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2 **The reporting of declarations and conflicts of interest in WHO**

3 **guidelines can be further improved**

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26

27 **Abstract**

28

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

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

36

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

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

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

47

48 **Background**

49

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

64

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

70

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

80

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

83

84

85 **Methods**

86 **Eligibility criteria and study selection**

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

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

93

94 **Data Extraction and analysis**

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

101

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

111

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

116

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

123

124 **Results**

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

128

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

132

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)

133 * One guideline could be included in multiple categories.

134 ** 63 focused on TB or HIV.

135

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

142

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

151

152

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)

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

154

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

158

159

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)

160 ^a Personal financial gain includes compensation, remuneration, travel allowance and other financial gain.

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

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

164

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

169

170

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)

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

174

175 Reporting of how DOI were collected and the process to assess DOI improved substantially between 2009 and
176 2011, and stayed relatively stable thereafter. Reporting of the judgements about whether COI existed changed little
177 over time (Fig. 2). When WHO was the sole author of a guideline, DOI was reported more frequently (131/143,
178 92%) than for guidelines that were co-developed with other organizations (26/33, 79%) (odds ratio [OR]= 2.9, 95%
179 confidence interval [CI] 1.1-8.2). The rates of DOI remained stable around 90% over time, except in 2010 when
180 only 67% reported DOI.

181

182 Discussion

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

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

190

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

200

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

211

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

219

220 Financial COI can substantially affect research findings, usually in favor of commercial entities
221 [11-13,16,36,37]. The effects of nonfinancial interests on research and decision-making are less clear-cut and
222 there is debate about whether or not such interests are an important source of bias [9]. Many researchers do feel
223 that nonfinancial COI can influence primary research, synthesis, and recommendations in guidelines [38-40]. One
224 study in fact suggests that nonfinancial COI might have an even greater impact on patients or volunteers [41], and a
225 survey reported that grant reviewers were more concerned about non-financial COI than financial interests [42].
226 The management of nonfinancial COI is particularly challenging, as all individuals, including content experts, have
227 such interests [43,44]. The only approaches to minimize the risk of bias from such interests are to try and balance
228 the perspectives, experiences, values and viewpoints across individuals contributing to the recommendations [5].
229 Both financial and nonfinancial COI were frequently reported in WHO guidelines, suggesting that WHO staff are
230 aware of the importance of both types of interests, and complete reporting enables end-users to appropriately

231 interpret the guidelines.

232

233 The number of organizations involved in guideline development may influence DOI reporting [20]. We found
234 that guidelines developed solely by WHO reported DOI more often than those co-developed with other
235 organizations. However, the difference was small and the statistical analysis was not able to provide strong
236 evidence of a true association. The small difference may be related to WHO's uniform requirements, regardless of
237 the number of collaborators. We also explored changes in reporting over the 9-year period of guideline
238 development since inception of the GRC. Although the rates of reporting DOI remained stable across the years, and
239 details of DOI collection and management were reported more frequently in recent years. This may be partly
240 attributed to continuous advances in the requirements for guideline development both internationally and at WHO
241 [6,45-47].

242

243 **Strengths and limitations**

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

253

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

260

261

262 **Conclusion**

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

272

273

274 **Declarations**

275

276 **Ethics approval and consent to participate** Not applicable.

277

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

279

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

281

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

285

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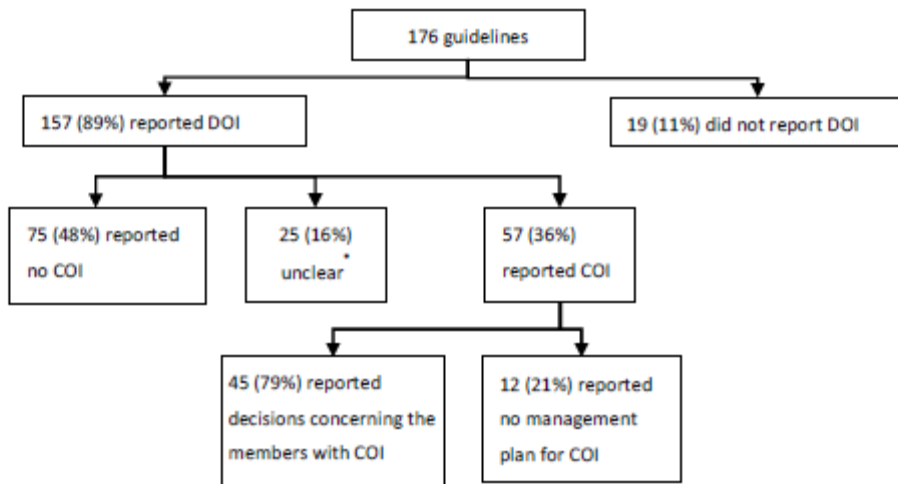


Figure 1. Information on declarations and conflicts of interest in WHO guidelines

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

COI, conflicts of interests; DOI, declarations of interest

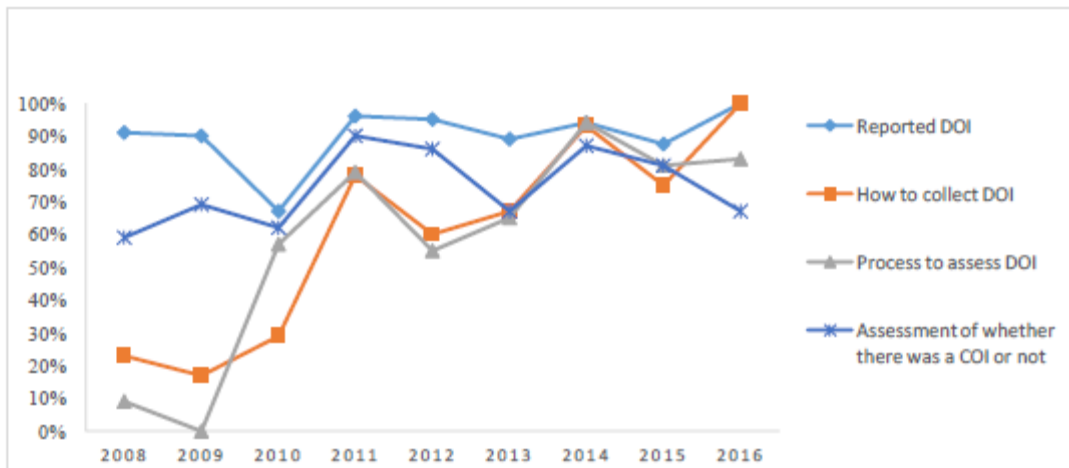


Figure 2. Reporting of declaration and conflicts of interests by year of publication

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