents the various stakeholders and indicates who may interact with whom. The Picture below offers you the hypothetical types of stakeholders and how they may interact.

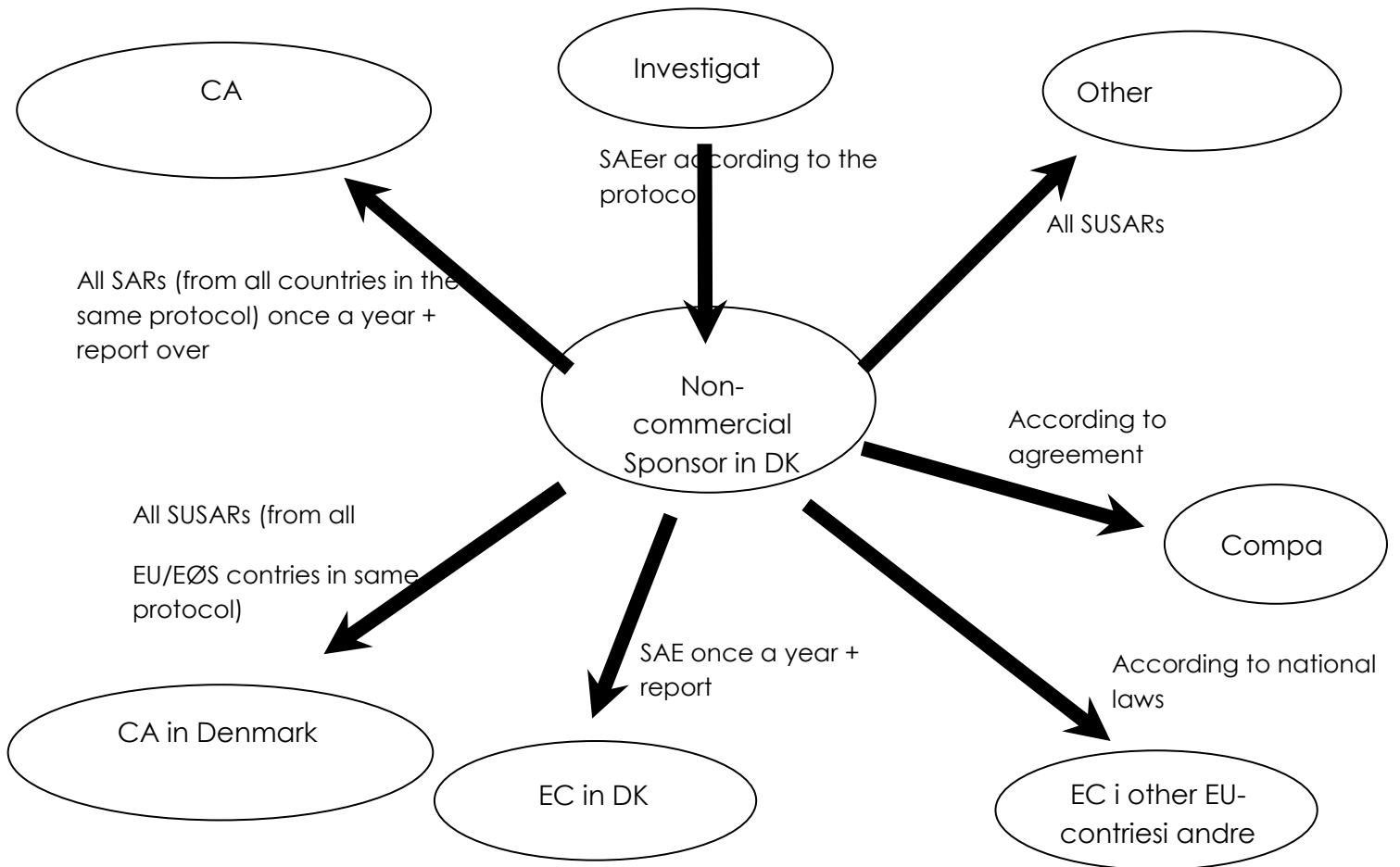


The following pages report the chart regarding each country.

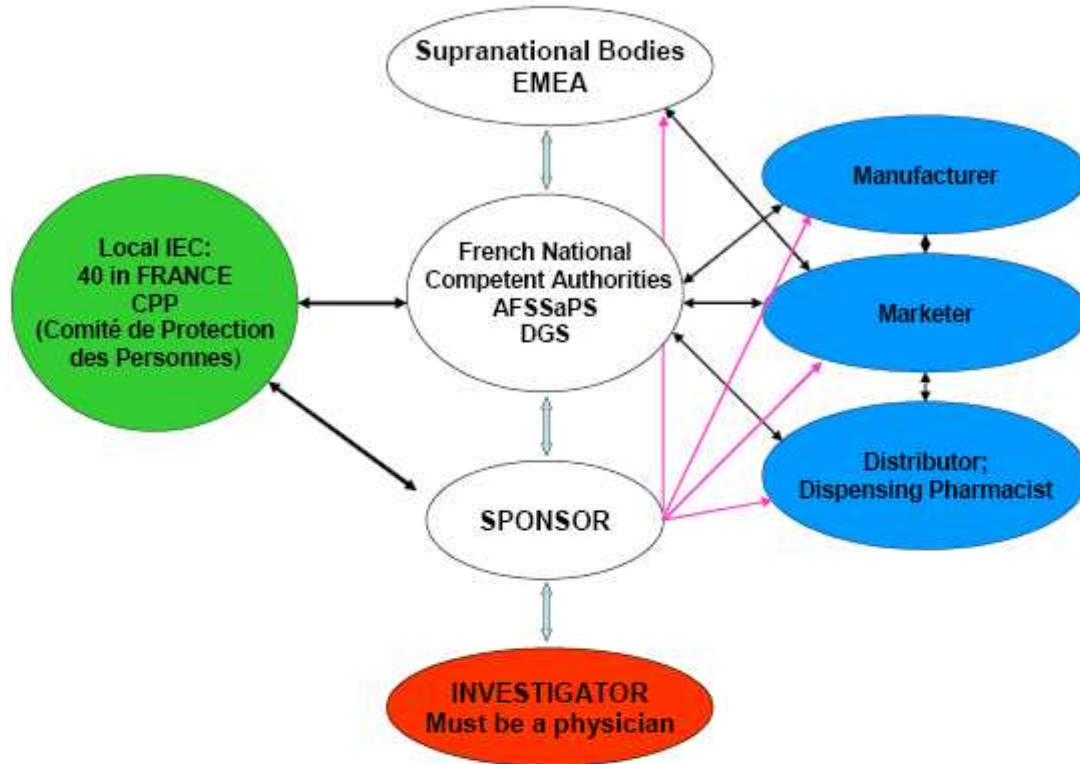
Austria

Notification flow diagram Austria





PRE-MARKETING FRENCH VIGILANCE SYSTEM : ROLE OF THE MOST IMPORTANT STAKEHOLDERS



The Agence Francaise de Sécurité Sanitaire des Produits de Santé (AFSSaPS) :

Direction de l'évaluation des médicaments et des produits biologiques

Direction de l'évaluation des dispositifs médicaux

- Receives from the sponsors all SUSARs, safety Issues and Annual Safety report of all clinical trials
- Controls the global safety of clinical trials
- Collaborates with EMEA and competent Authorities in EU.

The Direction Générale de la Santé (DGS) (for « physio-pathological studies »)

Politiques de Santé et Stratégies & Evaluation des programmes de recherche (will be integrated to the AFSSaPS in June 2008).

- Receives from the sponsors all SUSARs, safety Issues and Annual Safety report of all clinical trials
- Controls the global safety of clinical trials
- Collaborates with EMEA and competent Authorities in EU.

The Comité de Protection des Personnes (CPP)

- Receives from the sponsor all SUSARs, safety Issues and Annual Safety report of all clinical trials

The Academic sponsor :

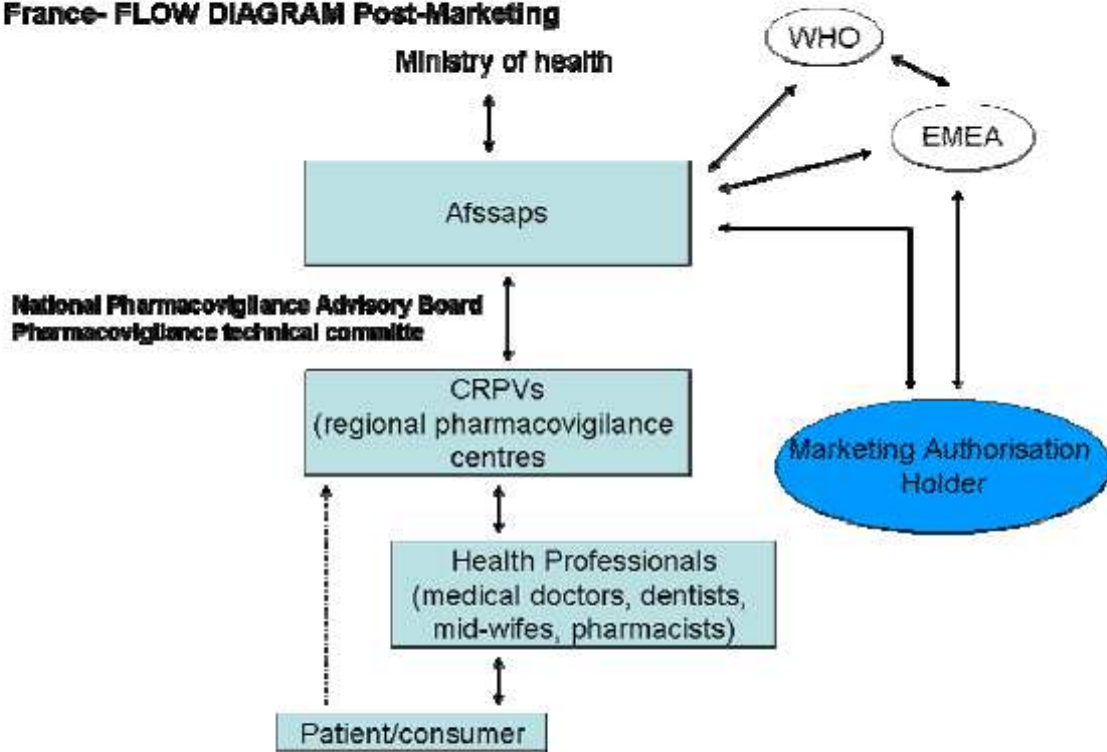
- Notifies all SUSARs, new safety Issues and Annual Safety report of all clinical trials
- Controls the global safety of the trial
- Interacts with manufacturer/pharmacies
- Inform pharmaceutical companies of serious adverse events if any signed agreement

The investigator :

- Must be a physician
- Notifies to the sponsor all serious adverse events that occurs in his clinical trial

POST-MARKETING FRENCH VIGILANCE SYSTEM : ROLE OF THE MOST IMPORTANT STAKEHOLDERS

France- FLOW DIAGRAM Post-Marketing



The French vigilance system is based on:

Health professionals (physicians, dentists, midwives, pharmacists) are under a legal obligation to report as rapidly as possible to the vigilance system any serious or unexpected adverse effect observed in a patient. The spontaneous declaration of the adverse events is carried out using the CIOMs reporting form .

The statements are made by the professionals of health and/or are collected by local and regional correspondents (regional Centers of pharmacovigilance, regional Centers of haemovigilance, Centre of "Evaluation and Information on dependency on medication"), charged of the collection and the transmission of the adverse effects to Afssaps.

The marketing authorization holder (MAH) must declare at the French Agency for the Safety of Health Products (AFSSAPS) the adverse effects of which they are informed through expedited reports for serious or unexpected AE.

The MAH is also required to provide Periodic Safety Update Reports and other relevant post-authorisation information.

Regional Pharmacovigilance Centres:

A network of 31 regional pharmacovigilance centres (CRPV- Centres régionaux de Pharmacovigilance) located throughout the country in order to promote local exchanges with healthcare professionals.

The CRPV are located within pharmacology, clinical pharmacology or clinical toxicology department at the university hospital centres and each covers a specific geographical territory.

Their missions are:

- collection, detection, validation of adverse events and registration in the national pharmacovigilance database
- transmission to Afssaps
- training and information of health professionals
- development of pharmacovigilance knowledge

Technical Pharmacovigilance Centre:

The centre, composed of all the CRPV managers, is in charge to prepare the work of the National Commission by coordinating the gathering of information on adverse reactions to medicinal products, evaluating the information gathered and coordinating, identifying and evaluating the inquiries and studies requested from the regional pharmacovigilance centres and MAH.

The National Pharmacovigilance Commission:

The commission based at Afssaps is in charge of the evaluation of the information on adverse reactions to medicinal products, of providing opinions and measures to be taken.

Afssaps (Agence Française de sécurité sanitaire des produits de santé):

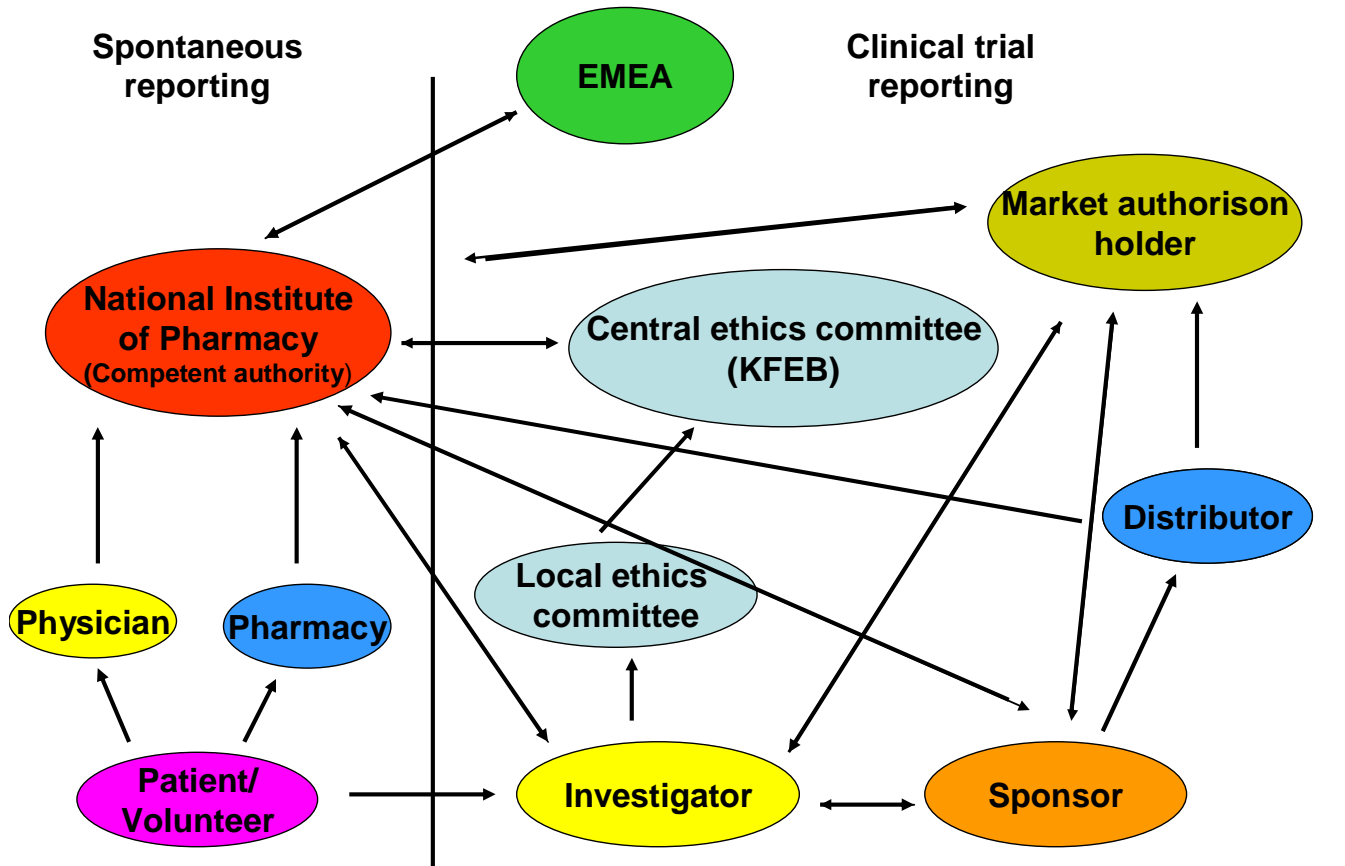
Afssaps applies the national pharmacovigilance system.

The agency organises and coordinates the implementation of the vigilance systems concerning healthcare products.

Afssaps has four principal missions:

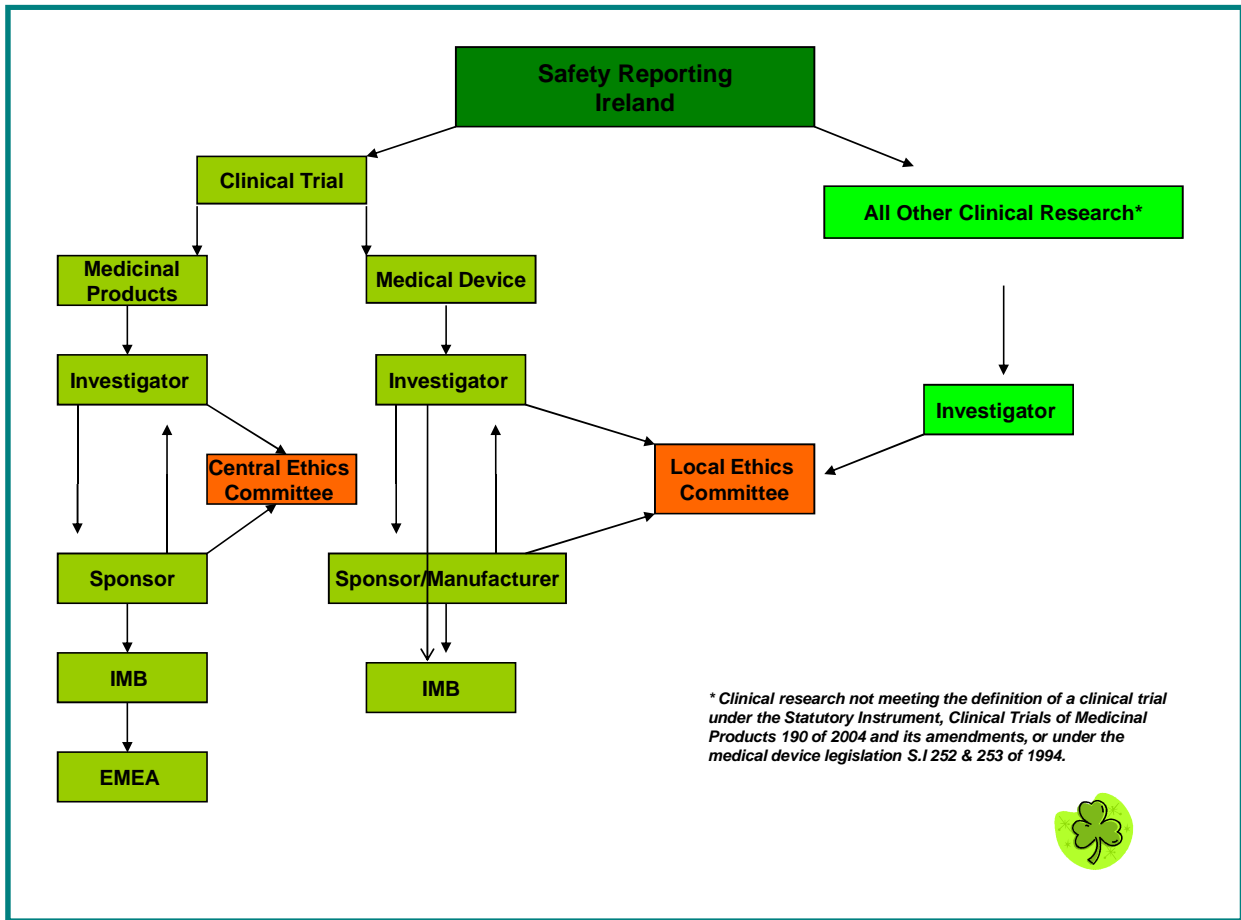
- scientific evaluation
- controls (including the advertising)
- inspection
- information for healthcare professionals and the generic public.

NOTIFICATION FLUX- HUNGARY

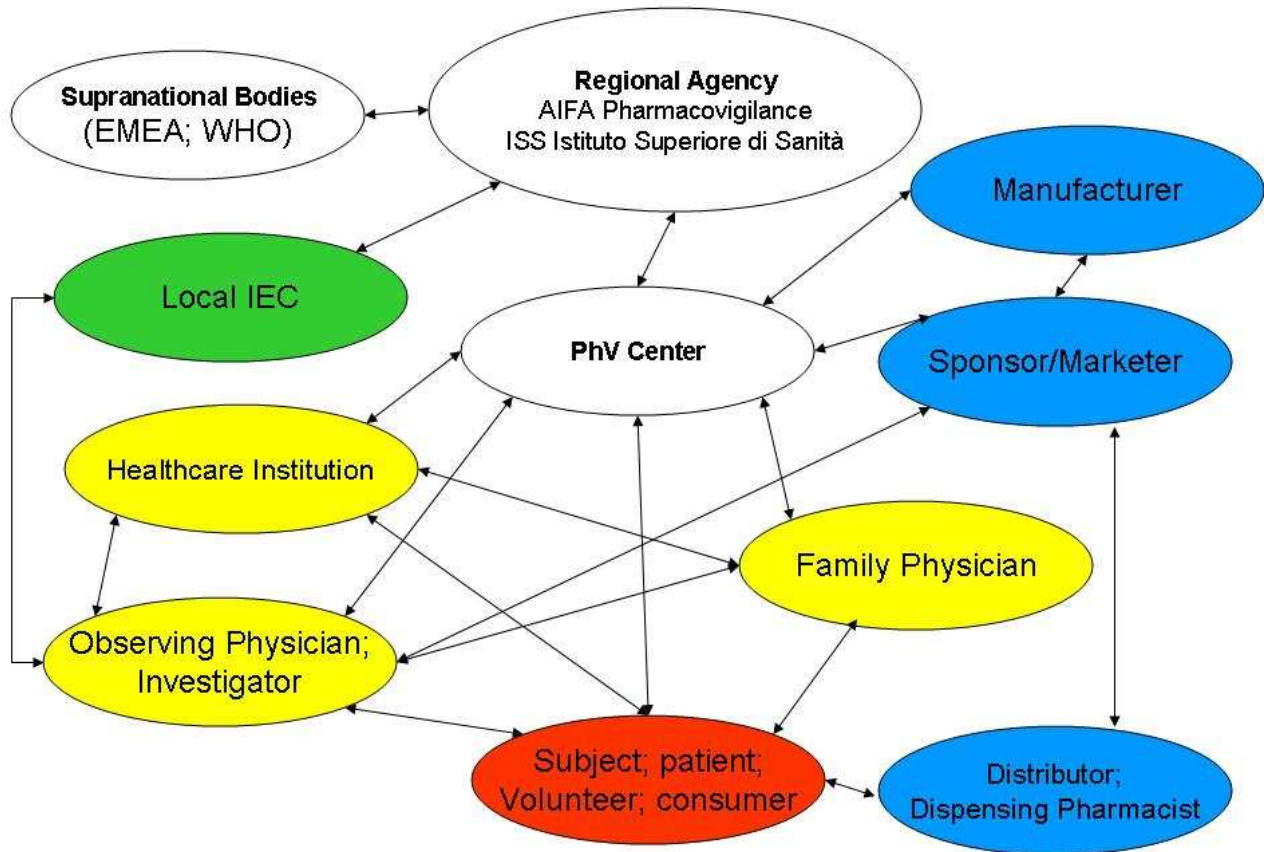


KFEB: Clinical pharmacological ethical committee

Ireland



ITALY FLOW DIAGRAM



Italian Pharmacological System. Role of the most important stakeholders

The National Pharmacological System is constituted by:

- Italian Drug Agency -Agenzia Italiana del Farmaco (AIFA) - that:
 - chairs the system
 - promotes all the fluxes required for pharmacovigilance,
 - coordinates the National Telematic Network that connects all health structures, Regions and pharmaceutical Companies,
 - collaborates with EMEA and competent Authorities in EU.

AIFA works through four commissions:

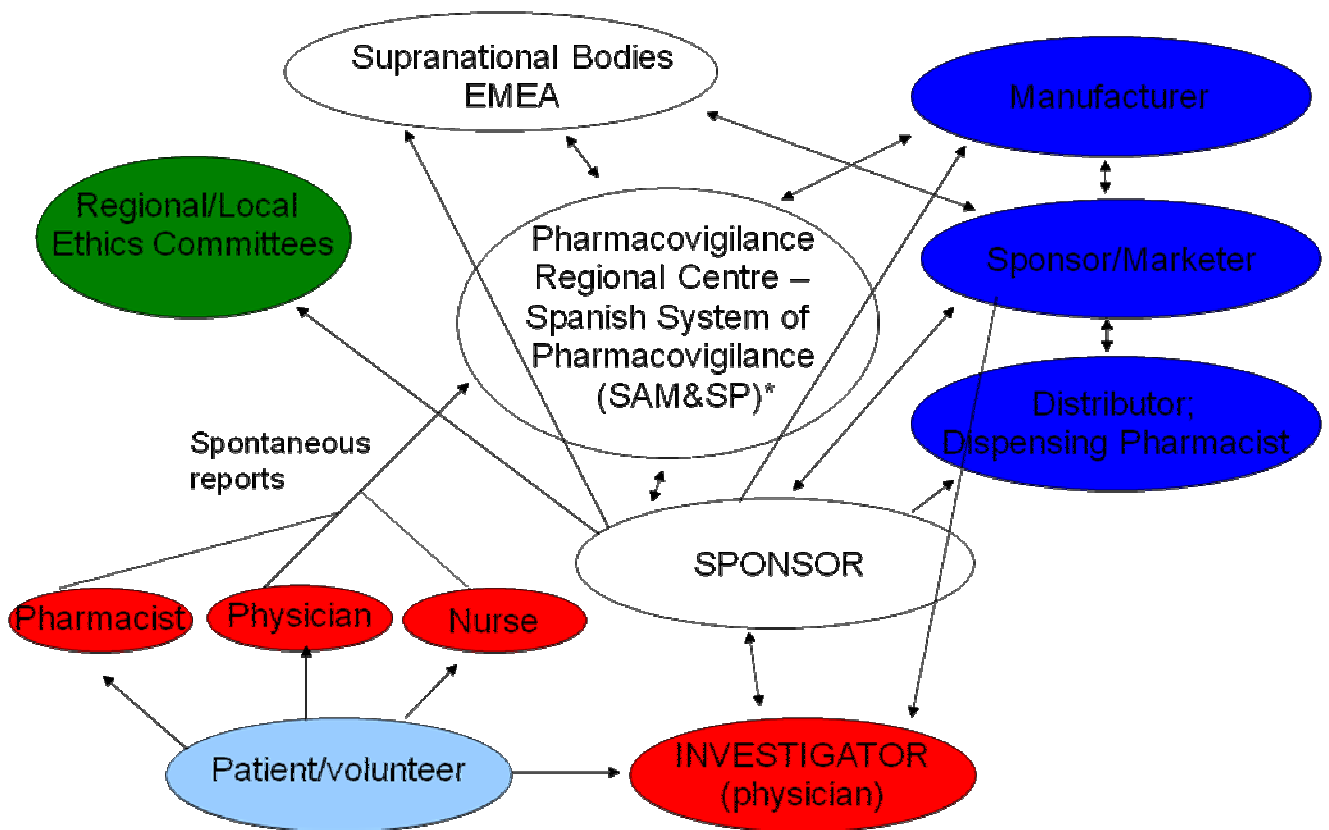
- *Technical-Scientific Commission* to evaluate new registration proposals
- *Price & Reimburse Commission* to define together with Companies the price reimbursed by the National Health System

- *AIFA-Regions Connection Centre* to promote with Regions the price determinants and the drug information flux, including pharmacovigilance
 - *R&D Commission* to promote scientific research including independent research
- The National Network of Pharmacovigilance that represents a tool of communication and information for all responsible for pharmacovigilance:
 - Regions,
 - Local Health authorities (ASL),
 - Hospitals,
 - Research Hospitals (Istituti di ricovero e cura a carattere scientifico - I.R.C.C.S.)
 - Pharmaceutical Companies.

The system works as a closed and private network, to which only operators of the above health structures and companies can enter; through them, notifications by doctors and pharmacists can be reported.

- Single Regions or Grouped Regions that can collaborate with AIFA in pharmacovigilance activity, by giving data at integration of data directly obtained by AIFA. The Regions for their own activity may organize Pharmacovigilance Centres.
- Local Health authorities (ASL), Hospitals, Research Hospitals (Istituti di ricovero e cura a carattere scientifico - I.R.C.C.S.), Private and Public University Policlinics and similar structures that have the duty to nominate a responsible of pharmacovigilance, who has to be registered in the National Pharmacovigilance Network in order to obtain the required qualification for managing the notification from health operators.
- Market Authorization Holders (Pharmaceutical Companies) have the duty to register all suspected adverse drug reactions observed in Italy, European Union or Third Country. Registration in Italy should be send within 15 days to AIFA.
- Doctors and health operators who have the duty to notify all suspected adverse reactions observed under their own activity; this notification is given through a specific form to the responsables of pharmacovigilance in their own health structure or, when not present, to the Local Health Authority. The responsible, after having controlled the congruity of the notification, has to send it to the databank of the National Pharmacovigilance Network within seven days, monitoring also its inclusion at Region and the pharmaceutical company level.

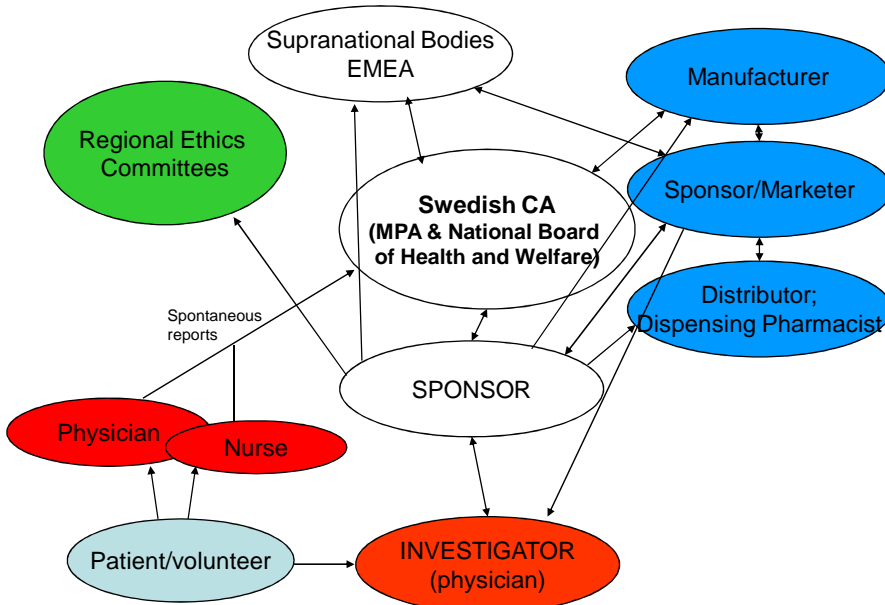
NOTIFICATION FLOW DIAGRAM; Spain



* Spanish Agency of Medicines and Sanitary Products

Sweden

NOTIFICATION FLOW DIAGRAM; Sweden



United Kingdom

