European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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2ND ENCEPP MEETING WITH CENTRES AT THE EMEA

MINUTES OF WORKING GROUP 2:
Independence & Transparency

18 April 2008

Chairperson: Helen Dolk

Present: Felix Arellano, Deborah Ashby *(ENCIAG)*, Vittorio Bertele, Helen Dolk (*Chair*), Zoe Doran, Hans-Georg Eichler *(EMEA, ENCIAG)*, Anders Ekbom, Stephen Evans, Henry Fitt *(EMEA, ENCIAG)*, Dr. David Haerry, Ron M.C. Herings, Ole Kirk, Joan Ramon Laporte, Nicola Magrini, Alain Micaleff (EFPIA representative), Ingemar Persson *(ENCIAG)*, Mauro Venegoni, Lesley Wise

Apologies: Milan Kriska, Anna Wiela-Hojenska

The main purpose of the meeting was to discuss and agree priority actions for the next two years in the field of Transparency and Independence. As a starting point for the discussions, the group were sent in advance a draft Mandate suggested by the ENCIAG. In addition, the following questions (see Annex-2) were used to focus the discussions.

1. Does the Working Group (WG) agree with the proposed mandate?
2. Are there additional topics which need to be included?
3. Possible conflicts of interest/issues which might preclude a specific topic being developed through a (successful) IMI proposal?
4. Are there topics which overlap with other groups; if so, how should this be addressed?
5. How would the WG suggest prioritising the topics?
6. How will the topics be addressed (including suggestions for lead persons for topics if appropriate)?

The main points discussed and recommendations reached are shown below:

- Proposed Set of Business Rules

It was mentioned that Rules might be very difficult to implement and that a "Code of Conduct" approach was preferred. Overall, it was felt that the development and subsequent adherence to a Code of Conduct was of paramount importance to achieve maximum transparency and independence. The Code of Conduct could be seen as a seal of recognition, where a standard statement (e.g. "This study was conducted under the ENCePP Code of Conduct for Independence

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& Transparency") could be included in the study report, in a similar manner to GCP compliance statements.

The group discussed whether the two aspects (i.e. Transparency and Independence) should be developed separately. It was decided that the two are inextricably linked and that the Code of Conduct should cover both aspects.

The point was made that it would be very important to ensure transparency translates into effective Public Communication (e.g. on the future EMEA Safety Portal - if this Commission proposal is implemented). This point was specifically added to the mandate.

Regarding data ownership and reproducibility, it was agreed that this is a very sensitive and complicated issue, as it depends on many factors. In any case, it should be clearly defined who own and who can access the data. There could be some form of commitment to share non-identifiable data upon request. Some members mentioned that data should available for inspection. In this respect, it should be clearly defined who has the right to request the data.

Regarding the submission of study results for publication, it was unanimously agreed that this is non-negotiable, and an obligation rather than a right. It was further suggested that ENCePP centres or other studies following the ENCePP Code of Conduct should undertake to submit the results of any ENCePP study for publication.

The EFPIA representative mentioned that Industry has some experience of contractual relationship between Industry and independent Investigators in the frame of "Independent Sponsored Trials" (usually interventional studies). This is best managed from a transparency and operational point of view in clearly established contracts (recognising that each Company may have their own requirements and template). As no universal Contract exists for these Industry/Investigators relationships, it was suggested that a standard or template contract between the study funder and the ENCePP centre, also addressing legal issues (e.g. legislation under which study is carried out), should be drawn up in order to guide relevant parties. This document should be annexed to the Code of Conduct.

[A post-meeting email from a member suggested that a clearer distinction be made between "sponsor" and "funder", and that independence should include consideration of funding modes which do not require a direct contract between industry and investigators (e.g. channelling through EMEA). This can be on the agenda of the next meeting.]

- Registry of non-interventional studies

The need to publish a study protocol or "register" a non-interventional study prior to the study being performed was discussed at length. At present one of the main difficulties when looking at the "available PhEpi evidence" on a given safety problem is that one has no idea of the magnitude of publication bias. The main objective of registries is to avoid or to limit publication bias. The group was in agreement with the principle of a registry as a means to reduce publication bias and achieve greater transparency regarding protocol changes during study conduct. Indeed, it was highlighted that in the clinical trials area, reputable journals will only publish results of previously registered clinical trials.

A member pointed out that it was sometimes difficult to determine when the study had actually started, as many database owners are asked to carry out pilot or feasibility studies, before a major project is undertaken. Such studies can sometimes show some preliminary negative findings, which lead to the protocol being amended or the study being altogether abandoned. Much PhEpi research, either case-control, retrospective cohort or a retrospective review of medical records or hospital registries, is based on the review of existing documents and registries (the review of "what has already happened"); for this kind of research, it is often impossible to determine when the project was started. This aspect needs more elaboration.
Should these pilot studies also be registered?

Interestingly the International Committee of Medical Journal Editors (ICMJE) has published a paper entitled "Is This Clinical Trial Fully Registered? A Statement from the International Committee of Medical Journal Editors", which addresses some of these points.
http://www.icmje.org/clin_trialup.htm

It was suggested to liaise with the ICMJE to obtain further advice on some of these issues, and explore a possible collaboration in promoting the creation of a registry of observational studies.

As regards the scope of the registry, some members mentioned that it should only apply to drug safety or PhV studies, whereas others would like the scope broadened to all observational studies (including drug utilisation studies), and would like regulatory authorities to agree that only registered PhEpi studies will be taken into account when a safety problem arises. It was agreed that, initially, the registry should focus on ENCePP studies, although the Registry subgroup will look into liaising with ICMJE and National Competent Authorities to explore the posssiblity of widening the scope of the registry.

Another point mentioned in the context of the registry was whether registered studies would undergo any type of peer-review.

- Interaction with Learned societies

It was agreed that the WG should liaise with Learned Societies where relevant (e.g. ISoP, ISPE, ISPOR, ICMJE, etc) in order to progress the WG's mandate and not to repeat unnecessary work which might already have been carried out. However, the group felt that Learned Societies should not be represented *per se* in the WG.

- Overlap with other WGs

It was felt that a certain degree of overlap with WG1 (Research Standards and Accreditation) was inevitable.

- Working method

The group was informed that the WG would be established for a minimum of 1-2 years. There would at least one further meeting in 2008. The need for topic leaders was discussed and two distinct topics were identified. The members were then asked to volunteer to one of the two groups as follows:

Code of conduct: Helen Dolk, Felix Arellano, Deborah Ashby, Vittorio Bertele, Zoe Doran, Anders Ekbom, Stephen Evans, David Haerry and Ole Kirk, Nicola Magrini and Lesley Wise.

Registry of Non-Interventional Studies: Joan Ramon Laporte, Ron M.C. Herings, Ingemar Persson and Mauro Venegoni.

It was agreed that the established groups would further communicate via email and that a permanent Chair of the WG on Transparency and Independence would be nominated at the next group meeting.

Conclusions

The mandate of the Working Group has been amended in line with the above recommendations and is attached to this report. Two subgroups have been established as follows:

- Code of Conduct subgroup
- Registry of Non-interventional studies subgroup

It was agreed that this WG would produce 2 deliverables:

1. A draft Code of Conduct for Independence & Transparency, including an Annex with a template contract.
2. A policy document discussing (and justifying) the need for a Registry of Non-interventional studies and a strategy implement such registry.

ANNEX – Amended Mandate of ENCePP Working Group 2

Working Group 2

Scope	***Independence and Transparency***
Chair: **Rapporteur(s):** **ENCIAG:**	Helen Dolk Henry Fitt, Hans-Georg Eichler Ingemar Persson, Deborah Ashby
Mandate	▪ To develop a Code of Conduct governing the responsibilities and interaction of stakeholders (Industry, Research centres, Regulators, etc) in the conduct of PhV studies in order to ensure scientific independence and transparency, including - Data ownership: raw data, analysed data - Centres' right/commitment to submit for publication - Centres' and MAHs'obligation to follow transparency rules - Authorships - Funders or Sponsors' rights: observer/presence in steering groups, information and comments on reports and manuscripts, time limits for comments, etc. - Regulatory requirements for reporting; interventional and non-interventional studies - Rules for financial interactions - Liability issues - Mandatory elements for standard contracts and legal issues (e.g. legislation under which study is carried out, copyright). - Introduce Annex with sample/template contract - protocol agreement, reporting of results etc - Define milestones when information details of a PhEpi study in progress shall be made available, or public, to stakeholders - Elaborate approaches/ways to ensure transparency, e.g. *web-publication* of the research protocol and/or the study results etc - Ensure transparency translates into effective Public Communication (e.g. on future EMEA Safety Portal) - Develop training programs ▪ Register of non-interventional PhEpi Safety Studies: develop a draft paper addressing the appropriateness, feasibility, scope and framework. Start with ENCePP studies. - Elaborate approaches for establishment of a register of initiated and conducted studies through ENCePP - Define rules for the *access of 3rd parties* to research data in the register - Develop a proposal for *standard forms* for website publication and entries in the register.