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This month we have our first JCE articles on Covid-19 coming through an expedited review process. The new submissions are reviewed weekly. Although we are only able to consider papers that methodologic in focus, it is good to see the substantial interest in the method challenges from authors. This is attracting the formation of new multidisciplinary author groups working virtually that may be the prelude to a new normal.

In this issue we have 2 series addressing important methods issues. The first series proposes a revolution of the ecosystems of systematic reviews. Ravaud et al argue dramatic changes are needed in the ecosystem world of systematic reviews and meta-analyses of therapeutic interventions if these are to be truly stakeholder-needs-driven. There is a mismatch between and among the primary research enterprise and the evidence synthesis enterprise; the planning, coordination and conduct of systematic reviews; there is fragmentation of available evidence that hampers providing useful information for health decision making. Some concrete solutions are proposed through the 4 papers and then vigorously commented on in 2 accompanying commentaries. These issues and their resolution is currently being actively debated within the Cochrane Collaboration.

The second series is a Controversy and Debate Series. This begins with a meta-epidemiology review to look at ‘subjective’ versus ‘objective’ when contrasting patient reported outcomes with other types of outcomes such as clinician reported outcomes, laboratory tests, imaging etc. Berthelson et al argue that their meta-epidemiology study demonstrated not only is the patient the most relevant source of data for patient care, but the clinimetric performance in terms of truth discrimination and feasibility of patient reported outcomes equals the performance of clinician reported outcomes, laboratory tests, imaging etc. This paper then becomes the focus of a debate over three subsequent papers on the methodological validity of such meta-epidemiological studies in avoiding a) various design related biases such as inadequate sequence generation and inadequate allocation concealment cause bias that inflate estimates of treatment effects; and b) misclassification of trial characteristics, non-reporting biases affecting the pool of trials available for analysis, and the generalisability of the meta-analyses sampled.

Just asking a question without any additional intervention can induce behavior change so this needs to be considered in any study. As part of a research program [MEasurement Reactions In Trials (MERIT)] to develop MRC/NIHR guidance on minimising the risk of bias in trials of healthcare interventions as a result of measurement reactivity, Miles et al report on an updated evidence-base for new guidance. They found further evidence for an overall small but heterogeneous effect after adding 10 new trials to the 33 trials across trials of conditions including alcohol, blood donation, diet, flossing, health checks, physical activity, screening, sexual behavior and vaccination. This reinforces the importance of considering this in such studies, especially where the effect size is likely to be small.

Publicly available protocols are increasingly felt to be essential for best practice in systematic reviews in most health disciplines—although this is still being debated amongst environment health journal editors. The most common approach is to register these on a publicly available database such as PROSPERO. However although this requires a standardised format this is not peer reviewed. Organisations such as the Campbell and Cochrane Collaborations require these to be peer reviewed but most other journals so not require this. In this issue Rombey et al report on a survey of 49 authors of systematic reviews registered on PROSPERO to assess the perceived importance of such protocols being peer reviewed. Many agreed that peer review would or did improve the protocol but less than half felt this should be required. This needs more empirical studies.

Searching for reports of studies presented at a conference is an acknowledged approach to study identification in systematic reviews, since this allows identification of newly emerging studies, or updated findings of on-going studies, potentially ahead of journal publication; thus identifying data that can help minimise the introduction of bias into systematic reviews, since a significant proportion of studies that are reported at conferences are never published. Handsearching has traditionally been the method used to search for reports of studies presented at conferences but it is resource intensive. Cooper et al report a case study of searching conference proceedings presented at the American Society of Hematology conferences between 2016 and 2018 to assess different approaches used to try and make this more efficient. Searching Embase, PubMed or Conference Proceedings Citation Index- Science were all inadequate; keyword searching performed better and did save some time. Efficiency of exporting would be improved if journals permitted bulk downloads.
The degree of robust trustworthiness of the science is the cornerstone of clinically important conclusions made in systematic reviews. This is assessed using validated instruments to assess risk of bias such as the Cochrane Risk of Bias measure. This does require expertise and judgment so it is recommended that this be assessed independently by two assessors. Bertizzolo et al. have previously shown that suboptimal agreement in risk-of-bias assessment, ranging from 81% agreement for random sequence generation to 57% for incomplete outcome data; such disagreement dilutes the confidence the conclusion. Sometimes this is due to one assessor missing the information due to it being placed in varying parts of reports but more than two-thirds of disagreements was related to differences in interpretation of the same information. In this issue these authors analysed external factors that might explain this beyond training—they found that assessors were more likely to allocate a good rating [low risk of bias] if any of the review authors are authors of the included RCTs and if the RCT in question is relatively old. Experience as assessed by number of reviews by the first author was not found to be a factor.

Systematic reviews to assess the efficacy and effectiveness of interventions require the assessment of the trade off between benefit and harm. However as Li et al point out journals and databases continue to favor assessment of benefits over assessment of harms despite increasing emphasis from reporting guidelines on harms such as the Cochrane Handbook and the PRISMA harms statement. Of 120 systematic reviews, including 60 Cochrane and 60 non Cochrane ones, only nine (7.5%) reviews clearly defined safety outcomes, and seven (5.8%) defined a primary safety outcome; none stated whether the primary safety outcome was pre-defined. Journal editors should require systematic review authors to report safety information.

Puljak et al report that 85% of 508 non-Cochrane systematic reviews published in Pubmed in June 2018 indicated they used the Cochrane Risk of Bias instrument. However in 41% this instrument was not correctly applied—most often due to the omission of the required details to justify the judgment of high/low/unclear risk of bias. If the non-Cochrane systematic reviews are to be used for policy and practice decisions these details need to be made available—if space in the written journal is limited this information should be made available in a web appendix.

Assessment of Risk of Bias in observational study designs is also controversial, even for the most widely used STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) instrument—a reporting guideline published in 2007 that consists of a checklist of 22 items that are considered essential for good reporting of observational studies. It has been widely endorsed by biomedical journals but few of these journals actually insist it is used and submitted with manuscripts. As part of a quantitative study on its use reported elsewhere Sharp et al report on over 150 qualitative comments made by respondents. Some of these are important for the clinical epidemiology community to consider given the increasing pressure to use such reporting guidelines. On the positive side the systematic process is an important part of scientific reporting and this structure is extremely useful for training of authors and journal reviewers. On the negative side several comments were made re timing—ie these issues should be addressed at the time of the study being designed; also some experienced investigators felt this was an inflexible overreach [forcing the researchers into a ‘straightjacket’] and not being taken seriously by the journals in their decision-making. The authors of this paper recommend a review of the STROBE instrument ’s content, training for early career researchers, and the need for better incentive and enforcement mechanisms.

Three articles address statistical issues. Bayesian analyses have enormous conceptual appeal over traditional frequentist analyses since Bayesian statistics better incorporates prior probabilities based on prior knowledge from previous experiments. This approach is slowly gaining acceptance in clinical epidemiology as reflected in many statistical texts, its acceptance by many leading journals, the recommendation by the US Food and Drug Administration for Phase III trials evaluating medical devices, and its acceptance by the Cochrane Collaboration for traditional and especially network meta-analyses. It is often chosen when trials do not achieve the sample size needed to meet type 1 and type 2 estimates for a frequentist analysis. In this issue Ferreira et al report on 49 trials between 2014 and 2016 that used a Bayes analysis as the main analysis. Although many were in major journals, few met best practice standards; especially concerning is the finding that a third failed to justify the priors and if those that did, few were based on robust prior studies. The authors emphasize the need for training in the use of Bayesian methods, especially in the context of validating medical devices. The use of Bayesian guidelines should be encouraged by the editorial boards.

Forecasting cancer prevalence is important for health resource planning but is a complex task, depending on past and future cancer incidence rates, past and future survival rates among cancer patients, the past and future population size and age-sex-distribution. Novikov et al report on the improvement over traditional approaches of the PIAMOD model(Prevalence Incidence Analysis Model) that used data from 1983 to 2013, to predict the cases in 2014-2016. Selecting forecasting models based on such “validation” is recommended.

Xu et al report that they are concerned about the practice of excluding studies with no events in both arms in meta-analyses. They identified 442 systematic reviews in the Cochrane Library where at least one RCT had zero effects in both arms and then excluded these results in the meta-analysis. There are methods such as the generalised linear mixed model for including these results. They demonstrate that if these are included over 10% of meta analyses the statistical significance of P-value and width of confidence interval is changed, often substantively. These results suggest the practice of excluding this data should be stopped.
Finally, as Tunji-Ajayi et al. report whilst there is now a significant body of research asking various methodological questions about recruitment and using an array of methods to answer these questions, the same cannot be said for retention. Missing data in trials is of concern as it has the potential to introduce bias and make the trial results unreliable or in some cases unusable. This is no doubt contributed to by the fact that most consent forms highlight the right to withdraw without describing the trial consequences. They argue that it seems much more sensible to mitigate problems of missing data by designing effective approaches and strategies to maximise data collection. These authors interviewed 21 individuals [trial participants, trial surgeons and research nurses]. Retention was rarely discussed during clinical trial consultations. If retention was discussed it only made up 3% (at best) of the consultation content. This needs to change.