Chapter 4.

Sequential meta-analysis to determine whether or not to start another trial: the high frequency versus conventional mechanical ventilation example

Sequential analysis shows value of new trials

Casper W. Bollen,

Cuno S.P.M. Uiterwaal,

Adrianus J. van Vught,

Ingeborg van der Tweel

Submitted

ABSTRACT

Background

Clinical trials can be stopped early based on interim analyses or sequential analyses. Sequential analyses could also be applied to decide if already enough evidence is gathered in previous trials. In a number of clinical trials, high frequency ventilation has been compared with conventional mechanical ventilation in premature neonates with idiopathic respiratory distress syndrome. Sequential meta-analysis was used to determine whether more trials have to be performed.

Methods

Five trials were selected that compared high frequency ventilation applying a high lung volume strategy with conventional mechanical ventilation using a lung protective ventilation strategy. Death or chronic lung disease and chronic lung disease in survivors were primary clinical outcomes of interest. Sequential meta-analyses were applied to these five studies.

Results

After including the first study of the last five trials in a sequential meta-analysis, the boundary of no clinically relevant effect was crossed for the outcome, death or chronic lung disease. A sensitivity analysis using a reduction in the size of assumed clinically relevant effect showed the same findings after two trials. The same result was found for reduction of chronic lung disease in survivors as outcome.

Conclusions

Sequential meta-analyses showed that already in the first out of five studies a lack of clinically relevant effect was established of high frequency oscillatory ventilation compared with conventional mechanical ventilation in premature neonates. This could have been an important argument in decisions to change the study design or even refrain from performing the last four trials.

Introduction

Whether or not to start a randomized clinical trial (RCT) should depend on the expected ability of the yielded evidence in such a trial to change current clinical opinion, taking into account previously obtained evidence. It is a matter of good statistical practice to make a prior estimate of the required size of a randomized clinical trial, based on the expected clinically relevant difference between treatments, the power 1-β and the significance level α. Stopping randomized clinical trials early, before the estimated fixed size is reached, is readily accepted for ethical or economical reasons. One or more interim analyses can be planned to determine whether enough evidence has been obtained to discontinue a trial prematurely. Interim analyses are performed on cumulative data of patients successively included in a RCT. Sequential testing is a collective noun for these interim analyses. We speak of continuous sequential testing, when cumulative data are analyzed after every new patient response.

Group sequential testing is a series of interim analyses after every new group of patient responses. A meta-analysis pools the results of a number of comparable RCTs in a systematic and quantitative way [1]. A cumulative meta-analysis can be viewed as a number of interim analyses on the aggregated data of successive, chronologically ordered RCTs. A cumulative meta-analysis is thus a group sequential test, but each group now represents patients from another trial [2]. In the following we will introduce the sequential meta-analysis as a particular form of a cumulative meta-analysis with adjustment for multiple testing and a guaranteed power (see Discussion for further comments). We applied a sequential meta-analysis to determine whether or not enough evidence was gathered already in a number of published RCTs.

Avoidance of ventilator induced lung damage is a major issue in research of mechanical ventilation. It is generally thought that prevention of repeated collapse of alveoli and limiting overdistension of alveoli protects the lung from the adverse effects of mechanical ventilation [3]. Therefore, lung protective ventilation strategies aim at reducing tidal volumes and maintaining higher mean airway pressures. A considerable number of randomized clinical trials have been performed to determine whether high frequency oscillatory ventilation improves pulmonary outcome in premature neonates with idiopathic respiratory distress syndrome compared with conventional mechanical ventilation [4-16]. High frequency oscillatory ventilation is a method of ventilation in which alveolar gas exchange is maintained by pressure swings initiating small displacements of ventilatory gases, considerably smaller than conventional tidal volumes, at frequencies generally from 5-20 Hz superimposed on a continuous positive pressure. High frequency oscillatory ventilation allows higher end-expiratory pressures with lower tidal volumes and higher mean airway pressures and is therefore proposed as currently the most optimal form of lung protective ventilation [17;18].

Two recent large randomized controlled trials failed to demonstrate a significant advantage of high frequency oscillatory ventilation over conventional mechanical ventilation, or showed only a small benefit [14;15]. A meta-analysis showed no reduction in mortality. However, a small reduction was shown in the risk of chronic lung disease at 36-37 weeks post-gestational age [19]. Our study used sequential meta-analysis to determine at what point in time additional trials did not contribute anymore to available evidence.

Methods

In a previous report we identified 13 studies in which high frequency ventilation was compared with conventional mechanical ventilation in the treatment of idiopathic respiratory distress syndrome in premature neonates [20]. The last five studies were comparable with respect to patient population, type of high frequency ventilation (oscillator) and ventilation strategies that were applied in both high frequency oscillatory ventilation and conventional mechanical ventilation [11;13-16]. These five studies were included chronologically in our sequential meta-analysis. The following data were extracted: gestational age or birth weight; time of inclusion; type of high frequency ventilator; ventilation strategies applied in both treatment arms; primary outcome measurements; power and estimated effect size upon which power analysis was based. The following outcome measures were identified: chronic lung disease, defined as oxygen dependency at the postconceptional age of 36 weeks; mortality to 36 weeks of age; intraventricular hemorrhage grade III and IV; and periventricular leukomalacia.

A high lung volume strategy with high frequency ventilation was assumed if two or more of the following items were explicitly stated in the methods: initial use of a higher mean airway pressure than on conventional mechanical ventilation; initial lowering of inspired oxygen before reducing mean airway pressure; and/or use of alveolar recruitment maneuvers. A lung protective strategy in the conventional mechanical ventilation group was based on specifying the PaCO2 goal, allowing permissive hypercapnia, and a high initial ventilatory rate and/or explicit avoidance of high peak inspiratory pressures, targeted at reducing tidal volumes.

Statistical analysis

An a priori estimate of the expected effect size of the primary outcome was deduced from reported expected clinically relevant differences in power analyses of included studies. A probability of 0.05 for a type I error and a power of 0.80 were specified in our sequential meta-analyses Sensitivity analyses were performed diminishing the expected differences in effect estimates and excluding studies by Thome et al [11] and Moriette et al [13] from the analyses. Those last studies were excluded in sensitivity analysis because of methodological reasons. Thome et al [11] used a different type of HFV ventilator and the HFV used by Moriette et al [13] was withdrawn from market. Reducing the size of clinically interesting effect would ordinarily require a larger sample size for that difference to be detected. Sensitivity analysis thus was conducted to rule out the need for more trials to establish smaller clinically relevant differences. All data were extracted according to the intention-to-treat principle. For the outcome chronic lung disease or death, the total number of randomized patients was put in the denominator with patients that died or with chronic lung disease in the numerator. To calculate the risk of chronic lung disease, the denominator was equal to the number of patients that survived and the numerator was equal to the number of patients with CLD.. Intraventricular hemorrhage grade III and IV and periventricular leukomalacia were determined with the number of randomized patients in the denominator. Statistical heterogeneity between trials was investigated by calculating the test statistic I^2 ($I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom) [21].

Sequential meta-analysis

The ith of the chronologically appeared RCTs contributes two quantities V_i and Z_i to the cumulative amount of information. V_i is a measure for the amount of information in that RCT, i.e. V_i is approximately proportional to the number of patients included in that RCT. Z_i is a measure for the effect

size in that RCT. After every new RCT the total amount of information is cumulated in $V = \Sigma V_i$ and $Z = \Sigma Z_i$. Z and V are thus the pooled results from different trials and the sequential meta-analysis can be viewed as a stratified analysis (see Appendix). Every new RCT thus results in a new (Z,V)-point, depicted in a graph with V on the horizontal and Z on the vertical axis. Four boundaries are plotted in the graph. These boundaries depend on the two-sided type I error α, the power $1-\beta$ and the expected effect size (in terms of the logarithm of the odds ratio (OR)) as stated under the alternative hypothesis. If the successive (Z,V)-points cross the upper or lower boundary, the sequential meta-analysis can be stopped: the null hypothesis of treatment equivalence is rejected in favour of the alternative hypothesis, i.e. significant evidence is gathered for the expected effect size. If the successive (Z,V)-points cross one of the inner, wedge-shaped boundaries, the sequential meta-analysis can be stopped for 'futility': the null hypothesis is accepted, i.e. it is very unlikely that the treatments will be concluded different in the amount as stated under the alternative hypothesis. If the successive (Z,V)-points remain within the triangular boundaries, results of a new RCT are added to the analysis. The outer straight-line boundaries represent the theoretical limits for decision-making. The inner, curved boundaries represent a continuity correction, because the unit of analysis is the trial (a group of patients) and not the individual patient. (For illustration see Figures 1 and 2). Specifically, when one of the inner boundaries is crossed one can stop the analysis.
For further details on the construction of the boundaries and on sequential analysis see ref. 1, 22 and 23 [1;22;23].

Results

Five high frequency ventilation studies were evaluated with a total number of 2152 patients randomized. Those five trials used both a high frequency

oscillatory ventilator with a high lung volume strategy in the high frequency oscillatory ventilation group, and a lung protective ventilation strategy in the conventional mechanical ventilation group. In Table 1 the exact numbers of the outcomes of interest are tabulated. The cumulative evidence of those five studies comparing high frequency oscillatory ventilation with conventional mechanical ventilation showed an OR of 0.92 (95% CI 0.77-1.09) for death or chronic lung disease, an OR of 0.98 (95% CI 0.80-1.21) for chronic lung disease in survivors, an OR of 1.01 (95% CI 0.79-1.29) for intraventricular hemorrhage grade III and IV and an OR of 0.90 (95% CI 0.62-1.33) for periventricular leukomalacia.

Table 1. Randomized Clinical Trials comparing high frequency ventilation with conventional mechanical ventilation.

	Author	Year	HLVS	LPVS	Death or CLD at 36 weeks or discharge		CLD 36 weeks in survivors	
					HFOV	*CMV*	*HFOV*	*CMV*
1	Thome	1999	Y	Y	43/140 (31%)	44/144 (31%)	32/126 (25%)	30/129 (23%)
2	Moriette	2001	Y	Y	55/148 (37%)	57/144 (40%)	24/105 (23%)	30/107 (28%)
3	Courtney	2002	Y	Y	103/244 (42%)	133/254 (52%)	70/201 (35%)	93/210 (44%)
4	Johnson	2002	Y	Y	265/400 (66%)	268/397 (68%)	165/300 (55%)	163/292 (56%)
5	Reempts	2003	Y	Y	49/147 (33%)	39/153 (25%)	24/122 (20%)	19/133 (14%)

	Author	Year	HLVS	LPVS	IVH		PVL	
					HFOV	*CMV*	*HFOV*	*CMV*
1	Thome	1999	Y	Y	19/140 (14%)	18/144 (13%)	3/140 (2%)	0/144 (0%)
2	Moriette	2001	Y	Y	34/148 (23%)	19/144 (13%)	14/148 (9%)	18/144 (13%)
3	Courtney	2002	Y	Y	45/244 (18%)	45/254 (18%)	18/244 (7%)	26/254 (10%)
4	Johnson	2002	Y	Y	38/400 (10%)	55/397 (14%)	8/400 (2%)	8/397 (2%)
5	Reempts	2003	Y	Y	14/147 (10%)	13/153 (8%)	11/147 (7%)	8/153 (5%)

Table 1. HLVS: high lung volume strategy in high frequency ventilation. LPVS: lung protective ventilations strategy in conventional mechanical ventilation. CLD: chronic lung disease at 36 weeks postconceptional age. HFOV: high frequency oscillatory ventilation. CMV: conventional mechanical ventilation.

Table 2. Study design of the last five trials.

Author	Year	Patients		Outcome	Power analysis		
		Age or Weight	*Time (hours)*	*Primary*	*Effect*	*alpha*	*power*
Thome	1999	≥24 and <30 wks	6	treatment failures	difference of 12%	0.05	0.80
Moriette	2001	≥24 and ≤29 wks	6	death or chronic lung disease at 28 days	improvement from 45% to 65%	0.05	0.80
Courtney	2002	601 to 1200 g	4	death or chronic lung disease at 36 weeks	improvement from 50% to 65%	0.05	0.90
Johnson	2002	23 to 28 wks + 6 d	1	death or chronic lung disease at 36 weeks	difference of 9-11%	0.05	0.90
Reempts	2003	<32 wks	6	death or chronic lung disease at 36 weeks	reduction of 60%	0.05	0.80

Table 2. Study design of the last five trials. Time: Age at randomization in hours.

In Table 2 the patient groups, primary outcomes and sample size specifications are mentioned. All studies included very low birth weight patients. Time prior to randomization was no more than 6 hours. Thome et al and Moriette et al used variants of the definition for the primary outcome upon which a power analysis was based [11;13]. However, in both studies death and chronic lung disease were part of the primary outcome. Overall, a reduction in death or chronic lung disease of 15% was expected (corresponding to an OR of 0.54). All trials specified a value of 0.05 for the type I error α. Power for detecting a difference was 0.80 or 0.90.

Treatment with high frequency oscillatory ventilation was comparable between trials (Table 3). Two trials used the SensorMedics ventilator, in two studies the Infant Star was used and Moriette et al used an OHF 1 Dufour ventilator [13]. Mean airway pressure was 2 cmH2O above MAP measured on conventional mechanical ventilation in 2 trials and varied from 6 to 16 cmH2O depending on gestational age of the patient or on FiO2 that was needed. In all but one trial, MAP was decreased only if FiO2

was less than 0.3-0.4. The ventilation strategy in the conventional mechanical ventilation groups did not differ much either between trials. Frequency was set at 60-80 breaths/min and a PEEP of at least 3 cmH2O was applied. Peak inspiratory pressures were explicitly limited in three studies and in all trials a certain amount of hypercapnia was accepted up to 50-70 mmHg. Inconsistency in primary outcome assessed by I^2 was 7.5%, indicating a low percentage of total variation across studies due to heterogeneity.

Sequential meta-analysis showed that one trial already provided enough evidence for no reduction in death or chronic lung disease of 15% (Figure 1). In a sensitivity analysis decreasing the effect to be a reduction of 10% it took only two trials before the boundary for no such reduction was crossed (OR=0.97 with 95% CI(0.68-1.41)). Sensitivity analysis excluding the studies by Thome et al and Moriette et al resulted in an OR of 0.98 (95% CI (0.68 ; 1.39) (data not shown). The same result was found with chronic lung disease as outcome with an estimated effect of 15% reduction (Figure 2). After one trial, by Thome et al, the boundary for no such reduction was crossed (OR=0.89 with 95% CI(0.50-1.58)) [11]. Sequential analyses were also applied with intraventricular hemorrhage grade III and IV and periventricular leukomalacia as outcome measures. For both outcomes there was not enough evidence to draw a definitive conclusion yet (data not shown).

Discussion

To be of value, a new RCT must add to current knowledge. Assessing whether clinical equipoise was present at the start of a new RCT should be general research practice [24]. *"Science is meant to be cumulative, but many scientists are not cumulating scientifically."* (Chalmers in his Comment

Figure 1. CLD or death: 50% (CMV) versus 35% (HFOV)

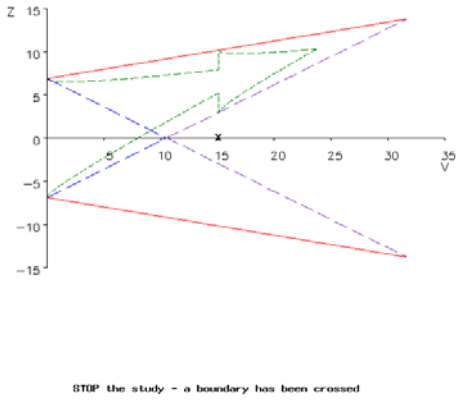
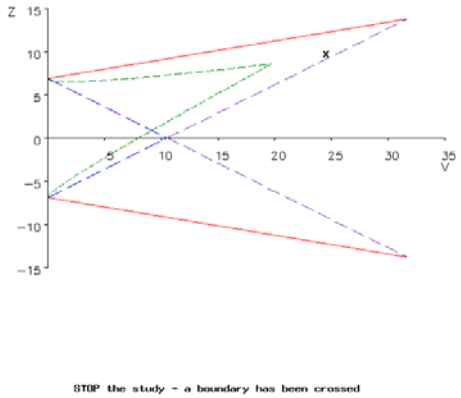


Figure 2. CLD: 50% (CMV) versus 35% (HFOV)



Legend of Figures 1 and 2.

CLD: Chronic Lung Disease. CMV: Conventional Mechanical Ventilation. HFOV: High Frequency Oscillatory Ventilation. The horizontal axis denotes the cumulative amount of information (V) (i.e. a function of the number of patients included). The vertical axis denotes a measure for the cumulative effect size (Z). When one of the upper or lower lines is crossed, the null hypothesis of treatment equivalence is rejected. When one of the inner, wedge-shaped boundariesis crossed, the null hypothesis is accepted. The x-symbol reflects the contribution of the one decisive study. The dashed lines within the straight-line boundaries represent a continuity correction. (see text and Appendix for further explanation.)

on Fergusson et al. (2005)) [25]. Cumulative meta-analysis is recognized as a systematic review technique. Various authors performed cumulative meta-analyses of RCTs on different research questions (amongst others, Lau et al. (1992); Fergusson et al. (2005)) [24;26]. The general approach used is to perform an analysis of the currently available studies and to test the null hypothesis that the two treatments are equally effective. If the test result is not significant, a new trial is added (when its results become available) and the analysis and testing procedure is repeated. This approach continues until a statistically significant result is found, i.e. the null hypothesis is rejected. Berkey et al. (1996) noticed that this general approach does not adjust for the multiple testing and lacks a formal stopping rule and a quantification of the power of the conclusion [27]. We performed a sequential meta-analysis according to the approach as described by A. Whitehead (1997) [28]. Using this approach the overall significance level α (the type I error) is preserved, thus preventing the increase of the cumulative α by multiple testing. Moreover, a prespecified power to detect a clinically relevant treatment difference is guaranteed. Furthermore, this approach permits stopping when enough evidence is gathered either to reject the null hypothesis of treatment equivalence or to accept it.

This is a second report that discusses the relevance of new trials using sequential meta-analysis. In trials with high frequency oscillatory ventilation versus conventional mechanical ventilation as an elective treatment of idiopathic respiratory distress syndrome in premature neonates, a reduction in the composite outcome of death or chronic lung disease at 36 weeks of 10% to 15% was expected. However, after one trial sequential meta-analysis showed no evidence for such reduction. Yet, four more studies were performed, powered to show the same amount of effect [14-16].

To compare trials, equality of treatment between trials is an important requirement. In a recent article we showed that ventilation strategies in high frequency oscillatory ventilation and conventional mechanical ventilation have changed in recent years [20]. In a cumulative meta-analysis ventilation strategies were an important source of heterogeneity between trials. In the last five trials, however, ventilation strategies were comparable and results were homogeneous between trials. A more formal approach showed that only a small amount of variation between trials was due to heterogeneity.

The most important differences between trials consisted of two major advancements in the therapy of idiopathic respiratory distress syndrome: the use of surfactant therapy and the application of a lung protective strategy in patients on conventional mechanical ventilation [20;29]. Both modalities have been applied in the last five trials. In the only trial that showed a reduction in chronic lung disease, the conventional mechanical ventilation therapy was most rigidly controlled [14]. Therefore, it seems unlikely that in daily practice the same difference between high frequency oscillatory ventilation and conventional mechanical ventilation will occur [30]. Various high frequency oscillatory ventilation devices have been applied in different trials. However, we showed that these differences did not explain heterogeneity between trials [20]. Sensitivity analyses excluding studies by Thome et al [11] for use of a flow interrupter type of HFOV and Moriette et al [13] for use of a ventilator that was subsequently withdrawn from the market showed the robustness of our analyses. Furthermore, it has been demonstrated that when applying the same ventilatory objectives, differences between devices are irrelevant because settings are adjusted to achieve the desired effect resulting in comparable high frequency oscillatory ventilation treatment [31;32].

Table 3. Ventilation strategies of the last five trials.

Author	Year	HFOV strategy				
		Ventilator	*Frequency*	*Mean Airway Pressure*	*FiO2*	*Chest X-ray*
Thome	1999	Infant Star	10 Hz	1-2 cmH2O above MAP on CMV; 10-12 cmH2O when primary HFOV	MAP increased until FiO2<0.3	ninth pair of ribs
Moriette	2001	OHF1	Not stated	14 cmH2O if FiO2 < 0.4; 16 cmH2O if FiO2>0.4	MAP increased until FiO2<0.4	Not stated
Courtney	2002	SensorMedics 3100A	10 to 15 Hz	≥2 cmH2O above MAP on CMV	Not stated	expansion to 8 to 9.5 ribs
Johnson	2002	Dräger Babylog 8000; SensorMedics 3100A; SLE 2000HFO	10 Hz	6-8 cmH2O	MAP increased until FiO2<0.3	ninth pair of ribs
Reempts	2003	Infant Star	Not stated	8 cm H2O if <29 weeks; 10 cm H2O if 29–31 6/7 weeks	Not stated	ninth pair of ribs
Author	**Year**	**CMV strategy**				
		Frequency	*PEEP*	*PIP*	*Tidal Volume*	*pCO2*
Thome	1999	60-80 /min	≥3 cmH2O	PIP as low as possible	Not stated	40-60 mm Hg; to 70 mm Hg after the 7th day
Moriette	2001	Not stated	4-5 cmH2O	PIP as low as possible	Not stated	40-50 mm Hg
Courtney	2002	≤60 /min	4-6 cmH2O	Not stated	4-7 ml/kg	40-55 mm Hg; 45 to 65 mm Hg if CLD
Johnson	2002	60 /min	Not stated	Not stated	Not stated	34-53 mm Hg
Reempts	2003	80 /min	4-8 cmH2O	20-30 cmH20	6–8 ml/kg	35-45 mmHg during the acute phase; up to 70 mmHg later

All trials were powered to show a relative reduction of chronic lung disease in survivors using high frequency oscillatory ventilation with a high lung volume strategy compared with conventional mechanical ventilation applying a lung protective strategy. In only one of these trials an improvement in pulmonary outcome was demonstrated that was statistically significant [14]. The inability of the last four trials to change the evidence that there was no improvement to pulmonary outcome was robust to smaller differences in effect size in a sensitivity analysis. With respect to other important clinical outcomes, intraventricular hemorrhage grade III and IV and periventricular leukomalacia, the last five trials did not result in enough evidence to draw definitive conclusions yet. Uncertainty remained as to whether high frequency oscillatory ventilation resulted in more intraventricular hemorrhage grade III and IV and/or periventricular leukomalacia.

In general, a clinical trial is undertaken to test relevant clinical treatment effects. The size of a trial is estimated by a power analysis that is based on an expected effect size and chosen probabilities for type I and II errors. However, this does not answer the question whether this new trial will be able to adjust the available cumulative evidence sufficiently to conclude that a clinically relevant effect can be refuted or accepted. By performing a sequential analysis, i.e. a sequential meta-analysis of earlier comparable trials it can be decided whether enough cumulative evidence has been gathered already to render another trial uninformative. Sequential analysis is already an accepted procedure within a trial. In this report we demonstrated that performing a sequential meta-analysis before starting three randomized trials comparing high frequency oscillatory ventilation with conventional mechanical ventilation could have resulted in a different study design aimed at investigating other more promising hypotheses (e.g. accepting smaller differences in primary outcome in the power analysis or choosing other primary outcome variables).

We think that, in addition to a power analysis, sequential meta-analysis of earlier comparable studies should be an integral part in the planning and design of new randomized trials. As we have shown in this report, the results of sequential meta-analyses can have major consequences for study design or even result in the decision to refrain from starting another trial.

Summarizing, before expanding existing experimental evidence by starting a new randomized clinical trial, it is useful to perform a sequential meta-analysis, to determine whether a treatment effect has already been convincingly established by cumulative evidence of previous trials. Sequential meta-analysis may result in decisions to change study design or even refrain from performing additional randomized trials designed to show the same objectives.

APPENDIX

Suppose k RCTs are available for a sequential meta-analysis. All RCTs compare the same experimental treatment E with a control treatment C and all have the same dichotomous outcome (event or no event). Results from the ith RCT (I=1,…,k) can be summarized in a two-by-two table (Table X).

Table X.

ith RCT	E(xperimental)	C(ontrol)	overall
event	S_{Ei}	S_{Ci}	S_i
no event	F_{Ei}	F_{Ci}	F_i
total	N_{Ei}	N_{Ci}	N_i

The proportions of events with the experimental and with the control treatment are

$P_{Ei} = S_{Ei} / N_{Ei}$ and $P_{Ci} = S_{Ci} / N_{Ci}$, respectively.

The logarithm of the odds ratio, as a measure for association between treatment and outcome, is defined as

$$\theta_i = \log\left\{\frac{P_{Ei}(1-P_{Ci})}{P_{Ci}(1-P_{Ei})}\right\}.$$

The test statistic Z_i is expressed as the difference between the observed number of events with E in the ith RCT (S_{Ei}) and the expected number under the null hypothesis of treatment equivalence.

$$Z_i = S_{Ei} - N_{Ei}S_i / N_i.$$

The statistic V_i, the variance of Z_i, is defined as

$$V_i = \frac{N_{Ei}N_{Ci}S_iF_i}{N_i^2(N_{i-1})}$$

The pooled estimate for the overall θ is equal to

$$\hat{\theta} = \frac{\sum_i \hat{\theta}_i w_i}{\sum_i w_i} = \frac{\sum_i Z_i}{\sum_i V_i}, \text{ with } \hat{\theta}_i = \frac{Z_i}{V_i} \text{ as the estimated log(OR)}$$

for the ith RCT and the weighting factor $w_i = V_i$.

An approximate 95% confidence interval for θ can be estimated by

$$\hat{\theta} \pm 1.96 \sqrt{\frac{1}{\sum_i w_i}}.$$

(For further details see References 1, 22 and 23.)

Reference List

1. Whitehead A,.Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat.Med.* 1991;**10**:1665-77.

2. Young C,.Horton R. Putting clinical trials into context. *Lancet* 2005;**366**:107-8.

3. MacIntyre NR. Current issues in mechanical ventilation for respiratory failure. *Chest* 2005;**128**:561S-7S.

4. Froese AB, Butler PO, Fletcher WA, Byford LJ. High-frequency oscillatory ventilation in premature infants with respiratory failure: a preliminary report. *Anesth.Analg.* 1987;**66**:814-24.

5. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. The HIFI Study Group. *N.Engl.J.Med.* 1989;**320**:88-93.

6. Carlo WA, Siner B, Chatburn RL, Robertson S, Martin RJ. Early randomized intervention with high-frequency jet ventilation in respiratory distress syndrome [see comments]. *J.Pediatr.* 1990;**117**:765-70.

7. Ogawa Y, Miyasaka K, Kawano T, Imura S, Inukai K, Okuyama K *et al*. A multicenter randomized trial of high frequency oscillatory ventilation as

compared with conventional mechanical ventilation in preterm infants with respiratory failure. *Early Hum.Dev.* 1993;**32**:1-10.

8. Wiswell TE, Graziani LJ, Kornhauser MS, Cullen J, Merton DA, McKee L *et al*. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics* 1996;**98**:1035-43.

9. Keszler M, Modanlou HD, Brudno DS, Clark FI, Cohen RS, Ryan RM *et al*. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome [see comments]. *Pediatrics* 1997;**100**:593-9.

10. Rettwitz-Volk W, Veldman A, Roth B, Vierzig A, Kachel W, Varnholt V *et al*. A prospective, randomized, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant [see comments]. *J.Pediatr.* 1998;**132**:249-54.

11. Thome U, Kossel H, Lipowsky G, Porz F, Furste HO, Genzel-Boroviczeny O *et al*. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure [see comments]. *J.Pediatr.* 1999;**135**:39-46.

12. Plavka R, Kopecky P, Sebron V, Svihovec P, Zlatohlavkova B, Janus V. A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respiratory distress syndrome. *Intensive.Care Med.* 1999;**25**:68-75.

13. Moriette G, Paris-Llado J, Walti H, Escande B, Magny JF, Cambonie G *et al*. Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome. *Pediatrics* 2001;**107**:363-72.

14. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N.Engl.J.Med.* 2002;**347**:643-52.

15. Johnson AH, Peacock JL, Greenough A, Marlow N, Limb ES, Marston L *et al*. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. *N.Engl.J.Med.* 2002;**347**:633-42.

16. Van Reempts P, Borstlap C, Laroche S, Van der Auwera JC. Early use of high frequency ventilation in the premature neonate. *Eur.J.Pediatr.* 2003;**162**:219-26.

17. Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! *Crit Care Med.* 1997;**25**:906-8.

18. Froese AB. The incremental application of lung-protective high-frequency oscillatory ventilation. *Am.J.Respir.Crit Care Med.* 2002;**166**:786-7.

19. Henderson-Smart DJ, Bhuta T, Cools F, Offringa M. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane.Database.Syst.Rev.* 2003;CD000104.

20. Bollen CW, Uiterwaal CS, van Vught AJ. Cumulative metaanalysis of high-frequency versus conventional ventilation in premature neonates. *Am.J.Respir.Crit Care Med.* 2003;**168**:1150-5.

21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.

22. PEST 4: Operating Manual. MPS Research Unit. 2000. The University of Reading.

23. Whitehead J. The design and analysis of sequential clinical trials. Chichester: John Wiley & Sons Ltd, 1997.

24. Fergusson D, Glass KC, Hutton B, Shapiro S. Randomized controlled trials of aprotinin in cardiac surgery: could clinical equipoise have stopped the bleeding? *Clin.Trials* 2005;**2**:218-29.

25. Chalmers I. The scandulous failure of science to cumulate evidence scientifically. *Clin.Trials* 2005;**2**:229-31.

26. Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N.Engl.J.Med.* 1992;**327**:248-54.

27. Berkey CS, Mosteller F, Lau J, Antman EM. Uncertainty of the time of first significance in random effects cumulative meta-analysis. *Control Clin.Trials* 1996;**17**:357-71.

28. Whitehead A. A prospectively planned cumulative meta-analysis applied to a series of concurrent clinical trials. *Stat.Med.* 1997;**16**:2901-13.

29. Froese AB,.Kinsella JP. High-frequency oscillatory ventilation: lessons from the neonatal/pediatric experience. *Crit Care Med.* 2005;**33**:S115-S121.

30. Stark AR. High-frequency oscillatory ventilation to prevent bronchopulmonary dysplasia--are we there yet? *N.Engl.J.Med.* 2002;**347**:682-4.

31. Hatcher D, Watanabe H, Ashbury T, Vincent S, Fisher J, Froese A. Mechanical performance of clinically available, neonatal, high-frequency, oscillatory-type ventilators. *Crit Care Med.* 1998;**26**:1081-8.

32. Gerstmann DR, deLemos RA, Clark RH. High-frequency ventilation: issues of strategy. *Clin.Perinatol.* 1991;**18**:563-80.