

Dear Dr Loder,

Thank you for the offer to resubmit our manuscript (BMJ-2019-051174).

We have addressed the Editors' and the Reviewers' comments below (in bolded text) and in the manuscript (using track changes).

Thank you for your time in consideration of our manuscript.

Sincerely,
The Authors

Editors' comments

We acknowledge this is a very important topic, and this version of the paper is more accessible than the original. Your results clearly show that funding of patient groups by industry is frequent, and, moreover, lacks transparency. We are less convinced about whether it adds sufficiently above and beyond the individual studies that are included, although we do think that bringing together all of this information in one location probably is useful. But it seems mainly a collection of case reports. There continues to be general dissatisfaction with the quality, completeness, and variability of the data. This is not your fault, of course, and is in fact part of the problem, but it limits the conclusions that can be drawn. It does of course point to the need for better reporting of these connections, and more research in the field.

RESPONSE: We thank the Editors for these comments and agree that we chose quite a challenging public health topic for our systematic review. We still believe it is important to systematically present what the research on this topic has shown so far in order to inform an evidence-based discussion, as well as future research and actions.

Our statistician notes: "This was a difficult area to evaluate using this design. In a way, it is mainly highlighting that no adequate research has been carried out and that this is an area that would be relevant to evaluate. Specifically in the methods, although it is probably not relevant due to only meta-analysing one outcome, you should have considered the potential overlap of organisations included in the studies. This would make the estimates uninterpretable.

RESPONSE: With regard to the potential overlap of organisations included in the studies, we have rechecked the year of data collection and location of study sample of the included studies to identify potential double counting. The timing is different for most of the studies that have been conducted in the same country. There could be an overlap between the two studies by Abola: they were conducted in the US in 2015-2016 and they both focused on

cancer groups. However, as showed in Figure 3, we placed the two studies in two different groups (“Consultation” and “Population sample”, respectively). When we pooled the data (as showed in Figure 1 of Supplementary File 4), we only included the studies based on population sample so only one of the studies by Abola was included.

One of our editors who is involved in drug decisions notes that patient groups "are far more influential than the healthcare professional organizations partly because they are professionalized. This is often their day job whereas for doctors this is an extra role. So they are influential, dedicated, and compromised. So they should be no less scrutinized than doctors."

RESPONSE: We agree with the Editor’s point. Moreover, while physicians’ interactions with the pharmaceutical industry have been extensively studied, the debate on the relationships between patient groups and industry is still not as advanced. This is what prompted us to conduct this systematic review.

Reviewers' Comments to Authors:

Reviewer: 1

Any attempt to draw attention to the negative impact of industry funding on the independence of patient groups is a step in the right direction. However, I can already hear the cacophony of outrage from those groups who spend most of their time trying to rationalize their decision to accept such funding. There are myriad holes that they can erroneously use to both support their position and undermine detractors. I do not bemoan their attempt to try to make sense of something so poorly studied, understood and subject to spin. This manuscript does its very best to make a silk purse out of a sow’s ear. From an independent patient perspective, it certainly provides more fodder for debate, but it is far from a silver bullet to support independent patient groups. The biggest problem with the study is related to the source material. The approach to and acceptance of industry funding varies greatly from country-to-country, province-to-province, election-to-election, group-to-group, individual-to-individual and web site-to-web site. Ultimately, the signal-to-noise ratio is so low that it is difficult to make any clear conclusions, which is a shame.

RESPONSE: We thank the Reviewer for understanding the challenges we faced to conduct a systematic review on this topic. It is true that due to the type of available data, we cannot make strong conclusions, but we still believe it is important to systematically present what the literature has found so far in order to inform an evidence-based discussion, as well as future research and actions on this topic.

As an independent patient advocate, I would have liked to have seen some guidance on how to determine the veracity of patient group motives. Or discussion on how to practically study this going forward would have been helpful. Finally, as someone at the coalface, how do I get the authentic patient voice front-and-centre?

RESPONSE: With regard to future research on the topic, in the Discussion we present some suggestions under the heading “Implications for research”. (page 17-18) In order to better assess the prevalence of industry funding, it would be important for future studies to use multiple sources of information such as patient groups’ websites, tax records, databases of industry payments to patient groups. These databases have been recently implemented in some countries and should be extended also to other jurisdictions.

Another important area that needs to be studied is the potential association between industry funding and organisational positions as we found only few studies that looked at this topic. There is a growing body of research identifying the extent and frequency of financial contributions from the pharmaceutical industry to the patient group sector. More research on the potential impact of this funding is needed using for example public submissions that patient groups make to regulatory and health technology assessment agencies.

The second question raised by the Reviewer on how to identify the authentic patient voice is quite interesting and at the same time challenging. Industry funding of patient groups could mean that certain views and perspectives gets disproportionately amplified and supported. In our Discussion we therefore stress the importance of financial transparency as it would at least assist those who listen to patient group voices (e.g., patients, health professionals, and policy makers) in the critical evaluation of those groups’ practices and positions. (page 19, lines 529-534) We have also added an additional recommendation to our Discussion with regard to alternative funding mechanisms: *“Consideration could also be given to whether there is a greater need for mechanisms for public financing of patient groups, for example provision of small grants allowing community organisations without corporate subsidies to participate in advocacy”*. (page 18, lines 514-517)

Reviewer: 2

Thank you for the opportunity to review this paper which uses a systematic review and meta analysis to look at issues linked to pharmaceutical industry funding for community-based organisations. These are very important research concerns and ensuring and expanding transparency for industry funding with both mainstream research and community activity is essential - and has long been a focus for the organisations involved.

The paper by Fabbri et al. is clearly the result of considerable work, with a large and extensive data search and analysis of important questions. However, most of the results do not add to our understanding of the specific questions better than some of the studies it is based on. More importantly, more direct research approaches would be more likely to answer the four key questions outlined as study objectives rather than this approach to use a literature review and meta analysis.

RESPONSE: We agree that more research is needed on the topic as showed by the conclusions that we could draw from the available evidence. However, we strongly believe that identifying grey areas and gaps in the existing evidence is still an important finding of a systematic review and could also stimulate further research on this topic.

Although many of the referenced studies have used various methods to collect information, including surveys and questionnaires and internet searches (mainly patient and industry websites), the wide heterogeneity in the results makes the outcomes from this meta analysis unclear on some of the four main research questions.

1 - The prevalence of industry funding is not addressed with an appropriate denominator, using only data from a small number of studies that themselves only include small numbers of patient organisations.

RESPONSE: We have used the per study denominators (e.g. patient groups within the study sample) and have identified when a study is population based or is based on a selected sample (e.g. respondents to consultations).

2 - The percentage of funding within each organisation that comes from industry - a key marker for understanding context of potential influence - is either not available or only low grade quality of evidence.

RESPONSE: We agree that the available data on this question are inadequate. We have stated this on page 16, lines 440-441. (*"Most of the included studies did not provide data on the amount and proportion of funding that came from industry"*).

3 - The percentage of industry-funded groups that report this funding online – roughly 27% – might now be out-dated because of changes in guidelines for industry funding over the 15+ years that

data is taken from. Calendar year is not referenced or adjusted for over absolute funding levels which will have changed over this time.

RESPONSE: As Figure 4 shows, the meta-analysis on proportion of industry-funded patient groups that disclosed information about this funding included only four studies published between 2008 and 2012. The publication year per study is stated in the forest plot. We agree that improvements in disclosure practices could have happened in more recent years, and we have added this sentence to the Results (page 12, line 346) and the Discussion (page 16, line 442): *“However, the four studies were published between 2008 and 2012, and there may have been additional shifts in disclosure of financial relationships with industry since 2012”*.

Finally we have not adjusted the data in Figure 4 for inflation rate as this is not a total amount of money, but it is the disclosure rate.

4 - The analysis of policy positions being shared with funders and organisations does include interesting examples that suggest less than independent views. However, this part of the paper doesn't refer to some of the larger studies that also addressed this question. For example, Rose et al reported high organisational importance and awareness of conflict of interest (>80%) and much lower (7%) perceived pressure to conform to interests of corporate donors.

RESPONSE: Under the outcome “Relationship between industry funding and organisational positions”, we included four studies that looked at actual positions/stances of patient groups on health-related topics. The positions were identified via analysis of documents that the groups published on their websites or submitted during public consultations.

The 2017 study by Rose that the Reviewer suggested we included under this outcome is different as it is not based on analysis of publicly available documents that can illustrate the groups' position on a certain topic. Rose et al conducted a survey where patient groups were asked whether they perceived pressure to conform their positions to the interests of corporate donors. It is an interesting results but it is based on the groups' perceptions which is not the outcome we aimed to analyse. We did not include studies of patient group representatives' impression of whether or not they are influenced.

Interestingly, there is a large literature indicating that doctors who receive industry funding do not believe they are influenced¹, but studies examining industry payments data and prescribing data from Medicare in the United States, found an association between

¹ Dana J, Loewenstein G. A social science perspective on gifts to physicians from industry. *JAMA* 2003; 290: 252-255.

payments and rate of prescribing.^{2,3} We could expect similar patterns among patient group representatives and therefore would not consider opinion of how much one is influenced to be a reliable indicator.

This makes the paper's results too indirect and dissociated from the key primary questions set by the researchers - all of which are critically important to ensure transparency. As an example, five out of the six criteria related to industry funding in Table 2 are graded either low or very low. Many of the key parameters are covered by less than 6 studies.

RESPONSE: We would like to clarify that when a systematic review finds limited evidence or poor quality evidence about a certain topic, this is still a very important result to report. In science there are no negative or positive results; there are just 'results' that are all important for advancing the debate on a topic. It is also important to identify research gaps.

And the large Kopp et al study included in Table 2 doesn't appear to be included in the references.

RESPONSE: We rechecked the References. The study by Kopp was cited (Ref 36, "Prescription for Power"), but the authors' names were missing due to a problem with the reference manager. We have fixed this and we thank the Reviewer for pointing this out.

The concern that industry funding can directly or indirectly influence the independence of community-based patient organisations is a real one. Over the last 15 years, at least in the UK, this had led to more restricted guidelines that govern such funding – and these include a high level of transparency for all financial support. A direct audit of these guidelines might therefore be a more effective and appropriate way to find out how closely they are being followed. Many other approaches for original research might be a better way to find out the current percentage of community organisations (of which there are thousands in the UK alone) that receive pharmaceutical funding. A similar approach would then find out the percentage of overall budget that come from this source - as this is mandated in producing annual accounts. Charities in the UK have to produce accounts and to highlight and name funders. This would seem a much better way to systematically find out levels of industry funding and the relative proportions each company contributes to the overall budgets. Although it is good practice for charities to include their financial accounts online, these are open access documents on the Charity Commission website.

²Yeh JS, Franklin JM, Avorn J, *et al.* Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts. *JAMA Intern Med* 2016;176:763–8

³ DeJong C, Aguilar T, Tseng C, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. *JAMA Intern Med.* 2016;176(8):1114–1122.

APBI and other guidelines have also changed probably several times during the years and combining results based on a metric of whether funding is reported on an organisations website are likely to be very different in 2019 compared to 2003, and yet calendar years isn't accounted for in answers to the key questions.

RESPONSE: The Reviewer is raising interesting suggestions for future original research on the topic. However, our aim was to assess the currently available evidence. By identifying grey areas and gaps, we hope that our review will stimulate further research on the topic.

The Reviewer also notes that improvements in disclosure practices could have happened in more recent years. We agree with the Reviewer and we have added this sentence to the Results and Discussion section where we present the four studies that assessed the proportion of industry-funded groups that disclose information about this funding: *“However, the four studies were published between 2008 and 2012, and there may have been additional shifts in disclosure of financial relationships with industry since 2012”*.

There are also now stricter restrictions on the overall percentage of income that a single company can contribute to an organisations overall budget - I think set at not being more than 20–25%. In the past though, requirements for transparency for funding have been set at much lower thresholds - perhaps when >5% of overall budgets. Similarly, several aspects of pharmaceutical funding that the paper highlights as being most important including the percentage that this makes to the overall organisations total budget, are either not available or are too poorly detailed to be useful.

RESPONSE: We agree that the available data on percentage of funding from industry are inadequate. We have stated this on page 16, line 440. (*“Most of the included studies did not provide data on the amount and proportion of funding that came from industry”*).

We find no reference to restrictions on the proportion of a patient organisation's budget that could come from a single company in any international overview, in a recent overview on UK patient group funding (<https://www.bmj.com/content/365/bmj.l1806>), or in any of the included studies.

Although the paper sets out to look at differences by country (high vs low income etc), all the selected studies are from high income countries (with one also including South Africa). There might be value in looking at difference between high income countries, especially for the US in terms of corporate guidelines.

RESPONSE: As stated in our protocol, we planned to undertake subgroup analyses by setting (high versus low income countries) for each outcome we meta-analysed.

However, due to the high level of unexplained heterogeneity, we could not present meaningful summary estimates for prevalence of industry funding and prevalence of organisational policies. The only outcome where we actually present a meta-analysis is the “Proportion of industry funded patient groups which disclosed information about industry funding on their websites” (Figure 4). The Reviewer raises an interesting suggestion on

potential differences between high income countries. However, the meta-analysis includes only four studies so we do not have enough data to look at country-by-country differences. With regard to the Reviewer's comment on the outcome related to policies governing corporate sponsorship, although we do not present a meta-analysis, in the Results we comment on potential differences by country: *"Among studies of high quality, the highest prevalence of policies was reported in two 2017 US studies (Rose and McCoy) possibly reflecting recent shifts in disclosure of financial relationship with industry"*. (page 14, lines 402-404)

Although a more minor point, the language of the paper sometimes has a bias that assumes there is a story here to be discovered. It is not scientifically neutral and neither are the assumptions behind the research. While the implications of inappropriate industry funding affecting the perceived independence of community organisations and their related agenda might easily be true, a more scientific approach should be to start from a position that is more neutral. For example, the implication of bias, whether conscious or unconscious, is never balanced by an awareness that community organisations might have the capability to construct their own agenda based on their direct experience of patient needs. And that they might similarly be able to independently analyse and report results on new treatments or indeed work with independent investigators and researchers to highlight any possible bias from industry-presented data.

RESPONSE: While we acknowledge the Reviewer's point that community organisations might have the capability to construct their own agenda, our aim was to present an evidence-based discussion on the topic. As we state in the Discussion (page 18, lines 506-508), there is increasing evidence that industry sponsorship can create bias in medical research, education and clinical practice; and patient groups may be subject to the same concerns. Moreover, we would like to point the Reviewer's attention to the section of the Discussion where we comment on the findings of the four studies that looked at the association between industry funding and groups' positions. We were very cautious in the interpretation of those findings and we mentioned that the groups' agenda might have been independently set by the patient organisations with no influence from the sponsor. For example, in the Discussion we state: *"this association of sponsored groups' and sponsors' positions does not necessarily reflect an influence by sponsors on a group's agenda. It is also possible that sponsors selectively funded groups with positions that were closely aligned with their interests"*. (page 16, line 457-459)

Similarly, and it is a point that runs throughout the paper, there is no recognition that community and industry goals can be independently similar for different reasons: patients who are desperately in need of treatment want better and more effective drugs, and the financial interests of manufacturers are of little concern to them (other than when prices prevent access to new drugs). The paper frames overlapping or similar goals as directional, actually saying that community "echo" industry, rather than independently setting out own agenda.

RESPONSE: We agree with the Reviewer that patient groups may advocate for access to a certain drug because they strongly believe that it will be beneficial to the people that they represent and receiving industry funding might have no role in developing this view. However, industry funding puts patient groups in a conflict of interest situation. The possibility that the views of patient groups may be influenced by industry funding is addressed even in the “Working Together Guide”, a document developed by Medicines Australia (the pharmaceutical industry trade association) and Consumers Health Forum of Australia. The guide states that it is important that *“when a health consumer organisation and pharmaceutical company collaborate, they consider how to avoid any perception that one party has unfairly or inappropriately influenced or compromised the other. As collaborations are often between organisations with different levels of resources, it is important that financial imbalances are dealt with appropriately to avoid any financial or other coercion”*.⁴

Moreover, even if we assume that industry funding helps patient groups to achieve their independently-set goals, then selective industry funding of aligned patient groups could enhance the impact of some groups over others. This might lead, for example, to advocacy efforts being mostly focused on drug access and subsidy rather than other non-pharmacological interventions.⁵ We have amended the Introduction to clarify these concepts: *“Although in some areas such as access and subsidy for drugs, the interests of the two parties might align, industry funding does put patient groups in a conflict of interest situation. The primary interest of pharmaceutical and device companies to maximize profits can conflict with the mission of patient groups to protect the welfare of the people they represent”*. (page 4, lines 112-115)

Similarly, the analysis of “shared positions” doesn’t include examples of when funded organisations actively disagree or criticise those of the pharmaceutical funders. One easy metric would be to see which organisations challenge inappropriate pricing for drugs. The paper doesn’t include a discussion of where challenging company pricing strengthens an organisation's independence. In research areas with many drugs, many companies accept that over time new data might sometimes show their drugs in a more favourable light and sometimes highlight new concerns. Independent community organisations (who take positions that are different to that of their funders) have the potential to be seen as more stable and less partisan - as should be their true role. So an analysis that looks at the presence or absence of comment about drug prices in an organisations work might be a useful surrogate for whether their funding has allowed them to remain independent. And there will be many industry-funded organisations where an absence of

⁴ Working Together Guide, 2015. Available at:

<https://medicinesaustralia.com.au/wp-content/uploads/sites/52/2015/08/Working-Together-Brochure-2015.pdf>

⁵ O'Donovan O. Corporate colonization of health activism? Irish health advocacy organizations' modes of engagement with pharmaceutical corporations. *Int J Health Serv* 2007;37(4):711-33

comment on pricing, shouts much larger than anything that proactively supports one drug or another.

RESPONSE: The analysis of organisational positions through an assessment of comments about drug prices is a very interesting idea for a future original research study.

Finally, if the paper is published, I suggest that the two current final bullet points for what this study adds are not appropriate. Perhaps one new bullet summary would refer to the limited data that this study could find for this analysis.

RESPONSE: We have added one bullet point to the section “What this study adds” to state that: *“The conclusions that can be drawn are limited by the low quality and variability of the available data”*. (page 4, line 89)

We believe that the third bullet point on association between funding and organisational position is framed in a cautious way and does not go beyond the data. (“Among the few studies examining funding status versus organisational position, industry sponsored groups tend to have positions that are favourable to the sponsor”) Therefore, we have not deleted it.

I also thought that the health fields analyzed were strange for not including any studies from the field of HIV, where activism significantly affected the research agenda, but where the relationship with industry funding has also been complex and sometimes controversial.

RESPONSE: We did not exclude any disease area from our literature search. Some of the studies that focused on patient groups from multiple disease areas included groups that work on HIV/AIDS (e.g. Colombo, 2012; Perehudoff, 2010). However, none of the studies we found searching five databases focused exclusively on the field of HIV.

To recognise the important role that patient groups had in the HIV/AIDS field, we have added a sentence in the Introduction to state that: “In some fields (e.g. HIV) patient groups were also instrumental in lowering the price of drugs, taking positions that did not align with manufacturers of HIV/AIDS drugs” (page 4, lines 103-104)

In the interest of transparency, I have been working for charities that over the last 20 years has including funding from both independent trusts and charities and from pharmaceutical companies. The funding has been critical to whether these services have continued and they have been run without direct input from funders into the programmes they support. In contrast, public funding - whether from the NHS or the complex history of commissioning bodies over that time - might have been preferable or carried advantages, but in practice has either not been available or not been sufficiently flexible to respond urgently to new situations. I work for an organisation that accepts industry support - but which also has policies for how this funding can only be used for specific projects. For example, industry funding is used to support some direct services but is never

used to support either publications or printing. Advertising is not allowed in publications for either health professional or lay readers (patients) - online or for any publication. We also have a history of taking positions that directly challenge funders over both pricing and marketing policies. All funding is reported online and itemised in the online annual accounts.

RESPONSE: We thank the Reviewer for sharing his experience with us. We strongly support better public financing of patient/consumer organisations. We also agree that organisational policies that address governance of sponsorships are important and we have mentioned this point in our Conclusion (page 19: “Greater transparency in reporting of industry funding, and policy development to govern corporate sponsorship are steps that are clearly needed and easy to implement”).

Reviewer: 3

Importance: This study explored the crucial and influential relationship between patient groups and industry sponsors. Financial transparency in healthcare has always been a seminal issue, and the influence of capital on the actions of those within healthcare organizations cannot be denied. This work is of particular importance to patients and policymakers. The general reach of the BMJ will provide this study with a good platform from which to reach its desired audience. However, this study may also be well suited to a Public Health Journal.

Originality: This systematic review with meta-analysis is a first of its kind study which explores the issue of industry funding of health consumer organizations. While there have been many individual studies and compelling incidents which expose the entanglement between patient advocacy organizations and for-profit companies, a high-quality systematic review has not yet been produced.

Research Question: The research question has been clearly defined under the sub-headings of

- i) Prevalence of industry finding
- ii) Transparency
- iii) Positions

However, it is not noted explicitly if this study sought to explore the industry-patient group relationship within a particular country/political jurisdiction (for example, the U.S vs. the E.U). Instead, it is left to the reader to elucidate this information on their own as it appears in the results section. This is an important dimension which should be addressed explicitly, and is relevant because different healthcare systems and governments have differing policies (if any) regarding the industry-patient group relationship.

RESPONSE: We thank the Reviewer for these comments. As stated in the Methods (page 7, line 181) we did not exclude studies based on study setting. However, most of the studies that we found through our systematic review of the literature were conducted in high-income countries. We state this at the beginning of the Results section (page 10, line 274). The location of study sample is also presented in Table 1 (Characteristics of Included studies). We agree with the Reviewer that different jurisdictions and healthcare system might have different policies regarding industry-patient group relationships. We intended to conduct a subgroup analysis by setting in our meta-analysis but this was not possible due to lack of available data (see Results section: page 10, lines 283-289)

Abstract

The abstract should include a brief overview of the importance of this topic in order to better represent the subject and convey to the reader why the study was undertaken.

RESPONSE: Our abstract follows the BMJ guidelines for an abstract of a systematic review. The guidelines require to start with a clearly stated objective and allow no room for background information.

Introduction

While this article has done a good job of consolidating available evidence regarding industry sponsorship of patient groups, some specific examples of this relationship at play in the introduction section might help provide some context about the scope of the issue and to ease the reader into the subject. Additionally, is suggested that examples of patient groups be provided in the introduction. For instance, some readers may not be aware that large influential organizations such as the American Heart Association and the American Diabetes Association are, in fact, patient groups.

RESPONSE: In the Introduction we now explain that the consumer group sector includes groups that work on specific diseases and groups that focus on general consumer health issues and that their size can widely vary in terms of number of members, number of salaried staff and budget: *“Patient and health consumer groups are non-profit organisations that aim to focus on the needs and interests of patients and communities affected by a specific disease/condition, or of health service users more generally. Their size can also widely vary from small organisations run by volunteers to big national organisations with salaried staff and thousands of members”*.(page 4, lines 95-98)

Lines 91-93: reference needed here. Patient and health consumer groups are defined without a supporting citation.

RESPONSE: We have added a Reference as suggested. (Ref #1: McCoy MS, Carniol M, Chockley K, Urwin JW, Emanuel EJ, Schmidt H. Conflicts of Interest for Patient-Advocacy Organizations. N Engl J Med. 2017;376(9):880-5.)

Methods and study design: The study design was robust. The methods are adequately described and transparency has been assured by the provision of supplementary material where needed. The relevant reporting standard is met. No ethical objections are evident.

RESPONSE: We thank the Reviewer for these comments.

In addition to sponsorship from the pharmaceutical and medical device industries, another source of financial support and potential conflict to interest for some organizations (such as the American Heart Association and the American Diabetes Association) is from health insurance companies. It would be helpful to know if the studies included in this meta-analysis addressed this.

RESPONSE: We agree that other industries active in health such as private insurance or food companies could be another source of conflicts of interest for patient groups. However, considering the complexity of the topic, the focus of this systematic review was specifically on relationships between patient groups and the pharmaceutical and device companies. We added a sentence to the limitation to state that the focus of our work was on pharmaceutical and medical device companies and it is possible that other conflicts are also relevant for specific groups within this sector, such as relationships with the food industry or with private health insurance providers: “Moreover, the focus of this systematic review was specifically on relationships between patient groups and the pharmaceutical and device companies and it is possible that other conflicts are also relevant for specific groups within this sector, such as relationships with the food industry or with private health insurance providers.” (page 17, line 473-476)

Page 9, line 235 – ‘Patient involvement’ should be changed to ‘Investigator involvement in patient groups’ since this section describes the involvement of the investigators of this study in various patient consumer groups.

RESPONSE: A paragraph on “Patient involvement” is required by the BMJ guidelines so we are not allowed to change the heading for this section of the manuscript. Since two of the study authors (PM and BM) have been involved with consumer groups, we thought it was appropriate to mention it under this section of the manuscript.

Results

Scientific reliability: Why were p-values not reported for the results?

RESPONSE: We reported 95% confidence intervals rather than p-values, as confidence intervals are more informative. Confidence intervals provide a range within which the outcome is likely to lie, and they indicate whether the range is wide (imprecise) or narrow

(precise). *p*-values, confidence intervals, and other statistical measures are all uncertain, and for this reason, there has been a shift in reporting in medical journals away from stating results are “statistically significant” because this indicates certainty in an association. Hurlbert, Levine, and Utts urge abandoning the use of “statistically significant” in all its forms and encourage journals to provide the following instructions to authors: *“There is now wide agreement among many statisticians who have studied the issue that for reporting of statistical tests yielding p-values it is illogical and inappropriate to dichotomize the p-scale and describe results as ‘significant’ and ‘nonsignificant.’ Authors are strongly discouraged from continuing this never justified practice that originated from confusions in the early history of modern statistics.”*⁶ For a more thorough discussion of this issue, see also: <https://www.tandfonline.com/doi/full/10.1080/00031305.2019.1583913>

Lines 50-51 ‘Estimates of prevalence of organizational policies ranged from 2% to 64%’. Needs clarification; would make more sense if it read ‘Estimates of prevalence of organizational policies regarding industry sponsorship ranged from 2% to 64%’.

RESPONSE: We amended the sentence as suggested (page 2, line 49)

Discussion

While the discussion section expresses the practical applications and implications of the results of this study, the overall message is somewhat scattered and unclear. It is suggested that a ‘Conclusions’ section be included so as to focus the main takeaways from this article.

RESPONSE: We added a “Conclusion” section where we summarised the main takeaways from the article and our recommendations: *“This systematic review shows that pharmaceutical industry funding of patient groups is common in many high income countries and clinical areas. The extent of industry funding of patient groups in low to middle income countries is unknown, as only one study included data from South Africa, an upper middle income country. Few groups have policies governing corporate sponsorship. Transparency concerning corporate funding is also inadequate. The few studies that assessed the link between policy positions and funding status raise concerns about industry influence. In conclusion, we encourage patient groups to critically evaluate the role of industry funding on their operations. Greater transparency in reporting of industry funding, and policy development to govern corporate sponsorship are steps that are clearly needed and easy to implement. In the long term, we would recommend a broader discussion around the role of industry funding in the patient group sector, both amongst patient groups themselves, and in the wider society, and exploration of alternate funding mechanisms”.* (page 19)

⁶ Hurlbert, S., Levine, R., and Utts, J. (2019), “Coup de Grâce for a Tough Old Bull: ‘Statistically Significant’ Expires,” *The American Statistician*, 73.

Key findings: This section is a summary of the key results and should be included in the results section as opposed to the discussion section.

RESPONSE: We wrote the Discussion following BMJ guidelines that require the authors to start the Discussion with a statement of the principal findings of the study.

Lines 434 – 436: ‘Four studies focused on a selected population of patient groups; prevalence ranged from 34% to 75%’. To which ‘selected population’ are the authors referring?

RESPONSE: We have clarified in brackets what we mean by selected population of patient groups: “(e.g. respondents to a consultation or patient groups that interact with regulatory agencies)”. (page 16, line 438)

Lines 444 - 451: The discussion of how industry-funded groups generally supported sponsors’ interests more often than non-funded groups is an important one. While the ensuing paragraph provides reasons as to why these results should be interpreted with caution, the discussion is incomplete without an exploration of whether or not the policy positions/sponsors interests are in opposition to available evidence (from the perspective of evidence-based medicine), or potentially harmful to the patient.

RESPONSE: Following the Reviewer’s suggestion, we rechecked the four articles that looked at association between funding and organisational positions.

1. The study by Jorgensen looked at the topic directly from the perspective of evidence based medicine. The authors looked at whether the information on mammographic screening presented on websites are balanced (i.e. reporting benefits and harms) and reflects recent findings.
2. The study by Lin looked at groups’ submission on guidelines developed by Centers for Disease Control and Prevention for prescribing opioids for chronic pain. Although the authors do not use explicitly the Evidence-based framework, the harm to public health from the opioid epidemic has created a strong public health incentive to develop guidelines to reduce opioid use. In the conclusion the authors state that “*a major concern is that opposition to regulatory, payment, or clinical policies to reduce opioid use may originate from groups that stand to lose financially if sales of opioids decline*”.
3. The study by Claypool looked at patient groups who opposed a Medicare proposal. As the authors state “*The proposed reform would study the effect of modifying reimbursement methods in a manner intended to decrease physicians’ perverse incentive to administer the priciest treatments, thus lessening the frequency these drugs are prescribed when lower-priced medicines would treat patients equally well, if not better*”. Patients would be expected to support measures to improve affordability of medicines when treatment outcomes are equivalent.

4. The study by Perehudoff looked at patient groups' opinions on a controversial European legislative proposal on industry-provided patient information. Several experts and groups raised concerns on some aspects of the proposal interpreting it as partial introduction of direct-to-consumer advertising in Europe.⁷ Interestingly, Mulinari analysed the evolution of the EU proposal showing the similarities it had with the drug information system already in place in Sweden. Using the case study of selective serotonin-reuptake inhibitor (SSRI), Mulinari showed that the Swedish model is not immune to industry bias and concluded that *"basing EU policy on a drug information system not resistant to corporate bias risks creating practices that violate the legally mandated mission of EU drug regulation, which is to promote and protect public health"*.⁸

We agree with the Reviewer's point that it is important to mention in the Discussion whether or not the groups' positions were in opposition to available evidence or potentially harmful to the patient. However, in order not to add too much to the Discussion we have added only one example from the four reported above. The Discussion has been amended as follows:

"Four studies analysed the relationship between organisational positions and industry funding. These studies addressed a range of highly controversial issues: overdiagnosis, pharmaceutical advertising, harm from opioid use, and high drug costs. All four represent situations in which a conflict existed between the interests of commercial sponsors and the interests of patients and/or the public. For example, the study by Claypool focused on groups who opposed a proposal aimed at decreasing the prescription of high cost drugs when less expensive and equally effective medicines are available. Access to equally effective but less costly medicines is in patients' interests as it improves affordability. The data available from the four studies points to positions reflective of sponsors' interests. However, this finding should be interpreted with caution as three of these studies had small sample sizes and all focused on a single policy or health issue. Additionally, this association of sponsored groups' and sponsors' positions does not necessarily reflect an influence by sponsors on a group's agenda. It is also possible that sponsors selectively funded groups with positions that were closely aligned with their interests."(page 16)

Implications for policy and practice: While the implications of the results of this study on patients, patient groups and the medical industry are explored in depth, the implications of these findings on physicians are not discussed in sufficient detail. Since a majority of the readership for this

⁷ Velo G, Moretti U. Direct-to-consumer information in Europe: the blurred margin between promotion and information. British journal of clinical pharmacology. 2008;66(5):626-8.

⁸ Mulinari, S. (2013). "Regulating drug information in Europe: a pyrrhic victory for pharmaceutical industry critics?" Sociology of Health & Illness 35(5): 761-777.

article is expected to be healthcare practitioners, a detailed discussion of the physician related consequences of these findings is suggested.

RESPONSE: The Reviewer is raising an interesting point. The implications of this paper are more at the policy level as patient groups are often involved in discussion around public coverage of medicines and treatments. We therefore believe our findings will likely be interesting not only for patient groups, but also for health technology assessment and regulatory agencies who often work with patient groups. However, a potential implication for physicians could be that patient groups face some of the challenges that also professional medical association face when they interact with industry. Therefore it could be interesting to further explore this issue in relation to professional medical associations. We have added a sentence on that in the Discussion: *“Finally, we examined industry funding of patient groups in this review because of the limited attention to conflicts of interest in this sector. However, financial conflicts of interest are a systemic challenge facing healthcare today and they can have an impact on many other stakeholders such as researchers, health professionals, and medical societies”.* (page 19, lines 537-541)

Page 18, line 522-524 - citation needed here: Two studies examining disclosure in patient group submissions to consultations with US governmental agencies reported very different disclosure rates: 0%, in submissions to the CDC and 91% in submission to the FDA.

RESPONSE: We have added the References as suggested. (Lin, 2017 and Abola, 2016b)

Tables and figures: Table 2. GRADE summary of findings: Industry funding of patient groups – a legend should be included for the interpretation of the $\oplus\ominus$ symbols.

RESPONSE: The legend is already included in Table 2 as the symbols are explained by the text next to them. For example, $\oplus\oplus\ominus\ominus$ means “low” quality of the evidence. If the Reviewer thinks this is not clear enough, we would be happy to add information.

Table 3. Details of industry funding – under the ‘mean amount’ column, the time period for this amount should be mentioned (e.g., per calendar year or fiscal year)

RESPONSE: We have rechecked the studies under the “mean amount” column in Table 3. For Kopp, 2015, the authors clearly state that they analysed the fiscal year 2015. For Perekhodoff, 2010 and van Rijn van Alkemade, 2005 we have reported the funding per year as reported by study authors and have assumed it to be by calendar year if only the year and amount was reported, without specifying that this was by fiscal year. As noted by the Reviewer, the data presented in Table 3 is quite limited. Any additional precision obtained by separating reports by fiscal and calendar year is unlikely to affect estimates.

Figure 1. Study flow diagram – should be labeled the PRISMA study flow diagram

RESPONSE: We have renamed Figure 1 as “PRISMA flow diagram of included articles”.

References

Areas which need references have been mentioned separately under each sub-heading in this review. Please see above for specific recommendations.

RESPONSE: We have added the References as requested.

Reviewer: 4

Relevant for patients: Yes, highly.

Areas of relevance that are missed: Given what the authors have written and changed the only thing missing is the part in the first article on the surveys on the opinion from patient groups about receiving industry funding. If it is still good data, I might be good to include it again, as it shows the discussions and ideas on industry funding. The articles quoted in this section are no longer included in the reference list. I'm OK with it if the authors can give a clear reason for this, but if not I would like it to be re-included. It is an indication about the internal (patient organisations) discussions on the subject of industry funding.

RESPONSE: The research question on “*What do patient and consumer organisations think about receiving industry funding?*” was excluded from the systematic review following the suggestions we received from the BMJ Editors during the first round of revisions. The comments from the Editors prompted us to carefully revise the research questions of our review in order to make them more focused. The rationale for excluding the question on opinions of patient groups is that it would be best addressed with qualitative research involving in-depth interviews. We have not included qualitative studies in the current review because a qualitative systematic review uses different methods for data synthesis and interpretation than a review of quantitative studies. We agree with the Reviewer that this is an interesting and important question, but that it should be the focus of a separate systematic review, with synthesis of qualitative research evidence. On reconsideration, we concluded that this question should be considered to be outside of the scope of the current review. We have therefore submitted a request for an amendment to our protocol to the Prospero team, which is currently under consideration. As the

Reviewer notes, deleting this research question led to the exclusion of the study by Leto di Priolo as it did not address any of the other research questions.

Methods used: I don't know enough of the statistics to judge if the changes made fit the questions asked in the first round of comments.

What can be improved: Compared to the previous version of the article, this one is clearer in its statements based on what can be found in the studies and does not add conclusions that can't be made (like the implication of bias by the patients organisation because of industry funding). The inclusion of the advice that this type of study would be needed is helpful.

RESPONSE: We thank the Reviewer for this comment.

What is missing: Are the questions the paper addresses relevant and important to patients and/or carers? Yes. Industry funding is an important issue that needs more research on the impact. Having the meta-analysis done in this study is already very helpful.

RESPONSE: We thank the Reviewer for this comment.

Are there topics or issues that are missing, or need to be highlighted more? Just the part on the surveys about the opinion on industry funding between patient organisations that was in the previous version of article. (p 17/100 previous version of the article.)

RESPONSE: Please see our response above where we explain why we excluded the research question on “*What do patient and consumer organisations think about receiving industry funding*”. We agree with the Reviewer that this is an interesting and important question, but that it should be the focus of a separate systematic review, with synthesis of qualitative research evidence.

Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges? Yes patients and patient organisations need to think about industry funding and the effect it has on their organisation and the freedom of expressing their opinions. As a patient involved in a patient organisation you need to think about the effects and consequences it has.

Are the outcomes described/measured in the study important to patients/carers? Yes. For this article these are the right outcomes to highlight and report upon.

Do you have any suggestions that might help the author(s) strengthen their paper?
I think the new version of the article is sufficient improvement.

RESPONSE: We thank the Reviewer for these positive comments on our manuscript.

Two small remarks for improvement:

(1) In the CONCLUSIONS (p4 L55-56) and in WHAT THIS STUDY ADDS (P4 l82-83) the authors write that “industry funding of patient groups is common in many higher income countries and disease areas”. This sentence is unclear. What disease areas do you mean? How many patients groups are there in middle and low income countries? What exactly are you saying? Later in the article the authors write that with the exception of South Africa all studies were conducted in high-income countries. Please amend the sentence in the article.

RESPONSE: With ‘disease areas’, we refer to the ‘clinical areas’ that the patient groups focus on. We have amended the text both in the Conclusion (page 19, line 546) and in the section on “What this study adds” (page 3, line 81) to clarify this.

We stated that industry funding is common “in many higher income countries” in order to accurately report the data we found. As showed in the Results and in Table 1, most of the included studies were conducted in high-income countries, primarily the United States and Europe. We found no data on low or middle-income countries therefore we cannot make any assumptions on the consumer group sector in those settings. We have added a sentence in the “What this study adds” section (page 4) and in the Conclusion (page 19) to state that “*the extent of industry funding of patient groups in low and middle income countries is unknown, as only one study included data from South Africa, an upper middle income country*”.

(2) Why has the part on the studies on survey data on the opinion of patients groups about industry funding been left out in the new article? It is an important section on the discussion about industry funding.

RESPONSE: As we stated above, the research question on “*What do patient and consumer organisations think about receiving industry funding?*” was excluded from the systematic review following the suggestions we received from the BMJ Editors during the first round of revisions. We agree with the Reviewer that this is an interesting and important question, but it should be the focus of a separate systematic review, with synthesis of qualitative research evidence.

Do you think the level of patient/carers involvement in the study could have been improved?
Yes it could have been improved, but they have improved some of it between the first and second

version of the paper. The authors have stated the of two of the authors engagement in women's health, consumers and community involved. A representative of a patient groups commented on the findings. The dissemination of the findings to patient groups through publicly accessible conferences, workshops and the media has been added. Which is positive. It would be good to do this both in the US and in Europe.

RESPONSE: We thank the Reviewer for these comments and for the suggestion to widely disseminate the research findings.

Reviewer: 5

Overall this article is important and useful. Should be published. Independence of interested parties that participate in EU decision-making and policy development need to be investigated and documented.

RESPONSE: We thank the Reviewer for these comments.

However important points need to be revisited (major comments):
Line 98-99: This view seems rather partial and oriented. Patient groups' actions target both public authorities (reimbursement/coverage) and industry (for example advocacy campaigns to lower the price of medicines (closing-down Wall Street on September 14, 1989 (seven ACT UP members infiltrated the New York Stock Exchange to protest the high price of the only approved AIDS drug, AZT. Several days following this demonstration, Burroughs Wellcome lowered the price of AZT from \$10,000 to \$6,400 per patient per year). Other actions in favour of generic products met to advocacy towards the World Trade Organisation which adopted rules on Compulsory Licensing and this advocacy movement was conducted by patient organisations that were largely funded by the pharmaceutical industry.

RESPONSE: The sentence the Reviewer refers to was just meant to give some examples of the activities that patient groups carry out. However, following the Reviewer's suggestion, we now mention the HIV as a good example of advocacy where patient groups were able to lower the price of medicines. The Introduction has been amended as follows: *"Patient and health consumer groups carry out many activities, such as: providing direct support, services, and education to patients and health consumers, funding of and participating in medical research, contributing to guideline development, and advocating for policies related to health services and/or health products. The latter may include lobbying for patient access and/or government subsidy for medicines and devices". In some fields (e.g. HIV) patient groups were also instrumental in lowering the price of drugs, taking positions that did not align with manufacturers of HIV/AIDS drugs".* (page 4)

237-241 Methods. Analysis by location of study sample is missing. Location of study sample reflects a large dominance of anglo-saxon culture: United Kingdom, USA, New-Zealand, Canada, Australia, Ireland mentioned 25 times out of a total of 37 locations. Given the very different practices/cultures in the anglo-saxon world (and also laws and practices on financial relations etc.) a separate analysis should have been done to account for contextual influence of different legal systems/sets of rules.

RESPONSE: As stated in our protocol, we planned to undertake subgroup analyses by setting (high versus low income countries) for each outcome we meta-analysed.

However, due to the high level of unexplained heterogeneity, we could not present meaningful summary estimates for prevalence of industry funding and prevalence of organisational policies. The only outcome where we actually present a meta-analysis is the “Proportion of industry funded patient groups which disclosed information about industry funding on their websites” (Figure 4). The Reviewer raises an interesting suggestion on potential differences between high income countries. However, the meta-analysis includes only four studies so we do not have enough data to look at country-by-country differences.

Results

361: At that time, HAI, Perehudoff is member of, adopted strong views that the directive proposal was a partial introduction of direct-to-consumer advertising in Europe which raises the impartiality of this analysis. Can you objectively assess/judge other's opinion when yourself adopted a strong one?

RESPONSE: Following the Reviewer’s comment, we have amended the sentence where we describe the European legislative proposal on industry-provided patient information that the Perehudoff study analysed as follows: “*Specific elements of this proposal were interpreted as partial introduction of direct-to-consumer advertising in Europe, whereas others were less controversial*”. (page 13, line 364) The sentence is supported by two scientific papers who raised concerns on the EU proposal and the impact it could have on patients’ health (Velo G. British Journal of Clinical Pharmacology, 2008; Mulinari, Sociology of Health & Illness, 2013).

Moreover, the Reviewer seems to have concern on the study by Perehudoff (2011) because of the views adopted by Health Action International. We would like to clarify that for all included studies, authors’ opinions were not considered relevant as the focus of a systematic review is on the study methods and results sections, and not discussion and conclusions. Additionally, the Perehudoff study report includes the study questionnaire, which can allow an assessment of the questions posed, and provide a detailed overview of how results were tabulated and analysed.

The work done by Perehudoff was based on 11 groups in official relations with the European Medicines Agency (EMA) out of 22 contacted, when there were 25 eligible organisations among 41 actually involved in EMA activities as of June 2009.

RESPONSE: The Reviewer seems to have concerns about the methods of one of the studies included in our systematic review (Perehudoff, 2011). We applied a standardised quality assessment (the Checklist developed by the Joanna Briggs Institute) to all included studies to assess the quality of the methods used, with a focus specifically on factors that have been shown to influence study outcome.

With regard to the study sample, Perehudoff states that: *“A sample group of 23 patient and consumer organisations (hereafter called organisations) were selected for their eligibility to work with the European Medicines Agency (EMA) as of 1 August 2009. These were identified from the list available at <http://www.ema.europa.eu/Patients/organisations.htm> (Footnote: Since the time of study, more organisations have become eligible to work with the EMA and they are named on the Agency’s website. Not all of these organisations were included in this study). HAI Europe was one of the 23 eligible organisations but has been excluded from the study, leaving a sample of 22 organisations”.*

In order to answer the Reviewer’s question, we have contacted the study authors to ask for a clarification on their sample. The authors told us that their sample came from the EMA list available on August 1st 2009. They raised the issue that there could have been a delay between an internal EMA list and its update on the EMA website. Since the EMA weblink available in the Perehudoff report is not active anymore, the authors used wayback machine to visit the old EMA link in order to answer our request for clarifications. (Wayback machine is a resource to retrieve old information). The authors were able to retrieve a list of organisations that is dated January 4th 2010. (They sent it to us in a PDF format that we are happy to share with the Reviewer if needed) The list shows that on January 4th 2010 there were 25 eligible organisations. The information about two of the 25 organisations was updated on January 4th 2010 (European Federation of Allergy and Airways Diseases Patients' Associations [EFA] and Global Alliance for Mental Illness Advocacy Networks [GAMIAN]) which means they were not included in the list from August 2009 that the authors used. The information about all the other 23 organisations was updated at the end of August 2009. One of the 23 organisations is HAI which was excluded by the study as stated in the report. We believe this additional information provided by the study authors clarifies why a sample of 22 organisations was contacted.

362-363: This statement can largely be discussed, it is partly false. The organisation I work for, for example, did not support an increased role for industry. It supported the view that pushed information for prescription medicines should continue to be banned

(communication/advertisement from industry), but pulled information (when patients or their organisations contact the marketing authorisation holder to obtain information) should become possible (this was the case in some member states but not all, introducing large disparity in access to life-saving information). Another proposal was to authorise industry to provide product information on websites in the jurisdiction of EU institutions, as most of these websites were registered/hosted in the US, and European authorities had no legal power to intervene in the information they provided (European users having to navigate on US based web sites to find information on a product, information which might differ from the European authorised reference documents), where my organisation thought the European Commission had a point there, but which did not mean my organisation advocated for industry to be authorised to post anything they wanted on Internet.

RESPONSE: Following the Reviewer's suggestion, we have amended the sentence where we describe the European legislative proposal on industry-provided patient information that the Perehudoff study analysed as follows: *"Specific elements of this proposal were widely interpreted as partial introduction of direct-to-consumer advertising in Europe, whereas others were less controversial"*. (page 13, lines 364)

430 - 533, Discussion section

The systematic review with meta-analysis as proposed here is interesting, however the discussion eliminated other works on the same topic. Their absence questions the completeness of the literature search on what is already known on this topic and/or the discussion. Publications from experts on conflicts of interests in the health care sector and on the financial links between patient organisations and industry funding include:

- Sebastien Dalgarrondo "Sida : la course aux molécules", Paris, EHESS, 2004
- Daniel Carpenter & David A. Moss (dir.), Preventing Regulatory Capture. Special Interest Influence and How to Limit it, Cambridge University Press, 2013.
- David Demortain, "The tools of globalization. Ways of regulating and the structure of the international regime for pharmaceuticals", Review of International Political Economy, 2015, 22, 6, 1249-1275.
- James Ferguson, «The uses of neoliberalism», Antipode, 2010, 41, S1, 166-184.
- Boris Hauray, Emmanuel Henry & Sébastien Dalgarrondo, «Conflit d'intérêts», dans Emmanuel Henry, Claude Gilbert, Jean-Noël Jouzel & Pascal Marichalar (dir.), Dictionnaire critique de l'expertise. Santé, travail, environnement, Presses de SciencesPo, 2015, p.71-79.
- Deborah Cohen & Philip Carter, «Conflicts of Interest: WHO and the pandemic flu "conspiracies"», BMJ, 2010, 340, c2912.

RESPONSE: We thank the Reviewer for bringing these references to our attention. The literature on conflict of interest in the health care sector is extensive and we cannot cite all these books and articles. Some of the references kindly provided by the Reviewer point to

the fact that conflicts of interest are an important challenge facing healthcare today and may influence many stakeholders beyond patient groups such as drug regulators, public health institutions, physicians, researchers, and professional associations. In this Systematic Review our aim was to examine industry funding of patient groups because of the limited attention to conflicts of interest in this sector. Following the Reviewer's suggestion, we have added the following sentence to the Discussion: "*Finally, we examined industry funding of patient groups in this review because of the limited attention to conflicts of interest in this sector. However, financial conflicts of interest are a systemic challenge facing healthcare today and they can have an impact on many other stakeholders such as public health institutions, researchers, health professionals, and medical societies*". (page 19, lines 537-541)

441-444: To discuss possible publication bias here. Many patient groups, if not most, do not publish their position on policy proposals, often because of lack of resources. They use other advocacy methods to make their voice heard. So what are these studies measuring ? The relation between industry funding and the position of patient groups? Or the relation between industry funding and the likelihood that a group publishes its position, thanks to the additional resources? This would favour the hypothesis of a link between industry funding and the group position when the group position is in favour of industry (and thus is more likely to receive funds from industry afterwards). In other words, does industry fund a patient group to influence its position towards industry interests? Or is the industry funding a "reward" to groups that adopt views that seem to be closer to industry interests? This would exclude groups that are against industry interests and therefore not likely to receive such rewards. The causality industry funding therefore favourable organisation position is not demonstrated. The competing interest exist, but this does not demonstrate the patient groups were influenced by industry. This is briefly discussed lines 449-451 but 3 lines do not really balance all what is explained above and after.

RESPONSE: The Reviewer is raising some concerns on the four studies that looked at association between industry funding and groups' positions. He mentions the possibility that these studies might be hindered by the fact that patient groups often do not have the resources to publish their positions on their website. Interestingly, not all the studies relied on positions expressed on the websites. For example Lin, et al looked at submissions to the Centers for Disease Control and Claypool looked at groups who signed a letter to oppose a Medicare program.

The Reviewer also highlights that causality was not demonstrated. We agree with the Reviewer and we were indeed very cautious in the interpretation of those findings. For example, in the Discussion we state: "*this association of sponsored groups' and sponsors' positions does not necessarily reflect an influence by sponsors on a group's agenda. It is also possible that sponsors selectively funded groups with positions that were closely aligned with their interests*". (page 16, line 457)

487-488: another indication of uncompleted literature search. Equivalent legislations were adopted in other jurisdictions, e.g. Belgium (betransparent.be), France (Decrêt 2013-414 of May 21st 2013) and probably many others.

RESPONSE: The sentence the Reviewer refers to (*“In this regard, legislations similar to the US Sunshine Act should be implemented also in other jurisdictions and expanded to cover industry payments to patient groups”*) was only meant to provide an example of a country where a legislation has been implemented. We are aware that legislations have been implemented in other countries (e.g. France) but in some jurisdictions there are still no reporting systems or voluntary systems that have flaws in terms of usability and comprehensiveness of the disclosed data. This is why we made that recommendation.

More minor comments:

Line 59-61: In Discussion, authors should address biases that might also exist among other interested parties, healthcare professional organisations in particular, also playing important roles in advocacy, education and research vis-à-vis funds they receive from industry, probably in higher proportions/amounts than patient organisations.

RESPONSE: We agree that other parties such as professional medical associations play an important role in advocacy, education and research. An in-depth discussion of conflict of interest of professional medical associations is beyond the scope of our systematic review. However, we have added to the Discussion the following sentence: *“Finally, we examined industry funding of patient groups in this review because of the limited attention to conflicts of interest in this sector. However, financial conflicts of interest are a systemic challenge facing healthcare today and they can have an impact on many other stakeholders such as researchers, health professionals, and medical societies”*. (page 19, line 537)

Line 68-69: more importantly patients groups are part of the decision-making and scientific evaluation§. This is important to recognise their role/impact, and also for the purpose of this research. The more sensitive aspects of dependency to industry, if there is one, are when this can influence decision-making (although no such case reported, but concern raised)

RESPONSE: We have amended the first bullet point of the “What is already known on this topic” section as follows: *“Patient groups play an important role in health care, including education of consumers, funding of medical research, and contributing to decisions on approval and public coverage of medicines and treatments”*. (page 3, line 67)

98-99: patient groups are not only advocating for access to new medicines and devices, but sometimes older ones also.

RESPONSE: We have deleted the word “new” so that we now refer also to older medicines and devices: *“The latter may include lobbying for patient access and/or government subsidy for new medicines and devices”*. (Page 4, line 102)

Discussion

The discussion part should address biases that might also exist among other interested parties, healthcare professional organisations in particular, also playing important roles in advocacy, education and research vis-à-vis funds they receive from industry, probably in higher proportions/amounts than patient organisations

RESPONSE: We agree that other parties such as professional medical associations also play an important role in advocacy, education and research. An in-depth discussion of conflict of interest of professional medical association is beyond the scope of our systematic review. However, we have added to the Discussion the following sentence: *“Finally, we examined industry funding of patient groups in this review because of the limited attention to conflicts of interest in this sector. However, financial conflicts of interest are a systemic challenge facing healthcare today and they can have an impact on many other stakeholders such as researchers, health professionals, and medical societies.”* (page 19, line 537)

103: it is good practice to cite older references. Authors should refer to full literature on the topic (some publications in 2004), not the most recent one (2017). One of the 26 studies was published in 2003 by one of the authors (Mosconi), and it certainly refers to documents relating concerns about financial relationships between patient groups and industry. The concern still can persist today, even if not new, and remedy measures have been implemented in some cases.

RESPONSE: We cited the article by Moynihan R., *Jama Int Med*, 2017 because it is a good and concise commentary on the issue of industry funding of patient groups. Following the Reviewer’s suggestion we have added also an older Reference (Herxheimer, *BMJ*, 2003)

148-151: Definitions are not so clear. An AIDS patient organisation can advocate for the rights of people who are at risk of acquiring HIV to access effective prophylaxis (they’re health services users, they’re not defined by a specific disease/condition). Furthermore, later in the article patient groups that include multiple conditions are described. Definitions should be changed.

RESPONSE: We have amended the definition of patient groups as follows: *“Population: patient groups, including both non-profit patient organisations that aim to represent the interests of patients at risk or affected by a specific disease/condition or set of conditions, and non-profit consumer organisations that advocate for the health rights of people and/or the interests of health services users”*. (Page 6, line 157).

323: Given the period during which most studies were conducted (from 2003 to 2018), email communication should have been the method of choice. Why not mentioned/measured?

RESPONSE: We reported the methods that the authors of the included studies used.

327-329: This seems to indicate communication only took place at the initiative of industry. This does not seem to take into consideration situations where patients/consumers disagree with industry, or need to contact them to advocate for the interests of patients to access a product, a compassionate use programme, to improve a clinical trial, to reduce the price of a medicine etc.

RESPONSE: We have rechecked the study by van Rijn van Alkemade and clarified the sentence as follows:

“A Dutch study reported that in a response to a query on how often they were contacted by companies in the last two years, 38% (36/96) of groups were contacted, on average 3.4 times. Reported reasons for communication included company requests to distribute an article on a medicine, requests to promote a medicine, and offers to produce information materials or fund awareness-raising activities. The study reported also that 38% (36/96) patient groups had requested support from pharmaceutical companies in the last two years.”

359: Results: Not only consumer but also patient organisations

RESPONSE: We now mention not only consumer but also patient organisation. (Page 13, line 362: “Perehudoff surveyed patient and consumer organisations”)

411-413: This seems to be an extremely small sample, out of a total number of patient groups in Germany that can approximate or exceed 8,000.

RESPONSE: We agree that the sample included in the study by Schubert is extremely small. This study has been rated as low quality for Item 3 (Sample size) of the quality appraisal checklist (see Figure 2).

510-512: not clear what this says. NICE has a procedure to involve patients in its discussion which includes a declaration of interests. See <https://protect-au.mimecast.com/s/RzEtCwVLQmimwgQMcvsvCV?domain=nice.org.uk>. So does this mean NICE does not use its procedure, or declarations are not complete?

RESPONSE: As the Reviewer notes, NICE has a disclosure policy. However, the policy requires patient organisations to disclose financial interests only if an organisation’s representative is nominated to give evidence to a decision making committee. In the study by

Mandeville et al⁹ that we cite in the Discussion, the authors found that 72% of the included organisations had received funding by companies with products under consideration or their competitors. Interestingly, Mandeville reports that *“NICE’s decision making committees were aware of less than half (30/73; 41%) of all declarable specific interests. For nearly two thirds (71/114; 62%) of the specific interests unknown to committees, declaration was not required by NICE’s disclosure policy”*. As Mandeville et al recommends, NICE should strengthen its disclosure policy to include patient groups as well as individuals. We have amended the Discussion to mention the loophole in the NICE’s current disclosure policy: *“NICE was rarely aware of these financial relationships, and in nearly two thirds of cases, NICE’s disclosure policy did not require declaration of these undisclosed conflicts of interest. Governmental agencies should therefore develop robust guidelines to ensure financial transparency from patient groups they interact with, including monitoring procedures and strategies to manage the disclosed conflicts of interest, as well as ensuring inclusion of patient groups without industry funding when obtaining input into decisions”*. (Page 18-19, lines 524-529)

512-515: Other interests that could influence the opinion of patients/experts should be mentioned. Public funding can also exert a strong influence on an organisation or an expert.

RESPONSE: We were interested in examining commercial influences specifically in this systematic review.

Moreover, we believe there is a difference between public funding and corporate funding. The first key difference is: who benefits financially? When the companies that are sponsoring a patient group produce a product for sale that is used by patients with that condition, they can benefit financially from this sponsorship. This does not happen with public funding.

Additionally, in a Cochrane review that assessed the relationship between funding source and research outcomes, industry funding was associated with more positive results in comparison with public or non-profit funding.¹⁰ And industry funding of health professionals has also been shown to influence prescribing.^{11,12}

⁹ Mandeville Kate L, Barker Rosie, Packham Alice, Sowerby Charlotte, Yarrow Kielan, Patrick Hannah et al. Financial interests of patient organisations contributing to technology assessment at England’s National Institute for Health and Care Excellence: policy review *BMJ* 2019; 364 :k5300

¹⁰ Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. The Cochrane database of systematic reviews. 2017;2:Mr000033.

¹¹ Yeh JS, Franklin JM, Avorn J, et al. Association of Industry Payments to Physicians With the Prescribing of Brand-name Statins in Massachusetts. *JAMA Intern Med* 2016; 176: 763–8.

¹² DeJong C, Aguilar T, Tseng C, Lin GA, Boscardin WJ, Dudley RA. Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries. *JAMA Intern Med*. 2016;176(8):1114–1122.

525-526: The authors could also add that ten Patients and Consumers' organisations eligible to work with the EMA published a Code of Practices guiding the Relations between Organisations and the Health Care Industry, as an illustration that indeed they are very aware of the importance to critically evaluate this role.

See : <https://protect-au.mimecast.com/s/KeFkCxnMRvtVWP06hYfzJF?domain=eurordis.org>

RESPONSE: We thank the Reviewer for pointing us to this Code of Practice. We now cite it in the Introduction where we mention the increasing attention to the relationship between patient groups and industry as demonstrated by the development of educational programs, codes and guidelines in recent years: *“In recent years there has been increasing attention to these interactions as demonstrated by the development of educational programs, codes and guidelines”*. (page 5, line 123)

532: There is no such thing as a neutral source of funding. Even crowdfunding activities or membership base funding impose certain conditions on an organisation strategy or action plan.

RESPONSE: Following also the suggestion by Reviewer 6, we deleted the last sentence of the manuscript.

548-549: The author in question could have declared being part of an organisation that hold strong positions against patient organisations being funding by industry. This might have affected the capacity to assess neutrally and objectively the link between industry funding and independence of patient groups. See Hayes, L. and Mintzes B (1997) ‘The ties that bind: drug industry sponsorship’. HAI Lights, 3(2-3):1-3. Shouldn't this haven been declared as a potential intellectual conflict of interest?

RESPONSE: In her conflict of interest disclosure, Dr Barbara Mintzes has already reported that she is a member of the European network of Health Action International (HAI-Europe). (page 20, lines 569) Her involvement with Health Action International was disclosed to the Editors and Reviewers since the initial submission of the manuscript to BMJ in March 2019. Moreover, we have clarified in the Conflict of interest statement that given this relationship with Health Action International, Dr Mintzes had no role in data extraction or risk of bias assessments for the two studies by Health Action International that have been included in our systematic review (Perehudoff, 2010; Perehudoff, 2011).

556: Is there a potential conflict here, as Katrina Perehudoff published several articles largely commented in this article and was also part of HAI, with strong views against patient organisations funded by industry?

RESPONSE: Katrina Perehudoff is not an author of the systematic review. She is mentioned in the acknowledgement section because she was asked to be one of the two duplicate independent coders for the article by Van Rijn van Alkemade.(full text in Dutch) She was only involved in the assessment of that study (of which is not an author) because she speaks Dutch. We do not think that this has created a conflict of interest.

Reviewer: 6

Overall impression: As the authors state, a major contribution of this study is that it is the first systematic review of a complex but important topic. They do a nice job summarizing the available data while also acknowledging some of the major limitations. In doing so, they raise some important questions, offer potential implications and establish a clear need for further research.

RESPONSE: We thank the Reviewer for these comments.

Intro: This section is well-written and clearly defines the terms, what is known on the subject, the goals of the paper, and why this review is necessary.

RESPONSE: We thank the Reviewer for these comments.

Results: How were the studies in different languages reviewed (translated or reviewed by native speakers)? How many languages were included and were discrepancies all resolved in the same manner (by consensus between investigators)?

RESPONSE: All but three of the studies were in English (one in Dutch, one in Spanish and one in German). The Dutch article was assessed by a Dutch speaking exchange student, Camilla Van Wijk (mentioned in the acknowledgements), who went through the article with one of the review authors who has a basic knowledge of Dutch; the second independent coder was a researcher who speaks Dutch and who is mentioned in the acknowledgement section (Katrina Perehudoff). The article in Spanish was assessed by two review authors who have a basic knowledge of Spanish. The German study was assessed by two review authors thanks to the help of two native-language collaborators who are mentioned in the acknowledgement section (Marc Torka and Yasmin Kroeger).

Is there any way to weight high-quality studies heavier than low-quality studies in the analysis? If so, would this alter the discussion in any kind of meaningful way?

RESPONSE: As stated in our protocol, we planned to undertake subgroup analyses by study quality for each outcome we meta-analysed. However, due to the high level of unexplained heterogeneity, we could not present meaningful summary estimates for prevalence of industry funding and prevalence of organisational policies. Therefore subgroup analyses also would not make sense to present. We did carry these out as supplementary sensitivity analyses (available in Supplementary File 4). They show that there was no significant difference between high quality and low quality studies.

The section titled “Relationship between industry funding and organizational positions” is also nicely organized and flows well. The second paragraph addressing legislative change to increase the industry’s role is interesting but has a very small sample size (11). This seems like an interesting area for future research but could be potentially biased given the small n.

RESPONSE: We share the Reviewer’s concern about the small sample size of the study by Perekhodoff. When commenting the studies on relationship between funding and organisational positions in the Discussion, we warn the readers and state: *“However, this finding should be interpreted with caution as three of these studies had small sample sizes and all focused on a single policy or health issue”*. (page 16, line 455)

In the fourth paragraph of this section, the authors state, “110/147 (75%) of patient groups that sided with pharmaceutical companies and opposed the proposal received industry funding (33).” Was this statistically significant in the original paper? What percent of the total of each group (industry vs non-industry funded groups) did these numbers represent? i.e. if the majority of patient groups surveyed had received funding then this percentage (and its significance) could be misleading.

RESPONSE: We rechecked the study by Claypool. The authors focused on groups that signed letters to Congress and to Centers for Medicare & Medicaid Services (CMS) opposing a Medicare Part B drug pricing reform. The authors identified 147 of the 388 groups as patients’ groups, then analysed each group’s website to identify pharmaceutical industry sponsorship. Additional industry sponsorships were identified via disclosures made on the websites of pharmaceutical companies. The only result the authors provide in the report is that at least 110/147 (75%) of the patients’ groups that signed on to letters received funding from the pharmaceutical industry.

The authors also acknowledge that these results might under-estimate the extent of industry funding of consumer groups as the analysis is based on voluntary disclosures on websites of patient groups and by pharmaceutical companies. Moreover, the amount of industry funding was mostly unknown. The study only examined groups that signed these letters. It did not have a comparison group. Therefore an assessment of whether there were statistically significant differences in position between industry-funded and non-funded groups could not be carried out.

No other information are available. This is an on-line report by Public Citizen (a non-profit organization in the US), and not a peer-reviewed article. Groups self-selected to sign these letters. They cannot be considered a representative sample of patient groups.

Discussion: Very strong overall. It is both a strength and a weakness that this paper compares studies across so many different countries with drastically different laws/regulatory policies. Ideally, this degree of inclusion would make the results more generalizable but it's also difficult to draw any meaningful conclusions from the reported outcomes when they vary so greatly between studies and countries. That said, I think the authors do a really nice job acknowledging this and don't overstate their conclusions. Consider eliminating/changing the last sentence as it feels like a little bit of an afterthought and the preceding sentence is stronger.

RESPONSE: Following the Reviewer's suggestion, we deleted the last sentence of the manuscript.

Reviewer: 7

Thank you for the opportunity to review this revised manuscript. In this new version, the study authors address a key weakness in the previous draft and acknowledge that in recent years, there has been increasing attention to the development of patient advocacy educational programs, codes and guidelines, referencing EUPATI, WECAN, and EFPIA. (lines 114-118 and references 3-6). This is a helpful addition and sets the landscape more clearly.

RESPONSE: We thank again the Reviewer for pointing us to these documents during the first round of revisions.

In the first draft the authors stated that “no patients were involved in planning and conducting this review”. It is a positive step that the authors now disclose that “Two of the study authors (PM and BM) have been involved for many years with women’s health and consumer groups and maintain strong community engagement,” and that the first draft has since been reviewed and commented on by the representative of a Canadian patient group. Although I would personally have preferred to have seen one of the umbrella organisations consulted over the study design and planning, it is clearly unrealistic to do so at this stage. I hope that the authors will consider this approach for future studies.

RESPONSE: We agree that for future studies we should plan since the beginning a stronger involvement of patient groups and their umbrella organisations.

It is puzzling that the number of studies reviewed in this paper has been reduced from 27 to 26 studies. On closer examination it appears that the Leto di Priolo study referred to in the earlier draft has been taken out. The authors give as their reason for excluding it that there were "no outcomes of interest". The conclusion of the Leto di Priolo study that ““Despite ongoing concerns about the openness and transparency of relations between pharmaceutical companies and patient groups, there is scope for these two sectors to work together on issues of common interest,” seems to me both interesting and relevant to the scope of the review, it is therefore disappointing that it has been excluded at this stage.

RESPONSE: As the Reviewer notes, in the revised manuscript we excluded the study by Leto di Priolo. This happened because following the suggestions we received from the BMJ Editors during the first round of revisions, we excluded one of the research questions from our systematic review (Question n. 4: “*What do patient and consumer organisations think about receiving industry funding?*”) The rationale for excluding the question on opinions of patient groups is that it would be best addressed with qualitative research involving in-depth interviews. We have not included qualitative studies in the current review because a qualitative systematic review uses different methods for data synthesis and interpretation than a review of quantitative studies. On reconsideration, we concluded that this question should be considered to be outside of the scope of the current review. We have therefore submitted a request for an amendment to our protocol to the Prospero team, which is currently under consideration. As the Reviewer notes, deleting this research question led to the exclusion of the study by Leto di Priolo as it did not address any of the other research questions.

I do not personally agree with all of the findings in this review article but this second draft has certainly benefited from the remarks made by myself and previous reviewers and the authors have clearly done their best to address the key points. Publication of this review article would facilitate healthy discussion with patient organisations and industry representatives.

RESPONSE: We thank the Reviewer for these comments.

Reviewer: 8

In my opinion, this is an important study that deserves publication. As the patient voice grows, organizations need to be cognizant of how their funding sources impact their influence, as well as the public’s perceptions.

RESPONSE: We thank the Reviewer for these comments.