RESEARCH LETTER

Sharing of Data From Industry-Funded Registered Clinical Trials

Access to individual patient-level data from clinical trials could be an important step forward in clinical research.1-4 Some pharmaceutical companies have committed to share such data. The largest repository is the Clinical Study Data Request (CSDR) website, wherein companies voluntarily list studies for which data can be requested.5 To evaluate the completeness of data sharing on CSDR, we investigated the proportion of randomized clinical trials (RCTs) registered at ClinicalTrials.gov that were listed at CSDR.

Methods | All drugs other than vaccines listed on CSDR by all sponsors actively involved in data sharing, defined as listing at least 100 studies in June 2014, were studied. One company listing less than 100 studies and 3 companies listing no studies were excluded.

ClinicalTrials.gov was searched by using the sponsor name in the “search field” on January 15, 2016. Studies were selected that were “completed” or “terminated” with a completion date of at least 18 months before the search date (to allow time for studies to be analyzed, published, and listed on CSDR); were recorded as “interventional” and “randomized”; and reported the drug name or any synonym (identified on the Drug Information Portal of the US National Library of Medicine) in the “intervention” field and the appropriate sponsor in the “sponsors” field. Single-group designs were excluded.

All available data were downloaded, including trial registry identification number for all studies listed at CSDR for the sponsors, and the ClinicalTrials.gov and CSDR databases were merged by trial registry number. All sponsors registered trials only at ClinicalTrials.gov.

Results | For the 61 targeted drugs from 4 sponsors (drugs: Roche, 13; Lilly, 3; Boehringer Ingelheim, 5; GlaxoSmithKline [GSK], 40), 966 RCTs (462751 participants) registered at ClinicalTrials.gov were identified; 512 RCTs (53%) (342271 participants; ie, 74% of the participants involved in these studies) were listed at CSDR. The availability of each document at CSDR (ie, raw data set, annotated case report form, protocol, analysis-ready data set, reporting and analysis plan, clinical study report) varied from 83% to 99%; records for 385 RCTs (40%) reported that all documents were available. The proportion of registered trials listed on CSDR varied from 33% for Roche to 66% for GSK and trials with all information available from 24% for Boehringer Ingelheim to 58% for GSK (Table).

Also, 440 RCTs (175177 participants) listed at CSDR but not registered at ClinicalTrials.gov were identified. These studies were sponsored by Roche (34 studies; 18420 participants), Lilly (2 studies; 512 participants), and GSK (404 studies; 156245 participants). For 359 of these RCTs (82%), the study start date recorded at CSDR was before 2005 (when registration was first required).

Discussion | Despite a delay of 18 months since the completion of drug trials by the company sponsor, only 53% of the RCTs from the 4 sponsors registered at ClinicalTrials.gov were listed at CSDR, with differences between sponsors. Data were available for a large number of participants, but an equally large amount of data was not available.

Limitations in this study need to be acknowledged. We did not evaluate whether data were actually made available. For this, a research proposal should be submitted, reviewed, and approved by an independent review panel, a data-sharing agreement signed, and the data obtained through the website. However, the number of submitted proposals is low and thus does not give a complete picture of the willingness of the companies to share data.6 Furthermore, all drugs manufactured by the sponsor and the results of trials were not considered, and therefore selective listing on the website cannot be excluded. Only studies that were listed at CSDR were considered, but data from studies that are not listed can be re-

Table. Sharing of Data by 4 Pharmaceutical Companies*

<table>
<thead>
<tr>
<th>Pharmaceutical Company</th>
<th>Roche (13 Drugs)</th>
<th>Lilly (3 Drugs)</th>
<th>Boehringer Ingelheim (5 Drugs)</th>
<th>GlaxoSmithKline (40 Drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs registered in ClinicalTrials.gov, No.</td>
<td>120</td>
<td>110</td>
<td>300</td>
<td>436</td>
</tr>
<tr>
<td>Participants, No.</td>
<td>54907</td>
<td>42474</td>
<td>177024</td>
<td>188346</td>
</tr>
<tr>
<td>RCTs registered and listed at CSDR, No. (%)</td>
<td>40 (33.3)</td>
<td>44 (40.0)</td>
<td>139 (46.3)</td>
<td>289 (66.2)</td>
</tr>
<tr>
<td>Participants, No. (%)</td>
<td>29878 (54.4)</td>
<td>20055 (47.2)</td>
<td>141639 (80.0)</td>
<td>150699 (80.0)</td>
</tr>
<tr>
<td>RCTs registered and listed at CSDR with all datasets and documents available, No. (%)</td>
<td>27 (24.5)</td>
<td>31 (27.2)</td>
<td>73 (24.3)</td>
<td>254 (58.3)</td>
</tr>
<tr>
<td>Participants, No. (%)</td>
<td>20870 (38.0)</td>
<td>13915 (32.8)</td>
<td>77250 (43.6)</td>
<td>120602 (64.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CSDR, Clinical Study Data Request; RCT, randomized clinical trial.

* For the 4 drug company sponsors and the 61 drugs listed, number of completed or terminated RCTs with a completion date of at least 18 months before the search that were registered at ClinicalTrials.gov and listed at CSDR.

b Raw dataset, annotated case report form, dataset specifications, protocol with any amendments, analysis-ready dataset, reporting and analysis plan, clinical study report.
Letters

The sponsor policy related to data sharing was not taken into account. Some sponsors agree to share only selected studies. However, the purpose of the study was to evaluate the amount of available data, regardless of whether a trial was not listed because of company policy or for another reason. In addition, only 1 repository was evaluated.

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Author Contributions: Drs Boutron and Baron had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Boutron, Dechartres, Ravaud.

Acquisition, analysis, or interpretation of data: Boutron, Dechartres, Baron, Li.

Drafting of the manuscript: Boutron.

Critical revision of the manuscript for important intellectual content: Dechartres, Baron, Li, Ravaud.

Statistical analysis: Baron.

Obtained funding: Ravaud.

Administrative, technical, or material support: Li.

Study supervision: Ravaud.

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Prenatal Vitamin D and Offspring Wheezing

To the Editor Dr Litonjua and colleagues reported the results of a randomized clinical trial investigating the effect of prenatal supplementation with vitamin D on asthma and wheezing in young offspring.1 The study provides an example of the problems with so-called “statistical significance” and the interpretation of P values with reference to an arbitrary threshold. The authors estimated that high-dose vitamin D given in pregnancy was associated with a reduced risk of the coprimary outcome of recurrent wheeze (hazard ratio [HR], 0.8 [95% CI, 0.6-1.0]), with an associated P value of .051.

The conclusion of the article emphasized that this result “did not meet statistical significance” (the P value was >.05). The implication is that, had the P value been just .002 lower (ie, P = .049), the authors might have presented their final conclusion with a different emphasis, noting “statistical significance,” and the trial results might have been interpreted more positively, with a conclusion that prenatal supplementation with vitamin D had a beneficial effect.

Yet the statistical meanings of both P = .051 and P = .049 are similar: if the null hypothesis were true (no real treatment effect), and the trial were repeated many times, a difference between the treatment groups at least as large as observed would be expected about once every 20 times due to chance variation alone.

The problems with arbitrarily dichotomizing results into statistically significant or nonsignificant have been noted for many years, and major journals now expect authors to present CIs and exact P values, offsetting some of the problems with this approach.2-4 Litonjua and colleagues rightly pointed out that their study may have lacked power and that the CIs did not preclude a clinically important protective effect of supplementation. Despite this, the focus on a binary notion of statistical significance still persists, and we think that it colors the interpretation of results in an overly simplistic way. We suggest that such terminology be avoided, with P values interpreted as a continuous measure of strength of evidence against the null hypothesis.

With this approach, this trial might have been interpreted as providing some, but not strong, evidence of a protective effect of supplementation during pregnancy on recurrent wheeze in offspring, and the range of possible clinically relevant benefits might have been better emphasized in key parts of the article. This interpretation would be similar with P = .051 or P = .049.

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