PEER REVIEW HISTORY

BMJ Medicine publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of age, sex and morbidity count on trial attrition: a meta-analysis of individual participant-level data from phase 3/4 industry-funded clinical trials
AUTHORS	Lees, Jennifer; Hanlon, Peter; Butterly, Elaine W; Wild, Sarah H; Mair, Frances; Taylor, Rod S; Guthrie, Bruce; Gillies, Katie; Dias, Sofia; Welton, Nicky J; McAllister, David A

VERSION 1 - REVIEW

REVIEWER 1	Kulkarni, Ameya; AbbVie, Genomics Research Center. Competing Interest: None
REVIEW RETURNED	01-Jun-2022

GENERAL COMMENTS	I recommend that the editors accept this manuscript titled- “The impact of age, sex and morbidity count on trial attrition: a meta-analysis of individual participant-level data from phase 3/4 industry-funded clinical trials” after minor revisions. This manuscript analyzes the potential associations between co-morbidities and trial attrition rate in a curated set of clinical trials. Using logistic regression adjusted for age and sex, the authors have shown that comorbidity count increases rate of trial attrition. Moreover, by calculating estimates from Bayesian linear models, they have examined this association within drug classes. The manuscript provides very valuable analysis for those who may want to act to improve participant retention. The study of estimates for each drug classes also provide a great resource for investigators. Minor comments (in order of priority) 1. The authors need further to delineate the idea of association vs potential causation, especially as this manuscript may be used by other reviewers and popular media to predict attrition within clinical trials. It may be worthwhile to add a causal inference analysis or at least mention how they would address this difference in a follow-up study. 2. Generally, individuals with co-morbidities and those taking medications are shown to have a higher biological age than others with the same chronological age, although this association may not be linear. The authors may want to mention that including biological age may change their estimates for comorbidities with attrition (using DNA-methylation- see Horvath 2013, Levine et al 2018 and Verschoor et al 2018). 3. The concept of polypharmacy needs to be addressed. For someone with comorbidities, it is very likely to be on more than one class of medication at a given time. Based on the model estimates, how can readers calculate the association between their trial participants with comorbidities, not just on concomitant

	medications? 4. For age-related diseases, frailty can be a major confounder between comorbidities and trial attrition. Many trials do utilize some metric of frailty (eg- frailty index- See Rockwood 2005). The authors may want to address this as a part of their discussion. 5. How were the covariates selected in the logistic regression model? Race and socioeconomic status warrant further analysis. Further discussion on covariate selection may clarify this idea.

REVIEWER 2	Riley, Richard; Keele University, School of Medicine. Competing Interest: None
REVIEW RETURNED	10-Jun-2022

GENERAL COMMENTS	This is a very interesting and unique study evaluating whether age, sex and comorbidities are associated with attrition rates in randomised trials that house their IPD within the YODA and CSDR platforms. It would be a useful contribution to BMJ Medicine, and it represents good use of IPD from existing trials. The major limitation (which is noted in the discussion) is that the number of comorbidities clearly depends on how many were even recorded. The more recorded, the more chance a patient has to have one or more of them. This will differ across trials, and may lead to attenuation (perhaps) of the relationships (and any non-linear trends) between comorbidities and attrition. This is difficult to address, but I still think this papers adds value regardless. I have some comments to help improve the article further, which I hope the authors find constructive. 1) I was left confused by the meta-analysis models used in this piece of work, based on the description in the methods section. That is, exactly how are the effect estimates synthesised in the second stage of the analysis? The authors says that Bayesian linear regression models are used, which can be used to fit 'standard' common-effect or random-effects meta-analysis models. Is this what is happening here? Looking at the supp material, I would call these Bayesian meta-regression modes really. The authors should explain whether there is weighting by inverse variances (and between-study heterogeneity), for example. And, from Figure 1 it looks like the variance matrix of effect estimates is taken forward – does this mean a multivariate meta-analysis approach is being used to account for the correlation (covariances) amongst effect estimates in some regard? 2) I was confused by the phrase 'partially pooled' – so I imagine most readers will be. Please explain better, for example in the sentence "models where there was partial pooling between either index conditions or drug classes, to the most complex model where the estimates were partially pooled across both drug classes and index condition" 3) "These meta-analyses were performed using the frequentist metafor package in R" – this is too vague. What models and assumptions were used, and how were CIs derived, etc? 4) In terms of examining non-linear associations, why is comorbidity count squared considered, but not a more general non-linear approach (e.g. using splines or fractional polynomials) that allows

	other shapes? Same with age. It could be a non-linear relationship has been missed by this restrictive approach. For example, the authors could fit a spline (at some knot positions) in each trial, to assess non-linear associations for age or comorbidity, and then pool these. See Gasparrini (https://pubmed.ncbi.nlm.nih.gov/22807043/). The second stage would then need a multivariate meta-analysis to account for multiple correlated parameters, but perhaps this has already been done for the comorbidity squared assessment? I'm not saying the authors have to do this for publication, but I think a broader consideration of potential non-linearity is needed (or better justification of their current choices). 5) "Age was not associated with attrition (Table 2): the odds ratio (OR) for attrition per 15-year increment in age was 1.04 (95% CI 0.98 to 1.11)." – most of the credible interval is above 1, so I am not convinced by the 'not associated' conclusion. There is some evidence of an association here, in my opinion – indeed, in the Bayesian framework, the probability of OR > 1 could be derived, and I expect it to be > 80%. So perhaps the authors might consider re-wording to say there is not clear evidence … or that, if there is an association, the impact is small? I might be wrong, but I do think it is worth re-evaluating the wording. 6) In the results the authors say:"There was no evidence of departure from linearity for this association" for comorbidity. But this relates to just assuming a squared term? So better to say no evidence of non-linearity defined by a squared term? 7) I struggle to identify any mention of heterogeneity of relationships for each meta- analysis. Is there heterogeneity in the effect of age, for example, across trials? Is it worth also reporting 95% predictive intervals for the effect? 8) Table 2 presents the meta-analysis results, but without telling us the number of studies and the estimated heterogeneity for each analysis. As mentioned, a 95% prediction interval may also be welcome here. 9) Figures 3 and 4 confused me – why not present the pooled result and CI at the bottom, like a usual forest plot, rather than provided the red dotted lines to present the CI. I must be missing something. 10) How were any missing values for age, sex and comorbidities dealt with in the modelling? Please clarify In summary, this article is generally very well done, and will make an excellent publication. I hope the authors can make the clarifications and changes recommended to improve things further, and potentially include additional analyses suggested (or justify against) too.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I recommend that the editors accept this manuscript titled- "The impact of age, sex and morbidity count on trial attrition: a meta-analysis of individual participant-level data from phase 3/4 industry-

funded clinical trials" after minor revisions.
This manuscript analyzes the potential associations between co-morbidities and trial attrition rate in a curated set of clinical trials. Using logistic regression adjusted for age and sex, the authors have shown that comorbidity count increases rate of trial attrition. Moreover, by calculating estimates from Bayesian linear models, they have examined this association within drug classes.
The manuscript provides very valuable analysis for those who may want to act to improve participant retention. The study of estimates for each drug classes also provide a great resource for investigators.

We thank the reviewer very much for the positive assessment of our manuscript.

Minor comments (in order of priority)

1. The authors need further to delineate the idea of association vs potential causation, especially as this manuscript may be used by other reviewers and popular media to predict attrition within clinical trials. It may be worthwhile to add a causal inference analysis or at least mention how they would address this difference in a follow-up study.

Thank you.

In future work we hope to examine both causal mechanisms linking comorbidity and attrition (e.g., difficulty following protocols, particular adverse events, changes in biomarker, the burden of trial participation) as well as to develop and validate a risk prediction model for trial attrition, but believe that this is beyond the scope of the current work, and mention some of these in the section on "unanswered questions and future research".

For this manuscript, we have been careful to describe only associations between comorbidity count and attrition.

"Secondly, though we have demonstrated a clear association between increasing comorbidity count and attrition, we cannot be sure that increased burden of comorbidity was the cause of attrition. An alternative explanation could be unmeasured confounding by other factors that may affect likelihood of trial completion (e.g., education, ethnicity and socioeconomic status) nor can we comment on potential mediators of the observed association."

2. Generally, individuals with co-morbidities and those taking medications are shown to have a higher biological age than others with the same chronological age, although this association may not be linear. The authors may want to mention that including biological age may change their estimates for comorbidities with attrition (using DNA-methylation- see Horvath 2013, Levine et al 2018 and Verschoor et al 2018).

This is an interesting point. Existing trial IPD do not measure biological age, though this would be a very interesting aspect for future study. We have added some discussion on this (along with

discussion of frailty, per the reviewer's comment below) in the following paragraph in the discussion (new text in bold):

"**There are two specific, potentially measurable indices of physiological well-being that may be associated with attrition and warrant further exploration. Increasing biological age (for example, measured by DNA methylation[28]) is associated with the accrual of comorbidity and predicts a variety of morbidity and mortality outcomes[29]. It may be that accounting for biological age would attenuate the association observed between comorbidity count and attrition; however, DNA methylation is not currently routinely measured or reported. Frailty is a marker of functional status that positively correlated with increasing (chronological and biological) age and comorbidity count, but is strongly and independently associated with mortality[30]. Availability of validated frailty assessment tools (such as Fried[31] or Rockwood[32] indices) permit simple recording of these data. Although some trials (especially in disease processes common in older patients e.g., dementia) do record participant frailty, the lack of uniform availability of these data from existing trial IPD prevents detailed assessment of the association between frailty and trial attrition. Assessing the impact of frailty on attrition constitutes an important avenue for further study, and particularly whether trial design could be adapted to improve inclusiveness of frailer participants. Specifically,** it would ~~also~~ be useful to examine whether associations differ according to trial characteristics which may improve completeness of follow-up, such as the use of wearables[24] or collection of routine data[25,26] to measure trial endpoints."

3. The concept of polypharmacy needs to be addressed. For someone with comorbidities, it is very likely to be on more than one class of medication at a given time. Based on the model estimates, how can readers calculate the association between their trial participants with comorbidities, not just on concomitant medications?

We agree with that the issue of polypharmacy is important and was not mentioned specifically in the previous version of the manuscript. We have adjusted the text under the heading "strengths and weaknesses of the study" as follows (added text in bold):

"First, the trials were not designed to study comorbidity, and as such our definitions were based on data collected for other reasons (and not redacted for privacy reasons when the IPD was shared): the medical and concomitant medication history collected at baseline. For this reason, we defined comorbidities broadly (e.g., asthma and chronic obstructive pulmonary disease were collapsed into a single category) and are likely to have missed some diagnoses. **Similarly, patients with comorbidities are likely to experience polypharmacy across multiple drug classes, or indeed be prescribed a single drug for multiple indications.** This may have biased associations between comorbidity count and attrition, most likely towards the null because of non-differential misclassification. Although we did not find any evidence for non-linearity in the association between comorbidity count and attrition, we would also caution against extrapolating the findings to comorbidity counts above 3, since there were very few individuals in the trial with comorbidity counts of this level."

4. For age-related diseases, frailty can be a major confounder between comorbidities and trial attrition. Many trials do utilize some metric of frailty (eg- frailty index- See Rockwood 2005). The authors may want to address this as a part of their discussion.

Thank you for this point. We agree with the reviewer that other factors – including those which correlate with comorbidity count – may be independently associated with attrition. We have added some additional discussion on frailty and biological ageing (per the reviewer's comment #2) above.

5. How were the covariates selected in the logistic regression model? Race and socioeconomic status warrant further analysis. Further discussion on covariate selection may clarify this idea.

Unfortunately, measures of socioeconomic status were not collected in these industry-funded trials. Per our data sharing agreements, we do not have permissions to examine race/ethnicity as a predictor of trial attrition. We are further aware that issues of race/ethnicity are nuanced, and politically and socially sensitive, and would be best explored as the main focus of some dedicated work involving experts in this area of study. We hope to explore this in future work.

Reviewer: 2

Comments to the Author
This is a very interesting and unique study evaluating whether age, sex and comorbidities are associated with attrition rates in randomised trials that house their IPD within the YODA and CSDR platforms. It would be a useful contribution to BMJ Medicine, and it represents good use of IPD from existing trials.

The major limitation (which is noted in the discussion) is that the number of comorbidities clearly depends on how many were even recorded. The more recorded, the more chance a patient has to have one or more of them. This will differ across trials, and may lead to attenuation (perhaps) of the relationships (and any non-linear trends) between comorbidities and attrition. This is difficult to address, but I still think this papers adds value regardless. I have some comments to help improve the article further, which I hope the authors find constructive.

We would like to thank Prof Riley for his positive general comments about our work and his constructive suggestions for improvement. We have responded to each of these more specifically below.

1) I was left confused by the meta-analysis models used in this piece of work, based on the description in the methods section. That is, exactly how are the effect estimates synthesised in the second stage of the analysis? The authors says that Bayesian linear regression models are used, which can be used to fit 'standard' common-effect or random-effects meta-analysis models. Is this what is happening here? Looking at the supp material, I would call these Bayesian meta-regression modes really. The authors should explain whether there is weighting by inverse variances (and between-study heterogeneity), for example.

Thank you. We did not use the term meta-regression as we did not wish to give the impression that the regression was at the level of trials, rather than at the level of individual patients. However, we agree that this is a form of meta-regression and so have described it as "meta-analysis of regression coefficients".

In terms of the second stage, we agree that we have been too brief in the methods section (albeit with a formal description of the model in the supplementary appendix) leaving readers unsure about the modelling. We have added the following text.

"We performed a range of meta-analyses for each regression coefficient. These meta-analyses were done within a Bayesian framework, where the final meta-analysed estimate was a summary of the trial level estimates. This summary is a product of the precision with which the association is estimated for each trial (i.e., the inverse of the squared standard error for the relevant coefficient), the between trial variation, the variation between other groups (e.g., drug class and/or condition) and the prior distributions (a vague prior for the overall effect, and weakly informative priors for the variation parameters). For the simplest model, only between trial variation was explicitly modelled. For the (progressively) more complex models, the variation between other groups was also modelled: drug class, condition and both drug class and condition. This modelling allowed estimates to differ for each group, while also allowing sharing of information between the groups (known as "partial pooling") which has the effect of improving precision as well as shifting extreme effect estimates towards the overall mean. The within group variation for trials, conditions and drug classes was reported as the respective standard deviations."

And, from Figure 1 it looks like the variance matrix of effect estimates is taken forward – does this mean a multivariate meta-analysis approach is being used to account for the correlation (covariances) amongst effect estimates in some regard?

Yes, we did export the variance matrix of the effect estimates. This was done in case we subsequently needed to do a multivariate meta-analysis. We wanted to give ourselves (and other researchers) maximum flexibility for subsequent re-analyses of the results after exporting these from the trial repository safe havens. Indeed – although discussion of this is outside the scope of this paper - we think it would be helpful if all researchers reporting results obtained using individual-level data (trials, cohort studies etc) would publish additional model outputs, such as the variance matrices. For that reason, we have provided all of the model coefficients and the variance matrices from the trial-level models in our GitHub repository in case these are of interest to other researchers.

In our case, we had planned, if the comorbidity-squared term had not been null, to model the comorbidity and comorbidity-squared terms simultaneously in a multivariate normal model. However, since the squared term was null, we were able to use a simpler univariate model.

We have described the reason for exporting the full variance matrix in the legend to Figure 1:

"Variance matrices of the effect estimates were exported to allow maximum flexibility in subsequent meta-analyses, if required."

2) I was confused by the phrase 'partially pooled' – so I imagine most readers will be. Please explain better, for example in the sentence "models where there was partial pooling between either

index conditions or drug classes, to the most complex model where the estimates were partially pooled across both drug classes and index condition"

Thank you for this comment. In response to comment #1 above, we have changed the description of the Bayesian meta-analysis of regression coefficients, which we also hope has improved clarity of the process of partial pooling.

3) "These meta-analyses were performed using the frequentist metafor package in R" – this is too vague. What models and assumptions were used, and how were CIs derived, etc?

We have clarified the procedure used to conduct this sensitivity analysis as follows:

"We fit a frequentist random effects model (which assumes effect estimates for each trial come from a normal distribution), using a restricted maximum likelihood estimator within the *metafor* package. This was fit using frequentist rather than the Bayesian software used for the main analysis, as the latter was not available within the trial repository."

4) In terms of examining non-linear associations, why is comorbidity count squared considered, but not a more general non-linear approach (e.g. using splines or fractional polynomials) that allows other shapes? Same with age. It could be a non-linear relationship has been missed by this restrictive approach. For example, the authors could fit a spline (at some knot positions) in each trial, to assess non-linear associations for age or comorbidity, and then pool these. See Gasparrini (https://pubmed.ncbi.nlm.nih.gov/22807043/). The second stage would then need a multivariate meta-analysis to account for multiple correlated parameters, but perhaps this has already been done for the comorbidity squared assessment? I'm not saying the authors have to do this for publication, but I think a broader consideration of potential non-linearity is needed (or better justification of their current choices).

Thank you very much to the reviewer for this suggestion.

We considered (at some length, and in discussion with co-authors) how best to model non-linearity for comorbidity account in these trials. We decided to use a second order polynomial as a trade-off between being able to capture some departure from linearity and simplicity in the model fitting and meta-analysis. As we were analysing data across multiple repositories, and then extracting results simplicity was an important consideration.

We have added the following statement to the limitations:

"Thirdly, we chose to explore non-linearity using a second-order polynomial (i.e., linear and squared terms for comorbidity count) as this was simpler to implement than other approaches such as splines or fractional polynomials, since we were analysing data across multiple repositories rather than on a

single platform. Had we been able to use these more flexible approaches, we may have detected non-linearity not apparent with the current method."

5) "Age was not associated with attrition (Table 2): the odds ratio (OR) for attrition per 15-year increment in age was 1.04 (95% CI 0.98 to 1.11)." – most of the credible interval is above 1, so I am not convinced by the 'not associated' conclusion. There is some evidence of an association here, in my opinion – indeed, in the Bayesian framework, the probability of OR > 1 could be derived, and I expect it to be > 80%. So perhaps the authors might consider re-wording to say there is not clear evidence … or that, if there is an association, the impact is small? I might be wrong, but I do think it is worth re-evaluating the wording.

Thanks for this suggestion. We agree that we understated the evidence in favour of there being an association between age and trial attrition. We now report Bayesian p-values in Table 2, to report the probability that there is a positive association between age and trial attrition. As the reviewer expected, this probability is high: around 89% for the result from the pooled model. We have therefore tempered the language as suggested (new text in bold):

"There was no clear association between increasing age and attrition (Table 2): the odds ratio (OR) for attrition per 15-year increment in age was 1.04 (95% CI 0.98 to 1.11), **although the probability of a positive association (Bayesian P-value) was 89% (Table 2)"**

The methods have been updated as follows:

"The probability (Bayesian P value) that comorbidity count was positively associated with attrition was estimated as the proportion of the posterior distribution of the log odds ratio which was above 0."

6) In the results the authors say: "There was no evidence of departure from linearity for this association" for comorbidity. But this relates to just assuming a squared term? So better to say no evidence of non-linearity defined by a squared term?

We agree that the modelling used to justify this statement requires clarification and have added the qualification that this assumes the use of a squared term to define non-linearity:

"There was no evidence of departure from linearity (estimated via the addition of a squared term to the model) for this association."

7) I struggle to identify any mention of heterogeneity of relationships for each meta-analysis. Is there heterogeneity in the effect of age, for example, across trials? Is it worth also reporting 95% predictive intervals for the effect?

Thank you for pointing this out. In the revised version of Table 2, we report the standard deviation for between-trial variation for pooled results, and after partial pooling across index condition, drug class

and both index condition and drug class.

We agree that prediction intervals – for estimating the likely attrition for future unobserved trials – would potentially be useful, particularly for trialists involved in design. However, we believe that this would be most useful in the context of a formal prediction score for trial attrition. Indeed, growing out of the current work we have been able to fund a PhD fellow who will begin working on such a model from October 2022.

8) Table 2 presents the meta-analysis results, but without telling us the number of studies and the estimated heterogeneity for each analysis. As mentioned, a 95% prediction interval may also be welcome here.

Thanks for this suggestion. In the revised version of Table 2, we include the number of trials included in each of the comorbidity, age and sex models, and the number of index condition and drug classes where relevant. We now additionally present the standard deviation for within group variation in pooled and partially-pooled models. We have added the following to the text of the results:

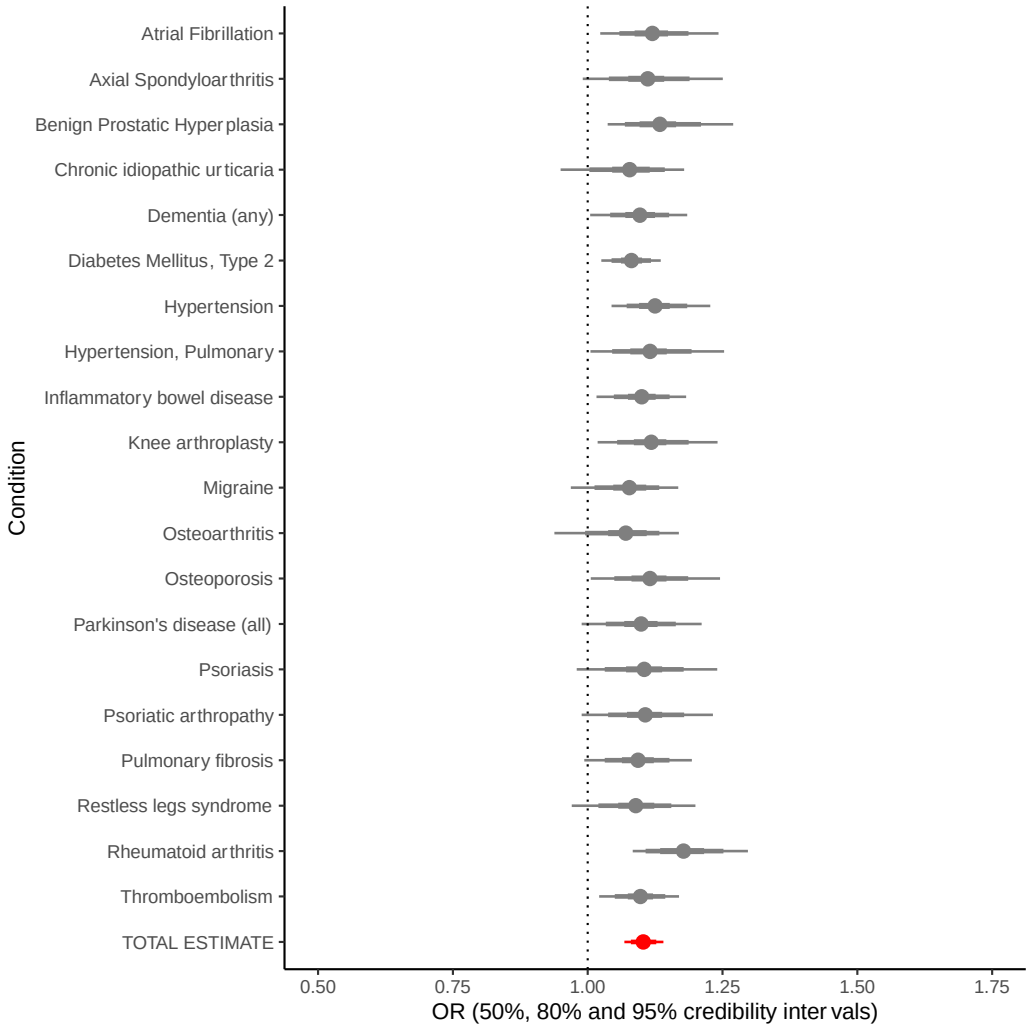
"For the association between comorbidity count and attrition, there was approximately twice as much variation between trials as between index conditions and between drug classes (standard deviation (on log-odds scale) 0.10, 0.05 and 0.04 respectively; Table 2)."

We have also updated the methods as follows:

"The within group variation for trials, conditions and drug classes was reported as the respective standard deviations."

9) Figures 3 and 4 confused me – why not present the pooled result and CI at the bottom, like a usual forest plot, rather than provided the red dotted lines to present the CI. I must be missing something.

We agree that the presentation of Figures 3 and 4 was unusual, and potentially confusing to interpret. In the revised version of the manuscript, we have provided the result from the pooled model (with 50, 80 and 95% credibility intervals) at the bottom. We have pasted an example plot (for comorbidity count with partial pooling across index condition) below for the convenience of the reviewers and editors:



10) How were any missing values for age, sex and comorbidities dealt with in the modelling? Please clarify

As expected for industry-funded phase 3 and 4 trials, the proportions of missing baseline data within trials were very small. Logistic regression models within trial repositories were therefore conducted on complete cases. We have clarified this in the methods as follows:

"Proportions of missing baseline data within trials were very small. Logistic regression models within trial repositories were conducted on complete cases."

VERSION 2 – REVIEW

REVIEWER 2	**Riley, Richard;** Keele University, School of Medicine. Competing Interest: None
REVIEW RETURNED	17-Jul-2022

GENERAL COMMENTS	I thank the authors for their detailed response to my previous comments, which are very clear and satisfactory. The revision is much improved, and this will make an excellent addition to the BMJ Medicine journal. My only remaining comment is for the authors to specify their choice of prior distributions in the methods section, and in particular to (briefly) examine the impact of changes to their choice of 'weakly informative' priors for the variance parameters (especially between-study variance), if there are other sensible alternatives. Or justify why not done.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Comments to the Author

I thank the authors for their detailed response to my previous comments, which are very clear and satisfactory. The revision is much improved, and this will make an excellent addition to the BMJ Medicine journal.
My only remaining comment is for the authors to specify their choice of prior distributions in the methods section, and in particular to (briefly) examine the impact of changes to their choice of 'weakly informative' priors for the variance parameters (especially between-study variance), if there are other sensible alternatives. Or justify why not done.
Best wishes,
Prof Richard Riley

In the original analysis, we ran the models for the overall effect of comorbidity, age and sex with a student t prior (mean = 0, SD = 100 and 3 degrees of freedom). For variance parameters, we ran the original models with a half-normal t distribution (equivalent parameters 0, 2.5 and 3).

For the best-fitting model for comorbidity count, we have now run a sensitivity analysis with wider priors on all of the variance components (trial, drug class and index condition), increasing the standard deviation to 10, and otherwise leaving the parameters unchanged. Reassuringly, running the models with these wider priors gave the same results to 2 decimal places for all of the estimated quantities.

We have added a statement referring to the selection of priors in the methods as follows:

"Details of the selected priors are available in the Supplementary Data file."

We have added the following description of prior selection to the supplementary data file:

"As a sensitivity analysis of the effect of the selected priors, the variance parameters were re-calculated using wider priors with half-t distribution as follows:

$\sigma_{trial} \sim half\text{-}student\text{-}t(df = 3, mean = 0, sd = 10)$

$\sigma_{cond} \sim half\text{-}student\text{-}t(df = 3, mean = 0, sd = 10)$

$\sigma_{drug} \sim half\text{-}student\text{-}t(df = 3, mean = 0, sd = 10)$"

The results are highlighted by the addition of the following statement in the results, Page 18, under "sensitivity analyses":

"Sensitivity analyses using wider priors for the variance parameters gave the same results to 2 decimal places for the between-trial, between-condition and between-drug class variances (Supplementary Table S3)."

This new table is pasted below for ease of review:

	Original priors[1]	**Wider priors[2]**
Partial pooling across index condition and drug class	N=20 index conditions; N=17 drug classes	N=20 index conditions; N=17 drug classes
Intercept (SD)	0.097 (0.026)	0.096 (0.025)
SD trial (SD)	0.091 (0.018)	0.092 (0.018)
SD index condition (SD)	0.044 (0.027)	0.043 (0.027)
SD drug class (SD)	0.036 (0.026)	0.035 (0.026)

"1 - Trial level models adjusted for age, sex and comorbidity count using original priors. 2 - Trial level models adjusted for age, sex and comorbidity count using wider priors for variance components. SD: standard deviations (and their SDs) for within-group variation for trials, index conditions and drug classes on log-odds scale. See supplementary methods below for full description of models and selection of priors."