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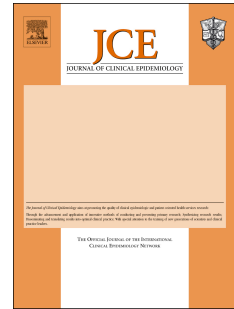


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Areti Angeliki Veroniki, Huda M. Ashoor, Susan P.C. Le, Patricia Rios, Lesley A. Stewart, Mike Clarke, Dimitris Mavridis, Sharon E. Straus, Andrea C. Tricco



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Retrieval of individual patient data depended on study

characteristics: A randomised controlled trial

Areti Angeliki Veroniki^{1,2,3*} e-mail: averonik@cc.uoi.gr

Huda M. Ashoor² e-mail: ashoorh@smh.ca

Susan P.C. Le² e-mail: les@smh.ca

Patricia Rios² e-mail: riosp@smh.ca

Lesley A. Stewart⁴ e-mail: lesley.stewart@york.ac.uk

Mike Clarke⁵ e-mail: m.clarke@qub.ac.uk

Dimitris Mavridis^{1,6} e-mail: dmavridi@uoi.gr

Sharon E. Straus^{2,7} e-mail: sharon.straus@utoronto.ca

Andrea C. Tricco^{2,8} e-mail: triccoa@smh.ca

¹ Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece

² Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

³ Institute of Reproductive and Developmental Biology, Department of Surgery & Cancer, Faculty of Medicine, Imperial College, London, United Kingdom

⁴ Centre for Reviews and Dissemination, University of York, York, United Kingdom

⁵ Northern Ireland Hub for Trials Methodology Research, Queen's University Belfast, Belfast, United Kingdom

⁶ Paris Descartes University, Sorbonne Paris Cité, Faculté de Médecine, Paris, France

⁷ Department of Geriatric Medicine, University of Toronto, Toronto, Ontario, Canada

⁸ Epidemiology Division, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

***Corresponding Author:**

Dr. Areti Angeliki Veroniki, MSc, PhD

Research Fellow at the Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece

Phone: +30 26510 05694; fax: +30 26510 05854; e-mail: averonik@cc.uoi.gr

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Abstract

Words: 199 (Max 200 words)

Objective: To examine the effect of providing a financial incentive to authors of randomized clinical trials (RCTs) to obtain individual patient data (IPD).

Study Design and Setting: Parallel-group RCT with authors identified in the RCTs eligible for two systematic reviews. The authors were randomly allocated to the intervention (financial incentive with several contact approaches) or control group (using the same contact approaches). Studied outcomes: proportion of authors who provided IPD, time to obtain IPD, and completeness of IPD received.

Results: Of the 129 authors contacted, 37 authors suggested or contacted a person/funder providing relevant details or showed interest to collaborate, while 45 authors directed us to contact a person/funder, lacked resources/time, did not have ownership/approval to share the IPD, or claimed IPD was too old. None of the authors shared their IPD. We contacted 17 sponsors and received two complete IPD datasets from one sponsor. The time to obtain IPD was >1 year after a sponsor's positive response. Common barriers included study identification, data ownership, limited data access, and required IPD licenses.

Conclusions: IPD sharing may depend on study characteristics, including funding type, study size, study risk of bias, and treatment effect, but not on providing a financial incentive.

Trial registration: Clinical Trials.gov (NCT02569411), registered on October 5th, 2015.

Keywords: meta-analysis, patient-level data, individual participant data, incentive, data retrieval, data sharing

What is New?

Key Findings

- Significant barriers were encountered in obtaining study individual participant data (IPD). These included identifying trial data based on published reports and other sources, negotiating data ownership (for both authors and sponsors), and limited data access (including time, ability to share data, and special software needed)

What this adds to what is known?

- Likelihood of sharing IPD may be associated with study-specific characteristics, such as funding type, study size, study risk of bias, and treatment effect. For example, authors of publicly-sponsored studies with medium-large treatment effect (i.e., an estimated treatment effect above 0.2 on the standardized mean difference scale) tended to respond positively to IPD requests. Availability of IPD from sponsors tended to be positive for large studies with a low risk of bias
- The time taken to obtain IPD was longer than a year after a sponsor's positive response. Data sharing agreements were required for all sponsors. Clarifications from sponsors regarding the agreements ranged between 0 and 24 days. Approval of data sharing agreements ranged between 86 and 168 days

What is the implication and what should change now?

- Sharing IPD has legal, ethical, and logistical constraints, which may deter researchers from embarking on these projects and may deter trial participants from participating. This may reinforce reliance on aggregate data (network) meta-analysis that may have inadequate statistical power and accuracy, reducing the quality of evidence available to health professionals, policymakers, and patients.
- Our findings show that obtaining study IPD can take longer than a year after a sponsor's positive response. Therefore, we recommend that future planning of IPD meta-analyses should provide sufficient time (e.g. at least two years) for the IPD retrieval process, particularly in clinical areas where the approach is not yet established.

1 **1. Introduction**

2 The synthesis of data from multiple randomized clinical trials (RCTs) may strengthen
3 scientific evidence used by health professionals and policymakers; the gold standard analysis
4 approach is pooling individual patient data (IPD) from RCTs of clinical interventions. [1-7]
5 Several methods have been developed to use IPD in meta-analysis [6] and network meta-
6 analysis (NMA) [8] and their use has increased over the years, [8, 9] because meta-analyses or
7 NMAs based on aggregated data have limitations. In particular, IPD can be used to explain the
8 variation of treatment effects between studies within pairwise comparisons (heterogeneity)
9 and the variation of treatment effects between pairwise comparisons (inconsistency). [9-13]
10 For example, a pooled estimate based on aggregate data with substantially heterogeneous
11 treatment effect estimates may not be informative and an exploration of whether the treatment
12 effects differ across pre-specified, clinically important subgroups may be needed. Although
13 meta-regression aims to answer this, it has many limitations, such as 'aggregation bias'. [14]
14 Aggregation bias arises when one incorrectly assumes that relationships observed at the group
15 level hold also at the patient level and is also known as ecological bias. [15-17] The use of IPD
16 can result in greater statistical power to detect patient-treatment relationships and help
17 individualise management for patients with certain characteristics. Hence, confidence in meta-
18 analysis results can increase by including IPD on all randomized patients, irrespective of
19 whether they were included in analyses of the primary RCT.

20 Technological advances, such as safeguarding confidential data through secured
21 platforms, have potential to increase the feasibility of obtaining IPD and there is a strong
22 impetus to share anonymized IPD from RCTs. [18-31] However, it has been suggested that
23 reluctance to share data is still the main obstacle for obtaining IPD and performing IPD meta-
24 analysis. [32, 33] Potential reasons for this include concerns about patient confidentiality, lack
25 of time to share IPD, not 'owning' the data, cost for de-identifying and formatting the data, or

26 lack of access to data by primary study authors after study completion. [32] A scoping review of
27 indirect comparisons with IPD showed that 67% of included studies obtained IPD through the
28 establishment of a collaborative group. [8] Hence, the cooperation of the authors of the primary
29 studies is crucial for providing IPD in a usable format and answering queries about their data.
30 Since sharing IPD has legal, ethical, and logistical constraints, we need to understand how to
31 optimize this process.

32 Our objective was to examine the impact of providing a small financial incentive to
33 authors of RCTs that were eligible for a systematic review and NMA, versus usual contact
34 strategies to obtain IPD. As a secondary objective, we aimed to describe potential barriers and
35 facilitators associated with the data sharing process.

36 **2. Methods**

37 The study protocol was registered with ClinicalTrials.gov (NCT02569411; October 5th,
38 2015). Our methods are described briefly here; additional details can be found in the protocol
39 publication and Additional File 1: Appendix 1, 2. [34] Our RCT conforms to the Consolidated
40 Standards to Reporting Trials (CONSORT) guidance [35] (Additional File 2).

41 We used RCTs identified through two systematic reviews and NMAs, [36, 37] and we
42 followed the process as depicted in Figure 1a. Overall, we contacted both study authors and
43 study sponsors (Additional File 1: Appendix 2) to obtain IPD. The process varied across
44 sponsors (Additional File 1: Appendix 3).

45 (Figure 1 here)

46 We performed a descriptive analysis using frequencies and percentages for all
47 characteristics we either abstracted from trial publications or collected through the author and
48 sponsor contacting process (Additional File 1: Appendix 2).

49 We compared author responses for which we received complete IPD, author response
50 type (positive vs. negative) and response rate (response vs. no response) between experimental
51 and control groups using the OR and its corresponding 95% CI. Upon IPD receipt, we assessed
52 data completion and time needed to share. Since only 2 IPD datasets were available across the
53 intervention and control groups at the time these analyses were done, we could not compare
54 the intervention group results according to the IPD characteristics. The OR and its
55 corresponding 95% CI was used to compare author and sponsor response type and response
56 rate in the following groups: low vs. high/unclear risk of bias, industry/mixed-sponsored vs.
57 publicly-sponsored studies, large vs. small-moderate studies, statistically significant vs. non-
58 statistically significant treatment effects, small vs. medium-large effect studies. We assessed for
59 a trend over publication years to respond using the Cox and Stuart trend test and the *trend*
60 library in R. [38] We assessed whether a linear relationship existed between year of publication,
61 absolute SMD or sample size and days to respond, and calculated a Pearson correlation
62 coefficient. The distribution of eligible studies by industry sponsor was plotted in a bubble plot
63 using the *ggplot2* library in R. [38] Finally, we outlined barriers and resource requirements that
64 prevented IPD from being obtained, challenges that delayed the process of obtaining IPD, as
65 well as monetary costs and personnel resources required to obtain IPD. We also describe the
66 barriers encountered at the different levels of the author and sponsor contact process.

67 **3. Results**

68 We included 137 studies (29 RCTs for type 1 diabetes mellitus and 108 RCTs for
69 Alzheimer's dementia) for which we attempted to obtain IPD by contacting the original authors
70 and trial industry sponsors (Additional File 1: Appendix 4). The deadline for receiving IPD to be
71 included in the analyses was February 28th, 2018 (internal deadline set in our team only). In
72 Additional File 1: Appendix 5 we present the number of eligible studies we requested from
73 authors and sponsors separately, and the number of studies we were able to acquire IPD. The

74 individual study characteristics are reported in Additional File 1: Appendix 6, 7. Additional
75 information on the results is reported in Additional File 1: Appendix 8.

76 **3.1 Contacting authors for the RCT process**

77 Of the 137 trials, we were unable to locate contact information for 8 authors and these
78 were subsequently excluded. Of the 8 trials, 3 were allocated to control and 5 were allocated to
79 intervention. These 8 trials were published between 1998 and 2010, had moderate to large
80 sample size, low to unclear allocation concealment bias, and low to high incomplete outcome
81 data bias. Of the 8 trials, 6 were industry sponsored and 2 did not report funding, 3 compared
82 NPH against glargine, and 5 compared galantamine, rivastigmine, or donepezil against
83 placebo/no treatment. In total, we included 26 type 1 diabetes studies, of which 20 (77%)
84 compared NPH, 14(54%) compared glargine, and 16 (62%) compared detemir to an alternative
85 treatment. Of the 103 Alzheimer's dementia studies, 57 assessed donepezil (55%), 25 assessed
86 memantine (24%), 23 assessed galantamine (22%), and 23 assessed rivastigmine (22%)
87 (Table1). Additional File 1: Appendix 9 presents a CONSORT flow diagram depicting the process
88 of the RCT and the IPD received across the 2 groups. [35]129 authors were contacted and 82
89 (64%) responded (of which 37 [45%] responded positively and 45 [55%] responded
90 negatively); 24 (19%) authors responded after the first invitation email, and the remainder
91 responded across the 4 other reminders. Of the authors who did not respond (47 [36%]), two
92 email addresses were deactivated at the second reminder (6 weeks after the initial email), one
93 email address was deactivated at the third reminder (10 weeks after the initial email), and one
94 email address was deactivated at the fourth reminder (14 weeks after the initial email) (Figure
95 2 and Table 2). According to authors of the primary studies, 15 (33%) of the negative responses
96 were due to lack of resources or time, lack of ownership or IPD, and old IPD that could not be
97 retrieved. Of the positive responses, none of the authors shared their IPD.

98 (Tables 1 and 2 here)

99 (Figure 2 here)

100 The response type (OR=1.13 95% CI [0.47, 2.69]) and the response rate (OR=1.25 95%
101 CI [0.61, 2.57]) were balanced in intervention and control groups (Additional File 1: Appendix
102 6). The response rates when the type 1 diabetes studies were categorized per treatment, ranged
103 between 70% (in NPH) and 85% (in glargine); in which the positive response rates ranged from
104 29% (in NPH) to 50% (in detemir). The response rates for the Alzheimer's dementia treatments
105 ranged between 52% (in rivastigmine) and 65% (in galantamine), with positive responses
106 ranging from 40% (in galantamine) to 50% (in donepezil) (Table 2). The response type and
107 response rate categorized per study characteristics are presented in Appendix 10.

108 The number of days required for an author to respond ranged from 0 to 117 days (mean
109 days=45, standard deviation [SD]=39), irrespective of the response type (mean days for positive
110 response=40, SD=38; mean days for negative response=49, SD=40). Similarly, the number of
111 days required for an author in the intervention group to respond ranged from 0 to 117 days
112 (mean days=40, SD=40), irrespective of the response type (mean days for positive response=32,
113 SD=35; mean days for negative response=48, SD=43), and the number of days required for an
114 author in the control group to respond ranged from 0 to 116 days (mean days=49, SD=38; mean
115 days for positive response=50, SD=40, range [1,113]; mean days for negative response=49,
116 SD=37, range [0, 116]).

117 **3.2 Contacting sponsors and IPD databases**

118 Of the 137 studies, 107 reported at least one industry-sponsored funder in their
119 publication. In the remaining studies, 11 were publicly-sponsored and 19 did not report any
120 information about funding. The 19 studies that did not report funding information were
121 published in journals requiring disclosures for: COI (1 [5%] study), COI/funding (2 [11%]
122 studies), funding (2 [11%] studies), sponsor (9 [47%] studies), and not available (5 [26%]
123 studies (Additional File 1: Appendix 6, 7). Across the 107 studies that reported sponsor
124 information, 17 different industry sponsors were reported in the publications and 24 (23%)
125 studies reported at least two different sponsors (Additional File 1: Appendix 11). In total, we

126 contacted 17 industry sponsors (4 of which collaborate with 2 IPD databases) for 133 studies
127 (or 107 unique studies, since some studies reported multiple sponsors, where 83 studies were
128 funded by 1 sponsor, 23 studies by 2 sponsors, and 1 study by 5 sponsors; see Additional File 1:
129 Appendix 12 for list of co-sponsored studies); 3 sponsors (18%) did not respond to any of our
130 contact attempts. We contacted industry sponsors only, as we were not able to locate the
131 contact information for the majority of the included public sponsors. In the following, we refer
132 to the term 'sponsor' to indicate an industry sponsor. CSDR and YODA databases facilitated data
133 sharing for 59 trials funded by 4 sponsors who made 18 trials available. In total, we included 25
134 type 1 diabetes studies, of which 20 (80%) compared NPH, 15 (60%) compared detemir, and 13
135 (52%) compared glargine to an alternative treatment. Of the 108 Alzheimer's dementia studies,
136 69 assessed donepezil (64%), 26 assessed galantamine (24%), 23 assessed rivastigmine (21%),
137 and 20 assessed memantine (19%) (Additional File 1: Appendix 13). Additional File 1: Appendix
138 14 shows the number of eligible studies per sponsor and per type of response regarding IPD
139 availability. The response rate when the type 1 diabetes studies were categorized per treatment
140 was 100% across all treatments. The positive response rates ranged from 15% (in glargine) to
141 80% (in detemir). The response rates for the Alzheimer's dementia treatments ranged between
142 85% (in memantine) and 100% (in galantamine), with positive responses ranging from 19% (in
143 galantamine) to 29% (in memantine). Of the total 133 studies, 38 (29%) unique studies were
144 deemed available by the sponsors. However, the majority (89 studies; 67%) of the IPD were
145 unavailable and the reasons for refusal of providing IPD varied, including difficulty with study-
146 identification (46%), non-ownership of IPD (26%), and the age of the study (too old, 12%)
147 (Table 3, Additional File 1: Appendix 15).

148 Up until February 28th, 2018 and within 318 days of contacting the sponsor, we received
149 2 complete IPD datasets from a single sponsor of 136 and 123 patients. We determined the
150 dataset complete according to the study protocol. Allocation concealment was rated as low risk
151 of bias for both studies; however, for incomplete outcome data, one study had low risk of bias
152 and one had a high risk of bias. Up until February 28th, 2018 we also had another data sharing

153 agreement signed by both parties for 12 unique studies. The time to clarify the data sharing
154 agreement process ranged between 0 and 24 days, whereas the time to approve the data
155 sharing agreement ranged between 86 and 168 days. All sponsors who agreed to share their IPD
156 with us restricted its availability through a password protected, software-restricted, and closed
157 environment within a certain period of time ranging between 28 and 730 days. The exploration
158 of response rate and response type across different study characteristics suggested effect sizes
159 with wide CIs for most point estimates (Additional File 1: Appendix 16,17).

160 (Table 3 here)

161 **3.3 Barriers and resource requirements associated with the IPD** 162 **acquisition**

163 Several barriers and challenges were encountered during the IPD acquisition process. In
164 Table 4 we provide the barriers we encountered during the author and sponsor contact process
165 separately. The barriers and challenges are also depicted with different icons at the various
166 levels of the author contact process in Figure 1b, and of the sponsor contact process in Figure
167 1c.

168 (Table 4 here)

169 An important barrier in obtaining study IPD was the identification of the underlying trial
170 data set, such as when an old study could not be easily located or when its data were lost by an
171 author. Also, studies may not have been identifiable by sponsors when certain information was
172 not available, such as the NCT number, due to the relatively recent widespread use of trial
173 numbers (since 2005). In some cases, even when conducting exhaustive searches (Additional
174 File 1: Appendix 18), an NCT number (or other related study ID) was difficult to find or did not
175 exist, and hence sponsors could not locate the study in their database solely based on the study
176 citation details. Being unable to match study publication to the underlying studies when
177 sponsors needed to be contacted was the most frequent reason for IPD being unavailable (see
178 Figure 8). Of the 98 studies with unavailable IPD, 41 (42%) studies could not be located by the

179 study sponsor. Another important barrier was data ownership. It was often the case that study
180 authors did not own the IPD, the study funder had to be contacted to request the IPD (56
181 [43%]). This also applied to sponsors. For instance, since 18 of the eligible studies were co-
182 sponsored by Eisai and Pfizer (see Additional File 1: Appendix 11), both sponsors were
183 contacted to confirm ownership. Data ownership was the second most frequent reason (25
184 studies [26%]) for unavailable IPD (see Additional File 1: Appendix 15). A barrier associated
185 with the analysis once IPD was received was that IPD were only available through proprietary
186 sponsor-specific platforms. This does not allow for IPD from different sponsor platforms to be
187 combined (and could be a challenge for those who are unfamiliar with the software provided in
188 the underlying platform). As the IPD could not be combined from all studies identified in a
189 systematic review in a single place and model, a one-stage analysis was impossible. Also, the
190 time that the platform permitted access to the IPD was often limited (e.g., 6 weeks) which is a
191 significant constraint given that IPD from different studies could be available at different time
192 points. However, this required knowledge of the data items and times for access available from
193 each sponsor.

194 **4. Discussion**

195 Our results showed that offering small financial incentives to study authors does not
196 improve IPD retrieval. In our particular example, by the end of July 2017 we were unable to
197 obtain any IPD datasets from trial authors, and were only able to obtain two IPD datasets after
198 contacting industry sponsors. We found that obtaining a response from authors to requests to
199 access IPD may depend on study characteristics. Authors of publicly-sponsored studies, those
200 that included between <50 and 150 patients, and those with a medium to large treatment effect
201 (i.e., an estimated treatment above 0.2 on the SMD scale) tended to respond positively to IPD
202 requests. Increased odds of a positive response were also found in studies at high risk of bias.
203 This is because small to moderate studies are typically at high risk of bias in most domains and
204 are associated with large treatment effects. In contrast, IPD availability from sponsors tended to

205 be positive for large (>150 patients), and low risk of bias studies, with small and non-
206 statistically significant treatment effects. This suggests that well-conducted industry sponsored
207 studies are more likely to be shared. It should be highlighted that there is a high risk of
208 confounding in our results, as large studies are typically associated with small treatment effects
209 and low risk of bias. In addition, these findings should be interpreted with caution, as our
210 estimated ORs were associated with wide confidence intervals. This high uncertainty in ORs
211 may be associated with low power to detect the true effect. Similarly, the marginally non-
212 statistically significant trend of positive author/sponsor responses across publication years
213 favouring newer RCTs may be associated with the low power of the test.

214 Sharing IPD may be constrained by a number of legal, ethical, and logistical factors,
215 which may deter researchers from undertaking them and trial investigators participating in
216 them. This may perpetuate reliance on the conduct of aggregate data meta-analysis and NMA
217 that may reduce statistical power and accuracy of results. Significant barriers in obtaining study
218 IPD from trial sponsors may include matching study publication to the underlying study,, issues
219 around data ownership, and acquiring of data dictionary licenses.

220 In general, time and cost may be a barrier to carrying out an IPD NMA. Costs include not
221 only staff wages, including administrative, legal, library, and research staff, but also license costs
222 (when applicable, e.g. WHO Drug Dictionary license approximate cost \$8,958.25 USD per
223 sponsor). We were surprised to encounter the licence cost issue as it has not been encountered
224 previously in the context of collaborative group IPD meta-analyses and could be an isolated
225 experience or an additional cost of obtaining data from trial sponsors and data repositories.
226 The longer time required to conduct this type of research may be considered an additional
227 barrier, especially when time-sensitive decisions need to be made. Our findings show that
228 obtaining study IPD can take longer than a year after a sponsor's positive response. Thus,
229 accessing data via repositories may not be as rapid as was hoped and therefore, we recommend
230 that in accordance with customary practice in collaborative IPD meta-analyses, future planning

231 of IPD meta-analyses that involve obtaining data from trial sponsors through data sharing
232 platforms should include sufficient time for the IPD retrieval process, (probably at least two-
233 years). For example, the IPD retrieval process for a recently published IPD-NMA of 10
234 antiepileptic drugs required 4 years to obtain the 65% of the included participants and 38% of
235 identified clinical trials. [39] Even if access to IPD is granted,, additional barriers may arise, such
236 as having to analyze IPD datasets using different sponsor data sharing platforms and software
237 making one-stage analysis impossible. Being able to access IPD only for a limited time (e.g. 4 to
238 6 weeks) is also a serious limitation and constraint as when analysing IPD from different studies
239 provided by different sponsors, the IPD datasets can be available at different time points. and
240 different data variables may be available.

241 A limitation of our RCT is that we did not anticipate that the trial authors would not have
242 authority to grant access to the data sets and that sponsors would need to be contacted instead.
243 We contacted each author about a single study to avoid contamination bias in our RCT. Through
244 this process, we avoided sending multiple requests to a single author. If an author directed us to
245 another co-author then we discussed all papers with them. However, in a usual IPD project
246 aiming to collect IPD from a number of studies, if multiple studies from the same research group
247 are of interest, one would probably request IPD from all these studies at once to maximise the
248 amount of data provided. Also, the time available to conduct the analysis in this study was
249 probably another barrier in obtaining IPD. Another limitation is that blinding to treatment
250 allocation was only possible for the statistician who conducted the analysis. Due to the nature of
251 the intervention and the study design, blinding was impossible for research personnel and
252 outcome assessors. However, given that neither group has contributed data, the unsuccessful
253 blinding has not impacted our success rate. To reduce potential bias in the author responses
254 received, we planned to send authors a debriefing letter at the end of the trial informing them
255 that they participated in a RCT. Also, to avoid misinterpretation of the small financial sum
256 offered as compensations for the effort involved in the preparation of IPD, we proposed our
257 IPD-NMA as a collaborative project. If the authors met the ICMJE criteria [40] and shared their

258 IPD, they would be included in the collaborative group authorship of the final publication. The
259 authors' reluctance to share their IPD could be due to the contact person's expertise outside the
260 clinical field relevant to the trial. However, to increase author responses, an experienced
261 Scientist (ACT) in the field of systematic reviews and meta-analyses contacted each author and
262 provided citations of our published protocols, where researchers with significant reputations in
263 the relevant fields were included as co-authors. Also, in our communication with the trialists we
264 indicated our experience in the fields through our published systematic reviews in the area,
265 which were funded through the Canadian Institutes of Health Research. An additional limitation
266 is that we used different outcomes across studies to explore the association between response
267 rate (and type) and the magnitude of treatment effect. In total, we used 62 studies with MMSE,
268 26 studies with serious adverse events, and 25 studies with A1c reported as the outcome
269 measure. Although it is expected that the treatment effect will vary across outcomes, this was
270 the only feasible approach to include the most data possible to explore this association. Another
271 limitation is that we used studies examining response rates from surveys to inform our study
272 size, [41-44] since to the best of our knowledge no studies assessing response rate in retrieving
273 IPD from RCTs using a financial incentive is available. This may have underestimated the
274 required sample size, producing imprecise results. Our findings represent retrieving IPD from
275 authors for two certain clinical areas (type 1 diabetes and Alzheimer's dementia), and these
276 might not be well generalized to other drug trials. It should be noted though that the majority
277 (77%) of the included RCTs were sponsored by pharmaceutical companies, and this may have
278 affected the IPD retrieval.

279 Before deciding to conduct an IPD meta-analysis or NMA, one should consider and
280 weigh up the benefits and limitations of the approach. Although the process of sharing IPD may
281 vary according to the disease, treatment, and clinical question addressed, [45] one should not
282 only consider the cost and time needed to conduct an IPD meta-analysis or NMA, but also the
283 possibility of being unsuccessful in retrieving IPD. [33] This may be particularly important for
284 NMAs that involved large numbers of studies. When IPD meta-analyses fail to obtain data the

285 impact of this on the analyses should be considered, especially when IPD are missing not at
286 random (e.g. when acquirement of IPD depends on the RCT characteristics). This could threaten
287 validity and in turn impact clinical decision-making as the practice of evidence-based medicine
288 relies on the availability of timely, relevant, and scientifically sound data on the risks and
289 benefits associated with medical interventions. Important initiatives to reporting study results
290 are currently being made by medical journals via encouraging authors to use the CONSORT
291 checklist, [35] as well as by study authors and organizations (see <http://www.alltrials.net/>).
292 [19-22] However, as our results showed, IPD sharing is not yet well-established in the fields of
293 type I diabetes and Alzheimer's dementia, and more efforts are required to achieve this goal.

294 **Declarations**

295 **Ethics approval**

296 Ethical approval was obtained from the Research Ethics Board of St. Michael's Hospital on
297 September 16th, 2015 to conduct this randomized controlled trial (REB # 15-240). The
298 information generated during our RCT was kept confidential and limited to the study's
299 purposes, as described in the protocol. We received anonymized IPD only as per our initial
300 request, where each patient was linked to a specific identifier.

301 **Consent for publication**

302 Not applicable.

303 **Availability of data and material**

304 The full dataset is available from the corresponding author upon reasonable request.

305 **Conflicts of interest**

306 ACT and SES are on the editorial board for the journal but were not involved with the peer
307 review process or decision to publish. All other authors declare that they have no competing
308 interests.

309 **Funding**

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314 in Knowledge Translation. ACT is funded by a Tier 2 Canada Research Chair in Knowledge
315 Synthesis.

316 **Role of the funder**

317 The funder had no role in the design and conduct of the study; collection, management, analysis,
318 and interpretation of the data; preparation, review, or approval of the manuscript; or decision
319 to submit the manuscript for publication.

320 **Authors' contributions**

321 AAV, SES and ACT conceived and designed the study. AAV coded author responses, abstracted
322 data, contacted sponsors, analysed data, interpreted results, and wrote a draft manuscript. SES
323 and ACT interpreted results and edited the manuscript. ACT and SPCL contacted the RCT
324 authors. AAV and SPCL contacted the study sponsors. SPCL collected the data and edited the
325 manuscript. HMA coordinated the RCT, coded author responses, extracted and categorized data,
326 appraised quality, resolved discrepancies, and edited the manuscript. PR coordinated the study,
327 extracted and categorized data, and edited the manuscript. DM, LAS and MC provided input into
328 the design, interpreted results, and edited the manuscript. All authors read and approved the
329 final manuscript.

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333 Matas for formatting the figures.

334 **List of abbreviations**

335 Clinical Study Data Request (CSDR); Coalition Against Major Diseases (CAMD); confidence
336 interval (CI); conflict of interest (COI); Consolidated Standards of Reporting Trials (CONSORT);
337 International Committee of Medical Journal Editors (ICMJE); individual patient data (IPD); Mini-
338 mental State Examination (MMSE); network meta-analysis (NMA); neutral protamine Hagedorn
339 (NPH); odds ratio (OR); Preferred Reporting Items for Systematic Reviews and Meta-Analyses
340 (PRISMA); randomized clinical trial (RCT); standardized mean difference (SMD); Yale University
341 Open Data Access (YODA)

342 **Tables**343 **Table 1: Author response per treatment**

	Type 1 Diabetes (N=26 studies)			Alzheimer's Dementia (N=103 studies)			
	Detemir	Glargine	NPH	Donepezil	Galantamine	Memantine	Rivastigmine
<i>Positive response</i>	6	4	4	17	6	7	6
<i>Negative response</i>	6	8	10	17	9	7	6
Response*	12	12	14	34	15	14	12
No response	4	2	6	23	8	11	11
Total studies	16 (62%)	14 (54%)	20 (77%)	57 (55%)	23 (22%)	25 (24%)	23 (22%)

344 **Footnotes:** * Combined total of positive and negative responses345 **Abbreviations:** NPH, neutral protamine Hagedorn

346 **Table 2: Author Response Summary**

# of authors contacted	129
# of authors who did not respond	47 (36%)*
# of authors who responded:	82 (64%)
# of authors who responded after first email	24 (0 to 15 days)
# of authors who responded after second email	21 (20 to 48 days)
# of authors who responded after third email	18 (50 to 83 days)
# of authors who responded via post mail	0
# of authors who responded after fourth email	14 (86 to 100 days)
# of authors who responded after fifth email	5 (105 to 117 days)
# of authors who responded via phone	5†
Negative response:	45
Contact funder/database	27 (60%)
Lack of resources/time	5 (11%)
Do not have approval/ownership	4 (9%)
Do not have data	3 (7%)‡
Old data	3 (7%)
Not interested	2 (4%)
Contact corresponding author	1 (2%)
Positive response:	37
Contact corresponding author/funder - provided contact person	20 (54%)
Contacted funder	5 (14%)
Interested but did not follow-up	12 (32%)
Time to respond (days)	0 to 117
Time to obtain data sharing approval (days)	467

347 **Footnotes:**

348 * Two email addresses were deactivated at the second reminder (6 weeks after the initial email), one
349 email address was deactivated at the third reminder (10 weeks after the initial email), and one email
350 address was deactivated at the fourth reminder (14 weeks after the initial email).

351 †5 calls were answered [Message left with admin (1); Language barrier (4)]

352 ‡2 authors mentioned that they did not have the data available. 1 author mentioned that the data was
353 destroyed

354 **Table 3: Sponsor Response Summary**

Number of sponsors/databases* contacted:	17
Number of sponsors who did not respond:	3 (6 studies) †
Number of sponsors where data was unavailable:	13 (89 studies) ‡
Cannot identify study	4 (41 studies)
Cannot share data	6 (22 studies)
Language	1 (1 study)
Old study	2 (11 studies)
Phase 4 study	1 (4 studies)
Potential business considerations under review	1 (1 study)
No details provided	1 (5 studies)
Do not own data	10 (23 studies)
IPD not available	1 (3 studies)
Number of sponsors who required a research proposal to be submitted first:	7 (91 studies) §
Research proposal approved	5 (64 studies)
Research proposal not approved (no reason provided)	1 (5 studies)
Research proposal under review	1 (22 studies)
Number of sponsors who required a research proposal and data sharing agreement (DSA) to be submitted congruently:	4 (24 studies) ¶
Research proposal approved and DSA approved	1 (15 studies)
Research proposal approved and DSA not approved (do not own data)	1 (2 studies)
Research proposal and DSA under review	2 (7 studies)
Number of studies where study identification number was required	62
Number of studies where author was contacted for study identification number	48
Number of studies where author provided study identification number	7
Number of studies where author did not provide study identification number:	41
No response	30
Does not have the information	4

Referred to sponsor	3
Does not have access to the information	2
Referred to lead PI of the study	1
Not registered	1
Number of studies where study identification number was found	13
Time to clarify data sharing process (days)	0 to 24 days
Time to approve research proposal (days)	22 to 121
Time to approve data sharing agreement (days)	86 to 168
Number of studies requested	137
Number of studies available	38
Number of studies shared	11

355 **Footnotes:**

356 * ClinicalStudyDataRequest.com (CSDR); Yoda.Yale.edu (YODA)

357 † Merz, ONO, Roivant

358 ‡ Abbvie, Daiichi-Sankyo, Eisai, Forest Laboratories/Allergen, GlaxoSmithKline, Janssen, Lundbeck,
359 Novartis, Novo Nordisk, Pfizer, Shire Pharmaceuticals, Takeda

360 § Abbvie, CSDR, Forest Laboratories/Allergen, Janssen, Pfizer

361 ¶ AstraZeneca, Lundbeck, Novo Nordisk, Shire Pharmaceuticals

362 **Table 4: Barriers and Resource requirements**

Activity/Item	Contacting Authors		Contacting Sponsors		Resources
	<i>Issue</i>	<i>Impact</i>	<i>Issue</i>	<i>Impact</i>	
Initial Contact	Cannot locate contact information (email address, mailing address and/or phone number)	Spent extra time finding current contact information for authors Unable to invite authors to participate	Unable to locate an 'obvious' contact for IPD requests Sponsors did not respond to initial contact	Spent extra time pursuing multiple avenues and contacting multiple sponsors (for co-sponsored studies) before finding the correct one	<i>Research staff</i> 1 research assistant 3 research coordinators 2 scientists <i>Administrative staff</i> 2 administrative assistants
Ongoing Communication	Emails become undeliverable Postal mail returned Initial contact directs to a co-author that is already part of the RCT Authors do not respond (either to initial contact or later communication)	Loss to follow-up: unable to pursue any further	No direct avenues for communication with sponsors (e.g. general inquiry only) Multiple departments/teams involved in communication	Difficult to follow-up with sponsors when no response is received Extra time needed to relay updates to sponsors	<i>Research staff</i> 1 research assistant 1 research coordinator <i>Administrative staff</i> 2 administrative assistants <i>Legal staff</i> 1 research contract specialist 1 research contract analyst <i>Incentives/communication</i> Gift cards (incentives for intervention) Post mail (reminder)

					Long distance phone charges (reminder)
Application Process	Not applicable	Not applicable	Differing requirements/processes between sponsors Additional items required by sponsors (e.g., additional training/agreements) Sponsors changed methods for application when application was in process	Significant delays to obtaining IPD	<i>Research Staff</i> 1 research assistant 1 research coordinator 2 scientists <i>Administrative staff</i> 2 administrative assistants <i>Legal staff</i> 1 research contract specialist 1 research contract analyst
Identifying Studies	Study is 'too old' to find/share data	Unable to obtain IPD from author	Could not identify studies with available information	Additional time/resources used to find trial identifiers/study information	<i>Research Staff</i> 1 research assistant 1 research coordinator <i>Library staff</i> 1 information specialist
Legal Agreements	Not applicable	Not applicable	Multiple revisions Regulations differ between countries Document formats (un-editable, need physical copies)	Time-consuming, lengthens agreement process Difficult to revise/edit documents	<i>Research Staff</i> 1 research assistant 1 research coordinator 2 scientists <i>Administrative staff</i> 2 administrative assistants <i>Legal staff</i> 1 research contract specialist 1 research contract analyst

Data Ownership	Study authors do not 'own' data	Authors unable to share IPD	Sponsors do not own data	We cannot identify who owns the data and thus cannot obtain IPD Extra time and resources needed to identify 'true' data owners	<i>Research Staff</i> 1 research assistant 1 research coordinator
Data Sharing/Receiving Data	Lack of available resources Ethics restrictions on data sharing	Authors unable to share IPD	'Out of scope' of data sharing policy Unable to share all data from different studies at once Data only available through sponsor platforms Additional licenses required to access the data Data only available for a specified amount of time	Unable to obtain IPD Access to data is limited Unable to conduct one-stage analysis Additional cost or unable to obtain IPD	<i>Research Staff</i> 1 research assistant 1 research coordinator 1 scientist 2 research managers <i>Licensing</i> WHO Drug Dictionary Approximately \$8,958.25 USD /sponsor

363 **Figures**

364 Figure 1. Process of study for acquisition of IPD (a) through an author (b), and a sponsor (c),
365 along with the barriers encountered at each step

366 Figure 2. Author response frequency by type of response and group author allocated per contact
367 reminder

368 **Additional Files**

369 **Additional File 1: Online Content**

370 Appendix 1: Deviations from planned analyses in the protocol

371 Appendix 2: Additional information on methods and analysis

372 Appendix 3: Application or data sharing requirements from study sponsors

373 Appendix 4: Study flow diagram

374 Appendix 5: IPD requested vs. IPD received

375 Appendix 6: Study characteristics

376 Appendix 7: Journal reporting requirements for included studies

377 Appendix 8: Additional information on results

378 Appendix 8a: Statistical significance based on author randomization group

379 Appendix 8b: Frequency of studies and type of response per study publication year

380 Appendix 8c: Scatterplot of number of days for authors to respond versus year of study
381 publication, treatment effect, and sample size

382 Appendix 8d: Sponsors response per study characteristic

383 Appendix 8e: Scatterplot of number of days for sponsors to respond versus year of study
384 publication, treatment effect, and sample size

385 Appendix 9: CONSORT flow diagram of the process of the randomized controlled trial

386 Appendix 10: Author response per study characteristics

387 Appendix 11: Bubble plot of individual sponsors.

388 Appendix 12: List of co-sponsored (or co-funded) studies

389 Appendix 13: Sponsor response per treatment

390 Appendix 14: Number of eligible studies per sponsor and per type of response regarding IPD
391 availability

- 392 Appendix 15: Sponsors' reasons for unavailability of IPD
- 393 Appendix 16: Author and sponsor response per year of study publication
- 394 Appendix 17: Sponsor IPD availability per study publication year
- 395 Appendix 18: Methods for locating NCT/ID Numbers
- 396 **Additional File 2: CONSORT Checklist**

ACCEPTED MANUSCRIPT

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Figure 1a

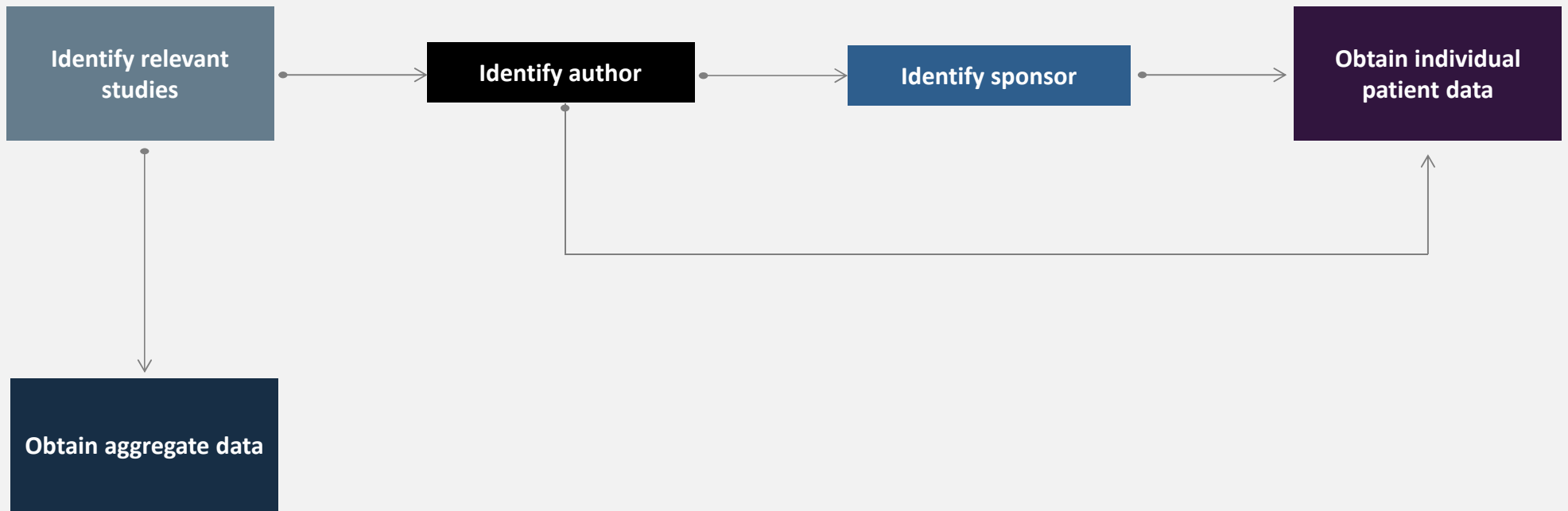
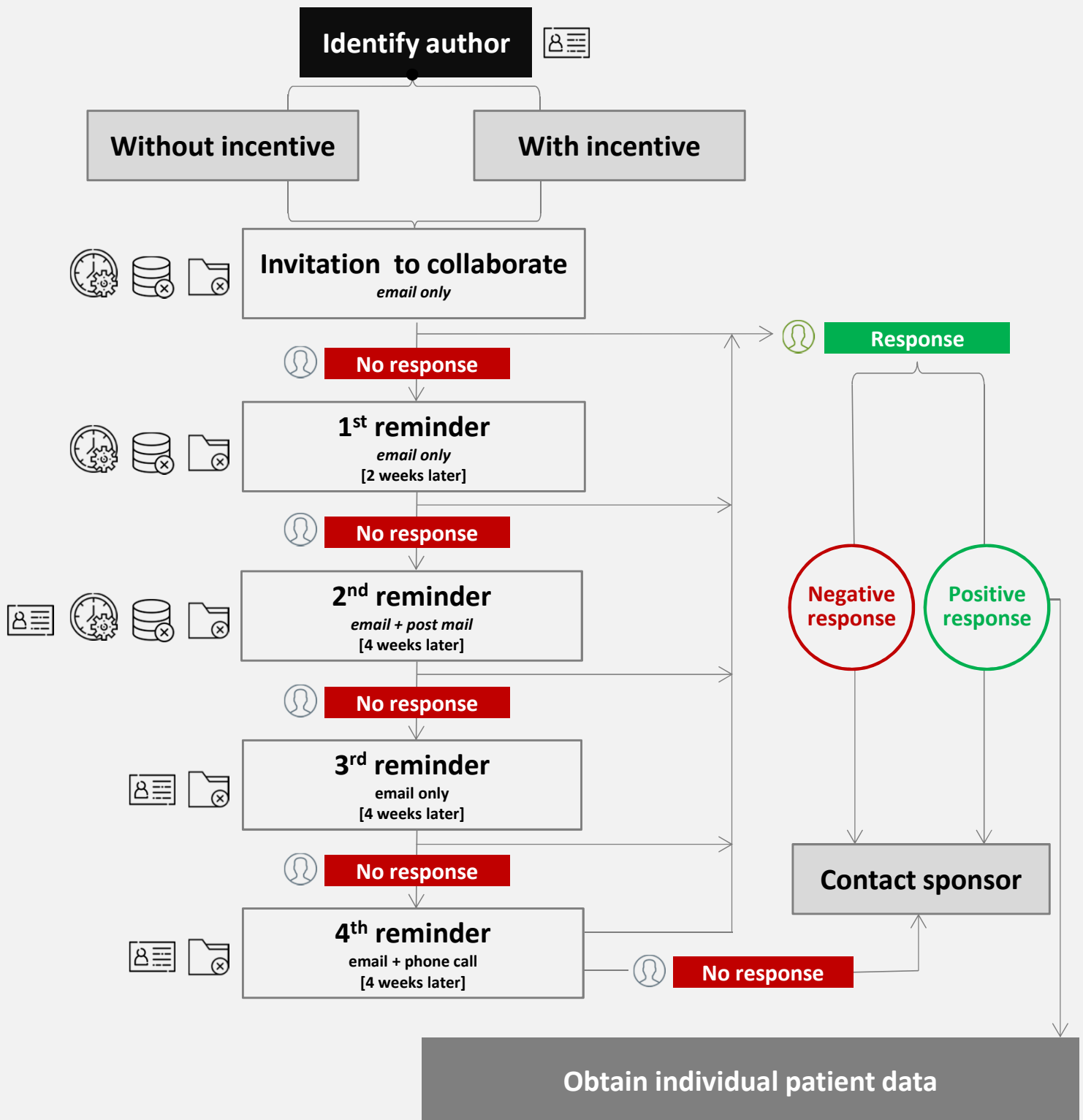


Figure 1b



LEGEND:





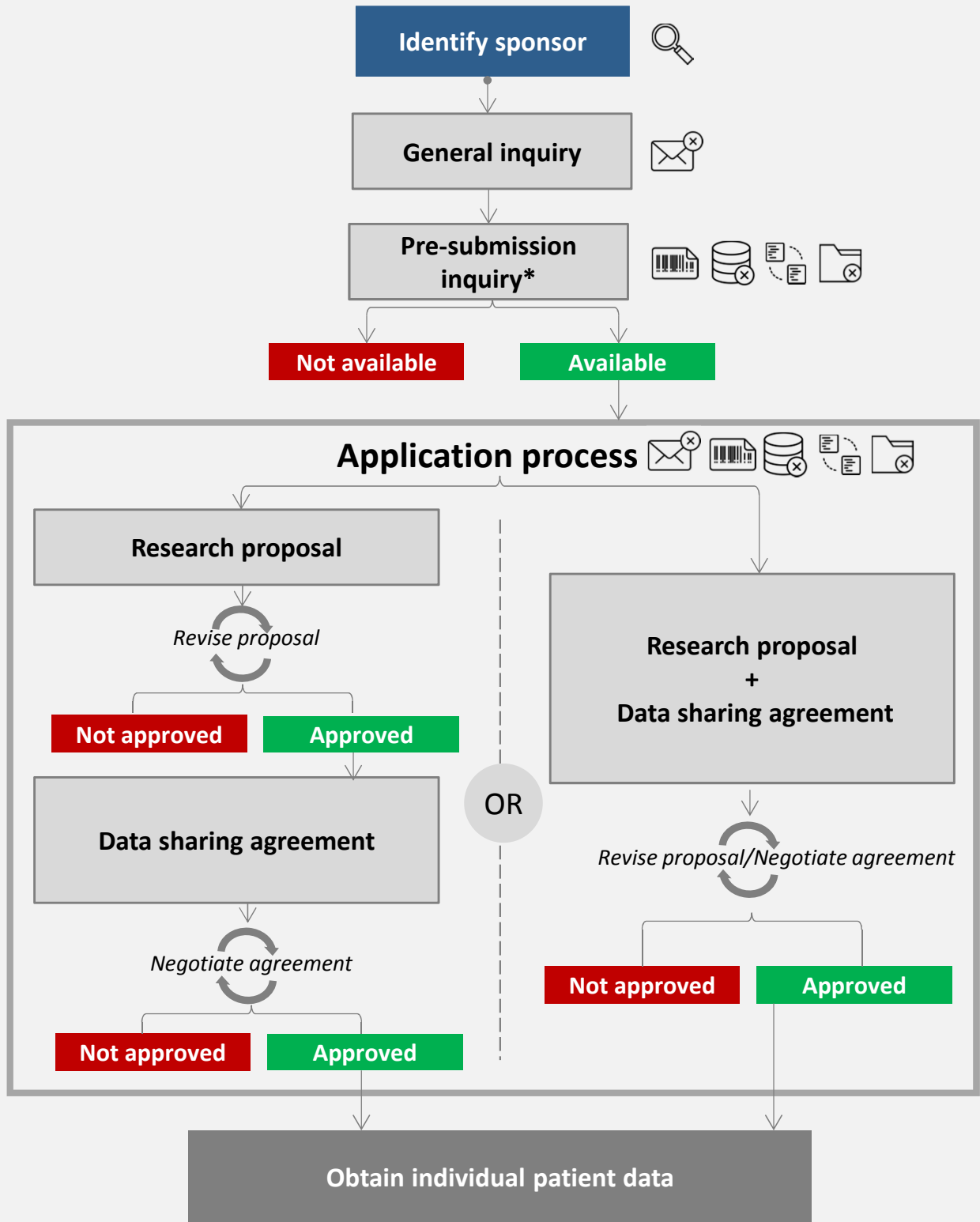






 <p>Contact information Unable to identify author's current/active contact information</p>	 <p>Lack of resources/time Resource/time limitation identified</p>
 <p>Data ownership Does not have ownership of individual patient data</p>	 <p>Do not have data Author does not have <u>any</u> data associated with the study</p>

Figure 1c

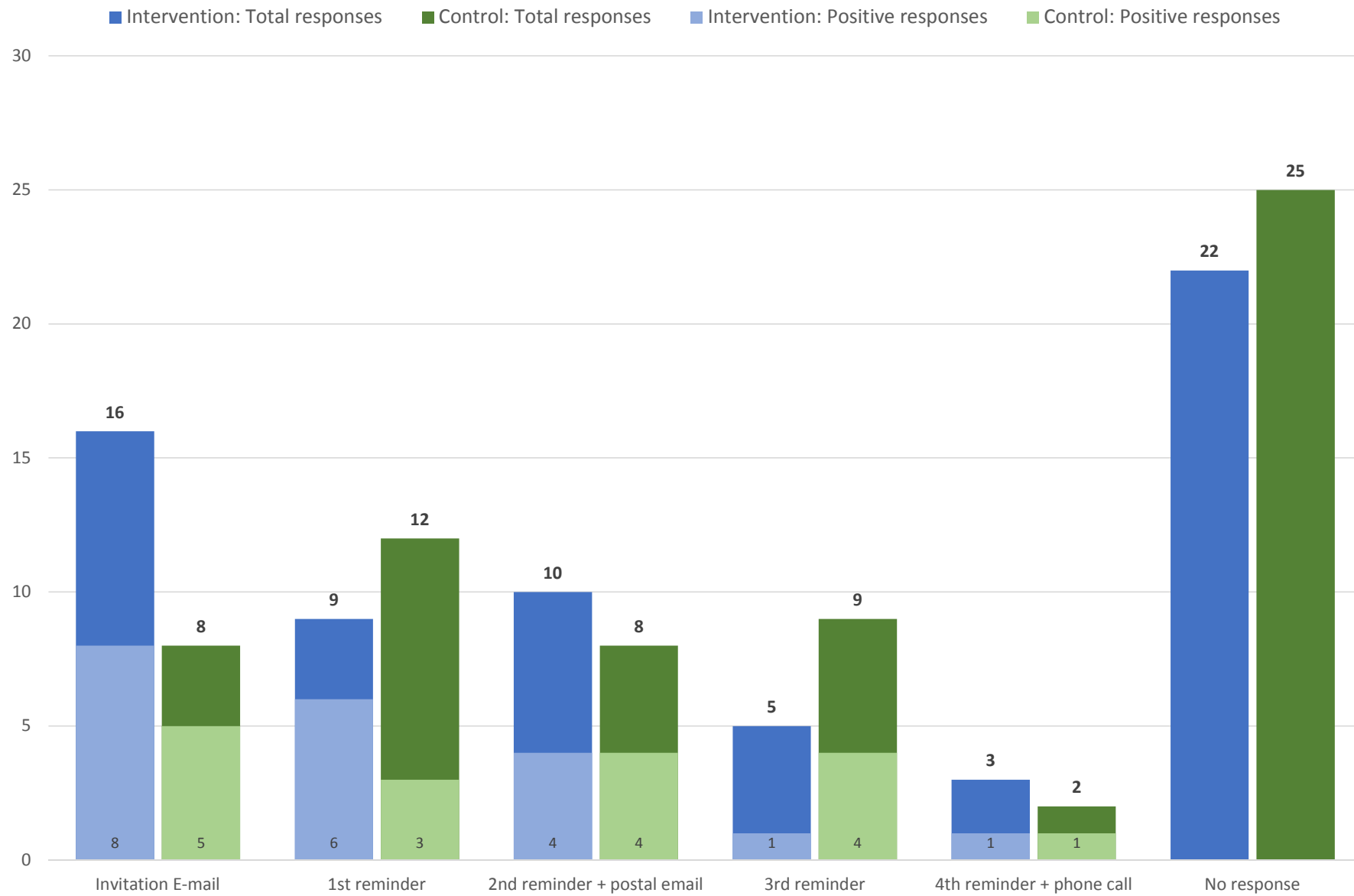


*Pre-submission inquiry step was not required for some of the sponsors

LEGEND:

 <p>Identify sponsor Unable to identify who sponsored the study via publication</p>	 <p>No response No response received from sponsor after multiple follow-ups</p>	 <p>Study ID number Not able to find trial identifiers (e.g. National Clinical Trial number)</p>
 <p>Do not have data Sponsor does not have <u>any</u> data associated with the study</p>	 <p>IPD not available Sponsor can share <u>some</u> data but not the requested individual patient data</p>	 <p>Data ownership Does not have ownership of individual patient data</p>

Author response frequency



What is New?

Key Findings

- Significant barriers were encountered in obtaining study individual participant data (IPD). These included identifying trial data based on published reports and other sources, negotiating data ownership (for both authors and sponsors), and limited data access (including time, ability to share data, and special software needed)

What this adds to what is known?

- Likelihood of sharing IPD may be associated with study-specific characteristics, such as funding type, study size, study risk of bias, and treatment effect. For example, authors of publicly-sponsored studies with medium-large treatment effect (i.e., an estimated treatment effect above 0.2 on the standardized mean difference scale) tended to respond positively to IPD requests. Availability of IPD from sponsors tended to be positive for large studies with a low risk of bias
- The time taken to obtain IPD was longer than a year after a sponsor's positive response. Data sharing agreements were required for all sponsors. Clarifications from sponsors regarding the agreements ranged between 0 and 24 days. Approval of data sharing agreements ranged between 86 and 168 days

What is the implication and what should change now?

- Sharing IPD has legal, ethical, and logistical constraints, which may deter researchers from embarking on these projects and may deter trial participants from participating. This may reinforce reliance on aggregate data (network) meta-analysis that may have inadequate statistical power and accuracy, reducing the quality of evidence available to health professionals, policymakers, and patients.
- Our findings show that obtaining study IPD can take longer than a year after a sponsor's positive response. Therefore, we recommend that future planning of IPD meta-analyses should provide sufficient time (e.g. at least a year) for the IPD retrieval process, particularly in clinical areas where the approach is not yet established.