Meta-analyses based on summary data can provide timely, thorough, and reliable evidence: don't dismiss them yet

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To the Editor - The inclusion of fraudulent trials in evidence synthesis may lead to unreliable or biased results, and so there have been calls to use individual participant data (IPD) exclusively when conducting meta-analyses of COVID-19 studies[1]. Certainly, with multiple high-profile cases of fraudulent trials during recent years, the collection of IPD would ensure that such trials are unearthed; but the time taken to collect and process IPD precludes rapid evidence synthesis. We argue that a prospective and collaborative approach to meta-analysis of summary data can provide timely, thorough, and robust evidence synthesis, and an extra level of scrutiny of trial results.

The work by Lawrence and colleagues[1] highlights important challenges for evidence synthesis exposed by the COVID-19 pandemic. As they diligently point out, fraudulent research included in numerous meta-analyses has led to swathes of support for an anti-parasitic drug, ivermectin, in the prevention and treatment of COVID-19. Whilst the issue of fraudulent or fabricated studies is not new or specific to COVID-19, the pandemic has expedited the immediate release of trial results through press releases or pre-prints[2], with multiple high-profile retractions[3]. Increasing the visibility of these issues is important, and a call for change in the way the scientific community approaches evidence synthesis is warranted. However, as meta-analysis researchers, we disagree that all “meta-analyses based on summary data alone are inherently unreliable”[1].

Systematic reviews and meta-analyses are commonly planned retrospectively, after eligible trials have reported their results, which can introduce bias into both review and analysis methods[4]. These reviews typically use summary data extracted from trial publications or other reports, and may overlook unpublished and ongoing trials[5]. Such summary data meta-analyses have the potential to be unreliable, and we agree that they risk including fraudulent trials, exacerbating this situation further. Meta-analyses of the effects of ivermectin for COVID-19 provides a good example of how standard approaches to evidence synthesis can lead to ungrounded claims of treatment benefit.

A prospective and collaborative approach to meta-analysis (PMA) of summary data, where methods are planned before results of included trials are known[4], is a viable alternative. Working with investigators can provide access to more detailed, standardised trial results, thereby reducing reporting and other data availability biases. PMA can also improve the breadth of analyses, enabling more nuanced meta-analysis results, such as whether treatment effects vary by participant characteristics. Importantly, investigators provide results directly to the review team, giving additional

scrutiny and less room for fabrication of data. In a sense, collaborative PMA of summary data brings advantages akin to those associated with IPD meta-analysis[6]. One such PMA approach, FAME[4], also involves prospectively monitoring how evidence from trials is accumulating, in order to anticipate the earliest opportunity for a potentially definitive meta-analysis, potentially months or years ahead of all study results being available. Hence, PMA of summary data can provide more timely and less biased evaluations of treatment effects compared to standard approaches[4].

An example is our recent collaborative PMA investigating the effects of interleukin-6 antagonists for patients hospitalised with COVID-19[7]. Due to the dynamic nature of the pandemic, and the need to align with WHO guideline publication[8], timely and robust synthesis of the accumulating trial results was vital. Firstly, representatives from all eligible trials were invited to weekly meetings to develop the protocol and analytical approaches prior to trial results being known. Then, during a set period, and again prior to most trials being published, we collected highly detailed summary data, employing rigorous procedures for cross-checking of baseline and outcome information with available trial reports. This allowed us to query and rectify any discrepancies with the trialists. Ultimately, we obtained results for 27/29 trials, relating to over 95% of participants randomised (at that time). As only 9 of the 27 trials had reported results at the time of the PMA publication[7], an equivalent meta-analysis based on published summary data would have been very limited, or delayed until more trials had reported results. The FAME approach to PMA[4] has also been used to provide timely evaluations of the effects of treatments for prostate cancer (see e.g., [9]).

Lawrence and colleagues recommend that “meta-analysts who study interventions for COVID-19 should request and personally review IPD in all cases”[1]. Whilst we agree that access to IPD from COVID-19 related trials is the ideal, even if trialists were to “immediately follow best-practice guidelines and upload anonymized IPD”[1] after publishing trial results, issues remain. Accessing IPD from different data sharing platforms, with variable modes of access can be a slow process, and thereafter, the datasets can be limited or heavily redacted (i.e., “careful anonymization”[1]) in order to protect participant privacy[10]. Obtaining IPD direct from investigators can also be lengthy, due to the increasing complexity of data sharing agreements and prolonged negotiations between legal teams[10], and the time taken to prepare IPD. Also, once shared, standardising and checking IPD requires substantial expertise and resource within the review team[6]. Thus, whilst the benefits of IPD meta-analyses are considerable, sharing of IPD is not yet widespread or streamlined enough to allow timely

evidence synthesis, which is paramount in a context of a global pandemic. In fact, if we had requested IPD for the PMA of interleukin-6 antagonists in COVID-19, we suspect that by the time this article was published (December 2021), we would still not have collected sufficient trial data – a delay that may have led to countless avoidable deaths.

There is a distinct possibility that a "study for which authors are not able or not willing to provide suitably anonymised IPD" could "be considered at high risk of bias … or excluded"[1]. However, there may be legitimate reasons for non-provision of IPD; and excluding evidence in this way, or labelling it as high risk of bias, may itself lead to increased bias or a lack of generalisability. For example, if only trials carried out in high-income settings with sufficient infrastructure for immediate data sharing were included, valuable evidence from lower-income settings might be disregarded. By contrast, in a prospective and collaborative approach to evidence synthesis, a combination of systematic data verification processes and close interactions with trialists[4] vastly reduces the possibility of including fraudulent data and reduces the burden of data preparation for trial teams.

In conclusion, we commend Lawrence and colleagues for their important work identifying questionable and fraudulent clinical trial data, and we also call for change. However, recognising that access to substantial and standardised IPD is still some way off, in the interim, we believe that adopting a prospective and collaborative approach to meta-analyses of summary data can provide timely, thorough, and reliable evidence.

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Author contributions

PJG and ER conceived the idea of the manuscript and wrote the first draft. All authors commented on draft versions of the manuscript for important intellectual content and approved the final version.

Competing interests

The authors declare no competing interests.

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