Declarations and conflicts of interest in WHO guidelines

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How to cite

WANG, Xiaoqin et al. Declarations and conflicts of interest in WHO guidelines. In: Journal of Clinical Epidemiology, 2017. doi: 10.1016/j.jclinepi.2017.12.021

This publication URL: https://archive-ouverte.unige.ch/unige:103894
Publication DOI: 10.1016/j.jclinepi.2017.12.021

The reporting of declarations and conflicts of interest in WHO guidelines can be further improved

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Abstract

Objectives: We aimed to examine the declaration of interests (DOI), management of conflict of interest (COI), and the funders for World Health Organization (WHO) guidelines.

Study Design and Setting: We examined all Guidelines Review Committee (GRC)-approved WHO guidelines published in English from January 2007 (inception of the GRC) to November 2016. We obtained a list of all such guidelines from the GRC Secretariat. Characteristics of guidelines including funders and individual contributors' DOI were independently extracted by two researchers. Binary logistic regression was used to assess the association between declarations and the number of organizations involved in development.

Results: 176 guidelines fulfilled inclusion criteria, encompassing 14 clinical or public health fields. Funders were reported in 128 (73%) of the guidelines: the most common were governments. DOI for external contributors were reported in 157 (89%) of the guidelines: 75 (48%) indicated no contributors with COI, 57 (36%) reported contributors with COI, and 25 (16%) reported collecting DOI but not whether COI existed. Financial COI were reported more frequently than nonfinancial COI. Of 57 guidelines that reported COI, 45 (79%) indicated how the COI were managed.

Conclusion: The majority of WHO guidelines reported their funding sources, and the DOI and COI of external contributors in their guideline documents. However, there is a need for improvement, in particular for reporting of funders and their role, declaration processes, and management of COI.

Key words: practice guideline; WHO; declaration of interest (DOI); conflicts of interest (COI); reporting quality

Background

Conflicts of interest (COI) - personal, organizational and financial factors which may affect the objectivity and independence of guideline contributors – are a potential source of bias in the development of clinical practice guidelines (CPGs) [1,2]. COI occur when professional judgment concerning a primary interest (such as the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain) [3]. Secondary interests can be classified as financial and nonfinancial, and include interests directly or indirectly (e.g., through relatives and close friends) related to the guideline contributor. Financial interests include shares or bonds in a commercial entity, personal financial gain (payment for work or research, consulting income or honoraria), gifts, proprietary interests and patents related to the topic, and grants or fellowships from a commercial entity that has an interest in the subject-matter of the guideline. In addition to the financial interests of individual contributors, funding for the guideline itself may also be a source of COI[4]. Non-financial interests of guideline contributors are also important and include previously published research related to the potential recommendations in guidelines, and personal political, religious or ideological beliefs that might influence evidence assessment and recommendation development [5-8]. There is no universally agreed upon taxonomy and management strategy for non-financial interests, which thus can be particularly challenging to manage [9].

Research findings are associated with the COI of authors and funders [10-17], thus management of COI of guideline contributors is critical to ensure the validity of recommendations in guidelines. Financial relationships between guideline organizations and biomedical companies are common but declarations of interest (DOI; the declaration of all potentially relevant secondary interests) are infrequently reported in guidelines [18-21]. Even when financial sponsorships are disclosed, few studies described the role of sponsors [10, 22,23].

The World Health Organization (WHO) produces guidelines to inform various stakeholders in the 194 Member States of the United Nations. These guidelines provide information about what policy-makers, healthcare providers or patients should do, assist in making choices between different interventions that have an impact on public health and resources, and help health care providers and recipients and other stakeholders to make informed decisions [6]. WHO has clear requirements for DOI and assessment of COI of contributors to its information products including guidelines, taking into account both financial and nonfinancial interests [6,24]. The WHO Guidelines Review Committee (GRC) was established in 2007 to ensure the use of internationally accepted best practice in WHO guidelines. The GRC critically reviews planning protocols and final versions of guidelines, and ultimately approves documents that meet the Organization's standards, including those related to COI [25].

The objective of this study was to examine DOI, COI, and funders reported in WHO guidelines, and the potential association between the reporting of DOI and whether WHO was the sole developer of a guideline.

Methods

Eligibility criteria and study selection

We included all GRC-approved, WHO guidelines published in English from January 2007 to November 2016, including those developed in collaboration with other organizations. We obtained a list of all such guidelines from the GRC Secretariat, and downloaded documents from the WHO website (http://www.who.int/publications/guidelines/en/). We included only the latest English-language version of each guideline. The full text of each guideline was independently screened by two researchers (XQW and QFW);

disagreements regarding inclusion were resolved by discussion or consultation with a third researcher (YLC).

Data Extraction and analysis

Data were independently extracted by two researchers (HXZ and RL) and disagreements were resolved by discussion or consultation with a third researcher (YLC). Referring to the requirements of WHO [5], the following data were extracted: 1) title, developers, year, topic(s); 2) funders, including their role in the development process; 3) DOI, including information on who declared their interests, and the methods and processes that were used to collect, evaluate, and report them; and 4) COI, including information on who declared them, their type (financial or nonfinancial), who assessed them, and how they were managed.

WHO, together with the other organizations involved in the development of a guideline, generally need to form four groups of contributors to complete the work: the steering group, the guideline development group, the external reviewer group, and the systematic review team. We investigated whether WHO guidelines reported DOI for all of these groups. DOI refers to declaration of all potentially relevant secondary interests, for example patent or stock ownership or prior authorship of a technical report on the same topic for the another group [24]. COI refers to the judgement that a declared secondary interest could potentially influence the guideline development process or outcomes, or the credibility of the final product. For example, if a guideline contributor declared owning stock in a drug manufacturer and that drug is being examined in a guideline, that is a COI. On the other hand, if the declared stock has no relevance whatsoever to the guideline at hand, that DOI is not a COI.

After extracting DOI from each guideline, we report if and how declared interests were assessed, and how conflicts, if any, were managed. If the guideline only reported DOI but did not indicate that the declared interests were assessed, we considered the situation to be “unclear”. We then examined DOI and the assessment process across publication years.

We used binary logistic regression to assess the potential association between WHO as the sole developer of guidelines (versus having multiple contributors) (independent variable) and reporting of DOI in guideline documents or their annexes (dependent variable). We hypothesized that guidelines that were developed collaboratively by several organizations may have lower rates of reporting DOI and COI management than guidelines developed by WHO because the other organizations may have less robust COI policies and practices. The regression analysis was conducted in SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA).

Results

We identified 208 guidelines approved by the GRC since its inception. Of these, 32 guidelines were excluded because they had been superseded by newer versions or were not published in English. Thus 176 guidelines fulfilled eligibility criteria (Fig. 1).

The characteristics of included guidelines are shown in Table 1. The number of guidelines published annually ranged between 6 and 29. Of the guidelines, 143 (81%) were developed solely by WHO, including its regional offices; the remainder were developed in partnership with external organizations.

Table 1. Characteristics of the included guidelines (n=176)

Characteristic		Number (%)
Publication year	2008	22 (13)
	2009	29 (16)

	2010	21 (12)
	2011	29 (16)
	2012	20 (11)
	2013	17 (10)
	2014	16 (9)
	2015	16 (9)
	2016	6 (3)
Developers	Developed by WHO	143 (81)
	Developed by WHO in partnership with other organizations	33 (19)
Type of funder*	No information on funding sources	48 (27)
	Governments	105 (60)
	WHO and its programs	25 (14)
	International non-profit organizations	24 (14)
	Foundations	21 (12)
	Institutes or societies	15 (9)
	Other (universities or hospitals)	3 (2)
Number of funders	No information on funding resources	48 (27)
	1	55 (32)
	≥2	73 (41)
Role of funders*	No information	120 (68)
	None	7 (4)
	Unspecified support for guideline development	26 (15)
	Meeting support	12 (7)
	Support the evidence review(s)	7 (4)
	Support publication and printing	7 (4)
	Provide technical support and consultation	3 (2)
	Appoint observers	1 (1)
	Supply products	1 (1)
	Edit	1 (1)
Topic	Infectious diseases**	76 (43)
	Maternal and child health	36 (20)
	Nutrition, chronic disease prevention	21 (12)
	Cancer	6 (3)
	Mental health and neurologic disorders	6 (3)
	Environment and health	6 (3)
	Smoking and substance abuse	5 (3)
	Health policy	5 (3)
	Public health emergencies including pandemics	4 (2)
	Food and health	3 (2)
	Non-communicable diseases	3 (2)
	Medical devices	3 (2)
	Disability	1 (1)
	Violence	1 (1)

* One guideline could be included in multiple categories.

** 63 focused on TB or HIV.

Funding sources for guideline development were reported in 128 (73%) of the guidelines. Of guidelines reporting funding sources, 55 (43%) were supported by one source and 73 (57%) received funding from two or more sources. The funders contributing to the greatest number of guidelines were governments (105, 82%), followed by non-profit organizations (24, 19%) and the WHO itself (25, 19%). Only 51 (40%) of the 128 guidelines reporting funding sources described the role of the funders. None of the included guidelines reported receiving funding from commercial entities.

A total of 157 (89%) guidelines reported the declared interests of external contributors (contributors who are external to WHO and participate in the guideline development process) (Fig. 1). Of the 157 guidelines, 97 (62%) reported the methods used to collect DOI (56 used a declaration form and 41 used a form plus verbal declaration), and 90 (57%) presented the process for assessing DOI (reported who assessed the DOI and by what criteria). Seventy-five (48%) of the 157 guidelines that reported DOI clearly indicated that no COI existed, and 57 (36%) reported one or more COI. The remaining 16% of guidelines provided the DOI without reporting if COI existed. Of the 57 guidelines that reported COI, 45 (79%) presented the management decisions that were made to deal with the COI (Table 2).

Table 2. The management decisions for conflicts of interest

Decision	Number (%)
The contributor should not contribute to deliberations on or formulation of the recommendations	34 (75)
Requires no action beyond declaration at the meeting and reporting in the final guideline	14 (31)
The contributor should not participate in evidence evaluation	8 (18)
The contributor should not provide comments on the final document	4 (9)
The contributor should not participate in relevant discussions and meetings	5 (11)
The contributor should not chair the screening discussion or identify the main sources of data	2 (4)
The contributor should not participate in developing provisional framework	1 (2)

Note: The total number is the 45 guidelines that reported this information.

Of the 57 guidelines reporting COI, 37 (65%) reported both financial and nonfinancial interests among the external contributors. The three most commonly reported types of COI were personal financial gain, personal research support, and participation in related research projects or presentations on related topics (Table 3).

Table 3. Types of conflicts of interest

Item (n, %)	Types of conflicts of interest	Number (%)
Financial (48, 86%)	Personal financial gain [a]	33 (58)
	Personal research support [b]	40 (70)
	Personal or organizational financial aid or scholarship	7 (12)
	Proprietary interests and patents	2 (4)
	Stock, shares or bonds	9 (16)
Nonfinancial (44, 79%)	Occupation or position, such as acting as chair or unpaid consultant for relevant organizations	29 (51)

Participation in related research projects or presentations on related topics	35 (61)
Personal political, religious or ideological beliefs	0 (0)

[a] Personal financial gain includes compensation, remuneration, travel allowance and other financial gain.

[b] Research support includes direct investment, device or product donation and other forms of support.

Note: The total number (n) is the 57 guidelines that reported this information. Different types of conflict of interest can exist in the same guideline.

A total of 145 guidelines (82%) reported the specific individuals or groups who declared their interests (Table 4). Members of the guideline development group (54, 31%), external or peer reviewers (48, 27%), and experts participating in meetings where recommendations were formulated (32, 18%) were the most frequent groups to provide DOI. DOI from the systematic review teams and from the guideline methodologists were rarely reported.

Table 4. Contributors declaring interests

Options	n (%)
Guideline development group	54 (31)
External reviewers or peer reviewers	48 (27)
Experts participating in meetings	32 (18)
Expert groups	31 (18)
Counselors/technical experts	24 (14)
Contributors/participants	11 (6)
Working groups	7 (4)
Core groups/members	4 (2)
Authors	4 (2)
Systematic review/ evidence groups	3 (2)
Methodologists	3 (2)
Steering groups	3 (2)
Observer, writing group, editor, external expert	8 (4)

Note: Because the labels for contributors varied across guidelines, some of these groups likely have similar roles to each other (e .g., guideline development group members and experts participating in meetings). The total number (n) is the 145 guidelines that reported this information.

Reporting of how DOI were collected and the process to assess DOI improved substantially between 2009 and 2011, and stayed relatively stable thereafter. Reporting of the judgements about whether COI existed changed little over time (Fig. 2). When WHO was the sole author of a guideline, DOI was reported more frequently (131/143, 92%) than for guidelines that were co-developed with other organizations (26/33, 79%) (odds ratio [OR]= 2.9, 95% confidence interval [CI] 1.1-8.2). The rates of DOI remained stable around 90% over time, except in 2010 when only 67% reported DOI.

Discussion

The majority of WHO guidelines reported their funding sources, however less than half presented the role of funders. Nearly 90% of the guidelines reported DOI, however of guidelines collecting DOI 38% did not provide details on how DOI were collected and nearly half did not report how DOI were assessed. In addition, 21% of guidelines that reported one or more COI gave no information on how COI were managed. Seventeen percent of

guidelines providing DOI did not report if COI existed. The most commonly reported type of COI was personal financial gain, and guidelines developed solely by WHO tended to report DOI more frequently than those co-developed with other organizations, although the difference was small.

Guideline development usually requires significant financial resources, and WHO staff may have to seek external funding in addition to mobilizing internal resources. External funding can, however, lead to biased recommendations [4,12,26] and thus many guideline developers and organizations producing systematic reviews set restrictions on the sources of funding. For example, the American Thoracic Society refuses any outright sponsorship [27] and the Cochrane Collaboration does not accept support for reviews from commercial sponsors that have a financial interest in the outcome [28]. Similarly, WHO does not permit guidelines funded by commercial entities [6]. Trustworthy guidelines must be transparent, including reporting of all funders [29, 30]. However, almost one-third of WHO guidelines did not provide this information, and less than half of those reporting funding sources described the exact role of funders.

Organizations including the Guidelines International Network [31], the New Zealand Guidelines Group [32], the British HIV Association [33], the U.K. National Institute for Health and Clinical Excellence [34], and WHO [6] all explicitly require DOI and the assessment of all disclosures for potential COI, followed by appropriate management of any conflicts. Standardized and complete reporting of DOI, COI and their management should be further improved at WHO. WHO requires the guideline development group, external reviewers, systematic review team and methodologists to declare their interests [6], but the results showed that the actual DOI varied greatly across contributors and guidelines. The labelling of guideline contributors varies across guidelines, which makes it difficult for end-users to understand the types of contributors and to compare rates of DOI and COI management across guidelines. In addition, there is no specific place for DOI reporting in WHO guidelines – the reader may have to look through the entire document and its appendices to find this information.

As this topic now receives more attention, DOI and COI are increasingly being reported in guidelines. George and colleagues reported in 2001 that only 3.7% of the included guidelines reported DOI information [35]. A 2012 study showed that only 60% of guidelines included in the US National Guidelines Clearinghouse (NGC) reported DOI and reporting of the management of COI was poor [20]. A more recent (2016) study of NGC guidelines showed that 65% of the guidelines reported DOI [21]. The results of our study suggest that reporting of DOI and COI management at WHO is better than that for other guideline developers: this may reflect rigorous implementation of the WHO COI policy and oversight by the GRC.

Financial COI can substantially affect research findings, usually in favor of commercial entities [11-13,16,36,37]. The effects of nonfinancial interests on research and decision-making are less clear-cut and there is debate about whether or not such interests are an important source of bias [9]. Many researchers do feel that nonfinancial COI can influence primary research, synthesis, and recommendations in guidelines [38-40]. One study in fact suggests that nonfinancial COI might have an even greater impact on patients or volunteers [41], and a survey reported that grant reviewers were more concerned about non-financial COI than financial interests [42]. The management of nonfinancial COI is particularly challenging, as all individuals, including content experts, have such interests [43,44]. The only approaches to minimize the risk of bias from such interests are to try and balance the perspectives, experiences, values and viewpoints across individuals contributing to the recommendations [5]. Both financial and nonfinancial COI were frequently reported in WHO guidelines, suggesting that WHO staff are aware of the importance of both types of interests, and complete reporting enables end-users to appropriately

interpret the guidelines.

The number of organizations involved in guideline development may influence DOI reporting [20]. We found that guidelines developed solely by WHO reported DOI more often than those co-developed with other organizations. However, the difference was small and the statistical analysis was not able to provide strong evidence of a true association. The small difference may be related to WHO's uniform requirements, regardless of the number of collaborators. We also explored changes in reporting over the 9-year period of guideline development since inception of the GRC. Although the rates of reporting DOI remained stable across the years, and details of DOI collection and management were reported more frequently in recent years. This may be partly attributed to continuous advances in the requirements for guideline development both internationally and at WHO [6,45-47].

Strengths and limitations

To our knowledge, this is the first study to evaluate the reporting of DOI and COI of guidelines related to both clinical practice and public health or health policy. Although the same principles for developing trustworthy guidelines apply to WHO guidelines as to clinical practice guidelines, WHO guidelines (which are usually developed for a global audience) may differ with respect to funding sources, diversity of end-users, the population focus, financial constraints, and the need to address issues of equity and human rights and incorporate issues related to social determinants of health. Thus the results of examination of other clinical practice guidelines may not necessarily be applicable to WHO guidelines. We obtained guidelines from the WHO website and the GRC Secretariat in order to ensure a comprehensive list. We assessed the reporting of DOI and COI of WHO guidelines according to WHO's own requirements, which are consistent with those of the US Institute of Medicine [29].

Our study results are based only on information reported in the guidelines. The completed DOI forms are not publicly available (only a summary of DOI and COI is published in WHO guidelines), and we did not contact guideline authors for further information, and there are data to suggest that self-report of interests is frequently inaccurate [48,49]. In addition, we did not examine differences in reporting across topics because for most topics only a small number of guidelines were published. There may be variation across the technical units at WHO, as experience and training levels may differ. These questions should be further investigated in the future.

Conclusion

The identification and management of COI, particularly nonfinancial interests, are challenging for all guideline developers; nonetheless the collection and assessment of DOI and the management plan for any COI should be consistently reported in all guidelines. The majority of WHO guidelines performed relatively well with respect to reporting of funders, DOI and COI of external contributors in their guideline documents. This may be related to the quality assurance process at WHO implemented by the GRC, and the careful attention paid to this issue by WHO staff. However, there is a need for improvement, in particular for reporting the role of funders, declaration processes, and management of COI. WHO and the guideline community need to continue to seek more efficient and effective approaches for identifying, quantifying and minimizing potential sources of bias in guideline development.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication All authors read and approved the final manuscript.

Availability of data and material All the data are presented in the manuscript.

Competing interests Dr SL Norris is an employee of the World Health Organization where one of her responsibilities is to help oversee the quality of WHO guidelines, including the implementation of WHO's conflict of interest policy.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions Conception and design: XQW, YLC and KHY. Analysis and interpretation of the data: XQW, YLC, QFW and SLN. Drafting of the article: XQW, QZ and LY. Critical revision of the article for important intellectual content: XQW, JE and SLN. Final approval of the article: XQW, QZ, LY, QFW, JE, QW, YLC, KHY and SLN. Statistical expertise: JE. Collection and assembly of data: XQW, QFW, QZ and QW.

Acknowledgements The authors thank Rui L, Qingyuan Q, Hongxia Z, Shujun X, Yang Y, Baosen W and Nan L (Medical School, Lanzhou University, Lanzhou, China) for extracting data. The authors also thank Xiping S (School of Public Health, Lanzhou University, Lanzhou, China) for helping with the statistical analysis.

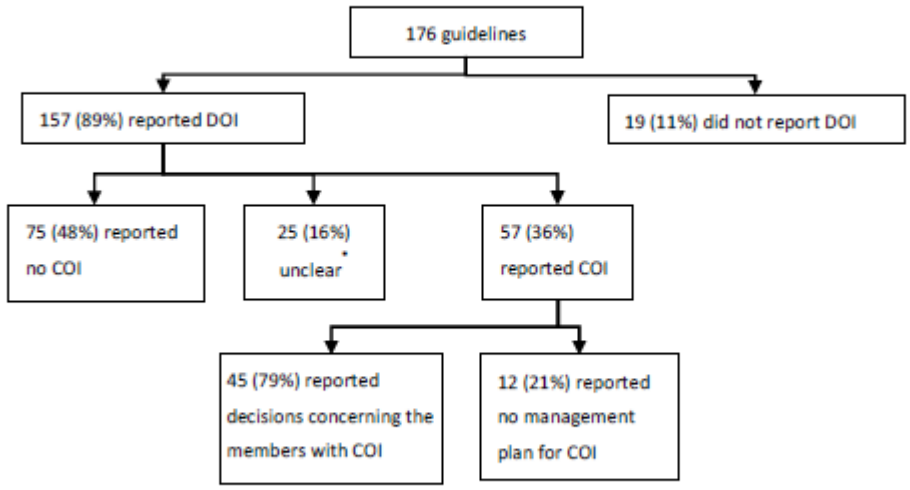

Figure 1. Information on declarations and conflicts of interest in WHO guidelines

* These guidelines provide only DOI information without reporting whether COI existed or not.

COI, conflicts of interests; DOI, declarations of interest

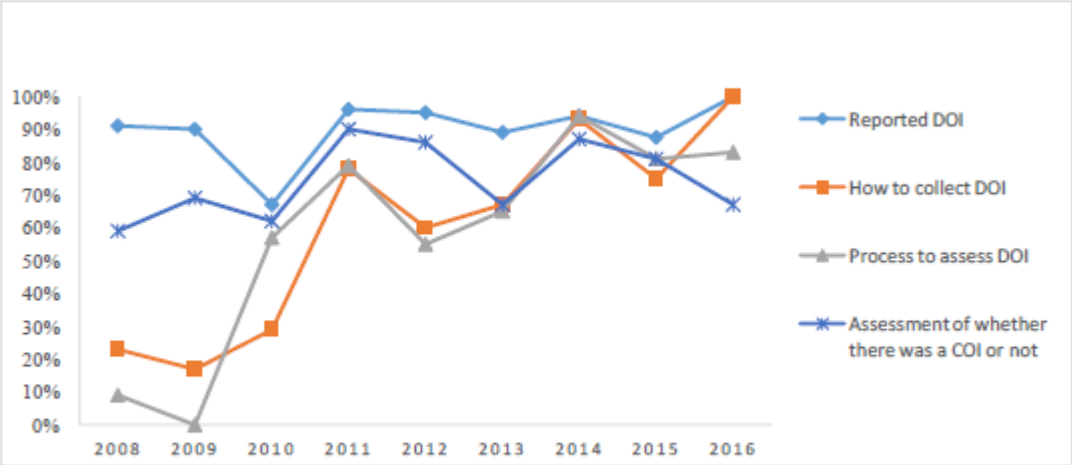

Figure 2. Reporting of declaration and conflicts of interests by year of publication

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