Report on the Italian National Workshop, October 28th

by

Nicola Fabris and Arrigo Schieppati

on behalf of

Consorzio Italiano per la Ricerca in Medicina

Istituto Mario Negri

1 - Structures and objectives of centres and networks

1.1 Centres

The MARIO NEGRI INSTITUTE

The Mario Negri Institute for Pharmacological Research is a not-for-profit biomedical research organisation. It was established in 1961 and started work in Milan on February 1st, 1963. There are now research units in Bergamo, at Ranica – near Bergamo – and at Santa Maria Imbaro, near Chieti.

The clinical research activities of the Institute are here briefly summarised by referring to the activities of the Departments of the Institute. This is only a brief description of some of the activities. A greater detail of all the activities of the institute are available at the Institute web site: http://www.marionegri.it/page.asp?idl=GB

Department of Cardiovascular Research

The areas of interest of the Department of Cardiovascular Research include the experimental, clinical, epidemiological aspects of acute myocardial infarction, cardiac failure, ventricular arrhytmias, peripheral arteriopathy and venous thromboembolic disease, as well as the clinical and epidemiological investigation on cardiovascular prevention, hypertension and stroke.

Following the successful experience of the GISSI-trials (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto) the activation of large collaborative networks in the setting of the National Health Service hospitals and in general practice has become a key characteristics of the Department, which can now relay on the permanent collaboration of over 300 clinical groups and several hundred general practitioners,

The GISSI project

In the twenty years since their beginning, the GISSI studies have obtained wide recognition in the international world of cardiology and are considered a methodological landmark.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI), born from the collaboration between the Mario Negri Institute and the Associazione Nazionale dei Medici Cardiologi Ospedalieri (ANMCO), is considered today one of the most characterised research team in the cardiovascular field. The GISSI has produced a series of large-scale clinical trials (GISSI 1, GISSI 2, GISSI 3, GISSI Prevention), that have involved more than 60.000 patients with myocardial infarction (AMI).

Department of Oncology

The Oncology Department is constituted by three preclinical experimental laboratories (Antitumor Pharmacology , Molecular Pharmacology and Biology and Therapy of Metastases Laboratory) and two laboratories dealing with clinical studies (Clinical Oncology Research Laboratory and Translational and Outcome Research in Oncology Laboratory). Research area of preclinical laboratories are the discovery , study and development of new antitumor and antimetastatic drugs and their new combinations; the study of tumor biology , not only to acquire new scientific knowledge, but mostly as a base for more selective therapeutic approaches and to identify and evaluate experimental models more suitable to discover and study new drugs or treatments. Clinical new drug development is based on a strong participation to the activity of SENDO (South Europe New drug Development Organization) and by studies driven by the Clinical Oncology Research Laboratory and the Translational and Outcome Research in Oncology Laboratory that are addressed to the evaluation of the effects of new therapeutic modalities. At the preclinical and clinical level there are studies of different human neoplasia, but a more intense activity is addressed to the study of ovarian tumors.

Department of Neuroscience

The Department of Neuroscience is formed by seven Laboratories and three Units of the Department; the activities of research are devoted to the study of neurological and psychiatric diseases. The purpose is to address at different levels, knowledge, therapy and clinical practice to the numerous questions, largely unresolved, proposed by the disorders of nervous system.

Department of Renal Medicine

The Department of Renal Medicine was established on 1999 at the Clinical Research Center for Rare Diseases " Aldo e Cele Dacco" -Villa Camozzi, Ranica to coordinate the activities of three Laboratories and two Units. The activities of the Department are mainly focused on the study of the mechanisms of progression of chronic nephropathies, of new prevention and intervention strategies for diabetic nephropathy, non diabetic chronic nephropathies, chronic allograft dysfunction, and cardiovascular complications of diabetes, chronic renal disease, dialysis and transplantation, and of the genetics pathogenesis and treatment of thrombotic microangiopathies.

1.2 Networks

IRCCS/CIRM - INSTITUTES OF CURE WITH SCIENTIFIC CARACTER / ISTITUTI DI RICOVERO E CURA A CARATTERE SCIENTIFICO

These are excellent hospitals, as defined by a specific law with the aims of research in the biomedical and in the health organization fields, according to the research areas of the single institutes themselves. Monitor of research results and of financial aspects are done by Ministry of Health.

The members are for integrate medical areas (no. 5 Institutes):

- Policlinico S.Matteo Pavia
- Ospedale Maggiore Milano

- Fondazione Centro S. Raffaele del monte Tabor Milano
- Fondazione Auxologico Italiano Milano
- Fondazione Salvatore Maugeri Pavia
-

For monothematic institutes (no. 24)

- Neurology & psychiatry - no 6
- Oncology - no 6
- Pediatrics - no 3
- Rehabilitation - no 2
- Orthopedics - no 1
- Cardiovascular pathologies - no 1
- Dermatology - no 1
- Gastroenterology - no 1
- Geriatrics - no 1
- Genetic diseases - no 1
- Infectious diseases - no 1

Some of these members are associated to CIRM

Financial support is given by the Health Ministry through two major areas: common research, i.e. the research developed by the institutes themselves and the targeted research, i.e. that one suggested by the Health Ministry.
The targeted research (more the 10 million €) has been suggested d by the Ministry to be used for the 10% of the total amount for independent clinical research.

1.3 Partners in the structuring of Clinical Research Infrastructures

1.3.1 Ministry of Health & Ministry of Education, University & Research

TUMOUR ALLIANCE – MINISTRY OF HEALTH / ALLEANZA CONTRO IL CANCRO

Tumor alliance is a network promoted by the Italian Ministry of Health with the following aims.
Objectives

- Foster the exchange of scientific know-how and results
- Increase the level of Italian research on tumour
- Favour homogeneity of cure of tumour patients
- Reduce the phenomenon of health care migration

Major activities

- Basic and clinical research
- Prevention and assistance for patients
- Education of health personell
- Communication to doctors and to the citizens.

Members:

- Tumour Inst of Milano, Genova, Roma, Napoli,Aviano (PN), Bari;
- Ist. Europeo di Oncologia – Milano
- Ist. Naz. Neurologico “Carlo Besta” – Milano
- Fondaz. “Salvatore Maugeri” – Pavia
- IRCCS San Raffaele – Milano
- Ist. Ortoped. Rizzoli – Bologna
- Lega Italiana Lotta contro i Tumori – Roma
- Centro St. e Prev. Oncol. – Regione Toscana
- Ist. Scient. Romagnolo – Forlì
- AIMaC (Assoc. It. Malati di Cancro) – Roma
- Federaz. Società Cure Palliative – Milano
- VIDAS – Milano

Some activities

Clinical trials: 351

- Phase II 51%,
- Phase III 46%

Sponsor: Industry 60%,

Independent 40%

- IRCCS 21%
- Scient. Ass. 11,4%
- Hosp. 6,1%
- Othar 1,3%

Multicenter trial 89,4%

National 53%

Financial support:

€ 4.212.000 (2,8% of current expenses for research of Italian Health Dept.)

Data management available in all members

CRO not available inside the network

ISTITUTO SUPERIORE DI ONCOLOGIA I.S.O. – MIUR / MINISTRY OF EDUCATION, UNIVERSITY & RESEARCH

Promoted by the University of Genova togheter with the following Italian Universities

L'Aquila, Bologna, Chieti, Genova, Insubria, L’Aquila, Messina, Modena e Reggio Emilia, Napoli "Federico II", Padova, Piemonte Orientale, Pisa, Roma "La Sapienza", Sassari, Torino e Trieste.

Objectives

- The consortium promotes and coordinates researches and other scientific and application activities in the field of oncology researches among the University Members , favouring collaborations among Universities, other Institutes and/or Industries and giving organization, technical and financial supports to University

Major activities

Major activity on translational research, but only some members have laboratories; in this case members may offer services to other institutes.

ISO is member of

- OECI (Organization of European Cancer Institute);
- GEIE-LINC (Groupe Européen d'Intérêt Economique "Liaison Network for Cancer")
- UICC (International Union Against Cancer);
- ECF (European Cancer Forum).

LOMBARDIA REGION NETWORK

This is not a real network, but a project aimed to number either the pharmaceutical companies having research objectives among their activity (in Lombardia are present more than 70% of the pharmaceutical companies of Italy), or the Health Settings making research and particularly clinical research. To give an idea clinical research in 2001 and 2002 has done for some 18 million €, 95% from industry. A portal has been develop by Region: www.sanita.regione.lombardia.it

2 - Financing, sponsoring

Italy spends about 1.07% of its GNP on scientific research (this figure is a combination of public and private investment in all fields of research, not only biomedical), a figure that is lower than average of the former 15 European Union countries. It is difficult to calculate exactly how much of this amount of goes specifically to biomedical research, and as a consequence how much money is specifically devoted to clinical research.

2.2.1 Public funding

Public support to biomedical research is provided by the Ministry of Health and the Ministry of Education, University and Research.

The Ministry of Health in Italy is supporting biomedical research with money coming from the Fondo Sanitario Nazionale, i.e. money that supports the National Health Care System in all its activity. The Ministry of Health financial support is given to all research activities that are aimed to improve health care, intended in a broad sense. Therefore either basic science and clinical research is supported.

The Ministry of Health supports the research of the "Istituti di Ricovero e Cura a Carattere Scientifico" (IRCCS) They are public or private hospitals, either connected or not to the University, which have won a distinctive status of excellence through their scientific production. There are 31 of such Institutes in Italy.

Grants are provided in different forms:

The term "Ricerca Corrente" is used to design the financial support that is given by the Ministry of Health to the IRCCS as a support the bulk of the research activity in the Institutes. The administration boards of the IRCCS allocate the money to support scientific projects of the Departments belonging to the Institute.

The term "Ricerca Finalizzata" designs the financial supports that is granted to IRCCS, Regional Health Care Systems, the "Istituto Superiore di Sanità" for specific research projects. These institutions can then

establish collaborations under the form of contracts with other private or public research institutions and enterprises that are not IRCCS themselves, for the development of those specific research projects.
The financial support for “Ricerca Corrente” are approx. 180 M € per year, while the money available for the projects Ricerca Finalizzata are approx. 61 M €. In 2003 the projects supported by Ricerca Finalizzata were 254. Among these project a significant number were basic research project, and very few clinical studies to test innovative treatments.
Public hospital, which are not IRCCS nor University Hospital have virtually no direct access to public funding for clinical research; hospital budgets do not have a specific allocation of money for research. In these hospitals clinical research is conducted only with industry support, or when funded by donations, charities etc. In summary, public funding of medical research is limited and access to financing is not extended to all potential beneficiaries.
Another important aspects that concern the public financing of medical research is the length of the approval time of the projects, and the time that elapse from approval to effective availability of money to the research institutions. As an example, it has been calculated that between deadline of project presentations to one of the call for proposal of the Ministry of University, and the approval of the projects there was an expectation time of 13 months; an first instatement of the grant was paid 10 month later, and the final instalment has not been paid yet.

2.2.2 Charity funding, foundations

There are several charities in Italy that collect money from people or sponsors and dispense the money in form of grants for specific proposals. The two main charities are

AIRC is the Italian Association for Cancer Research which has collected in 2003 25M €, which has used to support 204 basic reassert projects, 92 translational research projects and 34 clinical research projects. We do not have data to provide how much money has been used for clinical projects, but the numbers that we have reported clearly shows that there is a uneven distribution between basic and clinical studies. This is true also for TELETHON, the second big charity that collect money for independent biomedical research. TELETHON supports project on genetic disorders (most of which are rare disorders). Till now has supported more than 1200 projects and supports also core facilities projects. Last year has collected more than 26M €, mostly used for basic science research. Telethon would be indeed interested in increasing its investment in clinical research and drug trials, but in this field of rare diseases, it has been difficult so far to find interested parties, or good quality projects.

Sponsors
Pharmaceutical companies sponsor 76.7% of clinical trials in Italy, while the remaining 23.3% is co-ordinated by no profit entities (hospitals, local health units, scientific associations, institute of research and care, universities, etc). The therapeutic areas more studied by the pharmaceutical companies are antineoplastic and immunomodulating agents (21.4%), nervous system (13.0%) and general antiinfectives for systemic use (12.4%); while the no profit entities are focused mostly on antineoplastic and immunomodulating agents (63.1%). On one hand, the first 25 pharmaceutical companies cumulate 64.4% of the total clinical trials, the

first 50 cumulate 81.5% and the first 100 cumulate 93.7%; on the other hand, the first 25 no profit entities sponsor 65.7% of the total trials and the first 50 sponsor 84.2%. According to data issued from the Italian Association of Pharmacological Industry (Farmindustria), the total investments of industry for pharmacological research (including both basic and clinical research), is 812 M € in 2003 in Italy, as compared to 5.203 M€ in Uk, 3.590 M€ in Germany and 3.360 M€ in France.

3 – Ethics, Study registration

These two topics can be discussed together. The reason is that in Italy is effective since 1999 the "Osservatorio Nazionale per le sperimentazione cliniche" (National Monitoring Centre for Clinical Trials) which was designed as an instrument developed to guarantee registration and epidemiological surveillance of clinical trials on drugs conducted in Italy, and to offer co-ordination and information support to Local Ethical Committees.

In Italy, decrees issued in March 1998 transferred the responsibility of authorising the majority of clinical trials with drugs from the Ministry of Health to the local Ethics Committees. Following the implementation of good clinical practice guidelines, ethical committees were established in a great number of hospitals of variable dimension and importance. The first ethical committees to be established were in University and large national hospitals; then all hospital facilities where clinicians were involved in clinical studies, provided to establish their own committee.

Today, an estimated 96% of clinical trials are evaluated by Ethics Committees. The “Osservatorio” records show that, to date, 64.0% of all current Ethics Committees were established by the Ministry of Health after the date of enforcement of the above mentioned decrees. Regions with the highest number of Ethics Committees are Lombardia (55), Lazio (32) and Sicilia (27). It must be pointed out that Valle d’Aosta, Piemonte and Umbria work with the regional Ethics Committees of central authorities rather than local authorities, while in Lombardia the regional Ethics Committee sides the local Ethics Committees in authorising trials. The local Ethics Committees work mainly for Local Health Units (46.0%) and Hospitals (32.9%), and have been instituted mostly by the Director General of the health facilities (75.2%).

As for the members of the Ethics Committees, the average number for each Committee is 13 members and, even though a fair regional variation has been observed, an average 46.2% are not employed in the health facilities in which the committees work, while 53.8% are employees. A high prevalence is represented by clinicians (26.9%).

The “Osservatorio Nazionale per le sperimentazione cliniche” has conducted a survey and as for December 2003, has 304 registered local ethical committees. Currently, at the “Osservatorio” internet site, distribution and composition of each ethical committee can be inspected. Registered users can survey a number of information concerning the studies in which their institution are involved.

Current regulations establish that clinical trials are conducted in public health facilities such as public hospitals or private hospitals recognised equivalent, research institutes, universities, public and private scientific institutes (Law 833 of December 23rd 1978, articles 40, 41, 42, Ministerial decrees April 27th1992 and May 13th 1999). Phase IV studies can be conducted only in public facilities as the Ministerial decree of December 4th 1990 establishes. Phase I and bioequivalence/bioavailability studies on healthy volunteers can be carried out in private sites if the local health unit competent territorially have recognised them eligible to conduct clinical trials, after an inspection verifying that they have adequate requirements to do them (Annex to Ministerial decree March 19th1998). Phase I and bioequivalence/bioavailability trials on patients and phase II and III studies, instead, can be conducted in private sites too, provided that they are accredited for healthcare assistance by the Region and recognised eligible to conduct clinical trials, after an inspection verifying that they meet the requirements established by Presidential decree January 14th1997. At least one public site must participate in such a trial. At present, 27 private sites have been recognised eligible to conduct clinical trials by the Ministry of Health.

The goal of the "Osservatorio" is to assist investigators in answering the essential research questions that the National Health System has set forth, in order to lead a strategic and important process for public health.

Major activities to foster the Ethics Committees role has been:
Request for each study a systematic review of relevant studies for the study.
Have access to information on the studies on course (international registry of trials)
Have clear and public the criteria of evaluation of Ethics Committees.
Have public the conflict of interest of the member of EC.
Prevent the bias of publication and the vetos of selective suppression of negative results

The "Osservatorio Nazionale per le sperimentazione cliniche" provides the local ethics committees with informative support to build a cultural and effective network: indeed, each local ethics committee can have the opportunity to know, in real time, the status the clinical trials in which it is involved, to keep in touch with other local ethics committees on line and finally to access the outcomes of those clinical trials which it has approved.

For the sponsors, the "Osservatorio" can be a fast means to have their clinical trials approved. In fact, they may submit to the local ethics committees the electronic version of clinical protocols with all the information useful for evaluation and to learn the judgement of the ethics committee more rapidly than in the past.

The informative support of the "Osservatorio" consists of three on-line registers which form the database of clinical trials. The Ministry of Health, the local ethics committees, the sponsors, the Regions and the autonomous Provinces can access the information on these registers, according to their organisational needs. The registers are the following:

* a Register of the local Ethics Committees;

* a Register of private clinical sites;
* a Register of clinical trials.

The main features of the information system of the "Osservatorio" are:

* high reliability and timeliness in communication;
* adoption of safety standards to guarantee the confidentiality of the data;
* improved availability of information about clinical trials among the local ethics committees involved.

The aims of the "Osservatorio" are to:

* provide dialogue and co-operation among all the parties of the specific sector of clinical trials (the Ministry of Health, ethics committees, public administration, the pharmaceutical industry, scientific associations);
* modernise the Italian system of processing applied clinical research in the health sector;
* support the standardisation and the harmonisation of the local authorisation procedures;
* prevent duplication of research projects and to promote national and international co-operation;
* provide guarantees to citizens and patients, by improving transparency, credibility and access to clinical research.

During the period 2002-2003 2190 clinical trials were developed in Italy and registered by the "Osservatorio" and fully conducted to an end.
According to the data in the "*Osservatorio*", only two thirds out of the authorisations (9,959) give body to clinical trials, less than one third come to an end and a minimum percentage produces results which are published in national and international scientific journals.
As of now, many clinical sites are involved in the trial protocols in particular Phase III (90.1%) and Phase IV studies (73.9 %), even though an increasing percentage of Phase II studies has been noticed too. Moreover, in Italy there has been a significant increase of international clinical trials up to 70.7% in 2003.
Even if in year 2000 the percentage of Phase II trials increased from 27.8% up to 36.1%, in the first half of 2002 in Italy the most part of clinical trials (55.8%) are still Phase III. Also Phase I trials have increased up to 8 protocols approved in the first half of 2002, due to a new regulation issued in September 2001.

The Ministerial Decree issued on March 18th 1998 assigns specific responsibilities and importance to the co-ordinating clinical sites, which are deeply involved in the whole study. The first 25 Ethics Committees co-ordinate 68.9% of the trials, while the first 50 cover 85.3%. Hospitals (42.3%) and local health units (30.5%) are almost the three fourths of all the sites participating in clinical trials.
As far as the distribution on the Italian territory is concerned, clinical trials are mostly concentrated in Lombardia (21.9%), Emilia-Romagna (10.9%), Toscana (9.3%), Lazio (8.1%), Veneto 7.6% followed by all other regions which cover 42.2%.

In the second Annual National Report the clinical trials involving paediatric patients (<12 years) and elderly patients (>65 years) have been analysed.
Clinical trials involving paediatric population are basically Phase III trials (71.4%) and pharmaceutical companies sponsor 74.6% of them. International clinical trials are 54.3% of multicentre trials which in their turn are 88.7% of the whole.
In elderly population Phase II studies (36.9%) are well represented and 77.8% are sponsored by pharmaceutical companies. Multicentre trials are 86.2% and 64.2% of them are international.
The registration of clinical trials is a good instrument to monitor the state of the art of clinical investigation in Italy. However, at the present time, the registry of the "Osservatorio" is not avaialble to the public, and it is not intended to give public account on the results of ongoing clinical studies.

4 - Legislation, regulatory affairs, GCP, insurance

Italy adopted the European Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for clinical use by a LEGISLATIVE DECREE no. 211 of 24 June 2003, which came in effect on January 2004. The Italian decree is basically a complete transposition of the European Directive, and the complete text can be found at the site of the Osservatorio Nazionale per le sperimentazione cliniche also in English (http://oss-sper-clin.sanita.it/normativa/decreto_24062003_inglese.pdf) The Decree however is leaving some areas of uncertainty especially as far as the regulations of independent reassert. Indeed the Ministry of Health has disposed to prepare a number of implementation guidelines, which are supposed to explain further the content of the Decree. The content of the guidelines has unofficially circulated among experts in the field and even though at the time of the present report we can only offer hints from what should be the content of the guidelines, it is likely they would contain the following points.
The aim of these guidelines is to establish means to favour independent or non commercial clinical research (NCR), defined as clinical research not aimed to obtain registration of drugs and aimed to explore clinical problems currently neglected by mainstream industrial research. It is required that the promoter of NCR is not the holder of the patent or of the market authorisation, but is an independent, not for profit institution; it is possible that an individual person acts as a promoter. The promoter has the full responsability of the conduction of the research and should retain the full control of the data, being the only owner of the data.
The cost of all drugs which are used in the experimental protocols but already in the market, should be charged to the National Health System, while the cost of experimental drugs and all the adjunctive costs should be covered by a special fund that each hospital or institution involved in clinical research should establish. The fund should be constituted by moneys coming from different sources, including money from private industry, but it is essential that the non profit institution retaining the complete independence and full possession of all data generated by the research protocols.

In relation to the problem of standardisation in the field of Health Information and Communications Technology (ICT) a participant to the workshop, President of the Commission for Medical Informatics of Italian Entity for Normation (UNI), recognised in such a role by the European Directive 83/189/CEE/1983, has reported the following:

- The Commission is developing the ISO TC 215 for the “Standardisation in the field of information for health, and Health Information and Communications Technology (ICT) to achieve compatibility and interoperability between independent systems. Also, to ensure compatibility of data for comparative statistical purposes (e.g. classifications), and to reduce duplication of effort and redundancies”
- The ISO TC 215 Health Informatics has organised various Working Groups with the following aims:
WG1 Health Records and Modelling Co-ordination
WG 2 Messaging and Communication - Interoperability of telehealth systems and networks
WG3 Health Concept Representation - Controlled Health Terminology
WG 4 Security - Security Management in Health using IS17799
WG 5 Health Cards
WG 6 E-Pharmacy and Medicines Business. This last may be of particular relevance for:
Medication Records;
Adverse Drug Reactions;
Functional Requirements for Prescription Support Systems;
Patient Health Card Data e-prescription

5 - Pharmacovigilance, drug dispensation

Medicines are developed and tested for safety and efficacy through clinical trials.
These clinical trials involve a limited number of patients. Following their market authorisation medicines are used by millions of patients. In this transition the balance between risks and benefits established during the clinical trials can change radically. Pharmacovigilance is the process of collecting and analysing the adverse reactions to medicines following their market authorisation; as such it is an essential practice to ensure public health. The recognition and notification of adverse drug reactions (ADRs) is however a complex task requiring knowledge and expertise from both health practitioners and patients.
A “new pharmaceutical legislation” proposed by the European Commission in 2001 and currently under approval by the European Parliament and European Council will be in place in the near future. This legislation will strengthen pharmacovigilance requirements and will aim to an improved pharmacovigilance within the EU. One of these new requirements will be a more efficient ADRs recognition and notification.

The data model and the standardisation of the information items for the electronic ADRs notification have been the subject of a long debate that took place for nearly a decade and that has been concluded only recently within the International Conference on Harmonization (ICH) where a data model for the ADRs notification has been adopted (ICH M2) and where a standard medical dictionary for the annotations has been established (MedDRA dictionary). The MedDRA dictionary is currently available in a number of the EU languages (English, French, Spanish, German and Portuguese).

The European Agency has developed a data analysis pharmacovigilance system (EudraVigilance) which does not operate a direct data acquisition but that receive the data on ADRs (severe level only) from the national authorities systems and for the medicines authorised centrally from the MAHs. EMEA is not allowed, by legislation, to collect directly from health practitioners and other entities ADRs notifications.

In the majority of EU Member States with particular reference to the Mediterranean countries the notification process is devoted to the LHAs (Local Health Authorities), the Market Authorization Holders MAHs and Hospitals that represent the interface for health practitioners and patients.

In Italy the health practitioners (physicians and pharmacists) and the Market Authorization Holders (MAHs) as well have to notify ADRs through a procedure following the guidelines of the European Directive 2000/38/CE.
According to this procedure (Decreto Legislativo No.95 published on 03/05/03) the ADRs must be notify to the responsible peripheral authorities such as Local Health Administrations (LHAs) and hospitals. These authorities verify the quality of the notification card, translate the information in an appropriate digital format and forward it to the central database at the Ministry of Health.
The national authority then, when and if appropriate, passes on the notification to the European Medicine Evaluation Agency (EMEA) and to the World Health Organisation (WHO).
It is important to point out that the above-mentioned regulation also recognises a specific role to the regional authorities through the constitution of *ad hoc* Pharmacovigilance Centres. Moreover it is also request to the Regions an active collaboration for pharmacovigilance monitoring and specific support to the training courses.
Although this pharmacovigilance system has been working since 1997, “ADRs notification” is not reported as expected in terms either of number and quality. Indeed, in Italy, the notification rate is quite low, 82.45 cards/million of habitants, compared to the 300 cards/million of habitants that represent the *gold standard* for an efficient pharmacovigilance system, reported for instance in United Kingdom, Sweden and France.

6. Data management, quality management sops and audits

Centers involved in ECRIN in Italy have different kind of organization, and therefore practices in term of data management are wide variable. When involved in industry sponsored clinical trials, centers comply with the indications of the CRO in charge of the study. However a number of centers have developed their own expertise that is exploited in several task. As an example, the Mario Negri Institute has expertise in almost any aspects: from drafting the protocol, to preparation of case report form, from statistical planning to data management and analysis. In this process the Institute has adopted its own SOPs. Other centers in the Network have such facilities. Altogether in Italy both expertise and experiences are available outside of the industry to assure the possibility of conducting independent clinical research, but there there is a great variability of practice regarding data management, within different centres, and harmonization is surely needed urgently.

7. Communication

Information to the consumers concerning health issues is an important problem. There are in Italy a large number of patient associations, which are involved in activities that encompass information to the patients and consumers at large, lobbying, and fund rising. Most of the activities of the associations however are not

interconnected, and most often each association is concerned with its own program, without coordination with others. An example of co-ordination is offered by UNIAMO, an umbrella organization of rare disease support groups, that has established a common action plan. Another interesting initiative is "PARTECIPASALUTE", A pilot project, aimed at raising public awareness on health and health care-related issues and at broadly empowering consumers. It has been established as a consortium including The Mario Negri Institute, the Italian Cochrane Centre and Zadig Agency. Within the project a website has been launched with the aim of providing reliable information on the effects of health care interventions as well as to familiarize consumers with the world of clinical and epidemiological research.
"Partecipasalute" is aimed to establish a web site intended mainly for consumers, patients and their associations.

8- Education

A major concern in establishing an European common learning language is first of all the difference among the EU Member State in the way of conducting continuous medical education (CME), and secondly the still undefined way to conduct e-learning medical procedures. Continuing Medical Education (CME) is part of Continuing Professional Development (CPD), as addressed to medical doctors. CME is or will shortly be a legal requirement in Austria, France, Italy, the Netherlands, and Switzerland. In most instances the implementation is in the hands of the professional associations. Financial incentives for CME exist in Belgium and Norway. The professional associations themselves are engaged in structuring CME participation in Germany, the United Kingdom, Ireland and Spain. CME is completely voluntary in the Scandinavian countries, Luxembourg, Portugal and Greece.
This means that for 90% of European health practitioners some form of structured participation in CME programmes is effective.
European health practitioners will increasingly need a system for international exchange of CME credits as the national regulations tighten.
In Italy CME started only in 2002 and it is related and compulsory to all figures of health services. Till now the CME, called in Italy continuing education in medicine, has been promoted trough residential courses. At present is under experimentation the e-learning system, that will start officially in 2005. Credits are obligatory and will reach the final figure by 2005 with 50 credits per year.

As far as the training of research nurses, at the present, there are no official formal teaching courses for nurses, and the figure of study nurse is not officially recognised by the health authorities or by professional colleges. However a significant number of nurses are actively involved in clinical research and are officially included in the protocols that the promoter of the research presents to the ethical committee for approval. Their training is informal and based on practical experience. To circumvent this problem, a pilot experience has been conducted at the Mario Negri Institute, which has established a training course for research nurses. Nurses are involved in a two year program which include lecture hours and practical training by involvement in ongoing clinical trials. Nurses learn all the aspects connected to clinical trial design and implementation, and are involved in monitoring of the studies. This training has prepared more than 50

nurses in 5 years; however it is a single experience and does not yet provide an officially recognised diploma.

REFERENCES AND LINKS

Directive 2001/20/EC

Directive 2001/20/EC of the European Parliament and of the Council of 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 L 121/34 of 1 May 2001*

Decreto Legislativo n. 211 del 24 giugno 2003

Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico . Gazzetta Ufficiale n. 184 9/8/2003

Osservatorio Nazionale sulla Sperimentazione Clinica dei Farmaci / National Monitoring Center for Clinical Trial http://oss-sper-clin.sanita.it/index_ingl.htm