Editorial:

Recommendations and Guidelines in the JIMD: Suggested Procedures and Avoidance of Conflicts of Interest

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Author's contribution

Johannes Zschocke: designed and wrote the manuscript

Matthias R. Baumgartner: critical reading and revisions

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Verena Peters: critical reading and revisions

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Compliance with the Ethical guidelines

All authors were compliant and followed the ethical guidelines, according to the requirements of JIMD (see http://www.springer.com/medicine/internal/journal/10545).

Conflicts of Interest

J.Z. declares that over the last 3 years in the area of inherited metabolic diseases he has received travel and/or accommodation support from Merck Serono and Nutricia Metabolics. His institute has received research funding from Merck Serono as well as funding for educational activities from Nutricia Metabolics and Genzyme. M.R.B. declares that in 2014, he has served as a consultant to Promethera Biosciences and received reimbursement of travel. The University Children's Hospital Zurich 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. M.C.P. declares that over the last 3 years, he has received research funding from Actelion, travel and accommodation support from Actelion, consulting fees from Agios (Consulting), Alexion (formerly Synageva; Consulting), Amicus (DSMB membership), Actelion (Advisory Board), Genzyme (Consulting), Orphazyme (Scientific Advisory Board), Vtesse (Scientific Advisory Board), Stem Cells, Inc (DSMB membership). Research funding from Vtesse is currently in negotiation; MCP has resigned from the Vtesse Scientific Advisory Board for this reason. S.R. declares research funding from Vitaflo International Ltd. E. M. and V.P. declare no conflict of interest.

EDITORIAL

Clinical Practice Guidelines play an important role in the management of inherited metabolic diseases. Effective diagnosis and treatment is a particular challenge for rare diseases requiring specialist knowledge. The increasing availability of highly specific – and highly expensive – treatments for a rapidly growing number of rare conditions adds another dimension to the need for reliable guidelines. In order to justify the high costs of novel treatments it is essential that treatment is evidence-based and provided only to patients who will have a clear benefit. One of the main aims of the JIMD is to support the collation and publication of studies that provide a comprehensive, representative analysis of the clinical features, treatment and outcome of an inborn error of metabolism. The SSIEM's annual Archibald Garrod Award is given to the lead author of any such publication published in the preceding year in the JIMD. A major benefit of these studies is to provide an evidence base for the formulation of clinical practice guidelines, and the JIMD is very happy to consider such guidelines for publication.

Unfortunately limited resources are available to support the tedious and often undervalued effort needed to write reliable clinical practice guidelines. Frequently, only the pharmaceutical industry is willing to fund this work, sometimes because there is a strong interest in identifying additional patients who qualify for treatment and will generate revenue for industry. This creates immediate conflicts of interest that may be difficult to address (even if they are fully stated) in publications reporting clinical practice guidelines. On the other hand, close collaboration between clinicians and industry is often an important factor in optimizing care for patients with rare diseases including many inherited metabolic diseases. Furthermore, for some conditions it is difficult to find experienced clinicians who have no connections to industry. This also poses a particular challenge for the Editors and Reviewers of the JIMD when they assess a manuscript reporting clinical practice guidelines. Herewith we wish to state general principles for such manuscripts submitted to the JIMD. These principles address two aspects: (a) the consultation and review process leading to the formulation of clinical practice guidelines, and (b) independence from industry of the authors.

Rules for guideline development processes

Published clinical practice guidelines are of very variable quality and it has been long recognized that they may be influenced by industry funding (Choudhry et al. 2002). Many "guidelines" are in fact "expert consensus reports" based on expert opinion without systematic literature analysis and thus represent the lowest level of evidence (Shaneyfelt and Centor 2009; Shaneyfelt et al. 1999). In order to provide guidance for guideline development, an international collaboration denoted AGREE (Appraisal of Guidelines, Research and Evaluation) was established and a 23-item tool comprising six quality-related domains was released in 2003 and revised in 2010 (Brouwers et al. 2010). Details of this instrument including a user's guide are available at the collaboration website www.agreetrust.org (accessed 28.02.2016). Extensive information on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system of rating quality of evidence and grading strength of recommendations was published in a series of 15 articles in 2011 (Guyatt et al. 2011). National organisations such as the German Association of Scientific Medical Societies (AWMF; see http://www.awmf.org/leitlinien/awmf-regelwerk.html, accessed 28.02.2016) and the British Inherited Metabolic Diseases Group (BIMDG: see http://www.bimdg.org.uk/site/guidelines.asp, accessed 26.01.2016) have created framework structures for the publication of clinical practice guidelines on a wide range of topics (Muche-Borowski et al. 2012).

While a formalized review of the published medical evidence is clearly the preferred method for guideline development, this is not always feasible given the available resources. The Delphi method (Dalkey 1996) has been used to generate useful suggestions for the management of specific rare inherited metabolic diseases in a systematic fashion, based on the opinions of a large number of experts. This approach involves circulation of questionnaires to a large number of individuals across diverse locations, and repeated rounds of discussion, until consensus is reached. A review of the application of the Delphi method in medicine highlighted the need for adequate selection of panel members based on their knowledge and willingness to participate, and careful definition of study objectives and design of the questionnaire (Boulkedid et al. 2011).

The statistical evidence used to guide therapeutic choices in common disorders is not available for most rare diseases including inborn metabolic diseases. In many instances therapeutic choices are based on physicians' personal experiences, and "compassionate use" of drugs may be based on single case reports. In other cases the literature is not in agreement, or there is no reported evidence, just a known disease mechanism which is used to create a unique individualized treatment plan. This should be taken into account during prognostication and therapeutic counselling. It is hoped that establishment of networks of experts caring for larger numbers of "orphan" patients, together with good prospective data registration during observational or therapeutic trials, will overcome these problems in the future.

The JIMD considers it mandatory that the evidence underpinning recommendations or guidelines has been collated in a systematic and objective fashion. Patients entered into disease-specific registries must have an enzymatic and/or molecular confirmation of their disease, except in instances where a specific diagnosis can be reliably based on clinical and/or biochemical findings. Systematic review of the available medical literature should be performed using an established methodology. Alternatively, if the aim of the publication is an expert consensus report, the Editors of the JIMD require a (modified) Delphi method to be used. Authors are requested to describe the reason for selection of the panel experts and provide the questionnaires used, for publication as supplementary material. Authors should state in the title of their paper whether it constitutes "guidelines" or "consensus of expert opinion". Recommendations or guidelines arising from informal symposia and other meetings do not fulfil these criteria and therefore will not be accepted for publication in the JIMD.

Conflicts of interest

The need to consider possible conflicts of interest in the development of guidelines for diagnosis and treatment for rare diseases, and more generally in maintaining the scientific integrity and independence of future "European Reference Networks" (ERNs), has been highlighted in a recently published position statement (Hollak et al. 2016). It is the JIMD Editors' opinion that the general rules outlined in that manuscript also apply to

recommendations and guidelines published in the JIMD, as follows.

Groups that develop clinical practice guidelines should generally exclude as panel members individuals with conflicts of interest and should not accept direct funding for clinical practice guideline development from medical product companies or company foundations. 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 coordinator (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;
- publicly disclose the relevant conflicts of interest of panel members.

Healthcare professionals and patient representatives cannot take part in the publication of care pathways, treatment guidelines and diagnostic strategies if they have the following serious conflicts of interest relevant to the topic of the publication (at present, in the past three years, or in the foreseeable future):

- are employed by a company with commercial interest;
- have equity or other ownership interests in a company with commercial interest;
- receive fees for work related activities into a personal bank account;
- receive fees (paid to their institution, not for personal use) that are disproportionate to the work done (i.e., maximum fee more than locally agreed standards per hour).

A participant in the development of care pathways, treatment guidelines and diagnostic strategies can have the following conflicts of interest relevant to the topic of the publication, provided that these relationships are fully disclosed and compensation (not for personal use) is reasonable and in line with local standards:

- performing activities in the context of clinical trials;

- performing consultancies for a pharmaceutical company;
- giving presentations during meetings organized by a pharmaceutical company;
- receiving reasonable reimbursement of travel and hotel costs as part of meetings organized by a pharmaceutical company.

For background discussion of these rules see the full published position statement (Hollak et al. 2016). These rules should not be seen as discouraging fruitful interactions between industry, healthcare professionals, and patient representatives. Rather, safeguarding independence of diagnostic and treatment guidelines from commercial interests will give these guidelines more weight and will protect all parties involved from claims that the published statements do not represent current standards of care.

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