**Whither the Cochrane?**

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**Introduction**

On 27 July 2018, BMJ's Evidence Based Medicine published an article by Jorgensen, Gotzsche, and Jefferson (1) criticizing the Cochrane—formerly Cochrane Collaboration (CC)—of publishing a review (2) of the effect of human papilloma virus (HPV) vaccines on precursors to cervical cancer in which eligible trials were missed, and which breeched Cochrane policies and standards. In effect, the HPV vaccine review authors were accused of cherry-picking the data in support of conclusions that were incongruent with the totality of the literature.

# On 17 September 2018, the Cochrane Governing Board announced its intent to discipline Peter Gotzsche, a Cochrane founder and member of the Governing Board, for “bad behavior”. (3) [It should be noted that Gotzsche was a vocal and longstanding critic of corruption in medicine, and in 2013 had published the book, Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Healthcare.]

On 26 September 2018, The Governing board made known its vote from the day before to terminate Professor Gotzsche’s membership and positions in the organization. (4) Revelations by the disputants and bystander reactions to his ouster have shaken confidence in Cochrane both as a reliable source of integrative research reviews and as an organization free of conflicts of interest.

The controversy and conflicts of interest revealed, and the (increasingly well-known) lack of verifiability of clinical trial data, in general, that underpin its published meta-analyses, are formidable impediments to the production of reliable research reviews. Yet there is a dire need for accurate evaluations of drugs, vaccines and medical devices culled from the jungle of (both published and unpublished) biomedical data sets.

Our frame of reference in assessing the gush of disputant and bystander reactions is the same analytic model that undergirds Stegenga’s *Medical Nihilism* (5)—an empirically-grounded, logical demonstration of the essential malleability of all medical research. This includes in particular the randomized controlled trial (RCT), whose method is sometimes claimed as the “gold standard” to guide medical decisionmaking and policy.

**Reactions and Concerns for the Future**

Reactions to the Cochrane’s Governing Board statement came fast and furious both from within the organization and from without. Four of the 12 Governing Board members resigned in protest over Gotzsche’s expulsion from Cochrane and wrote a letter of explanation, concluding:

It is our hope and deepest desire that this event will encourage all Cochrane members and the wider community to reflect upon where we currently find ourselves and give serious consideration to what we want for the future of Cochrane and its principles, objectives, and ethos. (8)

The reactions were mostly critical of the Governing Board’s decision. They can be sorted into four categories: (1) arguments about “who did what to whom and the wherefores and whys” (8,9,10); (2) commentary offering historical perspective while pointing out methodological flaws in Cochrane meta-analytic aggregation of RTC reports (11,12,13,14); (3) explanations appealing to philosophy (15,16); and (4) commentary focusing on conflicts of interest and need for organizational reform (8,17). An ancillary source of dispute was Cochrane’s recent shift from a loose collaboration to centralized management and plans for expansion from a current staff of 50 (18) necessitating the need for more ample funding--which has been deemed fraught with moral hazard.

**Bystander Analyses**

One bystander, Nass (6), summarized the situation with respect to how the Pharmaceutical industry (Pharma) might benefit from Cochrane's crisis. She further noted that (in the US) a deliberately misleading literature review could subject the authors to a legal charge of scientific misconduct by falsification. (7) Her analysis:

* [If the Cochrane HPV review stands, it props the door open for Pharma's continuing capture of Cochrane’s work and reputation.](https://grants.nih.gov/grants/research_integrity/research_misconduct.htm)
* [For Pharma, if Cochrane is captured, big win.](https://grants.nih.gov/grants/research_integrity/research_misconduct.htm)
* [For Pharma, if the (sometimes pesky) Cochrane is not captured, but instead self-destructs, that too is a big win.](https://grants.nih.gov/grants/research_integrity/research_misconduct.htm)
* [For Pharma, the only loss would be if Cochrane tightens its belt and its standards, refuses Pharma-laundered funds and refuses to use authors with financial conflicts of interest.](https://grants.nih.gov/grants/research_integrity/research_misconduct.htm)
* [Right now, this looks like a position that is unlikely to result.](https://grants.nih.gov/grants/research_integrity/research_misconduct.htm)
* [But it appears to be the only option to preserve Cochrane as we knew it.](https://grants.nih.gov/grants/research_integrity/research_misconduct.htm)

David Healy puts in perspective the Cochrane’s longstanding commitment to systematically gathering all RCTs on treatment, winnowing out duplicate reports, and seeking to identify unpublished trials (11)—a good idea, but insufficient to overcome the known problems in the conduct and reporting of RCTs. Healy argues, “If RCTs don’t consistently give the same effectiveness result they are irredeemably flawed.” (12,13) In an earlier blog, Healy (14) argued that RCTs are “gold standard processors into which we have fed garbage and have got garbage back.”

There is a very large literature documenting the influence of corrupt medical research practices, such as concealing adverse events and negative data, penning names to ghostwritten clinical trial reports, publishing biased promotional reports, and hoodwinking the FDA by false reporting of efficacy and safety. (19,20). Jefferson aptly summarizes and uses the analogy “garbage” to describe these sources of fraudulent and misleading RCT evidence on which Cochrane meta-analytic reviews depend. (21)

The real issue is that there are numerous threats to reliability and validity at each of the major stages in the performance of a research review, including at least: (a) problem formulation, (b) identification of relevant studies, (c) judging research quality and controlling researcher and reviewer bias, (d) analysis and interpretation, (e) public presentation and f) interpreting effect size. (21)

Hilda Bastian (9) burrows into the minute details of process and personalities to handle an incendiary situation, seeing it as perhaps “our biggest chance to limit the damage, speed the recovery, and get something positive out of all this.” She discusses the problem of the omitted data identified by Jorgensen, Gotzsche, and Jefferson (1) and the Cochrane editors’ claim that it wouldn’t have changed the conclusions of the original Cochrane HPV review (2).

Trish Greenhalgh (15) expresses doubt that Cochrane is experiencing “a crisis of either morality or democracy.” Instead, she asserts “It’s brand, now as ever, stands for rigour, independence, and a commitment to using science to achieve high-quality patient care and social justice.”

Chair of NoGracias Abel Novoa et al. (16) argue to the contrary that Greenhalgh is over-simplistic in couching the decision to expel Gotzsche as a problem separable from organizational governance. Novoa relies on Stegenga’s (5) demonstration that the methodology of evidence synthesis does not produce random results, but disproportionately favors the products evaluated. Novoa points out the critical need for all scientific disciplines to identify and control researcher and organizational bias originating from conflicts of financial interest. A role of Cochrane governance should be to minimize bias in the production of credible integrative research reviews.

BMJ editor-in-chief Fiona Godlee (17) lends support for the position that the Cochrane crisis is much more than tension and clashes between strong personalities, and instead a struggle for the soul of the organization:

. . . the governing board’s vote to expel one of its founders and most vocal internal critics, Peter Gøtzsche, brings to a head years of growing tension between the collaboration’s radical academic roots and its more recent corporate identity ... beyond the personalities lies a deep seated difference of opinion about *how close to industry is too close*.

She expresses hope that “Cochrane remembers its roots, and that it comes through this episode reinvigorated, independent, and committed to holding industry and academia to account.”

In an October 12, 2018 BMJ "Second Opinion" piece about the scandal of vaginal mesh, Godlee (22) again raised the issue of how physicians, researchers and professional bodies are entangled with manufacturers. After so many revelations of how this entanglement worsens the care of patients, Godlee asserts,

"We don’t allow judges or journalists to take money from the people they are judging or reporting on. Doctors should be equally independent in their advice to patients...

As for industry sponsored research, we welcome the call by Paula Rochon and colleagues for journals to ensure that academic authors retain full control of the process...

Given that doctors and researchers do take money from the industry, should the details be readily available to patients and the public? My answer is yes. "

**Wherefore Cochrane?**

What can Cochrane do to survive its crisis? We offer suggestions based on disputant and bystander reactions, given increasing revelations of how medical industries have found ways to taint every aspect of the medical research endeavor.

*Conflicts of interest*. Cochrane must address and fix its conflicts of interest in securing adequate financing from industry and philanthropic and governmental agencies. (18) Godlee’s question, “how close to industry is too close?” needs a clear answer now.

Ideally, funding can be found without strings attached, but the harsh reality is, “Whose bread I eat his song I sing” (German Proverb). The Cochrane faces moral hazard and fierce competition in pursuit of adequate sustainable funding. Government funding, which provided a great deal of support to Cochrane, may pose as potent a threat to bias-free independence as industry. (25) and guidelines for government support need to be as transparent as those for industry.

*Advocacy for truth in labeling*. Cochrane might reinvent itself as a proactive advocate and lobbyist for truthful and comprehensive reporting of the effectiveness and harms of drugs, vaccines, and medical devices. All data, not only that derived from RCTs, need to be evaluated: clinical study reports, raw trial data, regulatory agency reports on how trials are conducted, evidence from litigation and enforcement agencies, as well as the professional and legal reputations of those engaged in conducting clinical trials. The FDA has in the past licensed drugs using clinical trial data obtained by clinicians who fabricated data—despite several going to prison for doing so. (26) The use of disreputable data to determine the proper use of therapeutics can never be acceptable—no matter by Pharma, the FDA, the CDC, European regulators, or Cochrane. (27) Labels describing the proper use of therapeutics must be accurate and comprehensive. Cochrane should exhort agencies such as FDA, CDC and EMA to use only verifiably accurate data and research methods that do not 'spin' data.

*Appropriate analytic methods.* There is also the matter of using appropriate statistical methods to calculate confidence intervals, perform null hypothesis significance tests, derive p-values, and calculate effect sizes. (29) FDA RCT requirements for drug approval do not adequately account for verified prior knowledge-- underscoring why so many RCT results are wrong, misleading, and a waste of money. (18,19).

There is need to end the common practices of (a) comparing a new drug to an inert placebo (or anything less than the current best treatment for efficacy assessment) (b) using subjects in clinical trials who are less likely to show adverse reactions than the population who will receive it (30); and (c) using active, adverse effect-inducing 'placebos' (usually novel adjuvants or other vaccines) in vaccine trials, obscuring adverse events caused by the vaccine being tested.

*Advocacy for full transparency*. Cochrane might reinvent itself as an advocate for full disclosure and sharing among researchers of verifiable. The goal would be to (a) promote truth in research reporting (32), (b) minimize opportunities for researcher manipulation of data and statistical analysis to produce biased conclusions, and thus (c) reduce the threats to reproducible science that “ . . . undermine the robustness of published research, and may also impact on the ability of science to self-correct.” (34)

*Reinvention as trusted conduit for verified data sharin*g. More ambitiously, Cochrane might reinvent itself as an independent recipient of verified RCT information via block-chain smart contracting. (34,35) This method permits researchers to transmit to an independent party (such as Cochrane) information about research hypotheses and the details of design and implementation, including data inputs on individual, anonymized RCT subjects. This method enables changes to data or analytic methods at any step of a trial to be identified. The Yale University YODA project (36,37) provides a template of conditions for allowing researchers, physicians and others who seek access to clinical trial data.

Cochrane’s reputation for excellence in producing unbiased literature reviews has been seriously tarnished. New scrutiny of the premises underlying the conduct of meta-analyses add to the jeopardy it faces. The likelihood of takeover by industry or government financial largess, if it has not happened already, seems greater than ever.

Will Cochrane recommit itself to seeking the strongest evidence available to assess therapies, recommit to transparent research methods and governance, and consider flexible research approaches as the problems with individual research methods are identified and understood? Can Cochrane seize this moment to disentangle the processes of medical research from those who have the most to gain by tainting them? Is Cochrane up to the challenge?

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