

# When to include clinical study reports and regulatory documents in systematic reviews

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## Abstract

Reporting bias is a major threat to the validity and credibility of systematic reviews. This article outlines the rationale for accessing clinical study reports and other regulatory documents (regulatory data) as a means of addressing reporting bias and identifies factors that may help decide whether (or not) to include regulatory data in systematic reviews. The article also describes the origins and current state of regulatory data access and summarises a survey of current systematic reviewers' practices in considering regulatory data for inclusion in systematic reviews. How to access and extract regulatory data is not addressed. Organisations and other stakeholders such as Cochrane should encourage the use of data from clinical study reports as an important source of data in reviews of pharmaceutical interventions particularly when the intervention in question is of high importance and the risk of reporting bias is great.

## Introduction

There has been a gradual realisation that sources of evidence historically considered to be reliable (such as peer-reviewed literature) are affected by reporting bias. Reporting bias generally refers to selective reporting of research depending on the nature and direction of research results. Reporting bias includes publication bias<sup>1-3</sup> and outcome reporting bias,<sup>1-5</sup> among many others.<sup>6</sup>

Systematic reviews of randomised controlled trials play an important role in health decision-making. Most of these analyse data extracted from journal publications despite there being good evidence that reporting bias is widespread. As trials with unfavourable results are less likely to be published and unfavourable outcomes less likely to be reported within publications, the evidence base is often incomplete and skewed towards a positive spin. Systematic reviews that use only published data perpetuate such bias and possibly compound the issue through the credibility afforded by the systematic review, particularly if carried out by a trusted source such as Cochrane.

In a survey of 348 systematic reviews published in 2014, around three-quarters relied solely on data published in peer-reviewed journals.<sup>7</sup> Of those that accessed other sources, data from trials registries (such as ClinicalTrials.gov), conference

proceedings or contacting authors were the most used. No reviews reported using or attempting to obtain regulatory information even though the majority of the reviews evaluated drug interventions.<sup>7</sup> A survey of 2184 Cochrane authors also found that contacting 'trialists/investigators' was one of the most common methods for accessing unpublished data and that data from manufacturers or from regulatory agencies were rarely obtained.<sup>8</sup>

Clinical study reports (CSRs) are documents prepared and submitted to regulators to obtain a marketing licence for a pharmaceutical. They represent the most complete account of the planning, execution and results of such trials. CSRs contain some of the same information as journal papers (ie, rationale, objectives, methods, results, discussion/conclusion), but are substantially more detailed with numerous large tables and figures, and datasets not constrained by page limits. A CSR for a single trial may be hundreds, thousands or even tens of thousands of pages in length but they are generally relatively straightforward to navigate owing to their standardised and structured format. CSRs generally contain, as appendices, important study documents including the study protocol and any amendments, statistical analysis plan and any amendments, blank case report forms, patient information sheet, blank informed consent forms and individual patient listings.<sup>9</sup>

There are indications that CSRs may be incomplete, and in some cases, may be internally inconsistent between different sections of the same CSR.<sup>10</sup> However, when comparing different data sources for the same trial, CSRs provide the greatest breadth and depth of information compared with journal articles, trial register data and grey literature. Aggregate data on subpopulations are often found in CSRs and can provide a source of further analysis. Such a wealth of information gives a fuller and more reliable picture of a trial's strengths and weaknesses, as well as a more reliable assessment of the benefits and harms of the studied interventions.

CSRs and other regulatory documents generally only exist for drugs and biologics. Non-pharmaceutical interventions (such as implantable devices, surgery, rehabilitation, behavioural (psychosocial) interventions and diagnostics) are responsible for a large part of healthcare expenditure and regulatory activity, but they do not generally produce CSRs. Transparency has generally



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been increasing in this area, although at a slower pace in the field of devices. Publicly funded trials, even of drugs and biologics, do not usually produce internationally standardised documentation, similar to a CSR.

In late 2010, the European Medicines Agency (EMA) began releasing CSRs of drugs and biologics on request under its Policy 0043.<sup>11</sup> In October 2016, the EMA began to release CSRs prospectively under Policy 0070 (<https://clinicaldata.ema.europa.eu>).<sup>11 12</sup> This policy applies only to documents received after 1 January 2015. Documents available from the EMA under Policy 0070 normally include the clinical overview, clinical summary and CSRs of individual trials.<sup>12</sup> In 2017, Health Canada published a report announcing an initiative to publicly release clinical information concerning drugs and devices under an eventual EMA Policy 0070-like mechanism.<sup>13</sup> In March 2018, the Food and Drug Administration (FDA) publicly released a CSR in a pilot programme that will eventually include nine new drug approvals.<sup>14</sup> Some manufacturers are making CSRs available to reviewers (<https://restoringtrials.org/insitutions-offering-data-access/>). GlaxoSmithKline (GSK), for example, allows CSRs to be freely downloaded from its clinical study register, although the documents may be heavily redacted and incomplete. Other manufacturers are making CSRs available to researchers on request and after review and approval of their project proposal.

### Rationale for the consideration of regulatory documents (including CSRs) as sources of data for inclusion in systematic reviews

Reporting biases can generally only be detected when two or more reports of the same trial are compared, for example, peer-reviewed publications compared with relevant regulatory documents. In addition to reporting bias, lack of transparency and lack of detail in journal publications may prevent or hinder detailed analyses of data which could be relevant to specific subpopulations potentially benefiting from or being harmed by the intervention.<sup>15</sup> This situation is likely to be the consequence of compressing thousands of pages of text and tables into the historically restricted confines of a printed journal article.<sup>15</sup>

Table 1 contains a selected and illustrative list of studies that have compared different sources of data for the same trial, such as publication versus CSR or publication versus trial register entries. Although this is not an exhaustive list of all such studies, it covers >50 different interventions and offers insights into the ways in which reporting bias affects the biomedical literature.

The studies in table 1 strongly suggest that discrepancies in the reporting of trials across different sources of data are common. There are, however, limitations when interpreting discrepancies. First, different types of trial documents may have very different objectives. CSRs, for example, inform regulators and, by law, provide a comprehensive record of a study. Trials registers, in contrast, are primarily a visible collection of trial data, yet their reporting can be either absent or incomplete. Under some circumstances (such as for non-phase I trials of FDA-regulated drugs, devices or biologics), reporting of trials within ClinicalTrials.Gov, including the submission of results, is compulsory.<sup>16</sup> There are also requirements for clinical trials funded by the US National Institutes of Health such as registration and reporting of results on ClinicalTrials.Gov,<sup>17</sup> but these requirements are not always adhered to nor adequately policed.<sup>18</sup>

The generalisability of each finding of the studies in table 1 to the larger population of trials or topic areas that exist is debatable, and it is unclear whether reporting biases are lessening over

time. Some journals have taken steps to limit the bias introduced by the current format of trial reporting, by requiring adherence to Consolidated Standards of Reporting Trials,<sup>19</sup> by publishing the trial protocol, statistical analysis plan or supplementary data as an online appendix or by requiring data sharing as a condition of publication.<sup>20-22</sup> As it is impossible to squeeze thousands of pages worth of information into a 10-page publication and the resulting information selection is based on unknown criteria, the authors of trial publications can, where these exist, provide links to the relevant CSR and other summary data.

We are currently aware of four systematic reviews (a Cochrane review of neuraminidase inhibitors,<sup>23</sup> twin reviews of recombinant human bone morphogenetic protein 2 (rhBMP-2)<sup>24 25</sup> and a review of reboxetine<sup>26</sup>) allowing an assessment of the contribution of regulatory data compared with the same trial data from published journal articles.

In the case of rhBMP-2, both CSRs and individual participant data (supplied separately by the manufacturer via the Yale Open Data Access Project) were included in the twin reviews,<sup>24 25</sup> while the Cochrane review of neuraminidase inhibitors and the review of reboxetine were based on CSRs.<sup>23 26</sup> In all cases, the conclusions were that important aspects of the reviews were changed with access to the more complete data available in the CSRs. Access to the CSRs also provided a deeper understanding of the strengths and limitations of the trial evidence. In the case of the review of reboxetine, the inclusion of CSR data changed the conclusions of the review and allowed quantification of the exaggeration in favour of the effects of reboxetine compared with placebo and other SSRIs.<sup>26</sup> The Cochrane review of neuraminidase inhibitors for influenza also found FDA drug-approval packages (medical and statistical officer reviews) to be an important source of data and detail.

As systematic reviews are considered as a gold standard of reliable research synthesis, we need to pay attention to the issue of reporting bias and to address whether, and how to decide when, accessing regulatory data, including CSRs, might offer a solution. The approach, however, is new and unfamiliar to most systematic reviewers and at the time of writing, regulatory data are not always immediately available. When available, using such documents can involve reviewing very large quantities of information, which may be time-consuming and resource intensive. Alternatively, it may be less time consuming than trying to assemble complete study data from information that is fragmented across several publications and unpublished sources such as trials registers. Thus, a framework to help identify where using data from regulatory documents is likely to matter most and prioritising those reviews which should adopt such an approach, will be helpful for groups grappling with how to respond to the increasing availability of these new sources of information.

### Current practice

To raise awareness of the above issues and to assess the level of familiarity with and experiences of using data from CSRs and other regulatory documents within systematic reviews, we surveyed Cochrane and non-Cochrane authors to gauge how many had considered using regulatory data and how many had actually included such data in their reviews. There were 160 respondents with results mostly showing a lack of familiarity with regulatory sources of data, barriers to access and lack of resources to do so. The main rationale for authors seeking regulatory data, however, was minimisation of bias.<sup>27</sup>

**Table 1** Examples of studies comparing different sources of data for the same trials

Reference	Type of study	Intervention comparisons	Source comparison	Take home message
Chan, <i>et al</i> <sup>22</sup>	Cohort study of 102 RCTs registered with scientific-ethical committees in Denmark, 1994–1995.	75% drug trials, 12% counselling/lifestyle trials, 11% surgery/procedure, 2% equipment	Protocols vs publications	'62% of trials had at least one primary outcome that was changed, introduced or omitted'. In 40 of 82 trials, prespecified primary outcomes were not presented as such in the journal publication. In 11 trials, outcomes not prespecified were reported as the 'primary outcome' in the publication. 'The reporting of trial outcomes is frequently incomplete and biased and inconsistent with protocols'.
Turner, <i>et al</i> <sup>33</sup>	Review of 74 RCTs for 12 antidepressants reviewed by the FDA, and their corresponding publication (or lack thereof) in the literature	12 antidepressants vs placebo	Medical officer reviews vs publications	Non-publication and selective reporting occurred frequently, and can change the apparent risk-benefit assessment of drugs. Publicly available medical officer reports are a valuable source of unbiased information about clinical trial design and results.
Eyding, <i>et al</i> <sup>26</sup>	Systematic review of 13 trials. 76% of patient data unpublished: 86% (1946 of 2256 patients) for roboxetine vs placebo and 67% (1760 of 2641 patients) for roboxetine vs SSRIs	Reboxetine for depression vs placebo or vs other SSRIs included in IQWiG HTA report	CSRs vs publications	The addition of unpublished data changed the direction and conclusions of the efficacy and harms analyses. Published data vs full dataset overestimate benefits by 99%–115% vs placebo and 19%–23% vs other SSRIs.
Jefferson, <i>et al</i> <sup>34</sup>	Cochrane review of 25 trials (15 oseltamivir, 60% unpublished, those published had been ghostwritten and corresponding 'authors' had no access to study data)	Neuraminidase inhibitors for influenza vs placebo	CSRs vs publications	Lack of detail in publication and unexplained discrepancies when compared with CSRs led the authors to change methods compared with previous version of the review and include only regulatory data, significantly changing the conclusions of the review.
Coyne, <i>et al</i> <sup>35</sup>	Review of the NHT run in the 1990s on 1265 haemodialysis patients with cardiac disease	Epoetin lower (9–11 g/dL) vs higher (13–15 g/dL) doses to increase haematocrit to reduce mortality and improve survival and QoL	CSR vs publication	'Disclosure of these (CSR) results in the 1998 publication or access to the FDA filed report on the NHT in the late 1990s would likely have led to earlier concerns about epoetin safety and greater doubts about its benefits'.
Wieseler, <i>et al</i> <sup>15</sup>	Systematic review of 29 studies included in 16 HTA reports prepared by IQWiG during 2006–2011	16 different pharmaceuticals mainly for depression and type I and II diabetes	CSRs vs publications vs register entries	CSR consistently reported more information than registers or journal publications.
Wieseler, <i>et al</i> <sup>36</sup>	Systematic review of 101 trials with full CSR available included in 16 HTA reports prepared by IQWiG. The study population is the same as Wieseler 2012 but in this study the authors quantified information gain for patient-relevant outcomes graded from 1 to 4	16 different pharmaceuticals mainly for depression, asthma and type I and II diabetes	CSRs vs publications vs register entries (unclear which trials have been registered where. Also some trials were conducted in the late 1980s)	CSRs reported complete information on 78%–100% of benefit outcomes vs 20%–53% in combined publicly available sources. The authors estimated 13% publication bias. CSRs reported complete information on 84%–92% of harm outcomes vs 27% to 72% of combined publicly available sources. 15% NR by publicly available sources for both general harms and withdrawals due to possible harms.
Rodgers, <i>et al</i> <sup>24</sup> and Fu, <i>et al</i> <sup>25</sup>	Systematic review of 13 trials and 4 single-arm studies (10 and 1 journal published)	Recombinant human bone morphogenetic protein 2 for spinal fusion vs iliac crest bone graft	IPD vs CSRs vs journal publications	Wealth of extra detail from CSRs provided by manufacturer. Fu <i>et al</i> conclude that 'Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication and under-reporting'.
Doshi and Jefferson <sup>9</sup>	Descriptive review of 78 CSRs	14 different pharmaceuticals and biologics	CSRs vs publications (comparison in size)	The ratio of CSR pages to publication pages for available full CSRs with a corresponding publication ('compression factor') ranged from 379 to 8805.

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Table 1 Continued

Reference	Type of study	Intervention comparisons	Source comparison	Take home message
Vedula <i>et al</i> <sup>31</sup>	Review of transparency and accuracy of reporting of the numbers of participants, description of types of analyses and criteria for including participants in the analysis in 11 published trials	Gabapentin vs placebo for four off-label uses (migraine prophylaxis, treatment of bipolar disorders, neuropathic pain and nociceptive pain)	CSRs accessed from litigation with their published counterparts (21 trials identified, 11 assessed, 8 trials excluded because unpublished, 1 not randomised, 1 no CSR available)	Probably biggest discrepancies occurred between protocol and publication. The authors conclude "we found that the trial publication was not a transparent, or accurate (presuming that the research report truly describes the facts), record for the numbers of participants randomized and analyzed for efficacy".
Maund, <i>et al</i> <sup>10</sup>	Review of nine trials in 1999–2001 (seven journal published)	Duloxetine vs placebo	CSR vs publications vs register entries; 1/9 R1 and 9/9 R2	7 S published 2 NS unpublished 1 NS published as S after post hoc analysis not mentioned in the paper. Harms 50% and 25% participant reporting inconsistency in two trials, one death in active arm in unpublished trial; lack of clarity on phase of deaths Suicide NR2% in register reports. SAE three articles failed to report, register entries unclear.
Le Noury, <i>et al</i> <sup>29</sup>	RIAT publication, restoring Glaxo SmithKline's trial 329 run in the 1990s and journal published in 2001	Paroxetine vs placebo and imipramine vs placebo	IPD with CRFs for 34% (93/275) participants and CSR vs publication	Paroxetine was reported as safe and effective in company-sponsored ghostwritten publications. Access to CSR data led the authors to conclude that the drug was no more effective than placebo and was toxic in adolescents. The authors identified four outcomes cited in the protocol but not reported in the CSR and publication.
Köhler, <i>et al</i> <sup>37</sup>	Systematic review of 15 dossier assessments by AMNOG submitted to IQWiG between 2011 and 2015. The authors assessed completeness of reporting in each document category	15 different drugs including anti-HIV and oncology	AMNOG documents: IQWiG dossier assessments and publicly available modules of company dossiers vs non-AMNOG documents: EPARS vs journal publications vs register entries available at market entry date point	'At the time of market entry of a new drug, a substantial amount of information needed for assessment of the corresponding clinical studies and for understanding of the drug's benefits and harms is missing in publicly available European public assessment reports, journal publications and registry reports (non-AMNOG documents)'. Dilution due to different coding of similar events (eg, 'nervousness', 'anxiety' and 'agitation'). Long-term harms not reported in publications. One suicide in active arm NR in publication; one death in active arm from CV causes identified from FDA drug-approval package not reported in either CSR or publication. Two suicide attempts not reported in active arm in publication and S dose-response with metabolic syndrome NR in a journal publication.
Beaumont, <i>et al</i> <sup>28</sup>	Cochrane review update of 4 CSR (three journals published in four publications)	Olanzapine vs placebo	CSRs vs publications	'Published literature gives the impression that vortioxetine is efficacious, safe and well tolerated, when in fact the data were not collected or analysed in a way that provides sound empirical support for this conclusion'. The authors note extensive sponsorship ties of 8/10 authors of published studies and comment on regulatory practice which focuses on an in-depth analysis of 'positive' trials rather than the whole evidence base.
Cosgrove, <i>et al</i> <sup>39</sup>	Review of data considered by regulators for registration vs other data available to them vs publications and comparison of regulatory vs SR process	Vortioxetine vs placebo (four RCTs) or active comparator (six studies) for depression	FDA drug-approval package (based on 10 short-term RCTs) and EMA EPAR (12 RCTs) vs publications. At least three studies were unpublished (38% of randomised participants). All unpublished studies showed no difference with comparator	

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Table 1 Continued

Reference	Type of study	Intervention comparisons	Source comparison	Take home message
Hodkinson <i>et al</i> <sup>40</sup>	Exploratory review to assess the reporting of harms in Orlistat trials	Orlistat vs placebo	5 Roche CSRs vs five journal publications	Journal publications provided insufficient information on harms outcomes compared with CSRs. Serious adverse events, were not reported or mentioned in the journal publications. Overall, CSRs provide extensive information about harms for study methods, including design, conduct, and analysis of the trial.
Jureidini <i>et al</i> <sup>40</sup>	Litigation documents vs publication	Citalopram vs placebo	Comparison of 750 documents from the Celexa and Lexapro Marketing and Sales Practices Litigation and publication	'The published article contained efficacy and safety data inconsistent with the protocol criteria. Procedural deviations went unreported imparting statistical significance to the primary outcome, and an implausible effect size was claimed; positive post hoc measures were introduced and negative secondary outcomes were not reported; and adverse events were misleadingly analysed. Manuscript drafts were prepared by company employees and outside ghostwriters with academic researchers solicited as 'authors'.
Schroll <i>et al</i> <sup>41</sup>	Descriptive review of seven RCTs to assess the reporting of AEs	Orlistat vs placebo	7 CSRs from Roche vs protocols vs journal publications	'Study identified important disparities in the reporting of adverse events between protocols, clinical study reports and published papers. Reports of the trials systematically understated adverse events. Based on the study findings, systematic reviews of drugs might be improved by including protocols and CSRs in addition to published articles'.
Mayo-Wilson, <i>et al</i> <sup>42</sup>	Impact assessment to determine whether disagreements among multiple data sources of the same trials affected meta-analytic effect estimates, statistical significance and interpretation	Gabapentin and quetiapine	21 gabapentin RCTs (74 reports, 6 IPDs) and 7 quetiapine RCTs (50 reports, 1 IPD)	'Disagreements across data sources affect the effect size, statistical significance and interpretation of trials and meta-analyses'.

AMNOG, Arzneimittelmarktneuordnungsgesetz (Germany's Act on reform of the market for medicinal products); CRF, case report forms; CSR, clinical study reports; CV, cardiovascular; EMA, European Medicines Agency; FDA, Food and Drug Administration; IQWiG, Institute for Quality and Efficiency in Healthcare, Germany; NA, not applicable; NHT, Normal Hematocrit Trial; NK, not known; NR, not reported (by the authors); NS, statistically not significantly different; QoL, quality of life; R1, registration 1 (in public register); R2, registration 2 (in manufacturer register); S, statistically significantly different; SAE, serious adverse events; SSR1, Selective serotonin reuptake inhibitors; IPD, Individual Patient Data; EPAR, European public assessment reports.

**Table 2** Criteria for assessing whether to include regulatory data of a drug or biologic in a Cochrane review (not in order of priority)

Criteria	Description of criteria
1	Monetary cost of the intervention on the healthcare budget (ie, considering both the price of a course and the number of people in the population that are being—or will be treated)
2	Burden of disease of the indication this product is meant to treat/prevent
3	Number of people using or likely to use the product
4	Product new to the market
5	Product from a new drug class or has a new mechanism of action
6	Has important interactions with other drugs (eg, drug-drug interactions)
7	High proportion of randomised controlled trials evaluating this product are industry funded
8	Prominent claims of safety and/or efficacy advantage of this product over currently available treatments
9	High degree of media attention surrounding this product
10	High proportion of trials of this product are unpublished
11	Postmarketing surveillance has identified safety concerns
12	Important or standard outcome measures (also known as 'end points') have not been published
13	Concerns regarding a lack of published data on potential harms of the product
14	Marketing authorisation based on surrogate outcomes (rather than clinical outcomes)
15	When protocol(s) are publicly available
16	When statistical analysis plan(s) publicly available
17	Known errors or concerns about trial publications of this product
18	Important discrepancies between the journal publication and the trial registry entry

### The circumstances under which CSRs and/or other regulatory documents should be considered for inclusion in systematic reviews

We concluded from the survey findings that the systematic review community is ready to consider using data from CSRs and other regulatory documents within systematic reviews. However, owing to the additional time and resource requirements that may be required to use these data sources, use should be focused on review topics where the data are needed most. We were unable to identify any research on the topic of how to decide whether to incorporate CSRs and other regulatory documents into systematic reviews, that is, a rule for determining which reviews would most benefit from the inclusion of such data.

We therefore created an initial list of reasons (or triggers) for seeking and using such data through discussion among our author group. Our list was a product of our opinion and experience. We then carried out a follow-up targeted survey in which we asked respondents to rate the importance of each criterion in our list. This survey was sent to the 21 (of 27) systematic review authors who had used, requested or considered using regulatory data in their review and had agreed to participate in a follow-up survey. Fourteen of 21 (66%) provided a response.<sup>27</sup>

Table 2 shows our final list of criteria (after addressing review authors feedback) for assessing whether to include regulatory data of a drug or biologic in a systematic review. The variables are self-explanatory, reflecting either known or suspected bias in published results or the potential for greatest impact in terms of

public health, for example, what are the human costs of acting on biased estimates of effectiveness or harm?

There is no proposed scoring or algorithm for combining criteria to identify priority topics or topic areas. The relative importance of criteria listed in table 2 will depend very much on context, and prioritisation is inevitably a somewhat subjective process. The list is not meant to be onerous. Systematic and formal evaluation of each of the 18 criteria is not required. We suggest reviewers instead focus on the items in the list that are most relevant to their research area of interest. The list is subject to revision and may even become obsolete over time as we learn more about the added value of using CSRs for systematic review, and if the ease of accessing CSRs becomes less problematic and burdensome in the future.

### Limitations when using CSRs

There are potential limitations when using CSRs as the data source for systematic reviews. First, CSRs are written for regulators and may contain sensitive information that needs to be redacted. Redactions may delay the time it takes to obtain CSRs and the applied redactions may be extensive, masking important information for inclusion in systematic reviews. Second, although data on adverse events are required to be included in CSRs at the individual participant level, these data may not be fully provided to regulators (although regulators can request these data) or to systematic reviewers who request CSRs directly from manufacturers. For example, completed case report forms are not always held by the EMA and serious adverse event narratives are redacted from CSRs on GSK's clinical trial register. Third, complete CSRs may not be held by the EMA, and some CSRs may not be held at all, although a complete list of all clinical trials conducted by a manufacturer does form part of the regulatory submission. Fourth, a CSR is a compiled report of a study and not the study's underlying raw data. Despite all their strengths as a rich source of data, some investigators have identified deficiencies in the reporting in CSRs, specifically the completeness and consistency of reporting of adverse events.<sup>28–31</sup>

### Conclusion

Regulatory documents are a complex and underused source of highly detailed data that could be included in systematic reviews. Although the steps to identify and extract and analyse data are broadly the same as for other sources of data, the resource implications of their use may not be. The results of our surveys and our own experience indicate that the use of regulatory documents should be considered, especially when the intervention in question is of high importance and when risk of reporting bias is great.

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Conference with *The BMJ* and the Overdiagnosis Conference with some international partners, which are based on a non-profit making model. He is Editor-in-Chief of BMJ Evidence-Based Medicine. LAS is an employee of the University of York. She previously received a research grant from YODA for her research team to independently analyse individual participant data and data from CSRs supplied by Medtronic.

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