



Fang-Fang Ji, Science Editor, Editorial Office

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July 30, 2015

Dear Dr. Ji,

Please find enclosed our "Answering Reviewers" document for manuscript 19436 submitted to the World Journal of Experimental Medicine, in the appropriate format, as directed.

Title: How reliable is online diffusion of medical information targeting patients and families?

Author: Pedro Xavier-Elsas. Sandra Epifânio Bastos, Maria Ignez C. Gaspar-Elsas (MD, PhD).

Name of Journal: *World Journal of Experimental Medicine*

ESPS Manuscript NO: 19436

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 00291404 made the following comment:

The authors have picked a usual yet interesting and important question regarding the diffusion

of medical information in the cyberspace. They have used the "ten warning signs of primary immune deficiency" as an object-lesson on the fate of scientific information. The article provides a nice documentation of the accurate/inaccurate spread of specific medical information and raises concerns regarding the standards for scientific or medical information provided online to physicians, patients and their families. This reviewer would recommend its publication in this journal.

Reply: We thank the reviewer for the encouraging comments and fair evaluation of our manuscript. As there are no criticisms, explicit or implicit, we will only point out that the ten warning signs of primary immune deficiency are not unique as a problem of uncontrolled diffusion online, but offer a unique opportunity for approaching this general problem, because they are very well-defined, have a known source, and an easily identifiable target public. Since the information contained therein is scientifically accurate and objectively written, uncontrolled variation online is not a matter of interpretation or improvement, but rather of corruption of the original message, which erodes its usefulness and credibility.

(2) Reviewer 00504024 made the following comment:

PID is not a good topic regarding online information propagation. Rather, AIDS or tuberculosis is recommended as a suitable topic. Anyway, this is a unique attempt and deserves Publication in WJEM.

Reply: We thank the reviewer for the encouraging remark concerning the merits of our manuscript for publication in the Journal. As to the criticism raised about the focus on PID rather than AIDS or tuberculosis, we would like to point out that we lack the necessary expertise in AIDS or tuberculosis to carry out the suggested investigations, and gladly leave this daunting task to others, far better qualified as ourselves, as it certainly would address a much larger body of evidence and encompass many different topics for individual evaluation. Such an endeavour would

clearly overstep the boundaries of an editorial, which should illuminate a topic of interest, rather than exhaustively examine it. Our admission of insufficient expertise on these alternative topics is now part of the final comments in the revised manuscript. On the other hand, we think the paper, as it is, sufficiently justifies our interest in PID: the ten warning signs list is a unique case for study because it is unambiguously defined as to content and origins, has a factual core that poses no problems of interpretation, and is undeniably useful to many people. The point we wanted to make is that online diffusion of expert opinion, as a concept, is meritorious, and PID in this respect is a suitable object for discussion. Those who diffuse the message of the ten warning signs are intent on helping patients and families. In practice, however, every time online diffusion undergoes uncontrolled variation from anonymous secondary experts, the credibility of the concept suffers. This loss of credibility will eventually curtail the usefulness of the practice. To raise awareness of this often overlooked issue is, I think, a proper task for an editorial. Besides, people depend nowadays on personal computers and on the Internet to such an extent that very few realize that the instant access to medical information online remains one of the most significant contributions of advanced technology to Medicine. In contrast to most of advanced medical technology, which is very costly, the personal computer and Internet access are everyday resources in many countries, including some which cannot afford advanced imaging technology and other high-tech devices. As a result, the worldwide impact of issues affecting medical information online is more significant than many suspect.

I have found no further criticisms from this reviewer, and did not receive any further set comments from other reviewers.

Additional comments on the final revision of the manuscript:

Language: On the other hand, I would like to point out that both reviewers, independently of

their scientific evaluation, considered the manuscript to meet the Grade A standards for language.

Formatting: As to the modifications requested in the edited manuscript, we have not found any that requires change in the body of the manuscript. Changes in the title length, table structure and reference list were made as directed.

Documentation: All other requested documents (numbered 1-7) are enclosed with the resubmission.

Plagiarism: Please note that the Google Report encompasses two searches, corresponding to exact or loose criteria for comparison. Both search reports are part of a single document. Please note that Cross-check has provided us with a lengthy list of comparisons which could not be managed by print screen procedures. For this reason, we are submitting the complete report of Cross-check.

Neither Google nor Cross-check reports provided any evidence of plagiarism.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Experimental Medicine*.

Sincerely yours,

Pedro Xavier-Elsas, MD, PhD

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Dr. Fang-Fang Ji,
World Journal of Experimental Medicine
Ref: MS 19436

Rio de Janeiro, August 24, 2015

Dear Dr. Ji,

We have received and revised MS 19436 according the the instructions contained in the copy of the manuscript. Changes include:

1. A novel, structured Abstract, following the word count limits per section indicated in the copy. Section highlighted.
2. A Comments section, following the instructions for this section indicated in the copy. Section highlighted.
3. Separation of Results and Discussion, without change in the contents of the original Results and Discussion section. Section headings highlighted.
4. A signed statement that the manuscript corresponds to an Invited Editorial, as requested by the original correspondence of the WJEM, and not to a systematic review.
5. A signed statement that no statistic treatment of any data in the contents of the manuscript was necessary, so there is no need to acknowledge the participation of a biomedical statistician.
6. A signed statement that this work generated no technical appendix or statistical code that required uploading to a repository.

Items 4-6 require further clarification, as detailed below:

#4 The Journal's query was: "SYSTEMATIC REVIEWS. Do you agree? You can see the format of SYSTEMATIC REVIEWS. And change the paper according it. Thank you!"

Strictly speaking, this is not a systematic review. I was asked to contribute an

Editorial, not a systematic review. If the invitation were to write a systematic review of the literature on any topic, I would not have accepted, as this is not an activity in which I am particularly qualified. I accepted the invitation to write an Editorial, which I understand is as a piece of opinion expressing the views of an author on a particular subject of interest to the journal's readership, based on his/her own experience and on evidence, which is not necessarily quantitative or experimental evidence, but which is both pertinent to the subject-matter and accessible for others to verify. This description fits our manuscript.

By contrast, a systematic review of the scientific literature must assess the contents and quality of published papers. These papers must be in sufficient number to justify a systematic review, and must fit specific categories. They must be published in recognized professional journals, undergo strict peer review, and concern a given subject or well-defined area. It is important that the systematic review author does more than recapitulate his/her own papers, for papers from third parties that meet the inclusion criteria should be treated the same way. This means several people, which may include the review authors, have studied Subject X, and published their results in peer-reviewed professional journals in good standing, which reach sufficient numbers and comprehensiveness to warrant a systematic review effort, and are retrievable through searches with the help of databases such as PubMed and others. Then the review authors analyze these results and extract the information reported by each, trying to define what is consistent or inconsistent relative to other similarly retrieved papers. This description obviously does not apply to our manuscript.

What we did is to identify active addresses at the Internet which can be retrieved with a simple Google search for the Ten Warning Signs of PID. This approach was purposeful, because we wanted to approximate the situation we are interested in, of a nonprofessional user consulting the Internet with nonprofessional search tools, in quest for answers on an uncommon medical condition. We did not analyze papers, because our

question was not: “What does this paper say, and is that confirmed by others?”.

Instead, we analyzed the presence or absence of a specific object in each site examined, because our question is: “Once a particular source (“JMF”) elaborated and distributed a particular piece of scientific information on PID (“the JMF list of 10 Warning Signs of PID”), did variant (i. e., nonconforming) versions of this information appear online, bearing the same name and referring to the original source, but departing from it in content, and can these variants be located through conventional Google searches?” The answer, as detailed in our manuscript, is Yes.

Please note that, even if our search uncovered just one case like that, we would be able to claim that uncontrolled variation occurs. If variants amounted to a much higher frequency, let's say one in every four recovered addresses, our conclusion would still be the same. It is a matter of whether it happens at all, not of how often it happens. So, no statistical treatment is necessary. But it turns out that it happens more frequently than we had expected, providing an opportunity to look into the types and nature of uncontrolled variation. We observed major differences relative to the JMF model, and a sizable sample of addresses encompassing such major changes is provided in Table 2.

The entire Editorial starts with the observation of (1) uncontrolled variation and (2) major factual changes, and proceeds to state and justify opinion. Therefore, my position is that the manuscript is an Editorial, and does not qualify as a systematic review. For these reasons, any attempt to force it into a systematic review format is not justifiable.

#5. As explained above, our opinion was based on evidence, but this evidence is available by assessing the links provided in the paper, and does not require statistical treatment. The conclusion that several sites provide information that is substantively different from that provided in the JMF model they claim to be reproducing is a matter of common sense. No

statistical analysis was performed, and there was no contribution of a biomedical statistician.

#6. As to the separate issue of a data sharing statement which is necessary for basic research and clinical research studies, I also see it as not applicable to this situation. Ours clearly is not a clinical research study, it is opinion based on searches done online. It is not basic research either, because it does not test a hypothesis, nor examines cause-effect relationships and mechanisms. Therefore, the Editorial does not have a Technical appendix or statistical code, so I cannot make it available at Dryad repository. We provided in Table 1 a list of addresses. The original listing in a separate file can be made available to the repository, if the Journal considers this necessary, but in this case we need instructions. Table 2 has summarized information from the analysis of several addresses, which are listed. If the information that has been summarized in Table 2 is deemed is necessary, we will make it available, but in order to so we need instructions about what is required, and in what format it should be provided. This effort will obviously consume some time, counting from the moment we receive such instructions.

Hopefully, these explanations will be acceptable to the Journal, and the review process will be completed.

Yours sincerely

Pedro Xavier-Elsas, MD PhD

Corresponding author