Re Sodium Cromoglicate: An Ineffective Drug or Meta-analysis Misused?‡

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Stevens et al. [1] describe some concerns they have with four systematic reviews of the effect of sodium cromoglicate in children, one of which was published in the Cochrane library [2]. As two statisticians involved in the Cochrane Collaboration, we wish to provide some background to Cochrane Collaboration reviews, and to comment on why some aspects of this review may have been done the way they were. As we were not involved in writing this particular review, we cannot comment on all of the specific criticisms. In particular, we do not feel able to comment on whether it was appropriate to include or exclude particular studies as we have not reviewed the individual studies.

The Cochrane Collaboration is an international, non-profit, independent organization. It aims to help people make well-informed decisions about health care by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health-care interventions (Cochrane reviews). These are updated regularly and published online in the Cochrane library. The Cochrane Collaboration is committed to involving and supporting people of different skills and backgrounds; reducing barriers to contributing; and encouraging diversity, open decision-making and teamwork. Over 12 000 people (mainly volunteers) in more than 90 countries are involved in the Cochrane Collaboration. This includes health-care providers across a huge range of clinical specialties, policymakers, patients, and their advocates and carers, and methodologists, who work together to provide evidence to help people make decisions about health care. Those who prepare the reviews are mostly health-care professionals who volunteer to work in one of the many Cochrane Review Groups. These groups focus on particular areas of health (for example, breast cancer, stroke), and are coordinated by an editorial team who edit and assemble completed reviews into modules for inclusion in the Cochrane library.

The Cochrane Collaboration aims to be transparent and open about everything that it does, by internally and externally fostering good communications, open decision-making and teamwork. A protocol is written and published prior to undertaking each review, which is peer reviewed both by editors within the Cochrane Collaboration, and by external peer referees, often including methodological and consumer input in addition to expert clinical opinion. Cochrane reviews are updated at intervals, so the results and interpretation will change as the evidence-base changes. There is a feedback system that can be used to inform review authors of alternative points of view, and Stevens et al. have quite rightly been conversing with the review authors directly. As an organization, the Cochrane Collaboration is open to discussing its views and methods, and as active members of the Collaboration, we appreciate the opportunity to join this particular debate.

A major criticism of Stevens et al. was that the primary outcome was reported in only four out of the 24 studies included in the review. There is an implication here that selection of the primary outcome in a systematic review should be based on what was most frequently considered in the trials, and not be based on the reviewers’ assessment of which outcomes they and others consider to be the most important and appropriate. Reviewing for the Cochrane Collaboration is a rigorous exercise. The protocol for a Cochrane pre-specifies the inclusion and exclusion criteria, the primary and secondary outcomes, and the methods that will be used. Outcomes in Cochrane reviews are generally selected on the basis of their value when making decisions about whether or not to use a particular intervention, rather than on the basis of whether they

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were used in the majority of trials. Cochrane reviews aim to help people make well-informed decisions about health care, so they try to select the evidence that matters to patients and decisionmakers, rather than summarizing everything that is available. Sometimes these outcomes are ones that are difficult to measure and are not assessed in many of the trials. Where important outcomes have not been measured, the Cochrane reviews draw attention to this fact, as they are reporting on the completeness and usefulness of the information, not just mechanistically summarizing what has been done. The Cochrane Handbook for Systematic Reviews of Interventions [3] quotes an example from cancer, ‘the quality of life is an important outcome, perhaps the most important outcome, for people considering whether or not to use chemotherapy for advanced cancer, even if the available studies only report survival data’. So in the sodium cromoglicate review, it is likely that the choice of primary outcome will have undergone careful thought, and was selected according to what experts and healthcare consumers in the field considered most important.

In their conclusions Stevens et al. suggest a re-examination of the review procedures that allowed all these systematic reviews to be published. In addition to peer review of protocols, Cochrane reviews are referred internally, by the Cochrane review group editorial team, and externally, by peer reviewers. It is virtually impossible to have a perfect refereeing system, but the Cochrane Collaboration’s procedures are probably more rigorous than most other peer-reviewed journals.

The Cochrane meta-analysis of sodium cromoglicate interprets the results across all studies despite significant heterogeneity. The Cochrane Handbook for Systematic Reviews of Interventions [3] encourages review authors to quantify the amount of heterogeneity present in any meta-analysis rather than concentrating solely on its statistical significance. As no two studies will ever be identical in every respect, heterogeneity will always be present to some extent. The handbook also describes in detail methods for dealing with heterogeneity, including exploring the potential sources of heterogeneity. The precise details of what should be done about heterogeneity have been debated at length amongst statisticians within and outside the Cochrane Collaboration, and there is still a variety of opinions about exactly what should appear in each individual review.

Stevens et al. question the authors’ use of the tolerance interval in the review. We agree that this is somewhat unusual. Tolerance intervals are not recommended in Cochrane reviewing guidelines, and this appears to be the only Cochrane review currently on the library that mentions them.

It is pointed out that there is only so much that can be done from published summaries and that this presents many challenges. We agree. The Cochrane Collaboration supports the prospective registration of clinical trials [4] and meta-analyses based on individual patient data [3], and recommends that all randomized controlled trials are registered at their inception (at the time of ethical approval and/or funding approval), and that registered information should be potentially accessible to all interested parties. Hopefully in the future there will be trial registration for all clinical trials, with associated publication of the full trial protocol, which will help in knowing what data were recorded in all studies. This may aid getting unpublished data from trial authors.

To put the criticism of the sodium cromoglicate review into perspective, there are currently 4539 reviews published on the Cochrane library, and Stevens et al. have pointed out concerns with two of them. There are a great many Cochrane reviews over which there is no controversy, and which have helpfully summarized the available evidence on a wide range of topics. Much of the work of the Cochrane Collaboration is done by volunteers or people on minimal funding. These enthusiastic individuals have achieved an astounding amount over the past 10 years, in reviewing many areas of the medical literature, review methodology, and in educating the medical professions in the art and science of meta-analysis. There are a great many statisticians within the Cochrane Collaboration. They have helped develop and write recommendations regarding rigorous methods for synthesizing evidence (even if they are not always implemented), supplemented by extensive guidance, training, and support. There is always a need for more people to get involved. Any statistician who is interested in joining the Cochrane Statistical Methods Group or in helping out in the reviewing process in any way should contact the authors.

REFERENCES