Retrieval of individual patient data depended on study characteristics: a randomized controlled trial: Protocol and Analysis Plan (NCT02569411)

Study Protocol

Study Design

Our study will be a pragmatic (or effectiveness) RCT comparing the financial incentive (i.e., intervention) against the standard process of contacting authors to obtain IPD (i.e., control). The participants will be the authors of RCTs included in our two systematic reviews for type 1 diabetes mellitus and for Alzheimer's dementia, and we will randomize these authors in two groups to request their IPD (see Control and intervention groups section).

We updated the literature search for our published systematic reviews for type 1 diabetes mellitus from January 2013 to June 2015, and for Alzheimer's dementia from January 2015 to May 2015. Briefly, we used the terms from our previous reviews to search MEDLINE, Cochrane Central Register of Controlled Trials, and EMBASE. Gray literature (i.e., difficult to locate and unpublished studies) was searched via trial registry websites, relevant society/association websites and conference abstracts. Reference lists of included studies and relevant reviews were also scanned. We used the Synthesi.SR tool to screen citations and full-text articles. To ensure reliability, we conducted a training exercise before screening titles and abstracts using our eligibility criteria. When high agreement (greater than 90 %) was observed, two team members screened each title and abstract for inclusion, independently (level 1). After pilot-testing, the same reviewers independently screened the full text of potentially relevant articles to determine inclusion (level 2). Conflicts were resolved by team discussion.

In the type 1 diabetes study, we included trials studying adults (aged 18 years or older) with type 1 diabetes and comparing long-acting basal insulin analogue preparations with other long- or intermediate-acting insulin. We included RCTs of any duration reporting glycosylated hemoglobin and severe hypoglycemia outcomes. Our updated search identified 179 citations with 15 potentially eligible studies, whereas 4 RCTs met the inclusion criteria. In total, 30 RCTs were included in the updated type 1 diabetes study, where 30 studies evaluated glycosylated hemoglobin and 24 assessed severe hypoglycemia.

In the Alzheimer's dementia systematic review, we included adults (aged 18 years or older) with Alzheimer's dementia diagnosed using various criteria (e.g., Diagnostic and Statistical Manual of Mental Disorders, Nursing Minimum Data Set criteria). Again, we focused on RCTs of any duration and we included the Mini-mental State Examination and overall serious adverse events outcomes. Our updated search identified 73 citations with 12 potentially eligible studies, whereas 1 RCT met the inclusion

criteria. Overall, 108 RCTs were eligible for the updated Alzheimer's dementia review, where 74 studies provided data on the Mini-mental State Examination outcome and 64 provided data on the serious adverse events outcome.

Participant recruitment

Corresponding authors of RCTs included in our previous and updated systematic reviews will be eligible for inclusion. We will attempt to obtain IPD from all eligible studies by contacting the corresponding author of each included RCT. In cases where the identified studies do not report authors' email addresses or include non-working email addresses, we will search authors' publications, PubMed, and profiles that are publicly available, including Research Gate and Google Scholar, to find contact information.

A challenge of this approach is that each author can only be contacted to ask for IPD from a single study. If a corresponding author of an eligible study has published more than one study, we will contact the first, last or the next in order author as presented in the paper. If a single author is included in more than one paper, then we will only contact him/her once for the newest study and the older study will be excluded. In such a case, for the IPD review and at the end of the RCT, we will contact the authors in the same way to obtain the IPD for all excluded studies. All authors who provide feedback during the conduct of the updated systematic review and IPD network meta-analysis for the type 1 diabetes study and the Alzheimer's dementia study, will become part of an active collaboration and will be included in the authorship in the final publication (only if they agree). This is in accordance with the International Committee of Medical Journal Editors (ICMJE) criteria.

Randomization and blinding

Eligible authors will be randomized to one of the two trial groups using a 1:1 procedure. Randomization will be performed using a computer-generated random number list, and adequate allocation concealment will be ensured as the sequence will not be revealed until the end of the study. The computer randomization will be done centrally and conducted by a statistician (AAV) who will be blinded to the authors' names. However, it is impossible to blind the corresponding authors and research personnel who will be in contact with them due to the nature of intervention. Blinding of outcome assessors is also not possible in this design.

Control and intervention groups

Control group

We will contact authors of eligible studies on Alzheimer's dementia and type 1 diabetes allocated to the control group to participate using four strategies, as per Dillman's method to optimize response rates and obtain IPD. First, authors will be sent an email requesting their IPD. Second, we will send four email reminders at 2-, 6-, 10-, and 14-week intervals after the initial email. Third, in week 7, we will send a reminder by post in addition to email. Fourth, in week 15 we will attempt to contact the corresponding author by phone. The duration of our study will be 19 weeks in total.

Intervention Group

Using the same approach used for the control group, we will contact authors using the four approaches described above. Authors allocated to the intervention group will be additionally provided with a

financial incentive (CAD100). Each participant allocated to the intervention group will receive an upfront CAD100 incentive as a gift certificate from Amazon (www.amazon.com) with the first email notification. In the same email we will clarify that at the end of the RCT, we will offer the same financial incentive to the authors allocated to the control group.

We will send two different letters by email, one for each group, simultaneously to the authors. The same letters will be sent to the authors' mail addresses, which will have been printed in two different files, one for each group. In both letters, we will ask authors of the original studies to be included in the group authorship on the understanding that they provide feedback on results and take part in writing and reviewing the systematic review manuscript for the final publication, as is common practice in collaborative IPD reviews. At the end of the RCT, we will send a debriefing letter to all the authors who participated to our study. All authors who will share their data with us will be appropriately cited and they will be acknowledged in our final manuscript if they wish.

Outcomes

Our primary outcome will be the proportion of RCT authors included in our published systematic reviews who provide complete IPD. We will define complete IPD as information on population, interventions, outcomes and randomization as outlined below for the two reviews:

1) Population: the type 1 diabetes RCTs should include: age, sex, pregnancy, initial baseline glucose control (e.g., baseline glycosylated hemoglobin level), presence of comorbid conditions, previous history of hypoglycemia, other medications used for each participant, drop-outs along with reasons for drop-out, and number of participants, and Alzheimer's dementia RCTs should include: age, sex, severity of the Alzheimer's dementia, previous response to treatment for Alzheimer's dementia, presence of behavioral disturbance, comorbid conditions (e.g., stroke), other medications used for each patient, drop-outs along with reasons for withdrawal, and number of participants
2) Interventions: including allocated treatment and dosage
3) Outcomes: including event and date of event for severe hypoglycemia in the type 1 diabetes review and serious adverse events in the Alzheimer's dementia review, as well glycosylated hemoglobin and Mini-mental State Examination values and measurement dates for type 1 diabetes and Alzheimer's dementia respectively
4) Date of randomization for each participant and overall method of randomization for all study participants

If any of the above items are not provided in the data we receive, but have been collected according to the RCT's protocol, the study's dataset will be considered partially complete. These items were chosen as the most vital data for IPD analyses based on input from clinicians on the relevant systematic review team.

Our secondary outcomes will be the time taken to obtain the dataset and the completeness of data. We will determine the duration between the information request and the authors' provision of their dataset to estimate the time required to obtain data from authors. In case the authors send multiple datasets (e.g., first received dataset is incomplete, but after exchanging several emails the final received dataset is complete) over a period of time, we will consider the last date of correspondence to estimate the time required to obtain IPD. The completeness of the received dataset is crucial to investigators, as missing

data might prevent inclusion of a RCT in the meta-analysis. An IPD meta-analysis may be biased if it is based only on a subset of trials. If an RCT author provides us with the requested information, but some variables are missing (e.g., age, sex, pregnancy) because these were not collected during the RCT, then we will consider the dataset complete if this was reported in the study protocol. This is because the data are not missing due to selection bias. However, in case the requested information is not provided and the data have been collected in the RCT, the dataset will be considered incomplete. In such cases, we will not be able to control for these variables for the particular RCT in the analysis.

Analysis Plan

We performed a descriptive analysis using frequencies and percentages for all characteristics we either abstracted from trial publications or collected through the author and sponsor contacting process.

We compared author responses for which we received complete IPD, author response type (positive vs. negative), and response rate (response vs. no response) between experimental and control groups using the odds ratio (OR) and its corresponding 95% confidence interval (CI). On IPD receipt, we assessed data completion and time needed to share. Because only two IPD datasets were available across the intervention and control groups at the time these analyses were done, we could not compare the intervention group results according to the IPD characteristics. The OR and its corresponding 95% CI was used to compare author and sponsor response type and response rate in the following groups: low vs. high/unclear risk of bias, industry/mixed-sponsored vs. publicly sponsored studies, large vs. small–moderate studies, statistically significant vs. nonstatistically significant treatment effects, small vs. medium–large effect studies. We assessed for a trend over publication years to respond using the Cox and Stuart trend test and the trend library in R. We assessed whether a linear relationship existed between year of publication, absolute standardized mean difference (SMD) or sample size, and days to respond and calculated a Pearson correlation coefficient. The distribution of eligible studies by industry sponsor was plotted in a bubble plot using the ggplot2 library in R. Finally, we outlined barriers and resource requirements that prevented IPD from being obtained, challenges that delayed the process of obtaining IPD, as well as monetary costs and personnel resources required to obtain IPD. We also describe the barriers encountered at the different levels of the author and sponsor contact process.