EDITORIAL

If there are no randomised controlled trials, do we always need more research?

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We have recently, partly by chance and partly through a blog called *Science-based Medicine*,[1] come across Cochrane Reviews in which evaluative research other than randomised controlled trials (RCTs), as well as logic and basic science, seem to have been largely ignored. Hence, the review questions cannot be answered in the manner that the authors set out to do, the implication being that more research is needed.

The Cochrane Review on Laetrile treatment for cancer may serve as an example.[2] Laetrile is a derivative of amygdalin, a substance extracted from apricots and other fruits and nuts. It contains cyanide and is used illegally as a treatment for cancer. The review's inclusion criteria limit the search to RCTs, but no RCTs were identified. In the discussion the authors describe various rationales for the possible effects of Laetrile, but none are deemed plausible. The authors state that: *"This is systematic review found no evidence for Laetrile to be effective as [an] anti-cancer agent. The claim that Laetrile has anti-cancer effects is not supported by data from controlled clinical trials. The potentially relevant studies identified were case series that do not provide good quality evidence as they do not include a comparison group. Therefore, Laetrile cannot at present be recommended as an anti-cancer treatment."*

But the review abstract concludes that:*"This systematic review has clearly identified the need for randomised or controlled clinical trials assessing the effectiveness of Laetrile or amygdalin for cancer treatment."*

One of the case series that the review authors identified, but excluded, looks at 178 patients with cancer who were treated with Laetrile plus a "metabolic therapy". The authors of the case series conclude: *"No substantive benefit was observed in terms of cure, improvement, or stabilization of cancer, improvement of symptoms related to cancer, or extension of life span. The hazards of amygdalin therapy were evidenced in several patients by symptoms of cyanide toxicity or by blood cyanide levels approaching the lethal range."*[3]

We question whether there is a need for RCTs to assess the effectiveness of Laetrile for cancer treatment. We also doubt whether such a study would be approved by any ethics committee. To suggest a need for RCTs (that will never be organised) to answer this question seems both illogical and unethical. It leaves us at a standstill. The authors have implicitly disapproved of the existing evidence and have given room to even more speculation.

Similar problems are encountered in the Cochrane Review of the MMR vaccine.[4] The objective of the effectiveness part of the review is: *"To review the existing evidence on the absolute effectiveness of MMR vaccine in children (by the effect of the vaccine on the incidence of clinical cases of measles, mumps and rubella)."*

The inclusion criteria are: *"Vaccination with any combined MMR vaccine given independently, in any dose, preparation or time schedule compared with do-nothing or placebo."*

The primary outcome is: *"Clinical cases: measles, mumps or rubella."* By using this outcome the authors exclude studies that assess antibody response to the vaccine as a measure of vaccine effectiveness. The question of whether or not antibody response is a good indicator of immunity (and if there is any reason to doubt the practice of measuring antibody response in vaccine studies) is not raised. The authors conclude that: *"As MMR vaccine is universally recommended, recent studies are constrained by the lack of a non-exposed control group. This is a methodologically difficulty which is likely to be encountered in all comparative studies of established childhood vaccines."*

Nevertheless, they go on to state that: *"We were disappointed by our inability to identify effectiveness studies with population or clinical outcomes."*

And, in the abstract:*"We could not identify studies assessing the effectiveness of MMR that fulfilled our inclusion criteria even though the impact of mass immunisation on the elimination of the diseases has been largely demonstrated."*

This is less dramatic than the Laetrile example, but still, in our opinion, not satisfying. As we will (hopefully) never have proper control groups for the MMR vaccine, the review's conclusions lead to a paradox: how can the effect of the MMR vaccine be proven through population or clinical outcomes (i.e. incidence of disease) when there is no non-exposed control group?

We can see the same disregard for non-RCT evidence in Cochrane Reviews of homeopathy. Homeopathy is, in essence, a placebo in itself, with no plausible mechanism of action.[5] Reviews typically have conclusions such as:

- *"There is insufficient evidence to recommend the use of homoeopathy as a method of induction [of labour] … Rigorous evaluations of individualised homeopathic therapies for induction of labour are needed."*[6]
- *"In view of the absence of evidence it is not possible to comment on the use of homeopathy in treating dementia."*[7]

These are, in our opinion, disturbing views. Is it really not possible to comment on the use of homeopathy in dementia without an RCT?

We acknowledge that there are many examples where findings from RCTs have led to necessary changes in established practice that had been based on logic and less rigorous evidence. Hence, we do fully agree that potentially (moderately) effective interventions should be evaluated, if possible, in experimental settings.

However, we need to discuss and refine our stance on what to think and what to broadcast when it is not possible to do so. When there are clear indications (e.g. from case series) that an intervention is dangerous, we need to let some hypotheses go and move on. Likewise, although empirical data trump theory, we must continue to think. And when something does not make sense at all (albeit within our belief system), we must have the courage to say so.

In our opinion, we need to be clearer about implications for policy, practice and research, when RCTs are lacking and unlikely to be done. On the other hand, it is understandable that authors (who often have a particular interest in a given intervention) sometimes find it difficult to declare something as 'not working' and move on. We think some guidance is needed for editors and authors in cases like this, and we would be interested to see what others have to say on the matter.

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Declarations of interest

The authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request) and declare (1) no receipt of payment or support in kind for any aspect of the article; (2) no financial relationships with any entities that have an interest related to the submitted work; (3) that the author/spouse/partner/children have no financial relationships with entities that have an interest in the content of the article; and (4) that there are no other relationships or activities that could be perceived as having influenced, or giving the appearance of potentially influencing, what was written in the submitted work.

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