EUROPEAN MEDICINES AGENCY
POST-AUTHORISATION EVALUATION OF MEDICINES FOR HUMAN USE

London, 30 May 2007
Doc. Ref. EMEA/240728/2007

CONCEPT PAPER

Model for **ENCePP**

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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May 2007

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LIST OF ABBREVIATIONS

7th FP	7th Framework Program for Research and Technological Development of the EC
ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordinating Group for Mutual Recognition and Decentralised Procedures – Human
DCC	Database Coordinating Centre
DG	Directorates-General
EBMT	European Group for Blood and Marrow Transplantations
EC	European Commission
EMEA	European Agency for the Evaluation of Medicinal Products
FUM	Follow-Up Measure
GPP	Good Pharmacoepidemiology Practice
HAART	Highly Active Antiretroviral Therapy
HMA	Head of Medicines Agencies
IMI	Innovative Medicines Iniziative
ISPE	International Society for Pharmacoepidemiology
MAH/A	Marketing Authorisation Holder / Applicant
MS	Member States
NCA	National Competent Authority
PC	Performing Centre
PhVWG	Pharmacovigilance Working Party
RA	Regulatory Agency
RMS	Rapporteur Member State
SO	Specific Obligation
SSRI	Selective Serotonin Reuptake Inhibitor
TCC	Therapeutic Coordinating Centre
UKCRN	UK Clinical Research Network

1. DEFINITION

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) is an EU-wide Network of Research Centres to be established by the EMEA.

2. SCOPE

In line with the new Pharmaceutical Legislation, the EMEA Road Map to 2010 lays out a vision of a more proactive conduct of Pharmacovigilance. This includes the establishment of the ENCePP, intended to further strengthen the post-authorisation monitoring of medicinal products in Europe. Using available data, expertise and research experience in the field of Pharmacoepidemiology and Pharmacovigilance across Europe, ENCePP will provide a unique opportunity to facilitate the conduct of multi-centre "independent[1]" post-authorisation safety studies (PASS). The ENCePP is a network of Pharmacoepidemiology Centres, Medical Care Centres, Health Care Databases and electronic Registries aiming to significantly contribute to identify, characterise and assess risks relating to medicinal products marketed in Europe. It will potentiate pharmacoepidemiological research in the EU by offering to Marketing Authorisation Holders/Applicants (MAH/MAA), Regulatory Agencies (RA) and Academics a rapid access to a robust network of resources working according to the highest scientific standards.

3. THE NEED FOR ENCEPP: EXAMPLES OF MULTI-CENTRE PASS

Increasingly, MAHs and National Competent Authorities (NCAs) are being requested to investigate and proactively monitor the safety of medicinal products through PASSs. Following are some examples of how the existence of the ENCePP would greatly facilitate the conduct of such studies within a European clinical setting. These studies can be initiated either by a MAH or a RA.

3.1 Initiated by the MAH/MAA

The MAH may be requested to conduct a specific safety study in the context of a Follow-Up measure (FUM) or Specific Obligation (SO) or due to an identified safety issue emerging in the post-marketing phase.
Following are some examples:

A new vaccine requiring a large safety follow-up (Cohort) study

In order to capture and analyse very rare events, studies with a large number of patients enrolled in a cohort and an efficient follow-up of events are needed. Such large cohort studies should preferably be organised and co-ordinated within the EU, in order to yield results that adequately reflect the experience in the different EU member states (MSs).
Past experience has demonstrated that Pharmaceutical Companies often have turned to the US, where the conditions for such studies have been perceived more favourable as compared with the nEU. Thus, it is highly desirable that networks are established with the participation of Centres in several MSs for (stand-alone) studies in the EU.

A new monoclonal antibody requiring intensive monitoring

Biological products, like monoclonal antibodies generated through recombinant DNA technology, or new advanced therapies, may be associated with serious and unpredictable long-term effects. These products need intensive monitoring in a clinical or academic setting in a large number of patients. Thus, a large network of Centres with competence in the specific therapeutic area is needed in order to allow for sufficient clinical data to be collected.

[1] " Independent" studies are understood as studies that are commissioned by MAHs/MAs or RAs to designated centres of Pharmacoepidemiology within the ENCePP and which are performed according to best standard practise for Pharmacoepidemiology and according to rules and principles that ensure compliance with regulatory requirements and full transparency.

The ENCePP would facilitate the collaboration between several clinical departments and thus provide access to a wider patient population.

The safety of biologicals in rheumatic diseases is currently being investigated by means of registries in several EU countries. This research concept could be generalised into a pan-European network, which would be more effective and would yield earlier and more robust safety data as compared with spontaneous ADR reports.

Marketed products with a new and serious safety issues

Occasionally, safety issues emerge when a product has been on the market for some time. In such situations data on both exposures and medical outcomes may already be available in several clinical databases. The use of already registered data makes a safety study relatively quick and inexpensive. In order to study rare and serious outcome data, however, it might be necessary to combine data from several databases.

Presently, MAHs often turn to the US where some well known large databases for the completion of such studies are consulted. Therefore, a network of Centres is needed that can access, combine and analyse data from several databases in the EU.

An example is the signal of an increased risk of urinary bladder cancer possibly associated with some new antidiabetic medicines based on animal studies. A multi-centre safety study on this topic is presently being carried out in the US.

3.2 Initiated by the RA(s)

Post-marketing safety issues can arise in a number of medicinal products belonging to the same class of medicines. Such adverse reactions, which are generally associated with a therapeutic class ('Class effects'), are commonly rare events, which are linked to long-term exposure. In such cases a number of products with the same mechanism of action need further evaluation and may require collection of extensive new safety data. ENCePP will facilitate the development and conduct of joint safety studies by MAHs.

Examples of recent product class safety issues are a) cardiovascular risks for Cox-2 selective and traditional NSAIDs; b) suicidal behaviour after antidepressant (SSRI) treatment; c) rhabdomyolysis after statin exposure, d) metabolic disturbances after HAART treatment of HIV positive patients, and e) suicidal behaviour following exposure to Tamiflu.

In these examples, combined studies have proven to be rather difficult to realise through joint actions by the responsible MAHs. Therefore, an adequate infrastructure obtained by co-ordinating research activities and data sources available to several Centres in a particular therapeutic field would generate sufficient sample sizes based on collection of the necessary data.

3.3 Evaluation of urgent drug safety issues

Not uncommonly, new signals of serious safety problems are generated through spontaneous ADR reports or through the literature. Such issues may challenge the positive benefit risk-profile of the product and give need for expeditious decisions. Access to data and resources to coordinate and analyse safety information from existing clinical databases will be pivotal to investigate whether the signal is strengthened or verified.

In summary, from a regulatory point of view, "independent", multi-centre PASS studies are urgently needed as they allow the best-standard pharmacoepidemiological research for comparative safety evaluation of products or classes of products within the therapeutic area of concern. Ideally, such studies could be conducted in a network of Centres provided by the ENCePP.

4. MODEL

(For overview, see the annexed *figures* depicting the elements of the model described below)

The proposed Model for ENCePP is based on a structure of Coordinating Centres (CC) and Performance Centres (PC) in specific area networks.

Centres within ENCePP will be generally organised in six specified *Therapeutic areas* (following prioritized areas for Central Authorisation in the European regulatory system):

(1) Neurological Disorders
(2) Oncology
(3) HIV and Immunology
(4) Diabetes and Endocrinology
(5) Cardiovascular and Blood Products
(6) Paediatrics
(7) Other

Therapeutic area networks
All specific area networks include a separate, designated, *Therapeutic Coordinating Centre (TCC)*, a Centre established and experienced in initiating, conducting and assessing Pharmacoepidemiological Research in the particular therapeutic area.

Data base network
In addition to the Therapeutic Networks, a *Database Network* would concentrate resources for research on methodologies and collection and compilation of safety data from clinical databases, taking into account the growing importance of database studies. The Database network would be headed by a *Database Coordinating Centre (DCC).*

4.1 Therapeutic Coordinating Centre (TCC)

Each Therapeutic Area has a 'Therapeutic Coordinating Centre' (TCC), which coordinates all research activities in its therapeutic area. The TCC shall ideally have an outstanding competence and performance capability in the area, and will work in collaboration with the other Performance Centres (PCs), to be organised within a particular therapeutic area. The TCC will coordinate the recruitment of suitable PCs for a particular study, based on their research experience and capabilities. Moreover, the TCC should have extensive experience in all relevant research methodologies and study designs together with profound experience in the planning and conduct of multicentre pharmacoepidemiological studies, e.g. pharmacoepidemiology, clinical pharmacology, the respective therapeutic area, biostatistics, data management, IT and communication.

4.2 Database Coordinating Centre (DCC)

The DCC is a separate and independent Competence Centre with the same status as the TCC. The DCC coordinates the tasks and responsibilities of the Database network, including the identification and/or establishment of as many clinical databases as possible, their coordination and formatting of data for effective compilation. The DCC would further manage the science, logistics and performance of these activities and act as an Advisory Centre to the therapeutic area networks in all questions related to database and registry-based studies. One fundamental task would be to develop, through innovative research, the methodologies for collecting clinical data from new sources in the health care systems in EU Member Sates, both in community and in hospital settings.
The DCC will need to incorporate competences as mentioned above and in addition staff with skills in database management.

4.3 General conditions and Reference for Coordinating Centres

Other existing networks, which have a similar scope and composition as ENCePP, frequently use a Coordinating Centre structure. Examples of Networks with a Coordinating Centre structure include the UK Clinical Research Network (UKCRN) and the European Group for Blood and Marrow Transplantations (EBMT). These Networks have been consulted in the planning for ENCePP.

The Coordinating Centres (TCC/DCC) are proposed to be supported financially by public funding. This Funding is envisaged to be provided by the EMEA and/or the European Commission [EC (DG Research)], to permanently support the basic administrative and scientific structure necessary to coordinate commissioned pharmacoepidemiological studies in the respective area. A standard contract between the funding organisation (EMEA/EC) and the CC will define the extent of funding and the associated roles and responsibilities of the CC. The contract should also contain general rules and principles for the conduct of a commissioned study. Outlines for such principles are specified under chapter 5.

4.3.1 Function and Responsibilities

The CC should manage all scientific, administrative, logistical and communicative tasks for commissioned studies in its respective therapeutic area. The responsibility associated with the being a CC will be defined in a contract between the funding body (EC/EMEA) and the Coordinating Centre. In this contract, the CC confirms to follow the Guidelines of Good Pharmacoepidemiological Practice (GPP) and to comply with a set of principles (see chapter 5) when planning, designing and conducting multi-centre commissioned studies. Further, the principles should ensure fulfilment of regulatory requirements and full transparency of the scientific process.
Moreover, the CC should agree to submit yearly reports to the EMEA, in which it will provide information on the utilisation of funding received during the reporting period, conducted studies and outcome(s) of commissioned studies.

4.3.2 Enrolment of Performance Centres and Preparation of Study

The CC shall be responsible to coordinate the recruitment of Performance Centres (PCs) to constitute the ad hoc Network that will be suited to conduct the particular commissioned study. These PCs are to be selected by the TCC from within the therapeutic group, but also from other groups if they offer some useful data (e.g. through the DCC to access databases) or methodologies necessary for the study.
The CC will initiate internal meetings and correspondence in order to organise the ad hoc network for the specific commissioned study.

4.3.3 Development of Study Protocols

The CC should also take the lead, together with the commissioning party (MAH/MA, or RA), in the development of the study protocol. Ideally, the study protocol should be developed, as appropriate, together with all Centres participating in the specific study to allow for the best possible utilisation of resources among the Centres and scientific consensus. The CC should submit a draft concept paper to the Scientific Advisory Board of the EMEA for comments at the earliest point in time, possibly in parallel with the consultation of the PCs.
If the MAH or RA submit a complete study protocol, the CC should be responsible for the review and the approval of the protocol, notwithstanding the agreement of the Scientific Advisory Board.

4.3.4 Conduct of the Study

The CC will be responsible for the coordination of the multi-centre study. Moreover it will be responsible to allocate funding for various research activities, on the basis of a contract between the commissioning MAH/MA or RA and the participating PCs. Furthermore, the CC will take the lead in the data compilation, biostatistical analysis and interpretation of study results. The CC will also be responsible for the final analysis, interpretation and conclusion on the study, in accordance to the PCs.

4.3.5 Finalisation of the Study

Upon finalisation of a pharmacoepidemiological study, it is the responsibility of the CC to draft a Study Report and to submit a copy to the EMEA /Scientific Advisory Board.
The CC will also be responsible for coordinating the scientific publication process resulting from the study.

4.3.6 Minimum Resources of the Coordinating Centres

Each CC should have the following basic resources available in order to satisfactorily fulfil the tasks and responsibilities of a CC:

Staff

- The TCCs should employ staff experienced in the relevant areas of pharmacoepidemiological research. More specifically the following disciplines should be represented at each CC, with an estimated need for staff with expertise in:

  Pharmacoepidemiology (Senior experts); Clinical Pharmacology; Clinical Medicine (expertise in the therapeutic field); Biostatistics; Data management; IT/database handling; and Communications/administration

- The DCC would need to be staffed with similar competences, perhaps with the exceptions of clinical medicine expertise and with the addition of expertise in database management.

These staff should be directly associated with the CC by employment contract. Additional staff could be hired and financed through project-related funding (MAH/MA or RA), as needed.

Databases

The CC will need access to clinical databases and registries necessary to conduct a specific pharmacoepidemiological study. For the TCCs to have access to database data covering the largest possible geographic region in the EU, close collaboration with the DCC will be necessary.

4.3.7 Funding

(For overview, see annexed *figure* illustrating the concepts for funding)
It is envisaged that DG Research funding is requested for research on drug safety or class drug safety issues that are perceived as being of public health importance. Funding for infrastructure and developing the ENCePP methodology is to be requested from IMI (ENCePP is already reflected in the Strategic Research Agenda).
The EMEA will provide the basic Secretariat and infrastructure (e.g. premises for regular meetings of Coordinating Centres) for the ENCePP Steering Committee.

4.4 Selection of Coordinating Centres

CCs for each Therapeutic network and the Database network could be selected by an ad hoc Selection Committee, consisting of representatives from therapeutic area societies, ISPE, and experts nominated by the CHMP and the PhVWP. The CC should be then endorsed by the Steering Committee [see chapter 4.6]. One possible procedure is a Call for Interest on the basis of a set of requirements, and in a second step more extensive review of the scientific qualifications. As part of the bid by a candidate CC, the potentials for forming adequate networks for studies in the respective area will be an important feature.

4.5 Performance Centres (PCs)

All Performance Centres (PCs) selected by a CC to be part of the ENCePP will be part of a therapeutic and/or the Database network. If a PC has expertise in more than one therapeutic area, this PC can be

part of more than one network. The same applies if a Centre has expertise and can significantly contribute to a therapeutic network and the Database network.

4.6 Steering Committee/ScientificAdvisory Board

4.6.1 Scientific Advisory Board.

An important component of the ENCePP is the Scientific Advisory Board. The role of the Scientific Advisory Board is to review and endorse the design and conduct of a study with regards to scientific quality assurance and transparency criteria. The Scientific Advisory Board is proposed to consist of representatives from the EMEA, CHMP/PhVWP, and experts and representatives from CCs. It is important that the interests of the responsible regulatory bodies are sufficiently represented. As for the scientific quality assurance, experts in pharmacoepidemiology, biostatistics, clinical pharmacology and relevant clinical disciplines available in the PhVWP/CHMP are expected to play key roles
Once the protocol is developed by the MAH, as foreseen in collaboration with the respective CC, the Scientific Advisory Board would endorse the protocol within a predefined timetable. If the Scientific Advisory Board does not raise any objections within the timetable, the study protocol should be considered accepted. Protocols for both safety studies commissioned by MAHs/MAs and by RAs need to be endorsed by the Scientific Advisory Board. In cases where a safety study is specifically requested by a National Competent Authority (NCA) in the context of a Follow-up measure (FUM) or Specific Obligation (SO), it is the responsibility of the Rapporteur or RMS to assess the protocol. It may be considered, for the sake of gaining efficiency and quality in the assessment, to employ the experts of the PhVWP, as mentioned above.

4.6.2 Steering Committee.

/To be completed after legal advice by the EMEA lawyers, and further considerations/

5. RULES AND PRINCIPLES FOR THE CONDUCT OF PASS

In order to ensure that studies conducted through the ENCePP meet the highest possible level of scientific quality, rules and principles for ensuring a *correct and trustworthy scientific process* are needed. Such rules and principles will likely be a condition for CCs and PCs to become active in the ENCePP. The overriding aim will be to ensure that the scientific process of the pharmacoepidemiological research is performed according to the best possible standards and that it is fully transparent.

5.1 Transparency

The first principle is to ensure *transparency* of the whole scientific process. The study protocol, elaborated by the MAH/MA in collaboration with a CC, following a request by the Regulatory Agency, is to be assessed and endorsed by the Scientific Advisory Board. Further, the finalised protocol is to be published electronically by the EMEA and the MAH/MA.
Further, the progress of the study should be monitored, reported and assessed, as specified in the Risk Management Plan (where applicable). This procedure should follow an adopted timetable, including reports on the enrolment of subjects, interim analyses, etc.
The Study Report should be made available to the RA as soon as it is finalised, independently from any other publication endeavours.

5.2 Scientific quality

The second principle is that the outcome of PASS should be of sufficient standard to meet the requirements for publication in a peer-reviewed scientific journal.
The Good Pharmacoepidemiology Practice (GPP) guidance (ISPE Commentary, Mark Epstein, Pharmacoepidemiology and Drug Safety 2005; 14: 589–595), as presented by the ISPE, should be adhered to.

If deemed necessary and in order to monitor that scientific standards are met, TCCs, DCCs and PCs, involved in a particular study, could be inspected (e.g. Good Vigilance Practice inspection).
In case of diverging views between a CC and the commissioning party on aspects of data collection, analyses, scientific reporting, interpretation or implication of results, the study protocol/data should be referred for second opinion to independent experts, e.g. those of the PhVWP, or other external experts.

5.3 Rules for contacts between the MAH/MA and Coordinating Centre

The responsible pharmaceutical industry MAH/MA may participate in the scientific process at the TCC or DCC of its own commissioned study, to oversee and/or comment on the processes of collecting and analysing data and reporting results. At all times, there should be full transparency as to changes in research protocols or deviations in the progress of the research work.
The payment of the commissioned study should take place according to an agreed budget and schedule.

5.4 Business contract

A standard business contract for commissioned studies shall be established, including standard clauses on data ownership, intellectual property, reporting obligations (regulatory), publication rights, conditions for payment, handling of conflicts, etc. The contract is to be signed off by the EMEA legal sector. The conditions of a contract shall be made publicly accessible in order to ensure that transparency criteria are met.

6. ROLE OF THE EMEA

The EMEA, in its interest to strengthen drug safety in the EU, forming an “umbrella” for the ENCePP, will support the establishment of the network and provide administrative support. This engagement will add credibility to the functioning and output of the network. The EMEA will further take part in and contribute to the organisation of the *Scientific Advisory Board and Steering Committee*. The EMEA will also provide logistical support for several meetings including two Annual Meetings and quarterly Meetings of CCs.

Annex

Figures

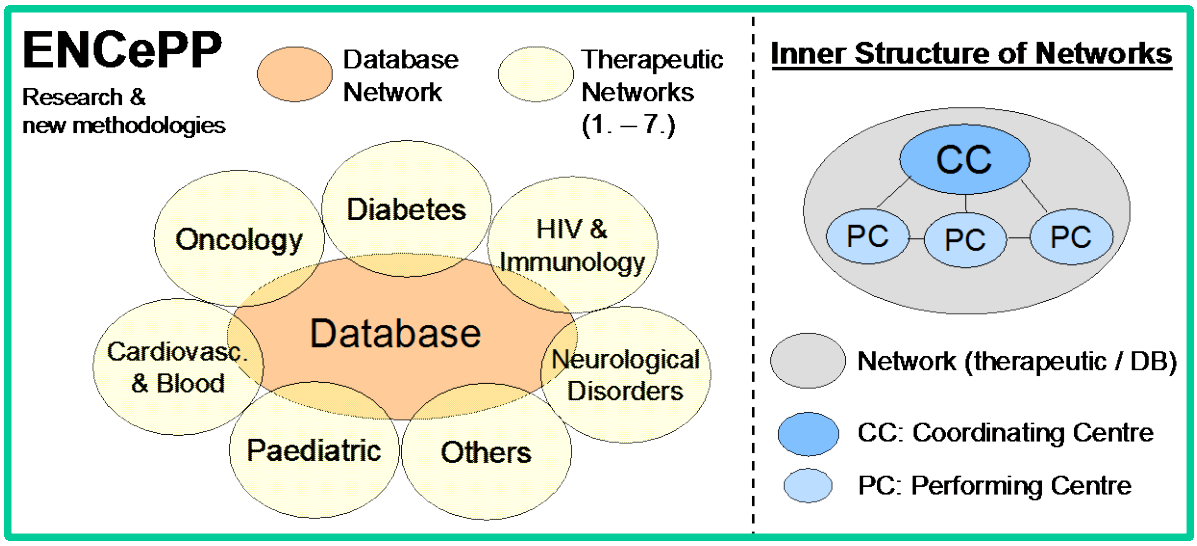

Figure 1 Network Structure of ENCePP

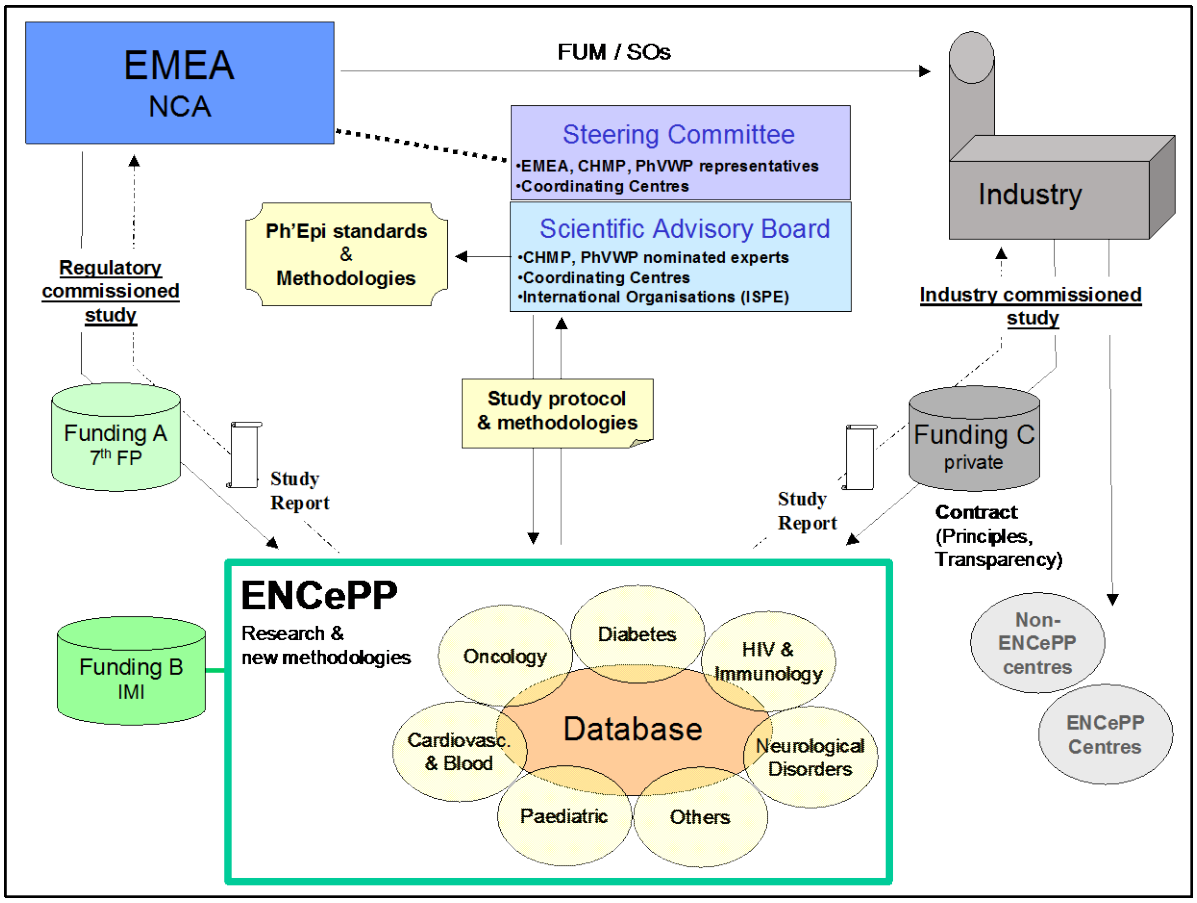

Figure 2 Model of ENCePP