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Undisclosed financial ties between guideline writers and pharmaceutical companies: a cross-sectional study across ten disease categories

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6 **Title:** Undisclosed financial ties between guideline writers and pharmaceutical companies: a
7 cross-sectional study across ten disease categories
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Abstract

Objectives: To investigate the proportion of potentially relevant undisclosed financial ties between clinical practice guideline writers and pharmaceutical companies.

Design: Cross-sectional study of a stratified random sample of Australian guidelines and writers.

Setting: Guidelines available from Australia's National Health and Medical Research Council guideline database, 2012-2014, stratified across ten health priority areas.

Population: 402 authors of 33 guidelines, including up to 4 from each area, dependent on availability: arthritis/musculoskeletal(3); asthma(4); cancer(4); cardiovascular(4); diabetes (4); injury(3); kidney/urogenital(4), mental health(4); neurological(1); obesity(1). For guideline writers with no disclosures, or who disclosed no ties, a search of disclosures in the medical literature in the 5 years prior to guideline publication identified potentially relevant ties, undisclosed in guidelines. Guidelines were included if they contained recommendations of medicines, and writers included if developing or writing guidelines.

Main outcome measures: Proportions of guideline writers with potentially relevant undisclosed financial ties to pharmaceutical companies active in the therapeutic area; proportion of guidelines including at least one writer with a potentially relevant undisclosed tie.

Results: 344 of 402 writers (86%; 95% CI 82% to 89%) either had no published disclosures (228) or disclosed they had no ties (116). Of the 344 with no disclosed ties, 83 (24%; 95% CI, 20% to 29%) had potentially relevant undisclosed ties. Of 33 guidelines, 23 (70%; 95% CI, 51% to 84%) included at least one writer with a potentially relevant undisclosed tie. Writers of guidelines developed and funded by governments were less likely to have undisclosed financial ties (8.1% vs 30.6%; risk ratio 0.26; 95% CI 0.13 to 0.53; P-value <0.001)

Conclusions: Almost one in four guideline writers with no disclosed ties may have potentially relevant undisclosed ties to pharmaceutical companies. These data confirm the need for strategies to ensure greater transparency and more independence in relationships between guidelines and industry.

Strengths and Limitations of this study

- Our study is the largest to date to examine undisclosed ties of guideline writers, and includes a broad sample of guidelines across ten disease categories
- Our study includes guidelines with different funding and development arrangements, enabling comparison of guidelines funded and developed by government, with other guidelines
- Our study did not investigate the undisclosed ties of guideline writers who had disclosed ties in the sample of guidelines analysed
- Study results likely underestimate the extent of undisclosed financial ties of guideline writers

peer review only

Introduction

There is global concern about the nature and extent of financial ties between pharmaceutical companies and health professionals, including those who develop influential clinical practice guidelines. (1-3) In 2009 a landmark Institute of Medicine report on conflicts of interest acknowledged the importance of collaboration with industry, but warned financial ties to industry were widespread and risked jeopardizing the integrity of medical education, research, and practice, and called for greater transparency and independence. (1) A subsequent Institute of Medicine report, titled “Clinical practice guidelines we can trust”, recommended that groups developing guidelines “optimally comprise members without conflict of interest.” (2) Systematic review evidence suggests most guideline writers disclose some form of industry affiliation, with estimates between 56% and 87%. (3) There are however few data on the extent of undisclosed financial ties of guideline writers. One study of North American cholesterol and diabetes guidelines estimated 11% of writers had undisclosed ties, (4) another study of American head and neck surgery guidelines found 6% had discrepancies between disclosures and an open payments database, (5) while a Danish study of 14 specialty society guidelines found 52% had undisclosed ties. (6) *

A conflict of interest is defined as “a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.” (1) A primary interest of a guideline writer may be maximising health outcomes, and a secondary interest could be personal gain derived from a financial relationship with a company active in the relevant therapeutic area. Evidence from other areas, such as clinical trials, has shown such conflicts of interest may introduce bias. A recent systematic review found drug trials sponsored by industry more often have efficacy results and conclusions favourable to the sponsor. (7) Similarly, a cross-sectional study of randomised trials found those authored by principal investigators with ties to pharmaceutical companies were more likely than other trials to report favourable results. (8) Such evidence has provoked debate about the optimum constitution of guideline groups, with calls for chairs and a majority of writers to be free of financial ties, (9,10) as well as recommendations for exclusion of any conflicted writer. (2)

**For consistency the term guideline writer is used throughout to refer to those who develop, draft and author guidelines.*

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3 In Australia, the publicly funded National Health and Medical Research Council (NHMRC)
4 is currently engaged in improving standards for guideline development, including in relation
5 to transparency and management of conflicts of interest. An internal analysis of nine years of
6 Australian guidelines made available via the NHMRC guideline portal, 2005-2013, found
7 only 12% of guidelines published declarations of the conflicts of interest of guideline writers.
8 (11) As part of work to improve standards of guidelines which can have direct impacts on
9 how clinicians deliver care to their patients, the NHMRC is developing new “guidelines for
10 guidelines”, and a draft released for public comment in 2017 included the recommendation:
11 “Organisations planning guidelines should aim to appoint a guideline development group
12 whose members have no financial or other links with relevant industry groups.” (12) In order
13 to inform on-going efforts to improve guideline quality in Australia and internationally, our
14 objective was to investigate the extent of undisclosed financial ties to industry, for a broad
15 cross-section of guideline writers from different categories of guideline developer, sampled
16 from a comprehensive national guideline database, across a wide spectrum of diseases.
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27 **Methods**

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29 We conducted a cross-sectional study of a stratified random sample of Australian clinical
30 practice guidelines and followed the STROBE checklist for reporting observational studies.
31 (see Supplementary file 1) (13)
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35 *Sampling guidelines*

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37 We identified a stratified random sample of clinical practice guidelines from within the
38 NHMRC guidelines database, across nine government designated health priority areas,
39 ([https://www.nhmrc.gov.au/book/nhmrc-corporate-plan-2016-2017/nhmrc-s-strategic-
40 direction/major-health-issues](https://www.nhmrc.gov.au/book/nhmrc-corporate-plan-2016-2017/nhmrc-s-strategic-direction/major-health-issues)), plus kidney/urogenital, published in the years 2012-2014. The
41 NHMRC database comprised guidelines made available on the publicly accessible NHMRC
42 guidelines portal, which aimed to include all Australian guidelines, defined broadly as
43 published articles making clinical recommendations. While the NHMRC portal at that time
44 included all Australian guidelines, it also **provided users of the portal with information on
45 quality indicators for these guidelines, such as whether the guideline was based on a
46 systematic review of evidence, whether the authors provided COI disclosures, and whether or
47 not the guideline had been approved by NHMRC.** From 2015, the NHMRC portal restricted
48 the inclusion of guidelines to only include guidelines which met certain quality standards, so
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3 to achieve a representative sample from the comprehensive collection of widely used
4 Australian guidelines, we analysed guidelines available on the portal in the three years
5 leading up to the change.
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8 In 2017 NHMRC staff (HJ) identified all guidelines in the database, published in the years
9 2012-2014, and used previous coding by NHMRC to exclude articles not relevant to the ten
10 health areas of interest, those not considered guidelines, including those coded as Evidence
11 Reviews, Posters/Flowcharts, Standards, and Summary guidelines. Following the initial
12 screen, each guideline was randomly ordered using Microsoft Excel, within each of the ten
13 health areas. Two authors (LB, RM) then assessed each guideline in the order they had been
14 ranked, against explicit inclusion criteria, and identified guideline writers to be included in
15 the analysis. Guidelines were included if they were associated with a professional
16 organisation or entity and made mention of medicines in recommendations. They were
17 excluded if they were a journal article unconnected from an external organisation, or if no
18 author names or full text was available. Guideline writers listed in the guideline were
19 included for analysis if they were explicitly engaged in developing, preparing or writing the
20 guideline, and excluded if they were external consultants, members of oversight committees,
21 or staff from a drug company, NHMRC, or administrative staff. Any discrepancies were
22 resolved by discussion.
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33 The primary unit of analysis was the guideline writer. Based on assumptions that 10% of
34 guideline writers might have an undisclosed relevant financial tie, and that guidelines would
35 have 4-20 writers each, we estimated a need for a minimum sample of 12 guidelines – aiming
36 for approximately 140 writers – to produce a confidence interval of a width of 10% around
37 our estimate of the proportion of writers with undisclosed ties. In addition, to obtain as broad
38 a cross-section as possible, we aimed to analyse up to four guidelines per health
39 priority/disease area, depending on guideline availability.
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45 *Guideline and author information*

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48 One investigator (either AL or RM) extracted all relevant information from each included
49 guideline into the REDCap electronic data capture tools hosted at the University of Sydney.
50 (14) The extracted information included the names of all included writers, classified in one
51 of three ways: disclosure of ties; disclosure of no ties; no disclosure present. Disclosures
52 were those included in the guideline document or associated publicly available documents.
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3 Information on whether the guideline had a statement on conflicts of interest, and the
4 developer/s and funder/s was also extracted.
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6 7 *Identification of potentially relevant undisclosed financial ties*

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9 For any guideline writer with no declaration present, or who declared no conflicts of interests,
10 one investigator (AL or RM) conducted a search of the writer's publications in the five years
11 before the year of guideline publication. The period of five years was chosen for the
12 following reasons: many guidelines are estimated to be at least two years in development
13 before the year of publication; disclosures are directly relevant at the start of the process of
14 guideline development; World Health Organization guidance suggests a period of 4 years
15 prior to publication is relevant when disclosing financial ties, (15); and many disclosure
16 policies have a recall period of 3 to 5 years. (16) Publications were also searched in the three
17 years following guideline publication, as some organisations, including the Institute of
18 Medicine, recommend guideline writers be free of conflicts for periods of time after guideline
19 publication. (17)
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28 The Scopus database was used to search for publications of guideline writers using their
29 names and affiliations. Full texts were obtained. Searches were conducted from the earliest
30 date, and as per Forsyth et al. (18) were stopped once a potentially relevant financial tie was
31 identified. A potentially relevant tie was defined as a financial tie to a pharmaceutical
32 company actively marketing or in late stages of bringing a medicine to market in the
33 therapeutic area relevant to the guideline, at the time of the guideline publication, determined
34 through searches of company websites and relevant product information material.
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Categorisation of ties was developed based on criteria set by the International Committee of Medical Journal Editors, ICMJE, and based on adaptations of ICMJE criteria used in a previous study, (18) including: grants (funding for research study); personal fees (consulting, advisory, speakers, honoraria, travel); patents/copyrights/royalties; miscellaneous. Once a potentially relevant tie was identified by one author (AL or RM), a second author (RM or LB) double checked the full text of the disclosure and verified the tie as a potentially relevant tie, and any discrepancies were resolved by discussion. Searches were conducted between August and December 2017.

53 *Outcome measures and statistical analysis*

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3 The primary outcome measures were specified as the proportion of guideline writers with
4 potentially relevant undisclosed ties, and the proportion of guidelines in the sample which
5 included at least one writer with an undisclosed tie. Secondary outcome measures were: the
6 proportion of writers with disclosed ties; the proportion of guidelines which have any
7 statement about conflicts of interest; and the proportion of guidelines developed and funded
8 by governments (state, federal or territories). We report data proportions using descriptive
9 statistics and including 95% confidence intervals. We examined the association between
10 having statements and the proportion of potentially relevant undisclosed ties of writers; and
11 the association between a guideline being developed and funded by government/s and the
12 proportion of potentially relevant undisclosed ties of writers. Potential associations were
13 tested using the chi-square test. Confidence intervals were not adjusted for clustering of
14 writers within multiple guidelines, or for clustering of guidelines within disease area.
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23 *Ethics*

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25 As all publications analysed for this study were on the public record, the chair of Bond
26 University's Human Research Ethics committee asserted that the study did not require ethics
27 review, if no individuals were identified or described.
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31 *Patient and Public Involvement*

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33 No patients or members of the public were involved in this study.
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36 **Results**

37 *Characteristics of Guidelines*

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39 There was a total of 347 guidelines in the NHMRC database, published 2012-2014. (Figure
40 1) The initial screen excluded 11 items not considered guidelines, coded by NHMRC as
41 Evidence Reviews, Posters/Flowcharts, Standards, and Summary guidelines, 62 because they
42 did not contain names of those who had developed the guideline and 129 published outside
43 the ten health areas in this study. The remaining 145 guidelines were assigned a random
44 number to establish a random order for assessment of the guidelines within each of the ten
45 health areas. We continued to assess guidelines within each area in random order until we had
46 included 4 for each health area or had completed assessing all the available guidelines in a
47 given health area. In total, LB and RM assessed 82 guidelines. Forty-nine of those
48 guidelines were excluded after assessment: because they were a publication only with no
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3 affiliation to any external organisation (n=22); had no recommendations about medications
4 (n=25); or the full text or author list of the guideline was not publicly available. (n=2) Sixty-
5 three were not assessed.
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8 We included 33 guidelines in our final sample: arthritis/musculoskeletal(n=3); asthma(n=4);
9 cancer(n=4); cardiovascular(n=4); diabetes (n=4); injury(n=4); mental health(n=4);
10 neurological(n=1); obesity(n=1); kidney/urogenital(n=4). (Supplementary file 2) The 33
11 guidelines involved a total of 402 guideline writers, with individual guidelines having
12 between 2 and 35 writers included for analysis.
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14

15 *Prevalence of undisclosed ties*

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17 Among all 402 guideline writers, 58 disclosed ties. (14%; 95% CI, 11% to 18%)(Table 1)
18
19 Among the 402 writers, 344 had no disclosed ties, (86%; 95% CI 82% to 89%) including 228
20 writers where no disclosures appeared, and 116 writers with statements that they had no ties.
21
22 Of the 344 writers with no disclosed ties, 83 had at least one potentially relevant undisclosed
23 tie, (24%; 95% CI, 20% to 29%), discovered in the published literature in the same year as
24 the guideline was published or the previous 5 years. Of those undisclosed ties, the first
25 category of tie listed in the relevant disclosure was: pharmaceutical company grant (64%), or
26 personal fees, (36%). If the time frame was extended to 3 years after the guideline, the
27 proportion of potentially relevant undisclosed ties rose from 24% to 28%. (95% CI, 23% to
28 33%)
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31
32 Of 33 guidelines, 23 included at least one writer with a potentially relevant undisclosed tie.
33 (70%; 95% CI, 51% to 84%). (Figure 2) Of those 23 guidelines, 14 guidelines had 20% or
34 more writers who disclosed no ties, but had potentially relevant undisclosed ties. Figure 2
35 also reveals the proportion of undisclosed ties of guideline writers who disclosed no ties, per
36 guideline, grouped by disease category.
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38

39 *Guideline Characteristics and Undisclosed Ties*

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41 Guidelines which included any statement about conflicts of interest were not significantly
42 different from those without statements, 59 of 223 writers (27%) had potentially relevant
43 undisclosed ties, compared to 24 of 121 writers. (20%) (risk ratio 1.33; 95% CI 0.88 to 2.03;
44 P-value =0.170) (Table 2) Guidelines both developed and funded by governments, as
45 opposed to non-government groups (including professional bodies, foundations, or
46 pharmaceutical companies), were significantly less likely to have authors with potentially
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3 relevant undisclosed ties, 8 of 99 writers (8%) compared to 75 of 245 writers. (31%) (risk
4 ratio 0.26; 95% CI 0.13 to 0.53; P-value <0.001)
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6 **Discussion**

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8
9 In this broad cross-sectional sample of Australian clinical practice guidelines, 14% of
10 guideline writers had published disclosures of conflicts of interest. Among those who either
11 had no disclosures or disclosed they had no conflicts, 24% – almost one in four – had at least
12 one potentially relevant undisclosed financial tie to a pharmaceutical company active in the
13 therapeutic area. More than two-thirds, or 70%, of the 33 guidelines in this sample had at
14 least one writer with an undisclosed tie. Undisclosed financial ties of guideline writers
15 appeared to be more common in some therapeutic areas such as diabetes and cardiovascular
16 disease, compared to other areas such as injury and mental health. Guideline writers working
17 on guidelines developed and funded by government were much less likely to have
18 undisclosed financial ties: 8% compared to 31%.
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27 There are important limitations to this study. First, the results likely underestimate the
28 frequency of undisclosed ties for several reasons: there is a general under-reporting of ties
29 published in medical journals as many important transfers of benefits to professionals, such
30 as hospitality or industry-subsidised education, are not routinely disclosed; Australia did not
31 at the time have a database with information on company payments to individuals; and we
32 did not search for any potentially relevant undisclosed ties of writers who made disclosures of
33 ties in the guideline, whether those ties were to pharmaceutical companies or other groups.
34
35 Second, our results may tend to a small degree to overestimate the frequency of undisclosed
36 ties, through what some may see as a broad definition of potential relevance; for example,
37 categorising a co-investigator of a study funded by a pharmaceutical company active in the
38 therapeutic area as a potentially relevant tie. Third, the sample of guidelines, while broad and
39 accessible, comes from 2012-2014 – the most recent years available for this sample from a
40 comprehensive collection – admitting the possibility of change since that time. And fourth,
41 we looked only at financial ties, not other non-financial conflicts of interest. The strengths of
42 the study lie in it being the largest to date in terms of guideline writers and undisclosed ties to
43 industry, as well as covering a broad cross-section of disease categories and guideline
44 developers – both government and non-government – with previous smaller studies limited to
45 specific therapeutic areas, (4,5) or guidelines produced only by specialty societies. (6)
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3 Neuman and colleagues investigated the prevalence of conflicts of interest among panels
4 producing 14 North American guidelines for high cholesterol and diabetes. (4) They reported
5 that among writers who formally declared no conflicts, 11% had one or more. Looking at a
6 small sample of 49 writers of head and neck surgery guidelines, Horn and colleagues found
7 6% had discrepancies between guideline disclosures and information available in the Open
8 Payments transparency database. (5) Analysing Danish specialty society guidelines, and
9 cross-checking disclosures against a public register of disclosures, Bindsley and colleagues
10 estimated 52% of 254 guideline writers had not disclosed ties. (6) A possible explanation of
11 why our estimate of 24% sits within these finding is that the North American studies used
12 narrower timeframes to search for undisclosed ties, while the Danish study defined a conflict
13 of interest as any affiliation with any drug company.
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22 As others have stated, guideline writer ties to companies with interest in the guideline's
23 outcome raise critical questions about potential bias in processes that may have great impacts
24 on the use of healthcare interventions, (4,12) disease definitions, (19) and patient care.
25 Findings of potentially relevant undisclosed ties compound the problem further and raise the
26 spectre of hidden bias, increasing the wariness of guideline users. Contemporary community
27 standards now demand total transparency, and our findings of undisclosed ties add weight to
28 calls for reforms like the Sunshine Act and Open Payments system in the United States, (20)
29 "publicly accessible registries of researcher conflicts of interest", (21) and more immediately,
30 enforcement of current disclosure policies to minimise undisclosed ties. In line with repeated
31 recommendations for greater independence between health professionals and industry,
32 (1,2,12) our incidental finding that almost one in five of these guidelines had less than 10% of
33 writers with any ties to industry, shows it is possible to assemble guideline panels almost
34 entirely free of financial conflicts of interest.
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45 The related reform processes of enhanced transparency and greater independence underway
46 in many nations creates clear opportunities for research comparing the quality of guidelines
47 developed by writers with and without links to industry, a research question beyond the scope
48 of this study, and where there is currently limited data. (22) Similarly, there is need for more
49 research investigating the impacts of links between industry and the professional
50 organisations which auspice guideline development, with one recent study suggesting such
51 ties are "common and infrequently disclosed." (23) Given their potential influence over
52 human health, and health system sustainability, such vital research on the independence and
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3 trustworthiness of guidelines will be greatly enhanced by complete transparency around the
4 financial conflicts of interest of those developing them.
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43 and, vi) licence any third party to do any or all of the above.
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49 **Conflicts of Interest:**

50
51 Competing interests: All authors have completed the ICMJE uniform disclosure form
52 at www.icmje.org/coi_disclosure.pdf and declare: RM and EB have received grant support
53 from NHMRC; LB is a member of the NHMRC committee developing the guidelines for
54 guidelines handbook.
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Contributor Statement:

RM, AL, HJ, GD, SG, LB conceived and designed the study. RM and LB supervised the study. RM, AL, EB, LB analysed the data. RM, AL, HJ, GD, SG, EB, LB interpreted the data. RM wrote the first draft of the manuscript, and RM, AL, HJ, GD, SG, EB, LB were involved in revisions of manuscript.

Contributor and guarantor information:

All authors contributed to the planning, conduct and reporting of this study, and RM and LB are guarantors.

Data Sharing Statement:

We will share data where possible, within confines of guidance from Bond University Ethics Committee that the paper does not identify or describe any individuals.

Transparency Declaration:

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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Supplementary File 1: Strobe checklist (attached)

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7 **Figure 1. Flowchart for sample**
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28 **Figure 2: Proportion of Australian clinical practice guideline writers with undisclosed**
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Table 1. Characteristics of guideline writers from a stratified random sample of guidelines, 2012-2014. (n=33)

Therapeutic area	Clinical practice guideline (ID #)	Total number of writers	No. with disclosed ties	Number with no disclosed ties	COI statement available	Developed & funded by government
Arthritis	1	15	0	15	Yes	No
	2	26	2	24	Yes	No
	3	6	0	6	No	Yes
Asthma	4	14	0	14	No	Yes
	5	7	0	7	No	No
	6	6	0	6	No	No
	7	6	4	2	Yes	No
Cancer	8	27	4	23	Yes	No
	9	6	1	5	Yes	No
	10	14	0	14	Yes	Yes
	11	31	0	31	No	Yes
Cardio-vascular	12	11	4	7	Yes	No
	13	4	0	4	No	No
	14	8	1	7	Yes	No
	15	34	0	34	Yes	No
Diabetes	16	4	0	4	No	No
	17	14	0	14	No	No
	18	5	5	0	Yes	No
	19	13	0	13	Yes	No
Injury	20	18	0	18	No	Yes
	21	2	0	2	No	Yes
	22	35	4	31	Yes	No
	23	9	0	9	Yes	Yes

Kidney	24	7	1	6	Yes	No
	25	9	2	7	Yes	No
	26	6	2	4	Yes	No
	27	13	0	13	No	No
Mental Health	28	10	10	0	Yes	Yes
	29	11	11	0	Yes	Yes
	30	9	0	9	Yes	No
	31	8	0	8	Yes	No
Neurological	32	2	0	2	No	No
Obesity	33	12	7	5	Yes	Yes
	Total	402	58	344		

Table 2. Proportion of guidelines writers with undisclosed financial ties by guideline type.

	Yes	No	Risk ratio (95% CI)	P-value
COI Statement in Guideline	59/223 (26.5%)	24/121 (19.8%)	1.33 (0.88 to 2.03)	0.170
Developed, funded by government/s	8/99 (8.1%)	75/245 (30.6%)	0.26 (0.13 to 0.53)	<0.001

Note: p value refers to chi-square test

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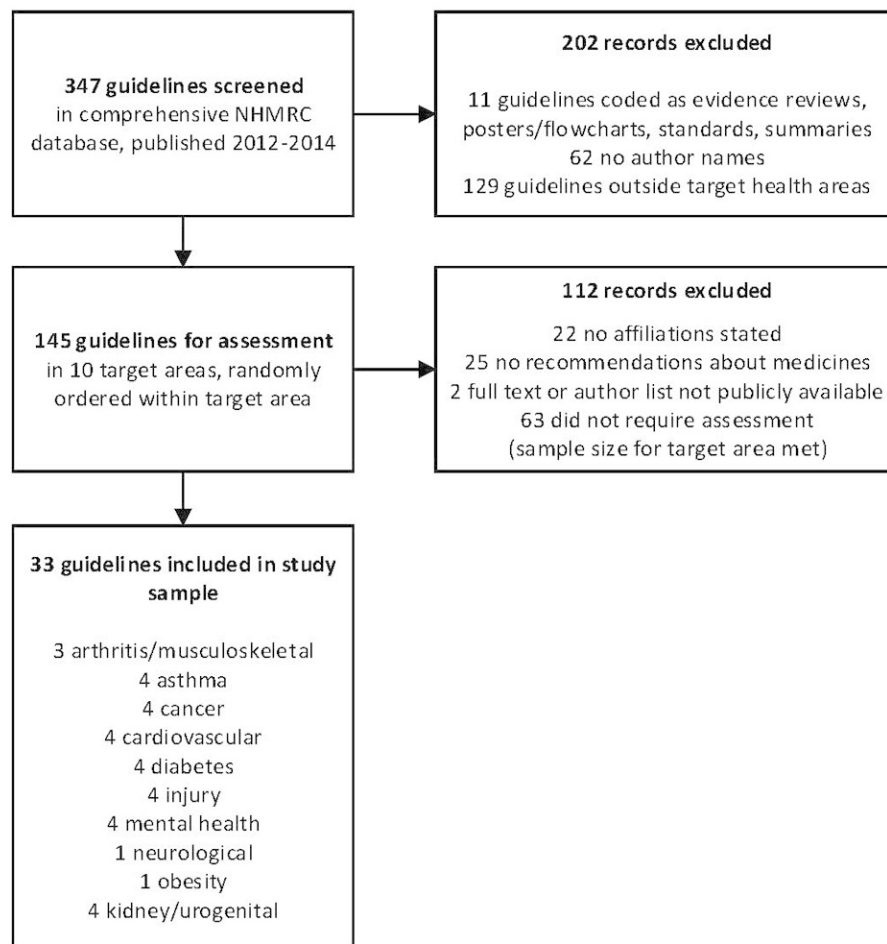


Figure 1. Flowchart for sample

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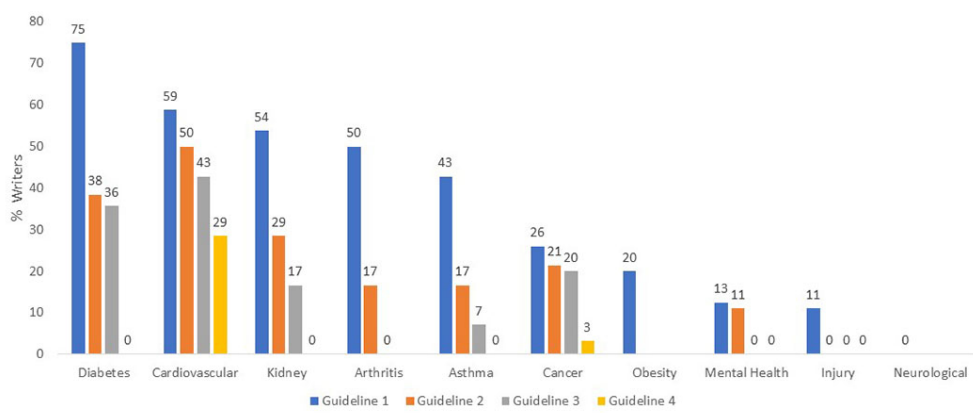


Figure 2. Proportion of Australian clinical practice guideline writers with undisclosed ties, 2012-2014

90x39mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies* (Page numbers refer to those on original submitted word document)

For manuscript: “Undisclosed financial ties between guideline writers and pharmaceutical companies: a cross-sectional study across ten disease categories”, submitted by Moynihan et al., 060818

	Item No	Recommendation	Item page nr
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study – eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 (plus Figure 1)
		(b) Give reasons for non-participation at each stage	7 (plus Figure 1)
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	7-8

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
2			(b) Report category boundaries when continuous variables were categorized	N/A
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
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6	Other analyses	17	Report other analyses done – eg analyses of subgroups and interactions, and sensitivity analyses	8
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11	Discussion			
12	Key results	18	Summarise key results with reference to study objectives	8-9
13	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
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15	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
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17	Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
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19	Other information			
20	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12
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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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BMJ Open

Undisclosed financial ties between guideline writers and pharmaceutical companies: a cross-sectional study across ten disease categories

Journal:	<i>BMJ Open</i>
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Primary Subject Heading:	Health policy
Secondary Subject Heading:	Public health
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, conflicts of interest, pharmaceutical industry

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6 **Title:** Undisclosed financial ties between guideline writers and pharmaceutical companies: a
7 cross-sectional study across ten disease categories
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Abstract

Objectives: To investigate the proportion of potentially relevant undisclosed financial ties between clinical practice guideline writers and pharmaceutical companies.

Design: Cross-sectional study of a stratified random sample of Australian guidelines and writers.

Setting: Guidelines available from Australia's National Health and Medical Research Council guideline database, 2012-2014, stratified across ten health priority areas.

Population: 402 authors of 33 guidelines, including up to 4 from each area, dependent on availability: arthritis/musculoskeletal(3); asthma(4); cancer(4); cardiovascular(4); diabetes (4); injury(3); kidney/urogenital(4), mental health(4); neurological(1); obesity(1). For guideline writers with no disclosures, or who disclosed no ties, a search of disclosures in the medical literature in the 5 years prior to guideline publication identified potentially relevant ties, undisclosed in guidelines. Guidelines were included if they contained recommendations of medicines, and writers included if developing or writing guidelines.

Main outcome measures: Proportions of guideline writers with potentially relevant undisclosed financial ties to pharmaceutical companies active in the therapeutic area; proportion of guidelines including at least one writer with a potentially relevant undisclosed tie.

Results: 344 of 402 writers (86%; 95% CI 82% to 89%) either had no published disclosures (228) or disclosed they had no ties (116). Of the 344 with no disclosed ties, 83 (24%; 95% CI, 20% to 29%) had potentially relevant undisclosed ties. Of 33 guidelines, 23 (70%; 95% CI, 51% to 84%) included at least one writer with a potentially relevant undisclosed tie. Writers of guidelines developed and funded by governments were less likely to have undisclosed financial ties (8.1% vs 30.6%; risk ratio 0.26; 95% CI 0.13 to 0.53; P-value <0.001)

Conclusions: Almost one in four guideline writers with no disclosed ties may have potentially relevant undisclosed ties to pharmaceutical companies. These data confirm the need for strategies to ensure greater transparency and more independence in relationships between guidelines and industry.

Strengths and Limitations of this study

- Our study is the largest to date to examine undisclosed ties of guideline writers, and includes a broad sample of guidelines across ten disease categories
- Our study includes guidelines with different funding and development arrangements, enabling comparison of guidelines funded and developed by government, with other guidelines
- Our study did not investigate the undisclosed ties of guideline writers who had disclosed ties in the sample of guidelines analysed
- Study results likely underestimate the extent of undisclosed financial ties of guideline writers

peer review only

Introduction

There is global concern about the nature and extent of financial ties between pharmaceutical companies and health professionals, including those who develop influential clinical practice guidelines. (1-3) In 2009 a landmark Institute of Medicine report on conflicts of interest acknowledged the importance of collaboration with industry, but warned financial ties to industry were widespread and risked jeopardizing the integrity of medical education, research, and practice, and called for greater transparency and independence. (1) A subsequent Institute of Medicine report, titled “Clinical practice guidelines we can trust”, recommended that groups developing guidelines “optimally comprise members without conflict of interest.” (2) Systematic review evidence suggests most guideline writers disclose some form of industry affiliation, with estimates between 56% and 87%. (3) There are however few data on the extent of undisclosed financial ties of guideline writers. One study of North American cholesterol and diabetes guidelines estimated 11% of writers had undisclosed ties, (4) another study of American head and neck surgery guidelines found 6% had discrepancies between disclosures and an open payments database, (5) while a Danish study of 14 specialty society guidelines found 52% had undisclosed ties. (6) *

A conflict of interest is defined as “a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.” (1) A primary interest of a guideline writer may be maximising health outcomes, and a secondary interest could be personal gain derived from a financial relationship with a company active in the relevant therapeutic area. Evidence from other areas, such as clinical trials, has shown such conflicts of interest may introduce bias. A recent systematic review found drug trials sponsored by industry more often have efficacy results and conclusions favourable to the sponsor. (7) Similarly, a cross-sectional study of randomised trials found those authored by principal investigators with ties to pharmaceutical companies were more likely than other trials to report favourable results. (8) Such evidence has provoked debate about the optimum constitution of guideline groups, with calls for chairs and a majority of writers to be free of financial ties, (9,10) as well as recommendations for exclusion of any conflicted writer. (2)

**For consistency the term guideline writer is used throughout to refer to those who develop, draft and author guidelines.*

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3 In Australia, the publicly funded National Health and Medical Research Council (NHMRC)
4 is currently engaged in improving standards for guideline development, including in relation
5 to transparency and management of conflicts of interest. An internal analysis of nine years of
6 Australian guidelines made available via the NHMRC guideline portal, 2005-2013, found
7 only 12% of guidelines published declarations of the conflicts of interest of guideline writers.
8
9 (11) As part of work to improve standards of guidelines which can have direct impacts on
10 how clinicians deliver care to their patients, the NHMRC is developing new “guidelines for
11 guidelines”, and a draft released for public comment in 2017 included the recommendation:
12 “Organisations planning guidelines should aim to appoint a guideline development group
13 whose members have no financial or other links with relevant industry groups.” (12) In order
14 to inform on-going efforts to improve guideline quality in Australia and internationally, our
15 objective was to investigate the extent of undisclosed financial ties to industry, for a broad
16 cross-section of guideline writers from different categories of guideline developer, sampled
17 from a comprehensive national guideline database, across a wide spectrum of diseases.
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29 **Methods**

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31 We conducted a cross-sectional study of a stratified random sample of Australian clinical
32 practice guidelines and followed the STROBE checklist for reporting observational studies.
33 (see Supplementary file 1) (13)
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37 *Sampling guidelines*

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39 We identified a stratified random sample of clinical practice guidelines from within the
40 NHMRC guidelines database, across nine government designated health priority areas,
41 (<https://nhmrc.gov.au/about-us/publications/nhmrc-corporate-plan-2017-2018>) plus
42 kidney/urogenital, published in the years 2012-2014. The NHMRC database comprised
43 guidelines made available on the publicly accessible NHMRC guidelines portal, which aimed
44 to include all Australian guidelines, defined broadly as published articles making clinical
45 recommendations. While the NHMRC portal at that time included all Australian guidelines, it
46 also provided users of the portal with information on quality indicators for these guidelines,
47 such as whether the guideline was based on a systematic review of evidence, whether the
48 authors provided conflict of interest disclosures, and whether or not the guideline had been
49 approved by NHMRC. From 2015, the NHMRC portal restricted the inclusion of guidelines
50 to only include guidelines which met certain quality standards, so to achieve a representative
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3 sample from the comprehensive collection of widely used Australian guidelines, we analysed
4 guidelines available on the portal in the three years leading up to the change.
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7 In 2017 NHMRC staff (HJ) identified all guidelines in the database, published in the years
8 2012-2014, and used previous coding by NHMRC to exclude articles not relevant to the ten
9 health areas of interest, those not considered guidelines, including those coded as Evidence
10 Reviews, Posters/Flowcharts, Standards, and Summary guidelines. Following the initial
11 screen, each guideline was randomly ordered using Microsoft Excel, within each of the ten
12 health areas. Two authors (LB, RM) then assessed each guideline in the order they had been
13 ranked, against explicit inclusion criteria, and identified guideline writers to be included in
14 the analysis. Guidelines were included if they were associated with a professional
15 organisation or entity and made mention of medicines in recommendations. They were
16 excluded if they were a journal article unconnected from an external organisation, or if no
17 author names or full text was available. Guideline writers listed in the guideline were
18 included for analysis if they were explicitly engaged in developing, preparing or writing the
19 guideline, and excluded if they were external consultants, members of oversight committees,
20 or staff from a drug company, NHMRC, or administrative staff. Any discrepancies were
21 resolved by discussion.
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34 The primary unit of analysis was the guideline writer. Based on assumptions that 10% of
35 guideline writers might have an undisclosed relevant financial tie, and that guidelines would
36 have 4-20 writers each, we estimated a need for a minimum sample of 12 guidelines – aiming
37 for approximately 140 writers – to produce a confidence interval of a width of 10% around
38 our estimate of the proportion of writers with undisclosed ties. In addition, to obtain as broad
39 a cross-section as possible, we aimed to analyse up to four guidelines per health
40 priority/disease area, depending on guideline availability.
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47 *Guideline and author information*

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49 One investigator (either AL or RM) extracted all relevant information from each included
50 guideline into the REDCap electronic data capture tools hosted at the University of Sydney.
51 (14) The extracted information included the names of all included writers, classified in one
52 of three ways: disclosure of ties; disclosure of no ties; no disclosure present. Disclosures
53 were those included in the guideline document or associated publicly available documents.
54 Information on whether the guideline had a statement on conflicts of interest, and the
55 developer/s and funder/s was also extracted.
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Identification of potentially relevant undisclosed financial ties

For any guideline writer with no declaration present, or who declared no conflicts of interests, one investigator (AL or RM) conducted a search of the writer's publications in the five years before the year of guideline publication. The period of five years was chosen for the following reasons: many guidelines are estimated to be at least two years in development before the year of publication; disclosures are directly relevant at the start of the process of guideline development; World Health Organization guidance suggests a period of 4 years prior to publication is relevant when disclosing financial ties, (15); and many disclosure policies have a recall period of 3 to 5 years. (16) Publications were also searched in the three years following guideline publication, as some organisations, including the Institute of Medicine, recommend guideline writers be free of conflicts for periods of time after guideline publication. (17)

The Scopus database was used to search for publications of guideline writers using their names and affiliations. Full texts were obtained. Searches were conducted from the earliest date, and as per Forsyth et al. (18) were stopped once a potentially relevant financial tie was identified. A potentially relevant tie was defined as a financial tie to a pharmaceutical company actively marketing or in late stages of bringing a medicine to market in the therapeutic area relevant to the guideline, at the time of the guideline publication, determined through searches of company websites and relevant product information material. Categorisation of ties was developed based on criteria set by the International Committee of Medical Journal Editors, ICMJE, and based on adaptations of ICMJE criteria used in a previous study, (18) including: grants (funding for research study); personal fees (consulting, advisory, speakers, honoraria, travel); patents/copyrights/royalties; miscellaneous. Once a potentially relevant tie was identified by one author (AL or RM), a second author (RM or LB) double checked the full text of the disclosure and verified the tie as a potentially relevant tie, and any discrepancies were resolved by discussion. Searches were conducted between August and December 2017.

Outcome measures and statistical analysis

The primary outcome measures were specified as the proportion of guideline writers with potentially relevant undisclosed ties, and the proportion of guidelines in the sample which included at least one writer with an undisclosed tie. Secondary outcome measures were: the proportion of writers with disclosed ties; the proportion of guidelines which have any

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3 statement about conflicts of interest; and the proportion of guidelines developed and funded
4 by governments (state, federal or territories). We report data proportions using descriptive
5 statistics and including 95% confidence intervals. We examined the association between
6 having statements and the proportion of potentially relevant undisclosed ties of writers; and
7 the association between a guideline being developed and funded by government/s and the
8 proportion of potentially relevant undisclosed ties of writers. Potential associations were
9 tested using the chi-square test. Confidence intervals were not adjusted for clustering of
10 writers within multiple guidelines, or for clustering of guidelines within disease area.
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17 *Ethics*

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20 As all publications analysed for this study were on the public record, the chair of Bond
21 University's Human Research Ethics committee asserted that the study did not require ethics
22 review, if no individuals were identified or described.
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26 *Patient and Public Involvement*

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29 No patients or members of the public were involved in this study.
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31 **Results**

32 *Characteristics of Guidelines*

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36 There was a total of 347 guidelines in the NHMRC database, published 2012-2014. (Figure
37 1) The initial screen excluded 11 items not considered guidelines, coded by NHMRC as
38 Evidence Reviews, Posters/Flowcharts, Standards, and Summary guidelines, 62 because they
39 did not contain names of those who had developed the guideline and 129 published outside
40 the ten health areas in this study. The remaining 145 guidelines were assigned a random
41 number to establish a random order for assessment of the guidelines within each of the ten
42 health areas. We continued to assess guidelines within each area in random order until we had
43 included 4 for each health area or had completed assessing all the available guidelines in a
44 given health area. In total, LB and RM assessed 82 guidelines. Forty-nine of those
45 guidelines were excluded after assessment: because they were a publication only with no
46 affiliation to any external organisation (n=22); had no recommendations about medications
47 (n=25); or the full text or author list of the guideline was not publicly available. (n=2) Sixty-
48 three were not assessed.
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3 We included 33 guidelines in our final sample: arthritis/musculoskeletal(n=3); asthma(n=4);
4 cancer(n=4); cardiovascular(n=4); diabetes (n=4); injury(n=4); mental health(n=4);
5 neurological(n=1); obesity(n=1); kidney/urogenital(n=4). (Supplementary file 2) The 33
6 guidelines involved a total of 402 guideline writers, with individual guidelines having
7 between 2 and 35 writers included for analysis.
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10 11 12 *Prevalence of undisclosed ties*

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15 Among all 402 guideline writers, 58 disclosed ties. (14%; 95% CI, 11% to 18%)(Table 1)
16 Among the 402 writers, 344 had no disclosed ties, (86%; 95% CI 82% to 89%) including 228
17 writers where no disclosures appeared, and 116 writers with statements that they had no ties.
18 Of the 344 writers with no disclosed ties, 83 had at least one potentially relevant undisclosed
19 tie, (24%; 95% CI, 20% to 29%), discovered in the published literature in the same year as
20 the guideline was published or the previous 5 years. Of those undisclosed ties, the first
21 category of tie listed in the relevant disclosure was: pharmaceutical company grant (64%), or
22 personal fees, (36%). If the time frame was extended to 3 years after the guideline, the
23 proportion of potentially relevant undisclosed ties rose from 24% to 28%. (95% CI, 23% to
24 33%)
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29 Of 33 guidelines, 23 included at least one writer with a potentially relevant undisclosed tie.
30 (70%; 95% CI, 51% to 84%). (Figure 2) Of those 23 guidelines, 14 guidelines had 20% or
31 more writers who disclosed no ties, but had potentially relevant undisclosed ties. Figure 2
32 also reveals the proportion of undisclosed ties of guideline writers who disclosed no ties, per
33 guideline, grouped by disease category.
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42 43 *Guideline Characteristics and Undisclosed Ties*

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45 Guidelines which included any statement about conflicts of interest were not significantly
46 different from those without statements, 59 of 223 writers (27%) had potentially relevant
47 undisclosed ties, compared to 24 of 121 writers. (20%) (risk ratio 1.33; 95% CI 0.88 to 2.03;
48 P-value =0.170) (Table 2) Guidelines both developed and funded by governments, as
49 opposed to non-government groups (including professional bodies, foundations, or
50 pharmaceutical companies), were significantly less likely to have authors with potentially
51 relevant undisclosed ties, 8 of 99 writers (8%) compared to 75 of 245 writers. (31%) (risk
52 ratio 0.26; 95% CI 0.13 to 0.53; P-value <0.001)
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60 **Discussion**

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3 In this broad cross-sectional sample of Australian clinical practice guidelines, 14% of
4 guideline writers had published disclosures of conflicts of interest. Among those who either
5 had no disclosures or disclosed they had no conflicts, 24% – almost one in four – had at least
6 one potentially relevant undisclosed financial tie to a pharmaceutical company active in the
7 therapeutic area. More than two-thirds, or 70%, of the 33 guidelines in this sample had at
8 least one writer with an undisclosed tie. Undisclosed financial ties of guideline writers
9 appeared to be more common in some therapeutic areas such as diabetes and cardiovascular
10 disease, compared to other areas such as injury and mental health. Guideline writers working
11 on guidelines developed and funded by government were much less likely to have
12 undisclosed financial ties: 8% compared to 31%.

21
22 There are important limitations to this study. First, the results likely underestimate the
23 frequency of undisclosed ties for several reasons: there is a general under-reporting of ties
24 published in medical journals as many important transfers of benefits to professionals, such
25 as hospitality or industry-subsidised education, are not routinely disclosed; Australia did not
26 at the time have a database with information on company payments to individuals; and we
27 did not search for any potentially relevant undisclosed ties of writers who made disclosures of
28 ties in the guideline, whether those ties were to pharmaceutical companies or other groups.
29 Second, our results may tend to a small degree to overestimate the frequency of undisclosed
30 ties, through what some may see as a broad definition of potential relevance; for example,
31 categorising a co-investigator of a study funded by a pharmaceutical company active in the
32 therapeutic area as a potentially relevant tie. Third, the sample of guidelines, while broad and
33 accessible, comes from 2012-2014 – the most recent years available for this sample from a
34 comprehensive collection – admitting the possibility of change since that time. And fourth,
35 we looked only at financial ties, not other non-financial conflicts of interest. The strengths of
36 the study lie in it being the largest to date in terms of guideline writers and undisclosed ties to
37 industry, as well as covering a broad cross-section of disease categories and guideline
38 developers – both government and non-government – with previous smaller studies limited to
39 specific therapeutic areas, (4,5) or guidelines produced only by specialty societies. (6)

41
42 Neuman and colleagues investigated the prevalence of conflicts of interest among panels
43 producing 14 North American guidelines for high cholesterol and diabetes. (4) They reported
44 that among writers who formally declared no conflicts, 11% had one or more. Looking at a
45 small sample of 49 writers of head and neck surgery guidelines, Horn and colleagues found

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3 6% had discrepancies between guideline disclosures and information available in the Open
4 Payments transparency database. (5) Analysing Danish specialty society guidelines, and
5 cross-checking disclosures against a public register of disclosures, Bindsley and colleagues
6 estimated 52% of 254 guideline writers had not disclosed ties. (6) A possible explanation of
7 why our estimate of 24% sits within these finding is that the North American studies used
8 narrower timeframes to search for undisclosed ties, while the Danish study defined a conflict
9 of interest as any affiliation with any drug company.

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17 As others have stated, guideline writer ties to companies with interest in the guideline's
18 outcome raise critical questions about potential bias in processes that may have great impacts
19 on the use of healthcare interventions, (4,12) disease definitions, (19) and patient care.
20 Findings of potentially relevant undisclosed ties compound the problem further and raise the
21 spectre of hidden bias, increasing the wariness of guideline users. Contemporary community
22 standards now demand total transparency, and our findings of undisclosed ties add weight to
23 calls for reforms like the Sunshine Act and Open Payments system in the United States, (20)
24 "publicly accessible registries of researcher conflicts of interest", (21) and more immediately,
25 enforcement of current disclosure policies to minimise undisclosed ties. In line with repeated
26 recommendations for greater independence between health professionals and industry,
27 (1,2,12) our incidental finding that almost one in five of these guidelines had less than 10% of
28 writers with any ties to industry, shows it is possible to assemble guideline panels almost
29 entirely free of financial conflicts of interest.

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41 The related reform processes of enhanced transparency and greater independence underway
42 in many nations creates clear opportunities for research comparing the quality of guidelines
43 developed by writers with and without links to industry, a research question beyond the scope
44 of this study, and where there is currently limited data. (22) Similarly, there is need for more
45 research investigating the impacts of links between industry and the professional
46 organisations which auspice guideline development, with one recent study suggesting such
47 ties are "common and infrequently disclosed." (23) Given their potential influence over
48 human health, and health system sustainability, such vital research on the independence and
49 trustworthiness of guidelines will be greatly enhanced by complete transparency around the
50 financial conflicts of interest of those developing them.

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6 for guideline writer publications.
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10 11 **Copyright/license for publication:**

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32 **Conflicts of Interest:**

33
34 Competing interests: All authors have completed the ICMJE uniform disclosure form
35 at www.icmje.org/coi_disclosure.pdf and declare: RM and EB have received grant support
36 from NHMRC; LB is a member of the NHMRC committee developing the guidelines for
37 guidelines handbook.
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42 **Contributor Statement:**

43
44 RM, AL, HJ, GD, SG, LB conceived and designed the study. RM and LB supervised the
45 study. RM, AL, EB, LB analysed the data. RM, AL, HJ, GD, SG, EB, LB interpreted the
46 data. RM wrote the first draft of the manuscript, and RM, AL, HJ, GD, SG, EB, LB were
47 involved in revisions of manuscript.
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54 **Contributor and guarantor information:**

55
56 All authors contributed to the planning, conduct and reporting of this study, and RM and LB
57 are guarantors.
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Data Sharing Statement:

We will share data where possible, within confines of guidance from Bond University Ethics Committee that the paper does not identify or describe any individuals.

Transparency Declaration:

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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Supplementary File 1: Strobe checklist (attached)

Figure 1. Flowchart for sample

Figure 2: Proportion of Australian clinical practice guideline writers with undisclosed ties, 2012-2014

Table 1. Characteristics of guideline writers from a stratified random sample of guidelines, 2012-2014. (n=33)

Therapeutic area	Clinical practice guideline (ID #)	Total number of writers	No. with disclosed ties	Number with no disclosed ties	COI statement available	Developed & funded by government
Arthritis	1	15	0	15	Yes	No
	2	26	2	24	Yes	No
	3	6	0	6	No	Yes
Asthma	4	14	0	14	No	Yes
	5	7	0	7	No	No
	6	6	0	6	No	No
	7	6	4	2	Yes	No
Cancer	8	27	4	23	Yes	No
	9	6	1	5	Yes	No
	10	14	0	14	Yes	Yes
	11	31	0	31	No	Yes
Cardio-vascular	12	11	4	7	Yes	No
	13	4	0	4	No	No
	14	8	1	7	Yes	No
	15	34	0	34	Yes	No
Diabetes	16	4	0	4	No	No
	17	14	0	14	No	No
	18	5	5	0	Yes	No
	19	13	0	13	Yes	No
Injury	20	18	0	18	No	Yes
	21	2	0	2	No	Yes
	22	35	4	31	Yes	No
	23	9	0	9	Yes	Yes
Kidney	24	7	1	6	Yes	No
	25	9	2	7	Yes	No
	26	6	2	4	Yes	No

	27	13	0	13	No	No
Mental Health	28	10	10	0	Yes	Yes
	29	11	11	0	Yes	Yes
	30	9	0	9	Yes	No
	31	8	0	8	Yes	No
Neurological	32	2	0	2	No	No
Obesity	33	12	7	5	Yes	Yes
	Total	402	58	344		

Table 2. Proportion of guidelines writers with undisclosed financial ties by guideline type.

	Yes	No	Risk ratio (95% CI)	P-value
COI Statement in Guideline	59/223 (26.5%)	24/121 (19.8%)	1.33 (0.88 to 2.03)	0.170
Developed, funded by government/s	8/99 (8.1%)	75/245 (30.6%)	0.26 (0.13 to 0.53)	<0.001

Note: p value refers to chi-square test

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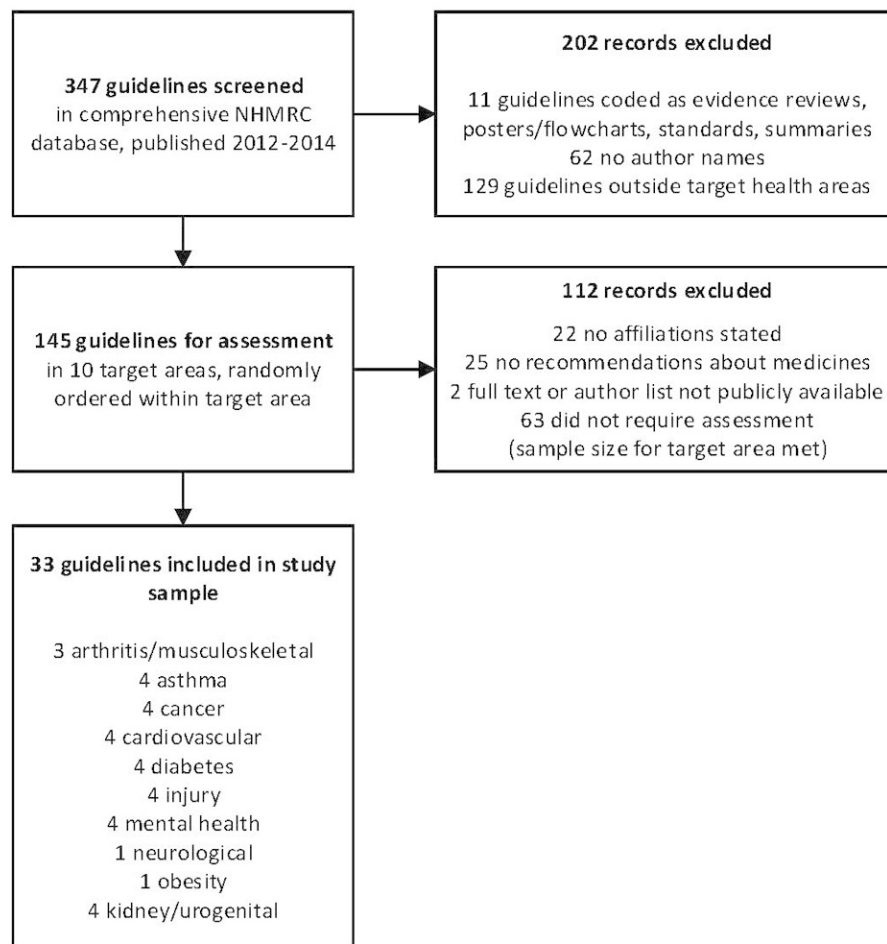


Figure 1. Flowchart for sample

88x90mm (300 x 300 DPI)

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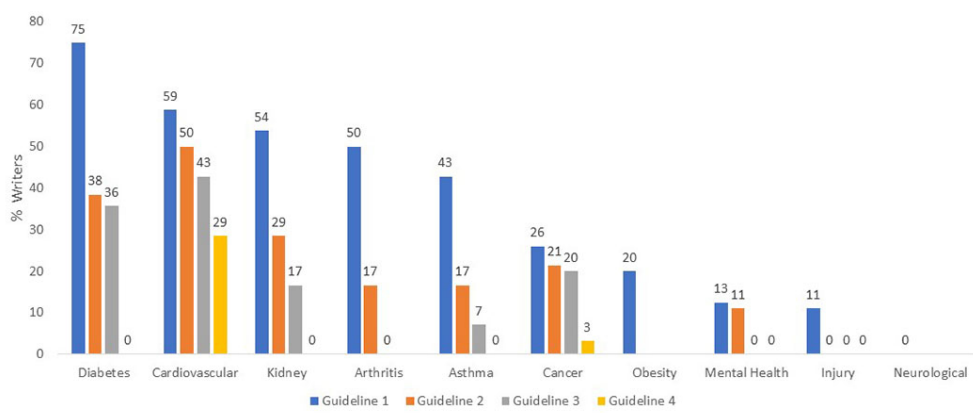


Figure 2. Proportion of Australian clinical practice guideline writers with undisclosed ties, 2012-2014
90x39mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies* (Page numbers refer to those on original submitted word document)

For manuscript: “Undisclosed financial ties between guideline writers and pharmaceutical companies: a cross-sectional study across ten disease categories”, submitted by Moynihan et al., 060818

	Item No	Recommendation	Item page nr
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	4-5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	N/A
		(d) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(e) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study – eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7 (plus Figure 1)
		(b) Give reasons for non-participation at each stage	7 (plus Figure 1)
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	7-8

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
2			(b) Report category boundaries when continuous variables were categorized	N/A
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
4	Other analyses	17	Report other analyses done – eg analyses of subgroups and interactions, and sensitivity analyses	8
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	8-9
7	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
8	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
10	Other information			
11	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

List of Guidelines

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