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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Abstract

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

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

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

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

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

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

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

There is already published methodology on the planning of future trials based on systematic reviews [8–10]. However, this methodology does not take into account the effect
of MOD on the sample size calculations for a future trial. Considering a fictional two-arm trial for illustration, Cook and Zea [11] performed a sensitivity analysis to investigate how the amount of MOD and different assumptions about the missingness mechanisms in the compared arms can influence the sample size calculations for a future trial. The authors demonstrated that the required sample size to achieve the desired power was dramatically larger when the calculations were based on the sensitivity analysis as compared to ignoring MOD altogether [11]. To the best of our knowledge, there is currently no research at the level of evidence synthesis to demonstrate the implications on sample size calculations when MOD from a series of relevant past trials are incorporated into the design of a future trial.

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

The present study aims to illustrate the advantages of using NMA rather than a trial or a 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 (≤ 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 β2-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
With $d_k$ we indicate the posterior mean of the log OR between intervention $k$ ($k = B, C, ..., T$) and reference intervention $A$. With $p_A$ we imply the underlying risk for the reference intervention that has been selected ideally from observational studies or relevant randomised trials (in the absence of the former) [15]. The GRADE approach advocates the risk ratio (RR) as a measure of the relative effect. However, we used the OR for its statistical advantages and for not requiring constraints to ensure that the probability of an event is within $(0, 1)$ – as opposed to RR [16]. Following Walter [17], we obtain the absolute risk in each intervention as a function of $d_k$ and $p_A$:

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

(1)

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

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

(2)

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

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

Figure 1B presents the network of four types of counselling for smoking cessation (no contact, self-help, individual counselling, and group counselling) [19]. We considered this network to illustrate the estimation of the absolute risk of success (smoking cessation) in each intervention under the assumption of transitive risks (Table S3 in Additional file 1). For illustration, we considered an 8% underlying risk of abstinence from smoking in ‘no contact’ (the reference intervention) which is the median risk across the trials that included that 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 $\alpha$, the required sample size in the absence of MOD is

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

(3)

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

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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

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

(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 10).
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.
patient population. Reliance on either evidence to calculate the required sample size led to an
underpowered future trial. The implications were also profound when MOD were not
considered in the sample size calculation.

We acknowledge that we used a simplified framework to select the target comparison and
perform the sample size calculation. This is the main limitation of our study. In real-life
practice, the costs, treatment availability, and priority for the development of clinical
guidelines are among the factors that affect the selection of the target comparison for a future
trial [9,22]. Furthermore, considerations on the optimal design of a future study to provide
conclusive results include sophisticated methods which are extensions of established methods
for clinical trials (e.g. [22,24]). Notably, the design of a future trial is the product of the joint
effort of a multidisciplinary group of experts, and is based on regulated processes.

Nevertheless, we expect the implications of MOD on the sample size calculation for a future
trial, as illustrated in the present study, to be fundamentally the same, regardless of the
framework.

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

The findings of the present study revealed the importance of incorporating MOD into the
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 β2-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.
Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The author declares no competing interests.

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Authors' contributions

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

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### Tables

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

| Intervention | Trials | Min. | 1st qrtl. | Median | 3rd 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. | 1st qrtl. | Median | 3rd qrtl. | Max. |
|--------------|--------|------|-----------|--------|-----------|------|
| LABA vs. PBO | 12     | 5    | 13        | 18     | 26        | 38   |
| ICS vs. PBO  | 5      | 6    | 16        | 29     | 38        | 39   |
| ICS vs. LABA | 3      | 29   | 31        | 32     | 33        | 34   |
| ICS+LABA vs. PBO | 5      | 6    | 9         | 31     | 35        | 36   |
| ICS+LABA vs. LABA | 4    | 3    | 23        | 30     | 30        | 31   |
| ICS+LABA vs. ICS | 3    | 28   | 29        | 30     | 33        | 36   |
| TIO vs. PBO  | 5      | 6    | 10        | 11     | 13        | 16   |
| TIO vs. LABA | 3      | 1    | 4         | 7      | 9         | 11   |

Note: ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; Max, maximum; Min, minimum; PBO, placebo; qrtl, quartile; TIO, tiotropium.

#### Table 2. Absolute risks using the assumption of transitive risks

| Comparison with | OR (95% CrI) | $p_k$ (95% CrI) |
|-----------------|--------------|-----------------|
| No contact      | -            | 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) |

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 β2-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 β2-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 β2-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 β2-agonist
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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 β2-agonist

Supplementary Files

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- Additionalfile1SupplementaryTables.docx
- Additionalfile2Technicaldetails.docx