Incorporating Missing Outcome Data in The Sample Size Calculation For a Future Trial: A Case Study Using a Single Trial, a Pairwise and Network Meta-Analysis

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**Incorporating missing outcome data in the sample size calculation for a
future trial: a case study using a single trial, a pairwise and network meta-
analysis**

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1 **Abstract**

2 **Background:** To illustrate the advantages of using network meta-analysis (NMA) as
3 compared to a trial or a pairwise meta-analysis to estimate the amount of missing outcome
4 data (MOD) for a target comparison in order to adjust the required sample size for possible
5 participant losses in a future trial.

6 **Methods:** We introduced the concept of transitive risks to obtain the absolute risks of MOD
7 for all interventions of the network. We used the network of a published systematic review on
8 a binary outcome to apply the proposed concept and to calculate the required sample size in a
9 future trial for a selected target comparison. For that comparison, we also calculated the
10 required sample size using the corresponding trials separately, and after pooling these trials in
11 a random-effects meta-analysis.

12 **Results:** Ignoring MOD from the sample size calculation led to the smallest sample size.
13 When either trial was considered, the risk of MOD ranged from 1% to 13% in the compared
14 intervention arms, therefore, increasing the sample size from 1% to 12%. Performing a
15 pairwise meta-analysis yielded a risk of MOD equal to 6% and 9% in the active and control
16 arms, respectively, which inflated the sample size by 8%. Using NMA, the corresponding
17 risks of MOD were 10% and 13%, which increased the sample size by 13%.

18 **Conclusions:** Provided that the transitivity assumption holds, incorporating the absolute risks
19 of MOD in the sample size calculation for a target comparison of the network led to better
20 planning of a future trial.

21 **Keywords:** Systematic review; Missing outcome data; Network meta-analysis; Sample size;
22 Clinical trial; Absolute risks.

1 **Background**

2 Patient dropouts are ubiquitous in clinical trials for various reasons, some of which may be
3 related to the design and conduct of the trial. Knowledge of the number of and reasons for
4 missing outcome data (MOD) is necessary to design a clinical trial that will deliver results of
5 high quality [1]. Information on the number of missing participants in the compared
6 interventions will ensure a sufficient sample size to detect the minimum clinically relevant
7 difference for a specific outcome and target population. Information on the possible reasons
8 for MOD will lead to a proactive design of the future clinical trial to retain most of the
9 randomised participants, and hence, increase statistical power [1].

10 Use of evidence synthesis to design a clinical trial has been long advocated as the key
11 against research and funding waste because it can reveal limitations in the conduct and
12 analysis of past relevant trials to prioritise future research [2]. The research community holds
13 a positive attitude to a research agenda for future trials based on the synthesis of past relevant
14 trials [3,4]. Evidence synthesis can also play a crucial role in uncovering the extent of MOD
15 in a specific patient population, set of interventions and outcome under investigation.
16 Applications of pairwise and network meta-analysis have revealed that trials with the same
17 patient population and intervention setting encountered variability on the amount of MOD [5–
18 7]. Selecting any of these past trials to inform the sample size of a relevant future trial would
19 be misleading. This is because failure to incorporate the variability in the amount of MOD (as
20 observed in a series of relevant trials) in the design of a future trial may result in an
21 underpowered trial, thus compromising any efforts to create an ecosystem of the best
22 available evidence.

23 There is already published methodology on the planning of future trials based on
24 systematic reviews [8–10]. However, this methodology does not take into account the effect

1 of MOD on the sample size calculations for a future trial. Considering a fictional two-arm
2 trial for illustration, Cook and Zea [11] performed a sensitivity analysis to investigate how the
3 amount of MOD and different assumptions about the missingness mechanisms in the
4 compared arms can influence the sample size calculations for a future trial. The authors
5 demonstrated that the required sample size to achieve the desired power was dramatically
6 larger when the calculations were based on the sensitivity analysis as compared to ignoring
7 MOD altogether [11]. To the best of our knowledge, there is currently no research at the level
8 of evidence synthesis to demonstrate the implications on sample size calculations when MOD
9 from a series of relevant past trials are incorporated into the design of a future trial.

10 It is legitimate to wonder about the ‘proper’ synthesis framework to inform the future trial:
11 pairwise or network meta-analysis. A pairwise meta-analysis restricts the synthesis of trials to
12 one comparison, therefore, providing only a fraction of the ‘underlying’ extent of MOD in the
13 compared interventions. Arguably, network meta-analysis (NMA) is the ideal framework to
14 base the planning of future trials on, as it synthesises a series of relevant trials investigating a
15 different set of interventions. Furthermore, it can inform decisions for comparisons never
16 investigated in a trial. Therefore, NMA can be used to prioritise the target comparison(s) to be
17 investigated in the future trial(s) [9]. In the context of MOD, NMA can maximise the
18 information on MOD contained in different sets of interventions across trials in order to
19 provide a sufficient sample size for a future trial on a specific comparison. Ergo, by taking
20 into account the variability in the amount of MOD within the network, we can adjust the
21 required sample size for the expected participant losses in the future trial for a target
22 comparison.

23 The present study aims to illustrate the advantages of using NMA rather than a trial or a
24 pairwise meta-analysis to estimate the amount of MOD for a target comparison in order to

adjust the required sample size for possible participant losses in a future trial. For that purpose, we introduce the concept of transitive risks across trials to estimate the risk of MOD for each intervention within the NMA framework [12]. We use a published systematic review as a motivating example to illustrate the concept of transitive risks and the implications of MOD on the sample size calculation for a future trial.

Methods

As a motivating example, we used the systematic review of Baker et al. [13] for the treatment of chronic obstructive pulmonary disease (COPD) exacerbations (Table S1 in Additional file 1). Figure 1A illustrates the network of five interventions alongside the extent of MOD in each intervention and observed comparison: the percentage of MOD (%MOD) signified moderate (more than 5% and up to 20%) and high attrition bias (> 20%) within the network. According to Table 1, %MOD varied substantially in all interventions ranging from low ($\leq$ 5%) to moderate in tiotropium and high in the remaining interventions. The %MOD also varied considerably within the majority of the observed comparisons (Table 1).

[Table 1]

For illustrative purposes, we focused on the comparison of tiotropium with long-acting β_2 -agonist (LABA) that was investigated in three clinical trials (Table S2 in Additional file 1). For this comparison, the publication reported an odds ratio (OR) of 0.82 (95% credible interval (CrI): 0.72–0.93) in favour of tiotropium (Figure 2 A in [13]). However, it is not explicit in the report how MOD were addressed in the NMA model. Therefore, we re-analysed the network while modelling MOD under the missing at random (MAR) assumption to acknowledge the uncertainty induced by MOD and maintain the randomised sample [7].

Transitive risks assumption

To be able to introduce the concept of transitive risks, we have assumed the transitivity assumption and its statistical manifestation (consistency) are plausible; otherwise, the transitive risks would be invalid [12]. The concept of transitive risks builds upon the transitivity assumption; namely, trials share similar clinical and methodological characteristics, and differ only in the interventions compared [12]. In essence, the assumption of transitive risks implies that the risk of the outcome in an intervention (hereafter, absolute risk) is similar across all trials of the network. In other words, an intervention is assumed to have an exchangeable absolute risk across all trials irrespective of the comparator intervention(s) in each trial [12]. This notion of transitive risks stems from the interpretation of the transitivity assumption in Salanti [14]: ‘There are no differences between observed and unobserved relative effects of AC and BC beyond what can be explained by heterogeneity’.

While the assumption of transitive risks might seem difficult to defend in practice, it facilitates the estimation of unique absolute risks for each intervention [12]. Specifically, for the calculation of the absolute risks, we only need (i) the estimated relative treatment effects from NMA (e.g. log OR) for comparisons with the selected reference intervention of the network, and (ii) a sensible assumption about the underlying risk in the reference intervention [12]. Below we illustrate the calculation of the absolute risks following the GRADE concept for binary outcomes [15]. We used the Bayesian framework to estimate the (posterior) median and 95% CrI of the absolute risk for each intervention.

Absolute risks under the assumption of transitive risks

1 With d_k we indicate the posterior mean of the log OR between intervention k ($k =$
2 $B, C, \dots, T$) and reference intervention A . With p_A we imply the underlying risk for the
3 reference intervention that has been selected ideally from observational studies or relevant
4 randomised trials (in the absence of the former) [15]. The GRADE approach advocates the
5 risk ratio (RR) as a measure of the relative effect. However, we used the OR for its statistical
6 advantages and for not requiring constraints to ensure that the probability of an event is within
7 $(0, 1)$ – as opposed to RR [16]. Following Walter [17], we obtain the absolute risk in each
8 intervention as a function of d_k and p_A :

$$p_k = \frac{\exp(d_k)p_A}{1 + p_A(\exp(d_k) - 1)} \quad (1)$$

9 Note that equation (1) is equivalent to the predicted risk for intervention k as described by
10 Dias et al. [18],

$$\text{logit}(p_k) = \text{logit}(p_A) + d_k \quad (2)$$

11 where $\text{logit}(p_A)$ is the log odds of an event in the reference intervention.

12 ***Illustration of obtaining absolute risk assuming transitive risks***

13 Figure 1B presents the network of four types of counselling for smoking cessation (no
14 contact, self-help, individual counselling, and group counselling) [19]. We considered this
15 network to illustrate the estimation of the absolute risk of success (smoking cessation) in each
16 intervention under the assumption of transitive risks (Table S3 in Additional file 1). For
17 illustration, we considered an 8% underlying risk of abstinence from smoking in ‘no contact’
18 (the reference intervention) which is the median risk across the trials that included that
19 intervention. We performed Bayesian random-effects NMA with the incorporation of the

equation (1) in the model. Information on the model implementation is found in Additional file 2.

Table 2 illustrates the estimated OR (posterior mean and 95% CrIs) for all comparisons with ‘no contact’ and the absolute risks for each intervention under the assumption of transitive risks. Group counselling was associated with the highest rate of smoking cessation (0.20 with 95% CrI: 0.10, 0.38), followed by individual counselling (0.17 with 95% CrI: 0.11, 0.25) and self-help (0.12 with 95% CrI: 0.06, 0.24). Note the wide width of 95% CrI in the absolute risks of all interventions, which may be partly attributed to the substantial between-trial variance (posterior median 0.79, 95% CrI: 0.54, 1.21).

[Table 2]

Sample size adjustments for MOD in a future two-arm trial

We plan a future two-arm trial, and we assume an event risk of p_1 and p_2 for the control and experimental intervention, respectively. We use a Z-test to assess the null hypothesis of no difference (i.e. $H_0: p_2 - p_1 = 0$) against the two-sided alternative hypothesis (i.e. $H_A: p_2 - p_1 \neq 0$). Under H_0 , $p_2 - p_1$ is assumed to follow a normal distribution with zero mean and variance $2\bar{p}(1 - \bar{p})/n$ where $\bar{p} = (p_1 + p_2)/2$. Under H_A , $p_2 - p_1$ follows a normal distribution with mean $\Delta \neq 0$ and variance $[p_1(1 - p_1) + p_2(1 - p_2)]/n$. For a pre-specified power at $1 - \beta$, and type I error at α , the required sample size in the absence of MOD is

$$n = \left(\frac{2Z_{1-\alpha/2}\sqrt{\bar{p}(1 - \bar{p})} + Z_{1-\beta}\sqrt{2p_1(1 - p_1) + 2p_2(1 - p_2)}}{p_2 - p_1} \right)^2 \quad (3)$$

where Z_q is the q^{th} percentile of the standard normal distribution [20].

When we expect MOD in the future trial, under the MAR assumption, the required sample size in the future trial with 1:1 randomisation is inflated by $1/(1 - q_k)$ where q_k is the probability of MOD in arm k . Then the required sample size to achieve a power of $1 - \beta$ after adjusting for MOD is

$$n^* = \sum_{k=1}^2 \frac{n}{2} \left(\frac{1}{1 - q_k} \right) \quad (4)$$

Implementation for the motivating example

We performed Bayesian random-effects NMA while modelling MOD under the MAR assumption [7] to adjust for MOD properly, and we incorporated equation (1) into the model to obtain the absolute risks p_1 and p_2 for LABA and tiotropium, respectively, while assuming $p_A = 0.39$ in placebo (median observed event risk across the placebo-controlled trials). We used the estimated p_1 and p_2 in equation (3) to calculate the required sample size before adjusting for the expected MOD in LABA and tiotropium in the future trial. We considered 80% power and 5% type I error.

Subsequently, for each trial, we calculated q_1 and q_2 as the ratio of MOD to the number randomised in each arm. At the pairwise meta-analysis level, we pooled the three trials that compared tiotropium with LABA for the dropouts outcome using the Bayesian random-effects meta-analysis model as described by Dias et al. [21] to obtain q_2 assuming $q_1 = 0.09$ (median event risk in LABA). For the NMA, we used the whole network (Figure 1A) and we worked in line with the pairwise meta-analysis to obtain q_1 and q_2 for LABA and tiotropium, respectively, while assuming $q_A = 0.18$ in placebo (median risk of MOD across the placebo-controlled trials). Finally, we applied equation (4) to obtain the adjusted sample size for that

comparison at (i) the trial level, (ii) pairwise meta-analysis level, and (ii) network meta-analysis level. Information on the technical details of the models is found in Additional file 2.

Results

Absolute risks of the primary outcome (COPD exacerbations)

Figure 2 illustrates the absolute risks of COPD exacerbations for all interventions in the network under the assumption of transitive risks. The posterior median (and 95% CrI) of the absolute risk of COPD exacerbations for LABA and tiotropium were $p_1 = 0.31$ (95% CrI: 0.24 – 0.39) and $p_2 = 0.27$ (95% CrI: 0.21 – 0.34), respectively. After adjusting for MOD, the posterior mean of the OR of COPD exacerbations in tiotropium versus LABA was 0.84 (95% CrI: 0.57 – 1.18) which was similar to the reported OR in the publication: 0.82 (95% CrI: 0.72 – 0.93). However, our results failed to demonstrate conclusive evidence in favour of tiotropium due to substantial missingness in the network. Using equation (3), the total *unadjusted* required sample size for a future trial on tiotropium versus LABA was $n = 4038$ (or 2019 participants per arm).

[Figure 2]

Total sample size adjusted for missing outcome data

Figure 3A summarises the adjusted and unadjusted sample size calculations for the three different levels of evidence. Figure 3B illustrates the corresponding absolute risk of MOD per intervention. At the trial level, q_1 and q_2 for LABA and tiotropium, respectively, were 0.09 and 0.05 in trial one, 0.13 and 0.09 in trial two, and 0.01 and 0.01 in trial three (Figure 3B). Then, using equation (4) for $n = 4038$, the total required sample size after adjusting for MOD in the compared arms was 4344, 4539, and 4079 in the corresponding trials (Figure

3A). Incorporating MOD in the sample size calculation inflated the required sample size by 8%, 12%, and 1% in the corresponding trials. The inflation varied across the trials: trials two and three received the highest and lowest inflation in the sample size calculation, respectively, for having the most and least MOD in the compared arms.

[Figure 3]

At the meta-analysis level, for $q_1 = 0.09$ (assumed) and $q_2 = 0.06$ (posterior median with 95% CrI: 0.03 – 0.10), the total required sample size after adjusting for MOD in LABA and tiotropium was $n^* = 4367$ which was 8% larger than $n = 4038$ (Figure 3A). Using NMA, the posterior median of q_1 and q_2 were 0.13 (95% CrI: 0.11 – 0.15) and 0.10 (95% CrI: 0.08 – 0.12), respectively, for LABA and tiotropium (Figure 3B). Then, using equation (4), the total required sample size after adjusting for MOD was $n^* = 4564$ (Figure 3A) which was 13% larger than $n = 4038$, 5% larger than $n^* = 4367$ in the pairwise meta-analysis, and 1% larger than $n^* = 4539$ in trial 2.

Discussion

This is the first study to illustrate the gains of using NMA instead of a single trial or pairwise meta-analysis to calculate the sample size for a future trial while accounting for expected MOD. With the present work, we aimed to contribute to the growing literature on the importance of NMA in the planning of future trials [22,23] by demonstrating another advantage of NMA to this direction: maximising the information on the extent of MOD to estimate a sufficient sample size for a future trial. Being an inevitable challenge in the conduct and analysis of a clinical trial, MOD should be an integral part of the considerations for the design of a new trial. We illustrated that individual trials and pairwise meta-analysis reflected only a fragment of the extent of MOD for a specific set of interventions and target

1 patient population. Reliance on either evidence to calculate the required sample size led to an
2 underpowered future trial. The implications were also profound when MOD were not
3 considered in the sample size calculation.

4 We acknowledge that we used a simplified framework to select the target comparison and
5 perform the sample size calculation. This is the main limitation of our study. In real-life
6 practice, the costs, treatment availability, and priority for the development of clinical
7 guidelines are among the factors that affect the selection of the target comparison for a future
8 trial [9,22]. Furthermore, considerations on the optimal design of a future study to provide
9 conclusive results include sophisticated methods which are extensions of established methods
10 for clinical trials (e.g. [22,24]). Notably, the design of a future trial is the product of the joint
11 effort of a multidisciplinary group of experts, and is based on regulated processes.
12 Nevertheless, we expect the implications of MOD on the sample size calculation for a future
13 trial, as illustrated in the present study, to be fundamentally the same, regardless of the
14 framework.

15 Furthermore, we considered only one network to illustrate the merits of incorporating
16 MOD from a series of trials into the sample size calculations. An empirical study on a
17 collection of networks from several health fields would demystify the degree of
18 underestimation in the sample size for a new trial when MOD are not accounted for in the
19 design. We acknowledge that an extensive collection of networks with complete information
20 on MOD for each intervention arm of every trial would be a challenging endeavour, as recent
21 evidence on the reporting quality of systematic reviews concerning MOD has been
22 underwhelming [25,26].

23 The findings of the present study revealed the importance of incorporating MOD into the
24 sample size calculation. However, the ubiquity of MOD in all levels of evidence renders

necessary the proper handling of MOD in the analysis. We view the collaboration between statisticians and clinicians as imperative for the successful handling of MOD, especially, at the level of systematic reviews where the extent of MOD is variable across the trials [7,27] and information about the characteristics of missing participants are not available without access to individual patient data [28]. In the light of these limitations, a panel of expert clinicians on the target condition and interventions is crucial for determining the plausible scenarios about the MOD mechanisms. Then, a team of statisticians can integrate these scenarios into a modelling framework (e.g. pattern-mixture model [7,29]) to adjust the NMA results for imminent attrition bias.

Conclusions

We regard the concept of the ‘conditional trial design’ proposed by Salanti et al. [23] as a promising framework to promote a healthy evidence ecosystem. Our proposed framework can be incorporated straightforwardly to the stepwise process of the conditional trial design [23]. Initially, the NMA model is extended to encompass the model for MOD to yield internally coherent relative treatment effects that are adjusted for potential attrition bias (step 1) [7,29]. After deciding on the target comparison(s) (step 2), and the evidence from the NMA is conclusive (step 3), the concept of transitive risks is used to estimate the absolute risk of MOD in the interventions of the target comparison(s). Then, these absolute risks of MOD are included in the sample size calculation for the new trial (step 4).

Abbreviations

COPD: chronic obstructive pulmonary disease; CrI: credible intervals; LABA: long-acting β_2 -agonist; MAR: missing at random; MOD: missing outcome data; %MOD: percentage of missing outcome data; NMA: network meta-analysis; OR: odds ratio; RR: risk ratio.

1 **Declarations**

2 **Ethics approval and consent to participate**

3 Not applicable.

4 **Consent for publication**

5 Not applicable.

6 **Availability of data and materials**

7 All data analysed during this study are included in this article and its supplementary
8 information files.

9 **Competing interests**

10 The author declares no competing interests.

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14 study design; in the collection, analysis, and interpretation of data; in the writing of the report;
15 and in the decision to submit the article for publication.

16 **Authors' contributions**

17 LMS conceived and designed the study; acquired, analysed and interpreted the data; drafted
18 and revised the manuscript. The author read and approved the final manuscript.

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1 Tables

2 **Table 1.** Distribution of percentage missing outcome data in the network

Intervention	Trials	Min.	1 st qrtl.	Median	3 rd qrtl.	Max.
PBO	19	5	13	18	22	44
LABA	14	1	10	14	21	32
ICS	5	0	13	27	31	40
ICS+LABA	5	5	12	28	30	32
TIO	7	1	5	8	9	12
Comparison	Trials	Min.	1 st qrtl.	Median	3 rd qrtl.	Max.
LABA <i>vs.</i> PBO	12	5	13	18	26	38
ICS <i>vs.</i> PBO	5	6	16	29	38	39
ICS <i>vs.</i> LABA	3	29	31	32	33	34
ICS+LABA <i>vs.</i> PBO	5	6	9	31	35	36
ICS+LABA <i>vs.</i> LABA	4	3	23	30	30	31
ICS+LABA <i>vs.</i> ICS	3	28	29	30	33	36
TIO <i>vs.</i> PBO	5	6	10	11	13	16
TIO <i>vs.</i> LABA	3	1	4	7	9	11

3 Note: ICS, inhaled corticosteroid; LABA, long-acting β 2-agonist; Max, maximum; Min,
 4 minimum; PBO, placebo; qrtl, quartile; TIO, tiotropium.

6 **Table 2.** Absolute risks using the assumption of transitive risks

Comparison with	OR (95% CrI)	p_k (95% CrI)
<i>No contact</i>	-	0.08
self-help	1.76 (0.76, 3.59)	0.12 (0.06, 0.24)
individual counselling	2.38 (1.49, 3.74)	0.17 (0.11, 0.25)
group counselling	3.28 (1.31, 7.16)	0.20 (0.10, 0.38)

7 Posterior median of between-trial variance: 0.79 (95% CrI: 0.54, 1.21)

Figure legends

Figure 1. A network of interventions for the maintenance treatment of the exacerbations of chronic obstructive pulmonary disease (network A) [13]. The different colours in the legend refer to the median percentage of missing outcome data across the trials. A network of four types of counselling for smoking cessation (network B) [19]. In both networks, the size of the nodes is proportional to the number of direct treatment comparisons that include that node, and the thickness of the links is proportional to the number of trials investigating the corresponding comparisons. ICS, inhaled corticosteroid; LABA, long-acting β 2-agonist

Figure 2. Barplots with error bars on the posterior median (and 95% credible interval) of the absolute risk of chronic obstructive pulmonary disease (COPD) exacerbation for each intervention in the network [13] under the assumption of transitive risks. Each bar indicates the number of COPD exacerbations per 100 participants who took the intervention. Placebo was the reference intervention in the network. We considered an underlying risk $p_A = 0.39$ for placebo to obtain the absolute risks for the remaining interventions in the network. ICS, inhaled corticosteroid; LABA, long-acting β 2-agonist

Figure 3. Plot A is a barplot on the total required sample size for a future trial on tiotropium versus LABA after adjusting for missing outcome data (MOD) in three different levels of evidence: individual trials, pairwise and network meta-analysis. The horizontal black line refers to the unadjusted total required sample size. On each bar, the percentage refers to the corresponding percentage inflation in the total required sample size when MOD are incorporated in the sample size calculation. Plot B is a barplot with heaped bars on the predicted number of MOD per 100 participants for each intervention of the target comparison in three different levels of evidence. LABA, long-acting β 2-agonist

Supplementary files

Additional file 1: Supplementary Tables (DOCX 39 KB)

Additional file 2: Technical details (DOCX 36 KB)

Figures

Figure 1

A network of interventions for the maintenance treatment of the exacerbations of chronic obstructive pulmonary disease (network A) [13]. The different colours in the legend refer to the median percentage of missing outcome data across the trials. A network of four types of counselling for smoking cessation (network B) [19]. In both networks, the size of the nodes is proportional to the number of direct treatment comparisons that include that node, and the thickness of the links is proportional to the number of trials investigating the corresponding comparisons. ICS, inhaled corticosteroid; LABA, long-acting β 2-agonist

Figure 2

Barplots with error bars on the posterior median (and 95% credible interval) of the absolute risk of chronic obstructive pulmonary disease (COPD) exacerbation for each intervention in the network [13] under the assumption of transitive risks. Each bar indicates the number of COPD exacerbations per 100 participants who took the intervention. Placebo was the reference intervention in the network. We considered an underlying risk $p_A=0.39$ for placebo to obtain the absolute risks for the remaining interventions in the network. ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist

Figure 3

Plot A is a barplot on the total required sample size for a future trial on tiotropium versus LABA after adjusting for missing outcome data (MOD) in three different levels of evidence: individual trials, pairwise and network meta-analysis. The horizontal black line refers to the unadjusted total required sample size. On each bar, the percentage refers to the corresponding percentage inflation in the total required sample size when MOD are incorporated in the sample size calculation. Plot B is a barplot with heaped bars on the predicted number of MOD per 100 participants for each intervention of the target comparison in three different levels of evidence. LABA, long-acting β_2 -agonist

Supplementary Files

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- [Additionalfile1SupplementaryTables.docx](#)
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