PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Exploiting science? A systematic analysis of complementary and alternative medicine clinic websites' marketing of stem cell therapies
AUTHORS	Murdoch, Blake; Zarzeczny, Amy; Caulfield, Timothy

VERSION 1 – REVIEW

REVIEWER	Nathan Lawrentschuk MBBS PhD FRACS University of Melbourne, Australia
REVIEW RETURNED	14-Sep-2017

GENERAL COMMENTS	This is an interesting topic. However, there are suites of papers demonstrating methodologies to assess quality of health information medical websites- why were none of the methodologies considered or referenced? e.g. Thoracic Surgery Information on the Internet: A Multilingual Quality Assessment. Davaris M, Barnett S, Abouassaly R, Lawrentschuk N. Interact J Med Res. 2017 May 12;6(1):e5. doi: 10.2196/ijmr.6732. PMID: 28500021 Free PMC Article Similar articles Select item 28044076 2. Quality of Health Information on the Internet for Urolithiasis on the Google Search Engine. Chang DT, Abouassaly R, Lawrentschuk N. Adv Urol. 2016;2016:8243095. doi: 10.1155/2016/8243095. Epub 2016 Dec 4. PMID: 28044076 Free PMC Article Similar articles Select item 26353845 3. Female urinary incontinence health information quality on the Internet: a multilingual evaluation. Saraswat I, Abouassaly R, Dwyer P, Bolton DM, Lawrentschuk N. Int Urogynecol J. 2016 Jan;27(1):69-76. doi: 10.1007/s00192-015-2742-5. Epub 2015 Sep 9. PMID: 26353845 In particular there is no great discussion of the WHO HONCODE or similar utilities patients and consumers may utilise to assess the quality of health information. Why not multilingual? the above mentioned papers assessed thousands of websites in each study.....

	Where the studies come up on a google search is important as people rarely look beyond 2-3 pages so the tertile rank is important- first 50 websites, second fifty websites , third fifty websites
	The discussion lacks any insight into prior works of health quality on the internet way of comparison and this needs to be addressed

REVIEWER	Spencer Hey Harvard Medical School, USA
REVIEW RETURNED	04-Oct-2017

GENERAL COMMENTS	==General comments== This is an interesting and clearly-written study, examining the language used to advertise stem-cell therapies on websites involving complementary and alternative medicine (CAM) practitioners. I have only two major concerns, both having to do with the framing and motivation for the work. First, I think the authors should better motivate their focus on CAM. Much of the introduction (and indeed, their findings) suggests that problematic use/marketing of stem cell interventions is not limited to CAM practitioners. Therefore, more needs to be said up front to explain why CAM, in particular, is being singled out. Second (and related), the concept of "scienceploitation" features prominently in the discussion and conclusion, and (I suggest) should be raised earlier to help frame the study and analysis. Indeed, concern about scienceploitation can help explain why CAM deserves particular focus here (as distinct from other concerns about MDs offering unproven stem-cell interventions). ==Specific Comments== =Abstract= Objective: An additional sentence describing the motivation (rather than just the aim) for the study is needed. The first bullet of the "Strengths and Limitations" would be excellent for this. Main outcome measures: The description of "representations as to" is hard to parse. Perhaps this is technical language unfamiliar to me, but I would suggest using more straightforward language (e.g., "Representations of expertise, such as …"). "Use of hype language" is also vague. It is defined in the main text (p.9). I recommend defining it in the abstract as well. Results: When reporting frequencies of information presentation, the text describes that "many websites lacked information," but then the frequencies report the number of websites that had the information. This is a bit confusing for the reader, since the text has prepared them to see high numeric values (despite the parenthetical comment). I suggest altering the text to something like "Few websites included important information…"—which better prepares the reader for the low values. =Strengths and Limitations= "CAM" appears here, but has not yet been defined. (Perhaps this is not a problem, depends on the formatting of the final version.)

| | =Methods=
A more detail of description of the "coding frame" is needed to properly interpret the results and limitations. I suggest both defining "coding frame" in general, and then giving at least a few details about the particular coding frame used for this study (perhaps in a box or table?). The reader can guess at some of the details from the results, but it would be helpful to provide more information in the methods. |

REVIEWER	Insoo Hyun Case Western Reserve University School of Medicine, USA
REVIEW RETURNED	08-Oct-2017

| GENERAL COMMENTS | This is an interesting study that draws valuable attention to a new dimension of the online marketing of dubious stem cell therapies. It is led by bioethics researchers who have previously published seminal work in this area. This new study could be seen as an important follow-up and update of this earlier work.

The research approach and conclusions drawn were well reasoned and persuasive. However, it would be helpful if the authors could address the following queries somewhere in the manuscript.

1. One could argue that CAM practitioners make many unsupported claims and offer many unproven services online that "exploit science," aside from the authors' observation that these online advertisements and statements are now starting to take advantage of the excitement around stem cells. Is there something especially salient or unique about CAM when it involves online claims about the power of stem cells? It seems that much of the concern raised by the study's authors could also apply to other types of CAM claims and interventions, and that the "truthful advertising" recommendation endorsed by the authors at the end applies just as well to many other CAM claims and practices. To what extent is the study driven by concerns about the inappropriate marketing of stem cell therapies vs. concerns about CAM practices in general?
2. Part of what motivates question 1 for me is that the authors analyze CAM claims that refer to plant stem cells and other treatments that merely make reference to stem cells (e.g. that they will stimulate the patient's dormant stem cells). But these categories seem to fall under the more general class of dubious claims often attributed to CAM practitioners by medical scientists. Targeting these types of claims (that do not involve the autologous or donor transfer of human stem cells) seems to be supported only on "truth-in-advertising" grounds and not on the further rationale employed by bioethicists and stem cell researchers that the unproven transfer of stem cells into patients could be dangerous. It may be helpful for the authors to point this out, or at least mention this distinction in the article.
3. The authors mention the notion of "scienceploitation". Is this different from "hype"? Hype is mentioned at the beginning of the article, but the authors offer no definition of what this means. Some clarification of how "scienceploitation" relates to hype would be helpful.

Finally, in the references George Daley's editorial in NEJM is listed twice (6 and 25). Is this an error? |

VERSION 1 – AUTHOR RESPONSE

Reviewer One – Nathan Lawrentschuk, University of Melbourne

1.   The reviewer stated that the study covers an interesting topic, and suggested that no methodologies for assessing quality of health information medical websites were considered or referenced. He noted that the manuscript does not discuss "WHO HONCODE or similar utilities patients and consumers may use to assess the quality of health information". We are aware of the important literature and policy activities associated with improving the quality of health information on the Internet. Our study is focused specifically on the marketing strategies of clinics offering stem cell therapies – a well-documented problem. We build on our past research on international stem cell clinics in order to demonstrate what is being offered. While some of our past work (e.g., D. Lau, U. Ogbogu, B. Taylor, T. Stafinski, D. Menon, T. Caulfield, Stem cell clinics online: The direct-to-consumer portrayal of stem cell medicine. Cell Stem Cell 3, 591–594 (2008)) has provided a more comprehensive analysis of the (lack of) evidence-base of the website representations, the goal of this piece is to explore how CAM providers are engaged in this topic. That said, we agree it is important to note the existence of entities like HONCODE. As such, we have added a reference. It looks like this reviewer has done some interesting research on point and we appreciate the references to his publications.

2.   The reviewer asked why the study was not multilingual. In our experience, the majority of studies of this type are undertaken in a single language, and while multilingual analysis can improve such research in some ways, it also introduces significant additional complexity in terms of interpreting and applying the coding frame. This can have the effect of decreasing the reliability of the data. Our team does not have the resources to do a multilingual analysis at this time, and we have noted the English language focus in our limitations section.

3.   The reviewer suggested that website rank on google search results is important due to the fact that people searching rarely look beyond the first few pages of a Google search. We agree that in some studies this would be important, but point out that our study was specifically focused not on the top results of Google and what health information is on them, but rather on the advertising claims made on websites by clinics with physical addresses. This method meant that many results were discarded, as they were not clinics but blogs, online stores, news reports, and other types of content.

4.   The reviewer suggested that the discussion "lacks any insight into prior works of health quality on the internet by way of comparison". As noted, this study is not one focused on assessing the quality of health information on websites, but rather is focused on establishing an inventory of marketing claims made and services offered by clinics. We have published this type of research extensively in the past, and we reference in the text publications where similar methodologies were used to study online representations (see, for example, footnote 11: Ogbogu U, Rachul C, Caulfield T. Reassessing direct-to-consumer portrayals of unproven stem cell therapies: is it getting better? Regenerative medicine. 2013 May;8(3):361-9. Another example of our work studying clinic marketing is Murdoch B, Carr S, Caulfield T. Selling falsehoods? A cross-sectional study of Canadian naturopathy, homeopathy, chiropractic and acupuncture clinic website claims relating to allergy and asthma. BMJ open. 2016 Dec 1;6(12):e014028.)

Reviewer Two – Spencer Hey, Harvard Medical School

Major Comments

1.   The reviewer stated that "more needs to be said up front to explain why CAM, in particular, is being singled out." This is a good idea and we have modified the introduction to explain that the growth of CAM practitioners presenting themselves as primary care providers, alongside their tendencies to offer unproven interventions, led us to hypothesize that such practitioners would begin to offer unproven stem cell therapies and make potentially misleading marketing claims about them.

2.   The reviewer also mentions that "scienceploitation" should be raised earlier on, and could help explain why CAM deserves particular focus. We have also added content to the early sections of the manuscript explaining that CAM practitioners often can use popular science terminology and knowledge to mislead the public and justify largely indefensible interventions.

Specific Comments

1.   "Abstract – Objective: An additional sentence describing the motivation (rather than just the aim) for the study is needed." We have added the first sentence from Strengths and Limitations as suggested. We have also added a sentence that notes the broader policy implications of this research.

2.   "Abstract - Main outcome measures: The description of 'representations as to' is hard to parse." We have changed the wording to clarify it, and have also defined hype language in the abstract as requested.

3.   "Abstract - Results:" We have changed the wording to better prepare reader for the low values in relation to additional information provided on websites.

4.   "Strengths and Limitations – 'CAM' appears here." We have changed CAM to complementary and alternative medicine.

5.   "Methods - A more detail of description of the 'coding frame' is needed to properly interpret the results and limitations." We have both defined coding frame and have added a summary of the coding from to the manuscript in a text box.

Reviewer Three – Insoo Hyun, Case Western Reserve University School of Medicine

1.   The reviewer makes a good point about explaining what is unique with CAM in relation to stem cells. The paragraph we have added to the introduction explains that there are additional special safety concerns with CAM practitioners offering stem cell therapies because of the fact that there is no guarantee of professional training in basic surgical and/or medical procedures. Indeed, this study is driven first by concerns about inappropriate marketing of stem cell-related therapies and products, but the study design was focused on CAM in order to provide valuable and novel insight that is currently lacking in the academic literature. Despite the methods, the results included more medical doctor clinics than expected, which was an interesting finding.

2.   The reviewer points out that the study looks at both the use of stem cell language for non-stem cell therapy products and services, as well as the potentially dangerous transfer of cells. We agree that this distinction is important, and have added a sentence in the conclusion in order to clearly point this out.

That being said, while the primary focus was on stem cell therapies, we did think it would be interesting and relevant to truth in advertising concerns to look at the stem cell-related claims while analyzing the websites, which is why we took the additional steps in our methodology.

3.   Due to our response to specific comment 2 from reviewer 2, we have now defined hype language in the abstract for clarity. Hype is not mentioned outside of the context of hype language. Additionally, due to our response to major comment 2 from reviewer 2, we have added more discussion of scienceploitation to the early part of the text. We explain its meaning and distinguish it from hype.

4.   This was a reference error that we have corrected (in relation to the Daley reference). Thank you for bringing this to our attention.

Thank you again for the thoughtful comments, and we look forward to hearing from you.

VERSION 2 – REVIEW

REVIEWER	A/Prof Nathan Lawrentschuk
	University of Melbourne, Australia
REVIEW RETURNED	06-Dec-2017

GENERAL COMMENTS	The paper has been approved but it cannot be stated that marketing is different form health quality of information- they are indeed related. Poor quality websites will generally be marketing (outrageous claims, lack of data etc) whilst more rigorous scientific publications will be better quality and have little or generally no marketing.
	So papers below very relevant and also the fact that categories were found in these papers means distinguishing quality and marketing is blurred at many junctions. Please reconsider a paragraph relating the two thought processes together.
	Health information quality on the internet for bladder cancer and urinary diversion: a multi-lingual analysis.
	Corfield JM, Lawrentschuk N.
	Minerva Urol Nefrol. 2017 Jul 12. doi: 10.23736/S0393-2249.17.02952-6. [Epub ahead of print]
	PMID: 28707843
	Similar articles
	Select item 28500021
	2.
	Thoracic Surgery Information on the Internet: A Multilingual Quality Assessment.
	Davaris M, Barnett S, Abouassaly R, Lawrentschuk N.
	Interact J Med Res. 2017 May 12;6(1):e5. doi: 10.2196/ijmr.6732.
	PMID: 28500021 Free PMC Article
	Similar articles
	Select item 28044076
	3.
	Quality of Health Information on the Internet for Urolithiasis on the Google Search Engine.
	Chang DT, Abouassaly R, Lawrentschuk N.
	Adv Urol. 2016;2016:8243095. doi: 10.1155/2016/8243095. Epub 2016 Dec 4.
	PMID: 28044076 Free PMC Article
	Similar articles

REVIEWER	Spencer Hey
	Faculty, Center for Bioethics, Harvard Medical School Research Scientist, Department of Medicine, Brigham and Women's Hospital; Boston, Massachusetts, USA.
REVIEW RETURNED	12-Dec-2017

| GENERAL COMMENTS | I find this draft to be much improved, and I now more clearly understand the aims, methods, and results. However, I think the discussion section could benefit from a few more additions.

First, it would be helpful to re-state the purpose and main findings in the first paragraph of the discussion. There is a lot of material to get through in the results section, so it would be good to remind the reader what this work is all about.

Second, I would like to see a few more paragraphs in the discussion that actually address some of the specific findings. The authors presented many tables of results, documenting a wide diversity of claims and practices across these web sites. Yet, they refer to few of these specifics in their discussion. In fact, the discussion section largely reads as though it could have been written without this investigation. What should we make of the distribution of stem cell modes? Or the distribution of targets? The lack of adequate risk information and the concentration of activities in the U.S. are touched upon, but I'd like to see more discussion of how these data in particular advance our understanding. |
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REVIEWER	Insoo Hyun
	Case Western Reserve University School of Medicine, USA
REVIEW RETURNED	13-Dec-2017

GENERAL COMMENTS	The authors' revisions adequately respond to the issues I had raised in my previous review. Furthermore, their responses to the other reviewers' concerns have considerably improved the quality of this manuscript.

VERSION 2 – AUTHOR RESPONSE

Reviewer One – Nathan Lawrentschuk, University of Melbourne

1.   The reviewer suggested we add content to the manuscript discussing the relationship between health information and the online marketing of products and services. We agree this is useful to explore and have expanded a paragraph in the introductory section discussing this. Among others, a reference of the reviewer's publication has been added.

Reviewer Two – Spencer Hey, Harvard Medical School

1.   The reviewer suggested that the discussion section include a restatement of the purpose and main findings, which we agree improves clarity. This has been added at the beginning of the section.

2.   The reviewer suggested that the discussion section be expanded to include a few more paragraphs discussing the specifics of the findings. We have added a significant amount of new content to help readers interpret the tables and the potential implications of the data.

Reviewer Three – Insoo Hyun, Case Western Reserve University School of Medicine

1.   The reviewer was happy with the initial revisions, and did not request any further changes or additions.

Thank you and we look forward to hearing from you.

VERSION 3 – REVIEW

REVIEWER	Nathan Lawrentschuk University of Melbourne, Australia
REVIEW RETURNED	08-Jan-2018

GENERAL COMMENTS	The paper now has been tightened and explores and reflects a concerning issue for the general and medical communities.

REVIEWER	Spencer Hey Harvard Medical School, United States of America
REVIEW RETURNED	08-Jan-2018

GENERAL COMMENTS	I find these additional paragraphs very helpful and have no further concerns.