Accounting for deaths in neonatal trials: Is there a correct approach?

Dr. Shalin Parekh[1], Professor David Field[1], Samantha Johnson[1], Edmund Juszczak[2].

Corresponding Author: Edmund Juszczak, Associate Professor, Director, NPEU Clinical Trials Unit, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Old Road Campus, OXFORD, OX3 7LF, UK. Email: ed.juszczak@npeu.ox.ac.u.k

Word Count: 2459 excluding title page, abstract, references, figures and tables.

No. of tables : 2 +1 box.

No. of References: 32.

Keywords or phrases: Death, clinical trials, primary outcome, neurodevelopment, impairment, disability .

Abstract/Summary

Survival in neonatal medicine has shown a steady improvement in recent years and, consequently, outcome measures in clinical trials have increasingly focused on quantifying neurodevelopmental impairment. However, whilst survival rates are improving, mortality is still significant in neonates requiring intensive care. This raises the question of how to account for deaths in clinical trials where neurodevelopmental impairment is the primary focus. This review details some of the approaches that have been used in studies and outlines the advantages and disadvantages of the options available.

Introduction

The Disability and Perinatal Care report published by the National Perinatal Epidemiology Unit (NPEU) and Oxford Regional Health Authority in 1994 emphasized that data on the neurodevelopmental outcomes of neonates requiring intensive care should be formally collected(1). Over the last 40 years, survival rates of high risk infants have improved but these have not been matched with parallel improvements in neurodevelopmental outcomes (2-4). Consequently, the focus of neonatal care has shifted increasingly towards reducing long term morbidity and neurodevelopmental impairment(1, 2). Improved long term neurodevelopment is now considered the “Holy Grail” in neonatology(1, 5).

These developments have led to a change in focus of perinatal trials, which have moved away from survival as the primary outcome towards using long term functional outcomes(2). This has raised the question of how to deal with deaths in those trials where neurodevelopmental impairment is of primary interest. In perinatal trials involving the recruitment of high risk infants, it is inevitable that some will die and quantifying outcome for these infants has led to a range of approaches, none of which are without compromise (6-9).

This issue has become even more pertinent since some interventions designed to improve neurodevelopmental outcomes may not necessarily have a biologically plausible effect on mortality, yet death still needs to be accounted for. Mortality is significantly higher in neonatology compared to other fields of medicine, particularly among very preterm infants(10), which strongly influences both trial design and analysis.

This review considers approaches that have been taken by trialists regarding the role of death in their outcome measures, the pros and cons of the various approaches, the effect on the outcomes measured and the subsequent interpretation of the trial's findings.

How is neurodevelopmental impairment measured?

There is broad global consensus that neurodevelopmental outcomes should be measured at 18-24 months of age corrected for prematurity. This is a pragmatic compromise between identifying adverse neurodevelopmental outcomes as early as possible, and using tools that are reliable and likely to be predictive of impairments in later life(11) (12). This also allows results to become available in a timescale that is not too far removed from the perinatal intervention, whilst minimising the duration and costs of the trial.

Neurodevelopmental outcomes are usually assessed using validated psychometric instruments which are designed to quantify a child's developmental progress. These have typically comprised formal standardised tests to assess multiple developmental domains including cognitive, language and motor development, but parent report measures have become increasingly popular as cost-effective alternatives to formal assessments. There are a variety of tools commonly used to assess neurodevelopment at 18 months to 2 years of age in perinatal trials (Table 1). One of the most widely used and recently standardised developmental tests is the Bayley Scales of Infant and Toddler

Table 1: Tools commonly used to measure neurodevelopmental outcomes at 18-24 months of age in perinatal trials.

Assessment	Domains measured	Continuous scores	Classifying neurodevelopmental impairment
Examiner administered tests			
Bayley Scales of Infant Development 2nd edition (BSID-II)(13)	i. Cognitive & Language ii. Motor	Standardised (Mean 100; Standard deviation [SD] 15) Mental Development Index (MDI) & Psychomotor Development Index (PDI) scores.	SD-banded cut-offs for moderate (Index score -2 SD to -3 SD) and severe (Index score < -3 SD) impairment.
Bayley Scales of Infant & Toddler Development 3rd edition (Bayley-III)(14)	i. Cognitive ii. Language iii. Motor	Standardised (Mean 100; SD 15) Cognitive, Language and Motor Composite scores.	SD-banded cut-offs for moderate (Composite score -2 SD to -3 SD) and severe (Composite score < -3 SD) impairment. Concern regarding underestimation of impairment has led authors to suggest cut-offs should be raised by up to 1 SD(15).
Griffiths Mental Development Scales - Revised: Birth to 2 years (GMDS 0–2).(16)	i. Locomotor ii. Personal-Social iii. Hearing & Language iv. Eye hand coordination v. Performance	Standardised (Mean 100; SD 16) Locomotor, Personal-Social, Hearing & Language, Coordination and Performance scores; and General Quotient (GQ).	SD-banded cut-offs for moderate (standardised score -2 SD to -3 SD) and severe (standardised score < -3 SD) impairment.
Parent report measures			
Parent Report of Children's Abilities-Revised (PARCA-R)(17)	i. Non-verbal cognition ii. Language	Parent Report Composite (PRC) score.	PRC composite score <44 for moderate/severe impairment(18); PRC <31 for severe impairment(19).
Ages and Stages Questionnaires 3rd Edition (ASQ-3)(20)	i. Communication ii. Gross Motor iii. Fine Motor iv. Problem Solving v. Personal-Social	Total scores for Communication, Gross Motor, Fine Motor, Problem Solving and Personal-Social domains.	Domain scores are compared to age-appropriate cut-offs for developmental delay to classify moderate/severe impairment (equivalent to standardised scores < -2 SD).
Clinical observation			
Gross Motor Function Classification System (GMFCS)(21)	Gross motor function in children with Cerebral Palsy	Five level classification system.	Moderate impairment Level 2; Severe impairment Levels 3, 4 or 5. Parent report versions are available.

Development 3rd Edition (Bayley-III)(14) which provides separate scores for cognitive, language and motor development. Perinatal trials typically use either the cognitive score or a combination of the domains to assess cognitive development(15). This 'outcome' is often combined with other measures of neuromotor and sensory impairment (e.g., vision, hearing, cerebral palsy) to establish a 'broad-spectrum' assessment of neurodevelopmental outcome (see Box 1). Opinions vary as to what combination should be used, but the broad approach to defining neurodevelopmental impairment is clear(11). However, there is no consensus on how death should be incorporated into the analysis of such composite primary outcomes.

Box 1. Recommendations for classifying neurodevelopmental disability at 2 years of age as a perinatal outcome (British Association of Perinatal Medicine & UK Royal College of Paediatrics and Child Health joint report)(12)

Domain	Moderate disability	Severe disability
Motor	Cerebral palsy with GMFCS Level 2	Cerebral palsy with GMFCS Level 3, 4 or 5
Hearing	Hearing loss corrected *or* partially corrected with aids.	No useful hearing even with aids.
Vision	Moderately reduced vision but better than severe impairment *or* blind in one eye with good vision in contralateral eye.	Blind *or* can only perceive light.
Speech & Language	Some words or signs but fewer than 5 *or* unable to comprehend un-cued command but able to comprehend cued command.	No meaningful words *or* unable to comprehend cued command.
Cognitive function	Score -2 SD to -3 SD below the normative mean.	Score < -3 SD below the normative mean.

Different approaches to accounting for death in clinical trials

Use of a composite outcome

One common approach in neonatal trials is to use a composite of death or neurodevelopmental impairment as the primary outcome. Neurodevelopmental impairment for these purposes is usually dichotomised (i.e. present or absent). In this approach, a score on a particular psychometric test or combination of measures may be used as a 'cut-off' for defining an adverse outcome (see Table 1). For example, standardised index scores more than 3 standard deviations below the normative mean of 100

(i.e., scores <55) on the Bayley Scales of Infant Development, 2nd Edition (BSID-II) (13) are generally accepted as defining severe impairment. Therefore a trial could be based on a primary outcome of infants who either died before two years corrected age or had a BSID-II index score <55. Several major national and international studies have used this approach (see Table 2).

Table 2: Recent neonatal and perinatal trials where neurodevelopmental impairment is included in the primary outcome

Trial	Year published	Region	Primary Outcome	Death as a part of primary outcome
Neurodevelopmental impairment as a binary outcome				
Benefits of Oxygen Saturation Targeting (BOOST-II UK)(22)	Ongoing 2 year outcomes pending	UK	Composite of death or serious neurodisability at age 2 years corrected age (serious neurodisability defined as a Bayley-III language or cognitive score <85 *or equivalent*; or severe visual loss or severe cerebral palsy or deafness).	Yes
Total Body Hypothermia (TOBY)(23)	2009	UK Finland Hungary Israel Sweden	Composite of death or severe neurodisability at 18 months of age (severe neurodisability defined as BSID-II MDI<70, GMFCS Level 3 to 5, or severe visual loss).	Yes
National Institute of Child Health and Human Development (NICHD) trial on total body hypothermia(24)	2005	USA	Composite of death or moderate (BSID-II MDI 70 to 84 or GMFCS Level 2 or hearing impairment with no amplification or persisting seizure disorder) or severe (BSID-II MDI<70 or GMFCS Levels 3 to 5 or blindness or hearing requiring hearing aids) neurodisability at 18-22 months of age.	Yes
GRIT (Growth Restriction Intervention Trial)(25)	2004	UK Belgium Czech Germany Greece Hungary Italy Netherlands Poland Portugal Saudi Arabia	Composite of death or disability at or after 2 years corrected age (Disability defined as Griffith GQ ≤70 or diagnosis of cerebral palsy or severe visual loss or deafness)	Yes
INIS (International Neonatal Immunotherapy Study)(19)	2011	UK Argentina Australia Belgium	Composite of death or major disability at 2 years corrected age. (Major disability defined as per criteria set out in the NPEU and Oxford Regional Health	Yes

		Denmark Greece Ireland New Zealand Serbia	Authority report(1) and includes any major disability in: neuromotor function, seizures, auditory function, communication, visual function, cognitive function and other physical disability. Cognitive delay defined as PARCA-R <31)(19).	
INNOVO Trial (Neonatal ventilation with INhaled Nitric Oxide versus Ventilatory support withOut inhaled nitric oxide for severe respiratory failure: a multicentre randomized controlled trial)(26)	2005	UK Ireland	Death and disability at 1 year corrected age (Disability defined by set clinical criteria, no psychometric scales used).	Yes
Trial of umbilical and fetal flow in Europe (TRUFFLE): a multicentre randomised study(27)	Ongoing	UK Austria Germany Italy Netherlands	Survival without neurodevelopmental impairment at 2 years corrected age (neurodevelopmental impairment defined as Bayley-III Cognitive composite score ≤70 or severe visual loss or GMFCS level ≥2 or deafness)	Yes
Neurodevelopmental impairment as a continuous outcome				
Neonatal ECMO Study of Temperature (NEST): A Randomized Controlled Trial(7)	2013	UK	Bayley-III Cognitive composite score at 2 years corrected age (24–27 months)	No
A RCT of peer-mentoring for first-time mothers in socially disadvantaged areas (the MOMENTS Study)(28)	2011	UK	BSID-II MDI and PDI at 1 year	No
I2S2 Iodine supplementation study in preterm infants(8)	Ongoing	UK	Neurodevelopmental status at 2 years' corrected (for prematurity). Neurodevelopmental status is defined by the three main domains of the Bayley-III scales, i.e. cognitive score, language composite score and motor composite score.	Yes

The main advantage of composite outcomes is that they add statistical efficiency, in terms of an increased number of events and therefore greater statistical power, as demonstrated by the NICHD trial(24) on whole body hypothermia for hypoxic ischemic encephalopathy. The authors reported that whole-body hypothermia was associated with a reduction (risk ratio 0.72, 95% confidence interval 0.54-0.95; P=0.01) in the primary outcome (death or moderate to severe neurodisability) compared to usual care in infants with moderate or severe hypoxic-ischemic encephalopathy. However the individual components of the primary outcome were not significant when analysed as secondary outcomes. This shows the benefit of using a composite primary outcome, especially when the components are important outcomes for clinicians and parents alike.

However, there are potential problems defining the primary outcome in this way. For example, it cannot always be assumed that all components of the composite outcome will be affected by the intervention in the same direction(29). Composites work best when an intervention anticipated to reduce morbidity is also expected to improve survival and this may not always be true; the SUPPORT trial(30) illustrates this. The oxygen saturation component of this factorial trial tested the hypothesis that a lower target range of oxygen saturation (85 to 89%), as compared with a higher target range (91 to 95%), would reduce the incidence of the composite outcome of severe retinopathy of prematurity or death among infants who were born between 24^{+0} weeks and 27^{+6} weeks' gestation. The results showed no evidence of a difference in the composite outcome overall. However the study found that a lower target range of oxygenation (85 to 89%), as compared with a higher range (91 to 95%) resulted in an increase in mortality and a substantial decrease in severe retinopathy of prematurity among survivors (30).

Treating neurodevelopmental impairment as a dichotomous outcome in analysis

A further layer of complexity of treating neurodevelopmental impairment as a dichotomous outcome is that it effectively becomes 'all or nothing'. For example, if a study defines a BSID-II index score of <70 as representing moderate to severe neurodevelopmental impairment, then a child with a score of 70 would be classified as unimpaired while a child with a score of 69 would be classified as impaired, even though the difference between these scores is not clinically significant. In addition, in this case, moderate or severe neurodevelopmental impairment is mathematically treated equally as important as death. Clearly this may be a reasonable compromise, but illustrates the problems that may arise when interpreting study results.

Furthermore an intervention capable of producing a clinically significant difference in the mean neurodevelopmental outcome of the population may be completely missed. The MOMS(9) trial, comparing prenatal surgery for myelomeningocele to postnatal surgery, used the BSID-II Psychomotor Development Index (PDI) score as a secondary outcome. There was a significant difference in the mean PDI score between the two groups (P=0.03). However when the proportion of infants who had a PDI score ≥50 was compared, there was no significant difference between the two groups (P=0.15). This was true even when a higher cut off of 85 was used (P=0.06). Dichotomising a continuous outcome measure using a cut off may lead to a loss of power(31). Thus a significant result on a continuous outcome may no longer be significant when the outcome is dichotomized.

Treating neurodevelopmental impairment as a continuous outcome and imputing a value for death

A number of studies have considered neurodevelopmental impairment as a continuous variable at analysis. Comparative analysis is performed on the scores attained on developmental tests between the intervention and control groups. How should authors account for death in such trials? Some studies have considered imputing a score for those participants who have died. For example, one option is to allocate an arbitrary low value on the Bayley scales for those participants who have died. This may be, for example, equivalent to 3 standard deviations below the normative mean, the conventional cut-off for severe disability.

Despite being consistent with an intention-to-treat analysis using complete data, this approach involves compromises. Allocating any single value (i.e. using single imputation) to participants who have died is technically problematic since the data may not be missing at random. There is not only the compromise of assigning a similar if not identical score to those participants who have died with those severely disabled, but also the scenario where one might impute a score for the deceased which is higher than the minimum possible neurodevelopmental score for survivors on that scale. Trialists need to guard against this possibility when considering imputation. However to impute a Bayley score implies that we know what the 'trade off' is between level of disability and death and imparts extraneous value judgements which could vary from individual to individual(32).

The use of a single imputation to assign a value to participants who have died also affects the precision and hence the interpretation of results, depending on the value assigned. At a more fundamental level, when planning a study, single imputation for participants who have died at analysis is likely to artificially inflate the overall standard deviation thereby adversely affecting the precision of the results. This will consequently impact on the sample size and the appropriateness of the statistical test used.

Focusing solely on neurodevelopmental impairment

An alternative to incorporating death into a composite primary outcome would be to consider the developmental test score within survivors only. In this case the study findings would reflect the impact of the intervention solely on neurodevelopmental outcome, and not on death. However, such an analysis is a non-randomised comparison and therefore subject to an increased risk of bias, the chances of which are affected not only by the magnitude of the death rate but also whether the death rate is differential across the groups being compared. Here the difference in test scores will be easy to interpret, but although death may be reported as a secondary outcome, the study would not normally be powered to show a difference in survival.

A study(7) that examined the effect of mild hypothermia for neuroprotection in infants requiring ECMO (extra corporeal membranous oxygenation) used this approach. The investigators argued that mild hypothermia was unlikely to influence mortality and thus they focused on the outcome for which there was biological plausibility for improvement(7). The primary outcome was analysed as a continuous variable and used the Bayley-III cognitive composite score.

However, studies that only focus solely on neurodevelopmental impairment may miss an important impact on survival, illustrated by the BOOST-II UK trial (22). The investigators compared the effects of targeting an oxygen saturation of 85 to 89%, as compared with a range of 91 to 95%, in infants born before 28 weeks' gestation. The primary outcome was a composite of death or serious neurosensory disability at 2 years corrected age. The trial was stopped early due to significantly increased mortality at 36 weeks' postmenstrual age in the group treated with the lower oxygen saturation target (22). Since deaths in neonatal trials mainly occur in the first few weeks of life, monitoring safety in such trials, typically by an independent Data Monitoring Committee, requires the uncoupling of such composite

primary outcomes for this purpose, given that the 'whole' primary outcome is not available until much later.

Other Approaches

The on-going OPPTIMUM(6) trial is examining whether prophylactic vaginal progesterone to prevent preterm birth has long term neonatal or infant benefit. For the analysis of the childhood primary outcome (Bayley-III cognitive composite scale at 2 years of age, a continuous measure), the investigators plan to incorporate deaths in a two-stage statistical model(6). Their rationale for the inclusion of deaths in the analysis is two-fold; the number of deaths may not be negligible and the distribution across the two groups may not be balanced. In the two-stage statistical model, deaths will be modelled using a binomial test, and survivors modelled using a generalised linear model. The two parts will then be combined to form the appropriate test statistic.

A different approach was used in the MOMs(9) trial in which the second primary outcome, at 30 months, was a composite of the BSID-II Mental Development Index (MDI) and the child's motor function. Each of the two components of this outcome was ranked across all infants. Foetal, neonatal and infant deaths were assigned the lowest rank. The composite score for each infant was the sum of the two ranks and this was compared across both groups.

For both of these approaches, the interpretation of the final results is potentially more difficult, but the advantage of the former is that it avoids the need to make value judgements and may well become the methodology of choice. However it remains to be seen if such an approach affects the interpretation and impact of the results. While taking deaths into account, the major disadvantage of the latter is that only P-values can be calculated and adjusted analysis is not possible.

The views of families

The opinion of the ultimate beneficiaries of treatment (patients and families) may well be highly useful in identifying the appropriate 'trade-off' between neurodevelopmental impairment and death, necessary when considering all of the above approaches. However it would not be possible to extrapolate the views of families involved in one trial to those in another, since the risk of death or disability will vary between trials. Hence parental views of what 'trade-off' is acceptable must directly relate to a particular intervention in a specific clinical scenario.

Conclusions

The recent change of focus within day to day neonatal care, with its increasing attention on reducing neurodevelopmental impairment, has been mirrored in the outcomes used in many perinatal trials. Clinical trials have increasingly incorporated neurodevelopment into their primary outcome and this has led to the question of how to deal with death in these studies. A range of possible solutions have emerged, each of which involves pragmatic statistical and clinical compromises, and there does not seem to be a correct approach.

The resources required to run large multicentre trials and the finite population of high risk neonates limit the potential size and feasibility of neonatal trials. Catastrophic events (i.e. the typical negative outcomes of interest) are thankfully uncommon but this drives up the sample size unless we compromise and create meaningful composites. Further work is needed to clarify how, and to what extent, each of the designs and chosen analysis used to date can affect the findings and the impact of the trial. Where value judgements are needed, views of patient groups should be considered and may enable trialists to make better judgements regarding which approach to choose for their particular trial.

Contributorship: SP, DF and EJ were involved in conception of this review article. SP wrote the initial draft manuscript. SP and SJ designed the tables. SP, SJ, DF and EJ were all involved in the design and contributed to subsequent drafts. All authors revised the final manuscript.

Competing Interests: none

References:

1. National Perinatal Epidemiology Unit. Disability and perinatal care: Measurement of Health Status at Two years: A Report of Two working Groups Convened by the National Perinatal Epidemiology Unit and the former Oxford Regional Health Authority. Oxford: National Perinatal Epidemiology Unit, 1994.
2. Stephens BE, Vohr BR. Neurodevelopmental Outcome of the Premature Infant. Pediatric Clinics of North America. 2009;56(3):631-46.
3. Robertson CMT, Watt M-J, Dinu IA. Outcomes for the Extremely Premature Infant: What Is New? and Where Are We Going? Pediatric Neurology. 2009;40(3):189-96.
4. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ : British Medical Journal. 2012;345:e7961.
5. Strand M, Jobe AH. The multiple negative randomized controlled trials in perinatology—why? Seminars in Perinatology. 2003;27(4):343-50.
6. Norman JE, Shennan A, Bennett P, Thornton S, Robson S, Marlow N, et al. Trial protocol OPPTIMUM-- does progesterone prophylaxis for the prevention of preterm labour improve outcome? BMC pregnancy and childbirth. 2012;12:79.
7. Field D. Neonatal ECMO Study of Temperature (NEST): A Randomized Controlled Trial. Pediatrics. 2013;132(5):e1247-e56.
8. Williams F, Hume R, Ogston S, Brocklehurst P, Morgan K, Juszczak E. A summary of the iodine supplementation study protocol (I2S2): a UK multicentre randomised controlled trial in preterm infants. Neonatology. 2014;105(4):282-9.
9. Adzick NS, Thom EA, Spong CY, Brock JW, Burrows PK, Johnson MP, et al. A Randomized Trial of Prenatal versus Postnatal Repair of Myelomeningocele. New England Journal of Medicine. 2011;364(11):993-1004.
10. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ : British Medical Journal. 2012;345:e7976.
11. Marlow N. Measuring neurodevelopmental outcome in neonatal trials: a continuing and increasing challenge. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2013;98(6):F554-F8.
12. British Association of Perinatal Medicine. Report of a BAPM/RCPCH Working Group Classification of health status at 2 years as a perinatal outcome Version 1.0; 8 January 2008. London: 2008.
13. Bayley N. Bayley Scales of Infant Development (Second Edition). San Antonio: Psychological Corporation; 1993.
14. Bayley N. Bayley Scales of Infant and Toddler Development (Third Edition). San Antonio: Harcourt Assessment; 2006.
15. Johnson S, Moore T, Marlow N. Using the Bayley-III to assess neurodevelopmental delay: which cut-off should be used? Pediatric Research. 2014;75(5):670-4.
16. Griffith R. The Griffiths Mental Development Scales from birth to 2 years, manual, the 1996 revision. Henley: Association for Research in Infant and Child Development, Test Agency; 1996.
17. Johnson S, Marlow N, Wolke D, Davidson L, Marston L, O'Hare A, et al. Validation of a parent report measure of cognitive development in very preterm infants. Dev Med Child Neurol. 2004;46(6):389-97.
18. Johnson S, Wolke D, Marlow N. Developmental assessment of preterm infants at 2 years: validity of parent reports. Dev Med Child Neurol. 2008;50(1):58-62.

19. The INIS Collaborative Group. Treatment of Neonatal Sepsis with Intravenous Immune Globulin. New England Journal of Medicine. 2011;365(13):1201-11.
20. Squires J, Twombly E, Bricker D, Potter L. The Ages and Stages Questionnaires-3 User's Guide. Baltimore, MD: Brookes Publishing; 2009.
21. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997;39(4):214-23.
22. Stenson BJ, Tarnow-Mordi WO, Darlow BA, Simes J, Juszczak E, Askie L, et al. Oxygen saturation and outcomes in preterm infants. The New England journal of medicine. 2013;368(22):2094-104.
23. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate Hypothermia to Treat Perinatal Asphyxial Encephalopathy. New England Journal of Medicine. 2009;361(14):1349-58.
24. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, et al. Whole-Body Hypothermia for Neonates with Hypoxic–Ischemic Encephalopathy. New England Journal of Medicine. 2005;353(15):1574-84.
25. The GRIT Study Group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. The Lancet. 2004;364(9433):513-20.
26. Field D, Elbourne D, Truesdale A, Grieve R, Hardy P, Fenton AC, et al. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: The INNOVO Multicentre Randomised Controlled Trial (ISRCTN 17821339). Pediatrics. 2005;115(4):926-36.
27. Lees C. Protocol 02PRT/34 :Trial of umbilical and fetal flow in Europe (TRUFFLE): a multicentre randomised study 2007. Available from: http://www.thelancet.com/protocol-reviews/02PRT-34.
28. Cupples ME, Stewart MC, Percy A, Hepper P, Murphy C, Halliday HL. A RCT of peer-mentoring for first-time mothers in socially disadvantaged areas (the MOMENTS Study). Arch Dis Child. 2011;96(3):252-8.
29. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA : the journal of the American Medical Association. 2003;289(19):2554-9.
30. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target Ranges of Oxygen Saturation in Extremely Preterm Infants. New England Journal of Medicine. 2010;362(21):1959-69.
31. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ : British Medical Journal. 2006;332(7549):1080-.
32. Rubin DB. Causal Inference Through Potential Outcomes and Principal Stratification: Application to Studies with "Censoring" Due to Death. Statistical Science. 2006;21(3):299-309.