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Title:

**The Decline of the Experimental Paradigm During the COVID-19 Pandemic: A Template for the Future**

Running head:

***Science decline during the COVID-19 pandemic***

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## **Abstract**

The current COVID-19 pandemic has exerted an unprecedented impact across the globe. As a consequence of this overwhelming catastrophe, long established prevailing medical and scientific paradigms have been disrupted. The response of the scientific community, medical journals, media and some politicians, has been far from ideal. The present manuscript discusses the failure of the scientific enterprise in its initiatives to address the COVID-19 outbreak, as a consequence of the disarray attributable to haste and urgency. To enhance conveying our message, this manuscript is organized in three interrelated sections: 1) the accelerated pace of publications coupled with a dysfunctional review process; 2) failure of the clinical trial enterprise; 3) propagation of misleading information by the media. In response we propose a template comprising a focus on randomized-controlled clinical trials, and an insistence on responsible journal publication, and enumeration of policies to deal with social media-propagated news. We conclude with a reconsideration of the appropriate role of academic medicine and journals.

Key-words:

COVID-19; scientific community, medical journals, media.

## Introduction

As of the most recent August 2020 update, the current COVID-19 pandemic has exerted an unprecedented impact across the globe. More than 21.5 million cases have been reported worldwide, including over 750,000 deaths<sup>1</sup>.

The World Health Organization (WHO) has recommended “lockdown” to limit the spread of the virus and many countries have closed their borders disrupting the global economy. Pressure has also increased on healthcare systems attributable to a steep increase of patients requiring acute care and respiratory and circulatory support, and also by increasing the demand for the rapid testing of the safety and efficacy of novel treatments. As a consequence, there has been a disruption of the evidence-based scientific paradigms that are essential for maintaining public health. The short-term consequences of this disruption can readily be observed. For example, off-label use of medications without credible proof of benefit (e.g., hydroxychloroquine), companies rushing to market vaccines without the requisite robust evidence of efficacy and safety, the downgrading of the role of disease control agencies, and distrust of scientific expertise<sup>2</sup>. While the long-term consequences are yet to be seen, a recent projection foreshadows a growing trend in anti-vaccination movements<sup>3</sup>.

In the context of this escalating chaos, how has the scientific community responded? What has been role of medical journals? How has scientifically rigorous information been disseminated? What follows is an overview of how the response to the COVID-19 pandemic has disrupted the norms for reliable data acquisition, analysis, and dissemination. We then adopt a constructive tenor and propose a template comprising a focus on randomized-controlled clinical trials, and an insistence on responsible journal publication policies to deal with social media-propagated news.

For ease of presentation we have organized this manuscript into three interrelated sections: 1) an accelerated pace of publication; 2) failure of the clinical trial enterprise; 3) media dysfunction and the propagation of misinformation. Importantly, we propose a template comprising a focus on randomized-controlled clinical trials, and an insistence on responsible journal publication policies to deal with social media-propagated news, with reconsideration of the appropriate role of academic medical faculties and journals.

### **Accelerated pace of publications**

The COVID-19 pandemic has resulted in a deluge of academic papers being published about the novel coronavirus in one of the greatest explosions of scientific literature ever observed. Professional organisations charged with grading scientific evidence are overwhelmed by the pace of publications. Researchers and clinicians have no time to keep up with the torrent of manuscripts coming out daily<sup>4</sup>. Moreover, many of these publications have not been peer-reviewed and are widely available solely as preprint manuscripts, while others have may have been peer-reviewed but lack quality and scientific rigour<sup>5,6</sup>. Regardless of their quality and whether or not they have been peer-reviewed, many of these manuscripts are treated equally and shared widely on social media and are frequently picked up by numerous news outlets. This has led the preprint server “bioRxiv” to add a yellow banner warning on all new publications of coronavirus research saying: *“A reminder: these are preliminary reports that have not been peer-reviewed. They should not be regarded as conclusive, guide clinical practice/health-related behaviour, or be reported in news media as established information”*. Consequently, it is appropriate to ask why publish them?

In a technological era where a tweet or a Facebook feed may provoke more impact than a well-planned and diligently executed scientific project, we must rigorously question

where the science stands currently, for the sake of transparency, rigour and public trust. The quantity of manuscripts being published suggests that many of these may be observational or small trials with poor oversight, resulting in an inappropriately hasty publication. But because good science requires discipline, caution, validation and replication, the current rapid pace of publications may be contributing to more confusion among the public and to an overall decline in scientific trust<sup>7</sup>. The failure to conduct large-scale hypothesis-driven randomised controlled trials, in concert with haste for fast-track publications has added little to the treatment, and especially the prevention of the novel coronavirus.

### **Failure of the clinical trial enterprise**

Randomised controlled trials (RCTs) are the gold standard test of whether or not a treatment is beneficial<sup>8-10</sup>. The numerous biases and limitations of non-randomised, observational studies have been thoroughly documented and are detailed in the *Table 1*. It must be emphasized, however, that underpowered and poorly conducted RCTs are equally prone to bias and spurious findings<sup>11</sup>. Regrettably, observational, poor-quality randomised and good-quality randomised studies are allocated similar press coverage and dissemination<sup>12</sup>. The growing access to large sets of data from thousands of patients and multiple data sources (i.e., “big data”) has prompted many researchers to erroneously claim an accurate determination of treatment effects from non-randomized studies<sup>13, 14</sup>.

Although, this approach may be used in unique settings wherein it is not feasible to perform a RCT, it should not be used to replace RCTs in settings where RCTs can (and should) be performed - as in the current coronavirus crisis<sup>10, 15-18</sup>. Additionally, using “big data” in the absence of a prespecified power calculation, expected event rates, treatment effects, and follow-up time (i.e., all prespecified parameters of RCTs) is fraught with errors<sup>19-21</sup>. *Table 1*.

During the COVID-19 outbreak many observational studies claiming treatment effects have been reported in top tier medical journals with the inherent limitations above (and in Table 1) described<sup>22-35</sup>; together with a few, small-scale, and/or open-label RCTs<sup>36-43</sup>, and no large-scale, international, well-powered, double-blinded RCT.

Observational studies can also jeopardize ongoing RCTs. For example, the recent publication (and subsequent retraction) of an observational study showing a possible deleterious effect of hydroxychloroquine and chloroquine for the treatment of COVID-19<sup>32</sup> has prompted many ongoing trials to withhold the hydroxychloroquine arm. Because of the context, the decision of pausing the randomisation to hydroxychloroquine might have been inevitable, simply because the patients started to express concern about participating in the trials<sup>44</sup>. While intermediate analysis could be informative, much more informative is to complete the trials as planned<sup>45</sup>. The recent retraction of manuscripts with data emanating from Surgisphere<sup>23, 32</sup>, highlights the failure of adherence to good science practices (access to the original data source denied by Surgisphere) and of peer-reviewing and editorial oversight (not having vetted quality control of the database before their publication). The confusion caused by these episodes expose to the “double whammy” of a) further disruption of RCT timely evidence generation and b) of loss of confidence of the patients eligible for inclusion in the ongoing clinical trials. In a constructive vein we have provided a framework to support and enhance the efforts of editors and reviewers in the handling of observational analyses is provided in the *Table 2*.

Along with the multiple observational studies, some RCTs have also been published. Many of these RCTs have important methodological caveats that render their conclusions non-definitive. A critical interpretation of these RCTs is presented in the *Table 3*. Overall our critique demonstrates a clear failure of the clinical trial enterprise, revealing a lack of



coordination and international cooperation required to facilitate large, high quality RCTs that could potentially respond to the patients` needs in a scientifically valid and timely manner<sup>46</sup>.

We propose that efficient coordination could have readily identified gaps in evidence, candidate hypotheses and interventions to be tested, consequently engaging international stakeholders in a cooperative effort that could lead to high-grade clinical evidence. Moreover, COVID-19 represents a condition where well designed RCTs should have been quick to deliver, because of the availability of patients eligible to be enrolled and a high rate of critical outcomes that develop rapidly and early<sup>47, 48</sup>. Successful coordination could have been achieved by the WHO engaging complementarity among international institutions. Unfortunately, this ideal role has been denigrated and compromised because of the end of multilateralism, and also, admittedly because of the many inefficiencies inherent in the processing of the WHO<sup>49, 50</sup>.

This lack of coordination between public institutions, countries, and scientists has led to an increase in ostensible “expert opinions” that are not supported by solid scientific evidence<sup>51</sup>. In order to deal with these issues, the International Coalition of Medicines Regulatory Authorities (ICMRA) emphasized the need and commitment by global regulators to cooperate and align their approaches to clinical trial management and pharmacovigilance<sup>52</sup>. To achieve this goal, a wider coordination of the media, medical academicians and journals is urgently required.

### **Media and the propagation of misinformation**

Evidence-based medicine has been readily adopted as the best standard of practice in most parts of the globe over the last decades. However, multiple digital sources that lack editorial

oversight or peer review have led to a point where regrettably evidence-based, “traditional” medicine, and fabricated facts are regrettably treated similarly<sup>53, 54</sup>. With billions of individuals online every day, health misinformation can spread at a very rapid pace<sup>55, 56</sup>. Many times, the spread of misinformation is supported by governments and public institutions, which may not only harm the public but may also enhance scientific mistrust<sup>55, 57</sup>.

This rapid spread of viral misinformation renders it impossible for anyone to distinguish between scientifically valid facts and completely false claims that can jeopardize health and well-being, compromise public health measures and ultimately undermine society as a whole<sup>55, 58, 59</sup>. Consequently, learning how to detect unsubstantiated medical news requires an important dose of critical thinking. The American Council on Science and Health has issued a list of “red flags” for facilitating the detection of the role of media and misinformation, taking into account the credibility of the journal, the use of exaggerated language, lack of appropriate methodology, and conclusions not supported by data<sup>60</sup>. These steps may be helpful if one has a strong background in scientific methodology, which unfortunately most readers lack. Consequently, we need a strong engagement of social media platforms for early detection, scrutiny and limiting the spread of the role of media and viral misinformation<sup>61</sup>. Fortunately, the rapid development of publicly available datasets and innovative methods that can rapidly cross-check facts and track misinformation (e.g., deep learning algorithms, natural language processing-assisted data mining, social network analysis), can facilitate the early detection of misinformation and be used for flagging users or groups that are contributing to the misinformation of the public<sup>62</sup>. Although the scientific community generally still enjoys relatively high levels of public trust, disturbingly 1 in 5 individuals express scepticism about scientists. These realities mandate that the medical

community vet health misinformation on social media<sup>54, 63</sup>. Potential solutions to achieve this goal are delineated in the *Table 4*.

The current crisis has clearly revealed the worrisome lack of understanding by the general public, lay media, decision makers and politicians of the basics of the hierarchy of evidence. Hopefully this crisis will contribute to an enhanced awareness about how medicine should transition from empirical-based practice to evidence-based practice. Education of the general public and political leaders about the simple, but critical principles of clinical evidence generation are urgently required<sup>64</sup>. To facilitate this goal, an easy-to-follow colour grading scheme for presenting medical evidence by the media and general public is presented in the *Figure 1*.

A search for the best available evidence should constitute a mainstay of society, but in order to achieve this goal a large scale and global coordination is required, for which participation by medical faculty and journals are essential.

### **How to leverage a pivotal role for academic medical faculties and journals is mandatory**

In many countries including Canada and the United States, medical faculties maintain close community relationships that provide communication platforms to counteract media-driven disinformation. Consequently, responsible journalism along with the public benefit from close and vibrant relationships with local medical faculties. This two-way communication (local medical faculty-to-the-public; and vice-versa) must be regarded as an essential responsibility for our academic medical institutions to counteract the impact of misinformation.

Scientific journals must also have active engagement in proactively counteracting misinformation. Despite being often perceived as inaccessible to lay public, many scientific

journals have more recently embraced the need to translate knowledge more broadly; for example, by adopting open-access “patient-pages” and/or brief summaries of the major research findings, often in the form of a “central illustration”. Most journals now have digital media tools and promote their articles in social media. Furthermore, many journals work in close alliance with medical societies and patient associations. We believe these elements serve collectively to position medical journals as potentially powerful agents-capable of mitigating and counteracting medical misinformation<sup>53</sup>. An increased involvement of the editors of medical journals, and the scientific community in general, is absolutely essential to help the public navigate a world rife with health-related misinformation<sup>59, 63</sup>.

Medical journals could play a leading role for achieving global consensus and prompting action on matters of public interest. Similar to the publication of guidelines for the treatment of specific conditions, and reporting of observational studies or RCTs checklists; medical journals should provide guidance and help regulate medical misinformation by enabling real-time fact-checking before the dissemination of medical information in the media (*Figure 1*).

Another innovation that medical journals should consider is to publish “theme issues” of global health interest (e.g., vaccination, climate change, or cardiovascular prevention). Such “theme issues’ can then be readily disseminated widely in the media, utilizing several outlets in a coordinated manner.

A social media strategy of Twitter promotion may increase the online visibility of research papers and also increase the number of citations<sup>65</sup>. Discussions are currently underway on whether Twitter should be used for continuous medical education<sup>66</sup>. While, a social media-based strategy can be utilized to promote good quality research, it cannot and

absolutely should not replace research itself. Moreover, the constant outpouring of information creates too many information inputs and options, and having too many options may be as bad as having none<sup>67</sup>.

A central issue that must be resolved is how medical journals will relate and coordinate with social media. Social media platforms are here to stay, but we must accept that they can be easily misused, prompting researchers to attempt to attain immediate recognition and feedback on Twitter, as a substitute for engaging in years of rigorous research. Clearly, the value of a scientist should not be measured according to social media feedback but rather by the quality and rigor of his/her research. To facilitate this evaluation, the scientific impact should be measured by long-term achievements rather than by short-term metrics. Instead of using metrics like Altmetric which aggregates short-term social media (e.g., Twitter, Facebook, and other sources) outputs and displays providing a composite score for each paper, medical journals should preferably deploy more long-term based metrics (e.g., citation indexes and clinical utility) that value work product over time<sup>55, 68</sup>.

Another important and glaring issue, that we perceive as despicable, that disrupts reliable data acquisition is “publication by press release”. Private companies, governments and research institutes are convening news conferences to report “potential breakthroughs”, that cannot be verified, because the complete dataset on which the announcements are based have not been peer reviewed<sup>69, 70</sup>. A recent example is Modena’s claim of “favourable” results from its vaccine trial, that was regretfully announced in the absence of supporting underlying data<sup>69</sup>. Nonetheless, the announcement may have had its desired effect i.e., it successfully added billions of dollars to the value of the company in a single day<sup>71</sup>.

To summarize, medical journals must play a pivotal role in reducing the incentive for “publication by press release” by restricting publication of results that have been previously presented to the media in the absence of supporting robust data. As an acceptable alternative, we propose that medical journals can simultaneously provide “fast-track” peer review and publications with a simultaneous press release. Furthermore, scientific journal editors must exercise more oversight and stricter publication control, dedicating themselves to publishing only a limited number of articles per edition, that are rigorous, data-driven and focused

Our proposal for achieving a more central role of medical journals and editors for retaining transparency and quality of evidence is detailed in the *Table 5*.

## **Conclusions**

The COVID-19 outbreak has exposed major gaps and serious flaws both within the scientific world, and how scientific information is disseminated in a technological world of “immediate information”. The lack of coordination between countries and institutions, in concert with the feverish haste of publishing, has regrettably led to a massive output of small studies, observational data, and poor-quality RCTs. We propose a wide array of discrete “next steps” to correct these deficiencies. International organizations such as the WHO and medical journals, must be rendered accountable and tasked to play a significant role in the coordination and quality control of scientific output. Simultaneously, a permanent and clearly identified fact-check system should be adopted by the media, clearly identifying to the reader what is misleading or false from what is likely true. To facilitate these goals, we have constructed a novel and user-friendly grading template for enhancing presentation of medical evidence by the media and general public.

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Table 1. Bias (deviation from the truth) of observational studies

| Bias                       | What is it?   | Example   |
|----------------------------|---|---|
| Selection bias             | The groups being studied are not comparable because they were not selected at random                                | Patients taking anti-hypertensive medication may have poorer outcome not because of the medication but because they are sicker i.e., they represent a group of sicker people  |
| Information bias           | Incorrect determination of exposure, outcome, or both   | Information regarding a treatment or an event is collected differently in across patient-populations e.g., hospital records vs. phone calls vs. face-to-face visits   |
| Confounding                | The association between the exposure and outcome is determined by another factor that can be measured or unmeasured | The association between a treatment for diabetes and outcome may be determined by the patients' income or access to health care e.g., poorer people may not have insurance to cover their health expenses   |
| Exaggeration of the effect | The magnitude of the effect seems greater on a relative scale than what it actually is on an absolute scale         | In the absence of a pre-specified sample size/events and expected treatment effect, an observational study may report an "important" relative effect even in the setting of a low event rate and small difference in events. For example, an outcome affecting 1.7% of the population on the "exposed/treated" and 1.3% on the "non-exposed/treated" may give an odds (or hazards) ratio around 1.3 which is usually translated by a "30% increase of event", but the absolute difference is 0.4%, which should be translated in a 0.4% increase and not 30%. |

Caption: given these limitations the results from observational studies should be regarded as "hypothesis-generating" to be tested in randomised controlled trials; observational studies should not guide treatment decisions.

Table 2. Framework to support editors and reviewers in the handling of observational analyses

| Checklist   | Comment   |
|---|---|
| ✓ Participants must provide informed consent for participation in the study   | Data coming from sources without proof of signed informed consent should not be taken seriously   |
| ✓ The study must have ethical approval from a clearly identified and reachable ethics committee   | Data that do not meet ethical standards should not be considered for publication  |
| ✓ Clear information about the data oversight and management must be provided  | The people responsible for the data oversight and data-management must be identified and reachable if required  |
| ✓ Clear information about the statistical approach must be provided and a statistical analysis plan (SAP) should be available                   | The statistical methods must be very detailed, including on the handling of missing data and rationale of the adjustment technique used; the statistician(s) must be reachable and accountable. Whenever possible the SAP should be published before the analysis is performed. |
| ✓ The data should be available upon reasonable request  | The full dataset used for the analysis should be available for independent verification. For example, upon request from a journal   |
| ✓ The study should be registered in an official agency  | It is strongly recommended a prior registry of the cohort along with its description (e.g., in ClinicalTrials.gov)  |
| ✓ The study should have well defined entry criteria, comparator arm, sample size calculation, outcomes of interest, and follow-up/exposure time | Observational studies should mimic the standards used for randomised trials   |

Table 3. Critical appraisal of the COVID-19 Randomised Controlled Trials (RCTs)

| Study  | Patients   | Treatments  | Main findings   | Methodological issues  |
|--|--|---|---|--|
| A trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe COVID-19. Chinese Clinical Trial Register identifier, ChiCTR2000029308   | 199 adult patients hospitalized with confirmed SARS-CoV-2 infection  | 1:1 assignment of lopinavir–ritonavir (400 mg and 100 mg, respectively) 2x/day plus standard care vs. standard care alone for 14 days   | Lopinavir–ritonavir was not different from standard care in the time to clinical improvement                                | The trial was not blinded, which could have influenced decision making and the use of concomitant treatments |
| Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. ClinicalTrials.gov identifier, NCT04276688 | 127 adult patients hospitalized with confirmed SARS-CoV-2 infection  | 2:1 assignment to a combination of lopinavir–ritonavir (400 mg and 100 mg, respectively) 2x/day, ribavirin 400 mg 2x/day, and three doses of 8 million IU of interferon beta-1b on alternate days (combination group) or lopinavir–ritonavir (400 mg and 100 mg, respectively) 2x/day (control group) for 14 days | The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab | The trial was not blinded, which could have influenced decision making and the use of concomitant treatments |
| Remdesivir in adults with severe COVID 19: a randomised, double-blind, placebo-controlled, multicentre trial.  | 237 adult patients hospitalized with confirmed SARS-CoV-2 infection  | 2:1 ratio assignment to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in 1x/day) or the same volume of placebo infusions for 10 days  | Remdesivir was not associated with statistically significant clinical benefits  | Exaggerated claims of treatment effect not supported by the data.  |
| Adaptive COVID-19 Treatment Trial (ACTT). ClinicalTrials.gov identifier, NCT04280705   | 1063 adult patients hospitalized with confirmed SARS-CoV-2 infection | 1:1 ratio assignment to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in 1x/day) or the same volume of placebo infusions for 10 days  | Remdesivir reduced the time to recovery (median: 11 vs. 15 days)  | Treatment cross-over. Early trial stop.  |
| Study to Evaluate  | 397 adult  | 1:1 ratio assignment  | No difference   | Open label.  |

|  |  |  |   |  |
|--|--|--|---|--|
| the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19). ClinicalTrials.gov identifier, NCT04292899                | patients hospitalized with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less (in ambient air), and radiologic evidence of pneumonia.  | to intravenous remdesivir ((200 mg on day 1 followed by 100 mg on subsequent days) for either 5 or 10 days.  | between a 5-day course and a 10-day course of remdesivir was found.   | No placebo control arm.  |
| A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for COVID-19. ClinicalTrials.gov identifier, NCT04308668  | 821 asymptomatic participants who had household or occupational exposure to someone with confirmed COVID-19  | Participants were randomly assigned to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days) within 4 days after exposure. | Hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection.   | No consistent proof of exposure to SARS-CoV-2 or laboratory confirmation. Young patients with few comorbid conditions who are less likely to develop severe disease. |
| Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19. Chinese Clinical Trial identifier, ChiCTR2000029757 | 103 participants with laboratory-confirmed COVID-19 that was severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation). | Convalescent plasma in addition to standard treatment vs standard treatment alone (control).   | Convalescent plasma therapy did not result in a statistically significant improvement in time to clinical improvement within 28 days. | Open-label. Trial terminated early after 103 of a planned 200 patients were enrolled. Trial likely underpowered.   |
| Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease. ClinicalTrials.gov                                 | 397 patients hospitalised with COVID-19 with oxygen saturation $\leq$ 94% while breathing ambient air, and radiologic evidence of  | Patients were randomly assigned in a 1:1 ratio to receive intravenous remdesivir for either 5 days or 10 days.   | No difference between a 5-day course and a 10-day course of remdesivir.   | Open label. Lack of a randomised placebo control group.  |

|  |   |  |   |   |
|--|---|--|---|---|
| identifier,<br>NCT04292899   | pneumonia.                                      |  |   |   |
| Randomised<br>Evaluation of<br>COVID-19 Therapy<br>(RECOVERY).<br>ClinicalTrials.gov<br>Identifier,<br>NCT04381936 | 6425 patients<br>hospitalised<br>with COVID-19. | Oral or intravenous<br>dexamethasone (6<br>mg once daily) for up<br>to 10 days or usual<br>care alone. | The use of<br>dexamethasone<br>resulted in lower<br>28-day mortality<br>among those who<br>were receiving<br>either invasive<br>mechanical<br>ventilation or<br>oxygen alone at<br>randomization but<br>not among those<br>receiving no<br>respiratory support. | Open-label.<br>Heterogeneity of<br>the treatment<br>effect with<br>benefit in patients<br>who were<br>receiving<br>respiratory<br>support and no<br>benefit (with<br>potential harm) in<br>patients who did<br>not require<br>oxygen. |

Table 4. Potential solutions to increase the quality of randomised trials and information diffusion

| Problem   | Potential solution  |
|---|---|
| Observational and RCT findings are given the same consideration/weight by the media and many scientists | <ul style="list-style-type: none"> <li>- Medical journals should diffuse in the media the differences between an observational study and a RCT;</li> <li>- A grading of evidence (e.g., “GRADE”) should be used along with the release of the study so that people can evaluate to what extent they should rely on the information;</li> <li>- Observational studies should generate hypothesis to be tested in RCTs and not inform about treatment decisions.</li> </ul>                         |
| RCTs (to date) are underpowered for assessing mortality and have many methodological caveats            | <ul style="list-style-type: none"> <li>- Coordination is warranted to allocate resources for performing larger and well-powered studies;</li> <li>- The WHO should be able to provide such coordination and multilateral approach by liaising with the coordinating agencies and the Country/Union level (e.g., EMA, NIH);</li> <li>- Independent DSMB should have the final decision on whether the trial should be stopped or not, and also inform about potential trial misconduct.</li> </ul> |
| Exaggerated claims about efficacy are presented in the study conclusions and abstract                   | <ul style="list-style-type: none"> <li>- Reviewers and journal editors should pay much attention to the wording and any suggestion of exaggerated effect, particularly in the abstract which is the most widely read part of the article.</li> </ul>  |
| Spread of “fake news”   | <ul style="list-style-type: none"> <li>- Social media platforms should improve their systems of “fake news” detection using real-time algorithms that can cross-check information, providing a grading on how reliable that information is. An easy-to-implement colour code could be used, with “green” = reliable, “yellow” = needs confirmation, “red” = unreliable/false;</li> </ul>  |

|  |   |
|--|---|
|  | <ul style="list-style-type: none"><li>- Media in general should be more informed about the conduct of medical research and the grade of evidence, while complying with the ethical principles of journalism*.</li></ul> |
|--|---|

Legend: RCT, randomised controlled trial; WHO, World Health Organization; DMSD, data monitoring and safety board; EMA, European Medicines Agency; NIH, National Institutes of Health; "GRADE", Grading quality of evidence and strength of recommendations. GRADE Working Group (<https://www.bmj.com/content/328/7454/1490>).

\* <https://www.spi.org/ethicscode.asp>

Table 5. The central role of medical journals and editors for retaining transparency and quality of evidence

| <b>Proposed role of medical journals and editors</b> |   |
|--|---|
| ✓  | Powerful agents for counteracting medical misinformation  |
| ✓  | Should join forces to achieve global consensus and take action on matters of public interest  |
| ✓  | Could provide guidance and regulation for information diffusion in the media  |
| ✓  | Social media platforms (e.g., Twitter) can be used to diffuse medical information (upon further regulation – see also the Table 3 & Figure 1), but they should by no means replace a full, thoroughly reviewed work                                   |
| ✓  | Reward systems should place more emphasis in long term scientific achievements, rather than immediate online rewards  |
| ✓  | Clinical impact metrics should be created. For example, by conducting surveys with clinicians from a certain area of expertise to gather information on how much they used a research article for their clinical practice                             |
| ✓  | Medical journals should reduce incentives on publications by “press release”. For example, publications that have been previously presented on media without robust data should no longer be considered suitable for publication in a medical journal |



Figure 1. Colour-code proposal for grading evidence on medical news in the media

(including social media)

| Credible   | Needs confirmation   | Misleading or false   |
|--|--|---|
| <ul style="list-style-type: none"><li>• Well designed and conducted RCTs;</li><li>• Findings replicated in independent RCTs;</li><li>• Findings replicated in 3 or more observational studies with adequate methodology to mitigate confounding;</li></ul> | <ul style="list-style-type: none"><li>• Methodologically weak RCTs (e.g., open-label, protocol violations, poor oversight);</li><li>• Observational studies without extensive replication;</li><li>• “Pre-prints” without peer review;</li><li>• Press releases;</li></ul> | <ul style="list-style-type: none"><li>• Claims without any backup data;</li><li>• Information based on “expert opinion” only;</li><li>• Information that has been proven wrong in RCTs or well designed and replicated observational studies;</li></ul> |

Legend: RCT, randomised controlled trial.

The colour-code fact check would appear as a bar or logo on top of the shared messages.