Position statement on the role of healthcare professionals, patient organizations and industry in European Reference Networks

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Abstract

A call from the EU for the set-up of European Reference Networks (ERNs) is expected to be launched in the first quarter of 2016. ERNs are intended to improve the care for patients with low prevalent or rare diseases throughout the EU by, among other things, facilitating the pooling and exchange of experience and knowledge and the development of protocols and guidelines. In the past, for example where costly orphan drugs have been concerned, industry has played an important role in facilitating consensus meetings and publication of guidelines. The ERNs should provide a unique opportunity for healthcare professionals and patients to lead these activities in an independent way. However, currently costs for networking activities are not to be covered by EU funds and alternative sources of funding are being explored. There is growing concern that any involvement of the industry in the funding of ERNs and their core activities may create a risk of undue influence. To date, the European Commission has not been explicit in how industry will be engaged in ERNs. We believe that public funding and a conflict of interest policy are needed at the level of the ERNs, Centers of Expertise (CEs), healthcare professionals and patient organizations with the aim of maintaining scientific integrity and independence. Specific attention is needed where it concerns the development of clinical practice guidelines. A proposal for a conflict of interest policy is presented, which may support the development of a framework to facilitate collaboration, safeguard professional integrity and to establish and maintain public acceptability and trust among patients, their organizations and the general public.

Keywords: European Reference Network, Rare diseases, Orphan diseases, Industry, Conflict of interest
Background

The launch of European Reference Networks (ERNs) for rare diseases should facilitate collaborations between centres of expertise (CEs) and improve the quality of patient care in EU member states and beyond. The call for the actual establishment of these networks is expected to be published in early 2016. At the second conference on ERNs in Lisbon [1], it was clear that there is no specific guidance from the European Commission (EC) on the interaction of care providers with the industry in either CEs or ERNs. In addition, at that time the EC had no plans to provide any funding for these networks. Whether there will be any financial support for ERNs at the level of member states is also unclear. This is unfortunate. The launch of ERNs creates an opportunity for healthcare professionals and patient organizations to work together to improve the quality of care for patients all over Europe, but for this to be effective, an infrastructure will be required. This will need financial support, which must be demonstrable independent of private interest.

The, mainly pharmaceutical, industry currently funds patient care, third party research and several of the activities that will become part of the core business of the ERN. Examples of such support are the set-up of care pathways, consensus guidelines and awareness studies in addition to the support of continuing medical education (CME). While these initiatives have sometimes led to valuable contributions to patient care, they have also raised concerns about the increasing participation and prominent role of the industry in programs that should be the sole responsibility of healthcare professionals [2, 3]. Going forward, to avoid any suggestion of an inappropriate mingling of private and public health interests, industry should not be directly involved in the funding or initial set-up of ERNs. Current guidance contained in EU law and the European Federation of Pharmaceutical Industries and Associations (EFPIA) code of conduct may not prove sufficient and we believe that more focused regulations and public funds are needed to guarantee the independence and scientific integrity of networks, member institutions and their collaborators.

European Reference Networks

In directive 2011/24/EU (Directive on the application of patients’ rights in cross-border healthcare, [4]) the EC commits itself and the EU member states to “support the development of European Reference Networks between healthcare providers and Centres of Expertise in Member States, in particular in the area of rare diseases” (Art. 12 and 13). These European Reference Networks (ERNs) are intended to support care for patients with low prevalent or rare diseases (RD) throughout the EU, and should provide the framework for healthcare pathways for RD patients through a high level of integrated expertise.

The European Union Committee of Experts in Rare Diseases (EUCERD), replaced by the Commission Expert Group on Rare Diseases, has developed recommendations on quality criteria for centres of expertise for RD as well as for specific needs for RD ERNs [5–7]. The core content of these recommendations is in agreement with the relevant sections of the EC Delegated and Implementing Acts [8, 9]. These Acts provide the binding, legal criteria and conditions that ERNs and their healthcare providers should fulfil, as well as the criteria for establishing and evaluating ERNs and their members. In summary, nationally designated centres of expertise (CEs) are the core participants in RD ERNs, but different forms of affiliation to an RD ERN (association, collaboration) are allowed for other healthcare providers in smaller countries. The main purpose of these networks is to improve clinical care for RD patients by, among other things, facilitating the pooling and exchange of experience and knowledge and the development of protocols and guidelines in order to ensure equal access to accurate information, appropriate and timely diagnosis and highly specialised and high quality care for RD patients. At a later stage, networks can apply for EU grants, which may benefit RD research as well. The Commission Expert Group on Rare Diseases has recommended to group rare diseases in thematic networks [7]. An EU call for the set-up of ERNs is expected for the first quarter of 2016.

Although the Acts are clear in how ERNs are to be set up and evaluated, they are not explicit in how industry can be engaged in ERNs. We believe that to clarify this issue for the various ERNs is of key importance to ensure and guarantee the independence of healthcare providers and the scientific integrity of medical research is fully guaranteed while allowing for the limited participation of industry in the work of ERNs where appropriate. Combining the work of ERNs and CEs with industry while maintaining professional autonomy and integrity as well as public acceptability and trustworthiness is a challenge. In the field of inborn errors of metabolism, a group of rare disorders in which a gene defect has a clinically significant impact on a metabolic pathway, initial discussions point to the importance of the subject and the relevance of conflicts of interest policies for ERN networks. This position statement is intended as a first step to support further discussions, which stretches well beyond our own field.

Objectives

All RD ERNs will be required to deliver added value in at least three of the objectives listed in Article 12 of the
Directive on patients’ rights in cross-border healthcare. In summary these objectives are:

a) To help realise the potential of European cooperation regarding highly specialised healthcare for patients and for healthcare systems by exploiting innovations in medical science and in health technologies;
b) To contribute to the sharing of knowledge regarding sickness prevention;
c) To facilitate improvements in diagnosis and the delivery of high-quality, accessible and cost-effective healthcare for all patients with a particular medical condition for which expertise and specialized healthcare facilities are concentrated and only available at a limited number of locations;
d) To maximise the cost-effective use of available resources by concentrating them where appropriate;
e) To reinforce research, epidemiological surveillance like registries and provide training for health professionals;
f) To facilitate the mobility of expertise, virtually or physically, and to develop, share and spread information, knowledge and best practice and to foster developments of the diagnosis and treatment of rare diseases, within and outside the reference networks;
g) To encourage the development of quality and safety benchmarks and to help develop and spread best practice within and outside the network;
h) To help member states with a low number of patients with a particular medical condition or lacking technology or expertise to provide highly specialised services of high quality.

Role of healthcare professionals, patient organizations and industry

Role of healthcare professionals
ERNs are networks of CEs providing healthcare for patients suffering from rare diseases: healthcare providers and the professionals working in such organizations will lead the networks. ERNs will not only need to collaborate with CEs and each other, but also with patient groups, social care providers, and affiliated research groups and diagnostic laboratories. ERNs should therefore have a robust and clearly defined governance with oversight structures and comprehensive methods for evaluation. The coordinating centre of an ERN will need to have and further develop its capability to coordinate the network, and this competence should be regularly evaluated as well.

Role of patient organizations
CEs should collaborate with patient organizations to bring in the patient perspective. In addition, patient organizations should play a role in ERNs and their evaluation. There is an ongoing discussion that the role of patients and patient organizations should be more robust and better defined at all levels. In several member states, patient organizations are increasingly involved in development of care pathways and research, such as in the French National Plan for Rare Diseases (Plan National Maladies Rares [10] and the Italian National Plan for Rare Diseases [11]). Experiences from these platforms can be used to strengthen the role of patients and their organizations in ERNs.

Role of industry
As ERNs primarily engage in clinical activities including the development of clinical guidelines and protocols such as diagnostic and therapeutic care pathways, there should be no role for industry in the governance of ERNs. Yet, for the discovery and development of new medications and medical devices that improve prevention, diagnosis, and treatment of health problems, research partnerships between industry, academia, public hospitals and government are essential. Such partnerships should be regulated in such a way that principles of professional autonomy of healthcare providers and scientific integrity of researchers are preserved and conflicts of interests are avoided for the ERN as such and in the member CEs. To prevent such conflicts of interest and to prudently handle situations in which they are at stake is not only in the interest of the ERNs, healthcare professionals and patients, but also in the interest of industry. For that reason we propose to adopt basic principles of independence for ERNs and CEs.

Proposal for a conflict of interest policy
Many healthcare professionals have relationships with industry. The increasing role of patient organizations in all aspects of patient care has also enhanced their interactions with industry. Many of these relationships concern the clinical development of innovative treatments, but industry also supports disease awareness
activities, diagnostic recommendations and management guidelines. Even when industry support for such initiatives remains solely financial, the relationships involved carry risks of conflict of interest and undue influence. These kinds of risks, which are well recognised for individual healthcare professionals and institutions or organizations, will also apply to ERNs. A conflict of interest policy is therefore needed with the aim of maintaining the scientific integrity and professional independence of ERNs and CEs. Such a policy usually includes i) the disclosure of financial relationships, ii) the prohibition of certain relationships, and iii) the management of potential conflicts of interest that have been identified [12]. In the paragraphs below, we will first give a short description of the concept of conflicts of interest, followed by an initial proposal for a conflict of interest policy for ERNs, their participating CEs and the individual healthcare professionals involved.

Conflicts of interest
According to the report of the USA Institute of Medicine (IOM) Committee on Conflict of Interest in Medical Research, Education, and Practice a conflict of interest is a set of circumstances that creates a risk that the professional judgment or actions regarding a primary interest (i.e. promoting and protecting the integrity of research, the welfare of patients, and the quality of medical education) will be unduly influenced by a secondary interest (i.e. financial interests). Secondary interests are unwanted only if they are more important than the primary interest in professional decision-making [12]. Conflict of interest policies aim to safeguard that primary interests guide professional decisions, and not secondary interests. Such policies have proven to work best when they are preventive and corrective rather than punitive [12]. Also, the likelihood of undue influence should be taken into account when developing a conflict of interest policy [12]. At the level of the individual healthcare professional, it is assumed that the probability increases when the value of the secondary interest is greater. Shareholding (or share options) in a pharmaceutical company, for example, creates a great risk for a conflict of interest, since positive results of a clinical trial may directly benefit the healthcare professional involved. Likewise, large fees for serving on a company advisory board carry a greater risk than small honoraria. Other aspects of the relationship, such as its depth and duration, may unduly influence professional decisions; the longer and closer the relationships, the higher the risk. Thirdly, whether the payments are transferred to the personal bank account of the healthcare professional or to the institution’s account is of importance when assessing the risk of undue influence [12]. Relationships with industry and conflicts of interest may not only exist at the individual level, but also at the institutional level and for patient organizations. For example, institutions may rely on industry funding for the appointment of research personnel, the development of treatment guidelines, or other activities. Similar risks may be greater for ERNs as, in the rare disease field, experts are involved in the development of innovative therapies and thus almost invariably have relationships with industry. Going forward, strategies should be developed which will avoid all potential conflicts of interest, but in the first instance, this may be an unrealistic goal. Taking all these things into consideration we propose the following recommendations.

Recommendations
Principles and regulations to protect scientific integrity and professional independence should be specified for (a) the governance of ERNs including the activities carried out by the ERN; (b) the CEs that will be its members and their activities; (c) external collaborative relations of ERNs and CEs with third parties:

(a) ERN governance and activities
- Costs for networking should be funded by the EC or scientific organizations. Direct funding by industry should be prohibited.
- ERNs should create a strong governance structure, with a steering committee, an independent board of trustees and transparent procedures to avoid and handle potential conflicts of interest and the handling of complaints
  - The board of trustees (adapted from [12])
    - has no members who themselves have serious conflicts of interest (see below) relevant to the activities of the ERN;
    - has no members who are directly in charge of running a CE that is part of the ERN;
    - has at least two patient representatives and a government/EC representative with relevant expertise;
    - creates adequate and independent arrangements for the day-to-day oversight and the management of institutional conflicts of interest;
    - submits an annual report to the steering committee, which should be made public.
- Activities within ERNs, specifically the development of clinical guidelines and protocols such as care pathways, treatment guidelines and diagnostic strategies should
- follow state of the art methodology, including the conduct of systematic and up to date reviews of the evidence and the linking of recommendations to that evidence
- include members that meet the criteria as listed in Table 1 [12]

(b) Centres of Expertise and their members
- CEs wishing to join an ERN should disclose their financial relationships with industry, which will be assessed against the criteria as delineated in Table 2
- CEs with serious conflicts of interest according to the criteria in Table 2 cannot be part of an ERN
- Healthcare professionals involved in CEs and ERNs should publicly disclose their financial relationships with industry
- Healthcare professionals involved in CEs and ERNs with serious conflicts of interest according to the criteria in Table 2 cannot participate in the development of clinical guidelines and protocols such as care pathways, treatment guidelines and diagnostic strategies

(c) External collaborative relations with third parties
Public-private partnership in the context of ERNs should be possible for the stimulation of innovation, in particular development of new treatments or medical devices and tools that ultimately offers benefit to patient care. The industry is a very valuable partner in this respect. It is expected that ERNs will engage with industry in future applications for Horizon 2020 research grants. These partnerships should be established in such a way that the principles of independence of an ERN and the CEs are maintained.

Table 1 Proposed criteria for participation in the assessment and approval of clinical guidelines and protocols for rare conditions/diseases (adapted from recommendation 7.1 in [12])

| Panels and groups that formulate and assess ERN guidelines for clinical practice should generally exclude as panel members individuals with conflicts of interest (see Table 2) and should not accept direct funding from medical product companies or company foundations. Such groups should publicly disclose with each guideline their conflict of interest policies and procedures and the sources and amounts of indirect or direct funding received for development of the guideline. In the situation in which avoidance of panel members with conflicts of interest is impossible because of the critical need for their expertise, then groups should:
| • Publicly document that they made a good-faith effort to find experts without conflicts of interest by issuing a public call for members and other recruitment measures;
| • Appoint a chair without a conflict of interest;
| • Limit members with conflicting interests to an agreed part of the panel;
| • Exclude individuals with serious conflicts of interest (see Table 2);
| • Publicly disclose the relevant conflicts of interest of panel members. |

Table 2 Proposed criteria for conflicts of interest

1. CEs that are members of an ERN can receive unrestricted grants as well as research grants from a pharmaceutical company provided full and timely (i.e., advance) disclosure of receiving such grants is given to the ERN’s Steering Committee and the amount does not conflict with other criteria
2. Centres of Expertise (CEs) cannot become a member of an ERN if it is primarily funded by and financially dependent on industry for a substantial part (to be defined by an independent body)
3. Healthcare professionals and patient representatives involved in CEs and ERNs cannot take part in the development of clinical guidelines and protocols, such as care pathways, treatment guidelines and diagnostic strategies, if they have the following serious conflicts of interest relevant to the CE or ERN:
   - a. being employed by a company with commercial interest
   - b. having equity or other ownership interests in a company with commercial interest
   - c. receiving fees for work related activities on a personal bank account
   - d. receiving fees that are disproportional to the work done (i.e., maximum fee more than locally agreed standards per hour)
4. Healthcare professionals and patient representatives involved in CEs and ERNs can take part in the development of clinical guidelines and protocols, such as care pathways, treatment guidelines and diagnostic strategies, if they have the following conflicts of interest, provided that they fully disclose these relationships and compensation is reasonable (according to local standards):
   - a. performing activities in the context of clinical trials
   - b. performing consultancies for a company
   - c. giving presentations during meetings organized by a company
   - d. receiving reasonable reimbursement of travel and hotel costs as part of meetings organized by a pharmaceutical company

The industry cannot be involved in development of clinical guidelines and protocols, such as care pathways, treatment guidelines and diagnostic strategies, as indicated above, nor can they be members of the ERN, steering committee or board of trustees.

Summary
A conflict of interest policy with respect to European Reference Networks, Centres of Expertise, individual healthcare professionals and patient organizations is needed to maintain scientific integrity and independence of ERNs. We propose criteria for a transparent structure, which could be used as a guideline for the future set-up of ERNs. The main elements are [1] a strong governance, with a Board of Trustees, whose task will be to monitor the activities and make sure that independence is maintained, and [2] a clearly defined set of criteria for CEs and their members. ERNs should seek endorsement from existing independent working groups. After the ERNs have been established, they can interact with industry for clearly described projects focusing on basic research. To
allow for an independent set-up of ERNs, a strategy for public funding should be developed by the EC as soon as possible.

Competing interests
CEMH declares that over the last 3 years, she has received reimbursement of travel and accommodation for serving at Shire’s charitable program. The Academic Medical Center has received educational and research grants from Genzyme and Shire and receives support for Registries. M Biegeleisen declares that she has not received travel and accommodation support from Genzyme to attend a symposium. MRB declares that in 2014, he has served as a consultant to Promethera Biosciences and received reimbursement of travel. The University Children’s Hospital has received educational and research grants from Actelion, Genzyme and Milupa Metabolics and receives support for the E-HOD Registry/Cystadane surveillance program from Orphan Europe. NB declares that she received fees for lectures, advisory boards and scientific committees for industrial registries (ICGG, GOS) and accommodation and travel support from Genzyme/Sanofi and Shire. The University Hospitals, Paris Nord, Val de Seine Hospital, Beaujon, has received grants. She serves as an expert at the French Social Security for metabolic diseases. BB declares that he has received grants and fees for advisory boards from Actelion, Genzyme, Shire. He is co-founder of Transactiva s.r.l., an academic spin-off of the University of Udine. AMB declares that she has been a member of advisory boards for SHS international, Nutricia and Merck Serono and has received funding for investigator initiated studies from SHS international and Nutricia. M Brouwers received honoraria for lectures from Shire and Genzyme, which were transferred to the institution’s account. M Brouwers received research funding from Synageva (currently Alexion Pharmaceuticals). HD declares that VKS has received unrestricted financial support for organising patient activities from Genzyme, Shire, Biomarin, Raptor, Sigma Tau, Sobi, Orphan Europe and Actelion in the past 3 years. DD declares that in 2014, he has served as a consultant to Promethera Biosciences and received reimbursement of travel. He has received accommodation and travel support for attending symposia and congresses. ME declares that he received consultancy fees from Minoryx Therapeutics and travel support from Actelion. MCG declares that over the last 3 years, she has received reimbursement of travel and accommodation from Orphan Europe for attending meetings. The Metabolic Power Foundation has received financial support for organizing fundraising activities from Shire, Genzyme and Biorizon (rate: 7% of the total income). HD declares that VKS has received unrestricted financial support for supporting patient activities from Genzyme, Shire, Orphan Biovitrum, Merk Serono and Orphan Europe. He has had unrestricted educational grant funding from Shire and Genzyme. Genzyme have supported the costs of a physiotherapist working in the CDMIU. RHL is chair of the scientific committee of the Recordati Rare Diseases Academy. JGL declares that over the last 3 years, she has received reimbursement of travel and accommodation expenses from Clinuvel for attending two EMA meetings in London, and a meeting organised by Clinuvel Pharmaceuticals, and she has received a separate research grant, all from Clinuvel Pharmaceuticals. ML declares that she has received travel and accommodation support from Genzyme to attend a symposium. GEL declares that over the last 3 years, he has received reimbursement of travel and accommodation for symposia from Shire and Genzyme. The Academic Medical Center receives support for Registries from Shire and Genzyme. SR declares that she received grant funding from Vitalfo International Ltd MEYG declares that over the last 3 years, she has received reimbursement for participating in two studies sponsored by Merck Serono. US declares that the University Children’s Hospital has received educational and research grants from Sobi, Orphan Europe, and Vitalfo. US has received fees for lectures and teaching material from Sobi, Orphan Europe and Vitalfo. U.S. has received travel and hotel accommodation from Nutricia, Orphan Europe and Shire. EPT has previously received honoraria for lectures from Shire and Genzyme. EPT’s Host Institution, Mater Misericordiae University Hospital is the recipient of a development grant from Shire Industries for the National Rare Diseases Office. RIAW declares that he has not received payment from industrial sources for consultancies or symposia. The department of Genetic Metabolic Diseases receives research support from Actelion and Synageva.

JZ declares that over the last 3 years he has received fees for an advisory board from Astra Zeneca, travel and accommodation support for attending scientific meetings from Merck Serono and Astra Zeneca, and accommodation support for attending scientific meetings from Nutricia Metabolics. His institute has received funding for diagnostic services as part of a clinical trial from Merck Serono, funding for educational activities from Nutricia Metabolics and Genzyme, and a research grant from Astra Zeneca. EM, BTIP and RH have nothing to declare.

Authors’ contributions
CEMH conceived the idea to write the paper, CEMH, MB and RH wrote a draft version. The position statement was distributed through their network, specifically healthcare professionals from the lysosomal/metabolic field. The boards of the Society for the Study of Inborn Errors of Metabolism, European Working Group on Gaucher Disease and European Study Group on Lysosomal Storage Disorders were informed. The recommendations are made by a group of healthcare professionals in their personal capacity and do not necessarily represent the views of professional societies. The co-authors on this position statement critically reviewed the draft, provided suggestions for improvement. All authors read and approved the final manuscript.

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