EUROPEAN CLINICAL RESEARCH INFRASTRUCTURES NETWORK - TRANSNATIONAL WORKING GROUPS

ECRIN-TWG

FP6-2005-Life Sciences and Health LSH-2005-3-4

Contract # 037199

DELIVERABLE N° 8

A REPORT ON THE COMPUTERIZATION OF ADVERSE EVENT REPORTING

Date of preparation: 09/09/2008 Draft version n. 1

Working Group 3 **Transnational Working Group on Adverse Events reporting**

Contact: Prof Nicola Fabris
Dir.Scuola Spec. Patologia Clinica - Univ. di Pavia e
Dir. Generale C.I.R.M. - Consorzio It. Ricerca in Medicina
General Office - Ist. Villa Marelli - Niguarda, Viale Zara 81- 20159 Milano (I)
Tel. ++39.02.66825289
E-mail nicola.fabris@cirm.net

List the members of the working group

Contact:

Nicola FABRIS, Chair - Italy
Arrigo SCHIEPPATI, Chair - Italy
Ove ANDERSEN, Denmark
Charlotte CALOV,Denmark
Jens Sandhal CHRISTIANSEN, Denmark
Evelyne JACQZ-AIGRAIN, France
Friedrich MITTERMAYER, Austria
Pirayeh EFTEKHARI, France
Delphine BERTRAM,France
Monika SEIBERT-GRAFE, Germany
Claudia MARX, Germany
Olga GRICHINA, Germany
Christine MULLER, Germany
Christian ROSÉ, Germany
Györgi BLASKO, Hungary
Ailbhe MURRAY, MSc Nursing Director, Ireland
Maurizio BONATI - Clavenna Antonio, Italy
Jaume TORELLO, Spain
Maribel LUCENA, Spain
Carina ALVFORS, Sweden
Sue TEBBS, UK
Jacqueline MATHEWS, UK

European Correspondents:

Diana WINTER, Austria
Kate WITHFIELD, Denmark
Tommi KOSKELA, Finland
Christine KUBIAK, France
Wendy ROBINSON, Germany
Gabriella KARDOS, Hungary
Siobhan GAYNOR, Ireland
Alfonso SASSUN, Italy
Nuria SANZ, Spain
Raquel HERNANDEZ, Spain
Hanna JOHANSSON, Sweden
Pegah SOURI, Sweden
Myriam CEVALLOS CHRISTEN, Switzerland
Svetozar MIHAYLOV, UK

Summary

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 Securité 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 committe)
CTA	Clinical Trial Authorisation
DMA	Danish Medicine Agency
DGS	Direction Générale de la Santé (french General Direction of Heath)
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
EMEA	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 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

For an introduction regarding the WP3 activity and more details concerning the survey (that allows collecting data as reporting in the Preliminary Considerations section) please see the ***Deliverable N° 6***.

Considerations on the analysis on results

Introduction

In relation to the specific data required by the deliverable n°8 the sections of the questionnaire selected were:

Section 1 PhV System Organisation

Question 1.02
Is Electronic Reporting available? How is it regulated? Is the purchase of MedDRA publicly restricted? How MedDRA training in 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 coursers 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).

Data model

See the same section in Deliverable N° 6 document.

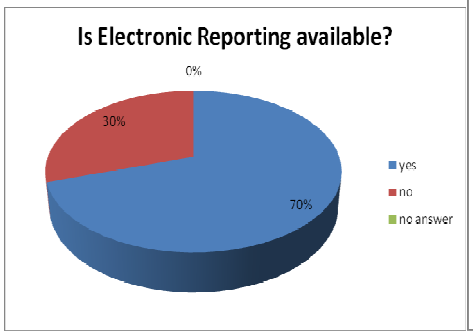
Data representation

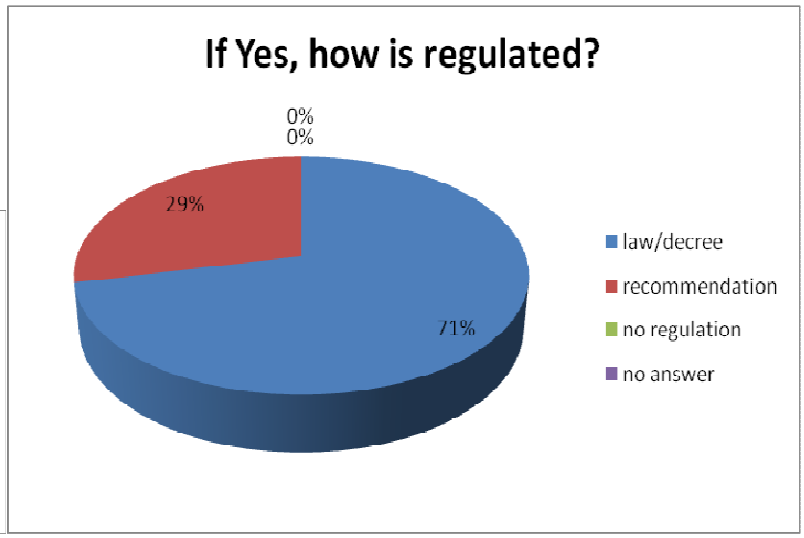
In order to achieve WP3 goals related to deliverable N° 8 here we report the data from the sections and the specific items selected, either specifically related to the electronic use for the adverse reporting or to the educational aspect that generally contains also information on how to use the electronic system.

The results were presented below.

Item N°1

Survey Question 1.02
Is Electronic Reporting available?





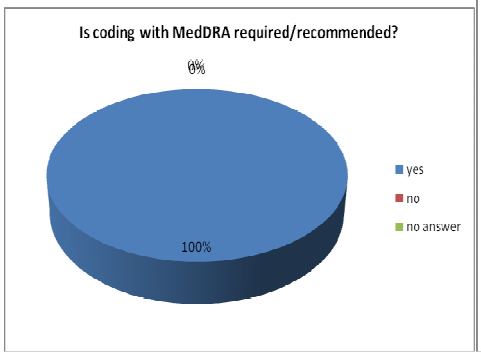
In this case we have a very significant percentage of countries (70%) that already have an electronic reporting available. The analysis of this percentage shows us that in the 100% of countries only 71% is regulated by law (71%) and in the other by recommendation (29%). We think that also the percentage of those countries where the Electronic reporting system is regulated by law is very significant (71%). We have also to notice that Spain declared that Eletronic reporting isn't available, but, at the same time, it's regulated by law/decree. In our analysis we considered that Spain answered "no" to main question.

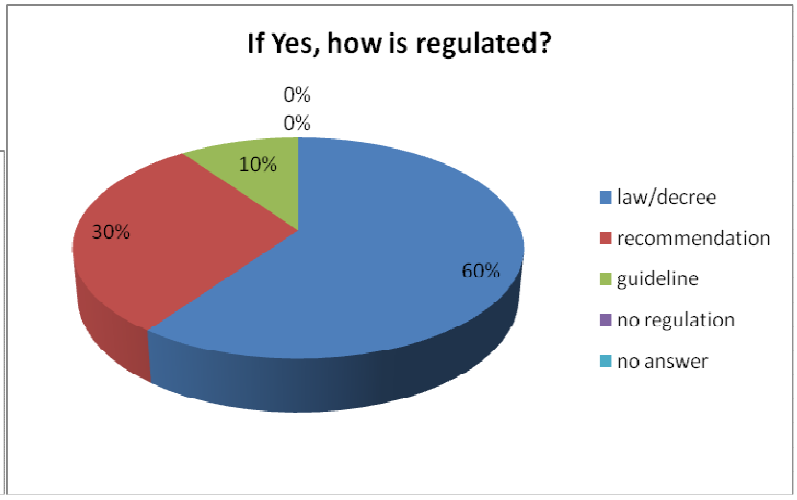
		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*	*How is regulated?*
Austria	**no**	-	-	-	-	-
Denmark	**yes**	-	-	yes	recommendation	CS to EV - non CS to CIOMS
France	**no**	-	-	-	-	not reported
Germany	**yes**	yes	yes	unclear	-	CS obligatory - non CS not obbligatory
Hungary	**yes**	yes	-	yes	-	by the NIP
Ireland	**yes**	yes	yes	yes	-	Obligatory
Italy	**yes**	-	-	yes	recommendation	Through PV Centers/AIFA
Spain	**no**	yes	yes	yes	-	not available
Sweden	**yes**	yes	yes	yes	-	Each Sponsor should report to MPA through EV. No electronic reporting to EC2.
United K	**yes**	yes	yes	-	-	Through MHRA

Item N°2

Question 1.03

Is coding with MedDRA required/recommended?





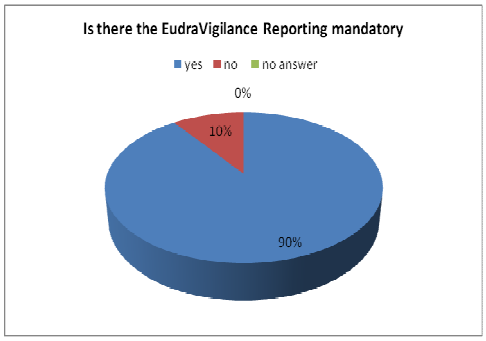
The result of the survey is that in the 100% of countries the coding with MedDRA is required / recommended also if with different approaches (law/decree, recommendation, guideline). We notice that the percentage of countries in which the coding with MedDRA is regulated by law /decree (60%) is an important percentage.

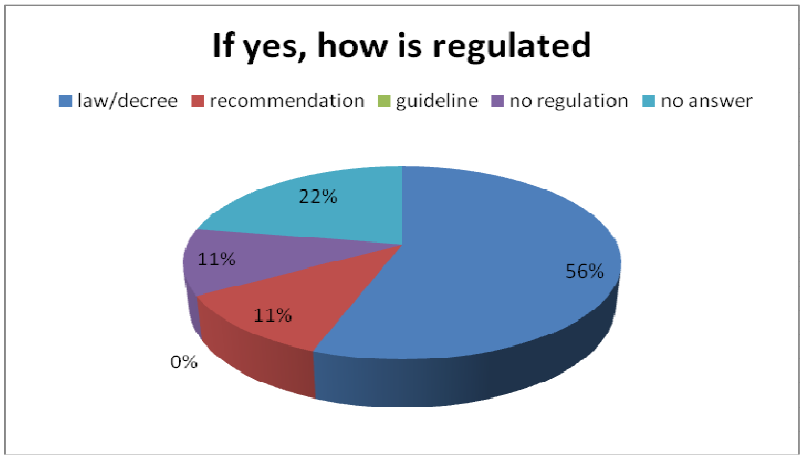
		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*	*MedDRA publicly subsidised*
Austria	**yes**	-	-	yes	recommendation	not reported
Denmark	**yes**	yes	yes	yes	-	not reported
France	**yes**	no	no	yes	recommendation	not reported
Germany	**yes**	yes	-	-	guideline reported in the law	yes
Hungary	**yes**	yes	-	yes	-	required
Ireland	**yes**	yes	yes	yes	-	no
Italy	**yes**	-	yes	-	guideline	no
Spain	**yes**	yes	yes	yes	-	no
Sweden	**yes**	yes	yes	yes	- mandatory/available in the EV database	no for CS - free for non CS
United K	**yes**	-	-	-	recommendation	no

Item N°3

Question 1.04

Is EudraVigilance Reporting mandatory?





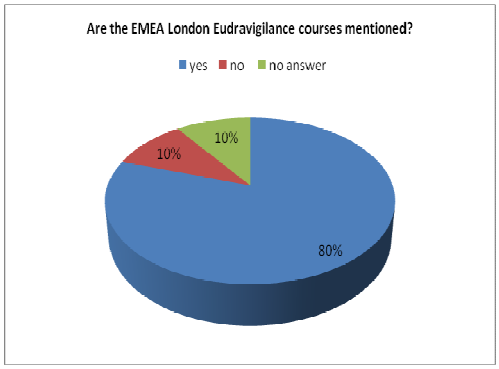
In this case we have a very significant percentage of countries (90%) where EudraVigilance Reporting mandatory. Although this data, the further analysis shows that only in the 67% of countries is regulated by law (56%) or recommendation (11%).

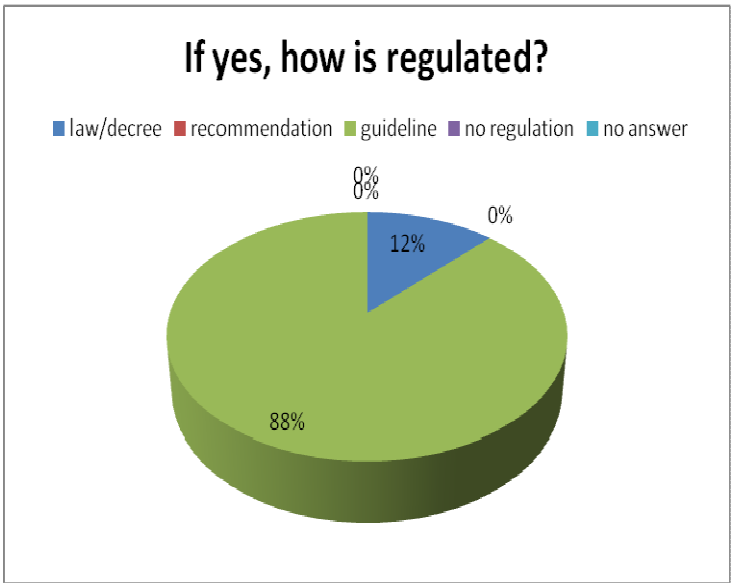
We have also to notice that Spain declared that EudraVigilance Reporting is not mandatory, but, at the same time, it's regulated by reccomendation. In our analysis we considered that Spain answered "yes" to main question.

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*	*Who must report?*
Austria	**no**	-	-	-	not mentioned	-
Denmark	**yes**	yes	yes	yes	-	Danish Agency
France	**yes**	yes	yes	yes	-	Sponsor
Germany	**yes**	-	-	-	not mandatory - EV only possibility	MAH
Hungary	**yes**	-	-	-	-	Sponsor
Ireland	**yes**	yes	yes	yes	-	Sponsor
Italy	**yes**	-	yes	yes	-	AIFA
Spain	**no**	yes	yes	yes	recommended	Sponsor
Sweden	**yes**	yes	yes	yes	-	Sponsor
United K	**yes**	yes	yes	yes	-	MHRA or Sponsor

Item N°4

Question 1.05.1
Are the EMEA London Eudravigilance courses mentioned?



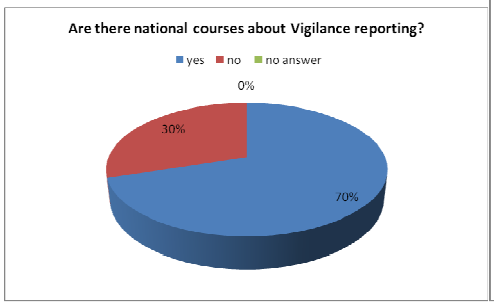


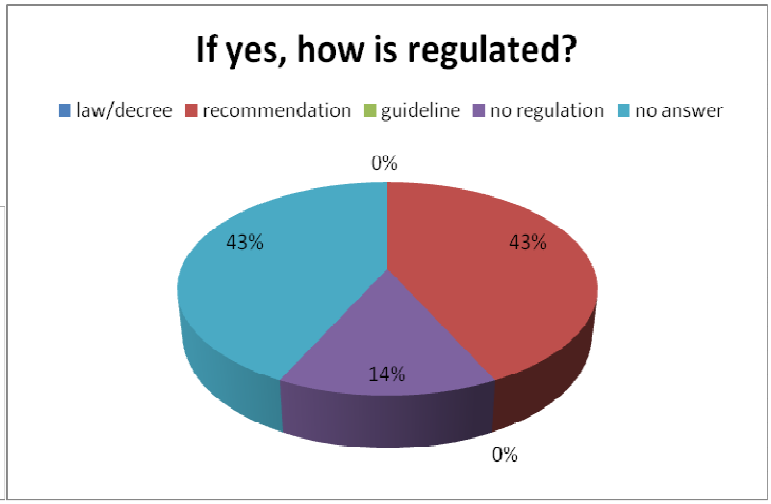
The result of the survey is that in the 80% of countries the EMEA London Eudravigilance courses are mentioned also if with different approaches (law/decree, guideline). We notice that the percentage of countries in which the present issue is regulated by guideline (88%) is a very important percentage. Only in the 12% of countries is regulated by law/decree. Italy answered "no" to main question but declared that they have a guideline, so we considered that Italy answer "yes" to main question..

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*	For whom?
Austria	**yes**	yes	yes	yes		MAH
Denmark	**yes**	-	yes	yes	guideline	CS
France	**yes**	-	yes	yes	guideline	qualified person
Germany	**no**	-	-	-	-	-
Hungary	**yes**	-	-	-	Other procedures/guidelines	MAH
Ireland	**yes**	-	yes	yes	Other procedures/guidelines	MAH - NCA - Md - PHV
Italy	**no**	-	yes	unknown	Other procedures/guidelines	undefined
Spain	**yes**	-	-	unknown	Other procedures/guidelines	undefined
Sweden	**yes**		yes	yes	Other procedures/guidelines	undefined
United K	**-**	-	-	unknown	Other procedures/guidelines	undefined

Item N°5

Question 1.05.2
Are there national courses about Vigilance reporting?





In this case we have a very significant percentage of countries (70%) where there are national courses about Vigilance reporting. The analysis of this percentage shows us that only in the 43% of countries is regulated by recommendation. We have a significant percentage of countries where it seems that the issue isn't regulated (57%): no answer (43%) and no regulation (14% - France).

		law/decree	*article*	*EU compliance*	*Other procedures/guidelines*	Please specify
Austria	**yes**	-	-	-		Medical Ass
Denmark	**yes**	-	-	-	Recommendation	DMA
France	**yes**	no	no	no	-	private
Germany	**no**	-	-	-	-	-
Hungary	**yes**	-	-	-	-	PHV Academy
Ireland	**no**	-	-	-	-	-
Italy	**yes**	-	-	-	-	Medical Societies
Spain	**no**	-	-	-	-	-
Sweden	**yes**	-	-	-	Recommendation	private; general courses but not certifying for entering data into EV
United K	**yes**	-	-	unknown	recommendation	Private and academic

Conclusions

Taking into account the requirements of specific procedures, as defined by Volume 9, EudraVigilance has identified issues from a regulatory, implementation and technical perspective, as applicable.

Similar issues have been discussed in the present online questionnaire and quite similar considerations have been achieved.

In order to reach harmonised electronic expedited reporting it is necessary that electronic reporting is not simply available in the MSs but mandatory; the use of recommendation does not assure the utilization of the electronic system; the obligation of using electronic system has to find a precise law or decree, that at present is not found in all MSs. To foster this point a circular from the DG Enterprise to all MSs is required.

In addition to the harmonization of the electronic tool, it is necessary to organize specific courses devoted:

- to the use of MedDRA dictionary;
- to learn the management of EudraVigilance
- to learn the electronic tool.

Courses are available at EMEA in London and in a few MSs, but in the majority of MSs there are no possibilities, mainly for cost reasons, to participate in EMEA courses or to have similar courses in their own country. Moreover in the majority of situations, only NCA members have been allowed to participate in such courses. Other pharmacovigilance professionals are prevented from participating.

The fostering of such courses, likely from the Ministries of Health or from the Drug Agencies, where present, is an impellent procedure to over come the actual disharmony.

The implementation needed to overcome the disharmony requires specific intervention from the Commission; it is hoped that the new Directive in course of consultation might include some issues in relation to both electronic obligation and extended courses for all actors of adverse event reporting.

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 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 in 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 coursers 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 casuality 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).