Appendix A

Study Protocol for the study: "*Clinical significance in pediatric oncology randomized controlled treatment trials: A systematic review*"

Background:
The sample size calculation of a randomized clinical trial (RCT) should be based on a delta value that reflects the minimal clinically important difference. The limited prior research suggests that RCTs in the literature do not provide sufficient information on clinical significance, including the use of a minimal clinically important difference, that enables readers to draw their own conclusions, nor do they provide their own interpretation of the clinical importance of their results. The degree to which clinical significance has been reported or determined in RCTs in pediatric cancer, a rare disease, remains unknown.

Primary Objective*:*
Assess clinical significance in the pediatric oncology RCT literature by evaluating, 1) the relationship between the treatment effect and the delta value as reported in the sample size calculation, and 2) the concordance between statistical and clinical significance.

Methods:

Population: Pediatric patients diagnosed with cancer and the primary outcome of the trial was a relevant cancer treatment outcome (e.g., a treatment regimen assessing overall survival, event-free survival, etc.).

Study inclusion criteria:
- RCTs that reported a sample size calculation where a delta value was reported or could be calculated for the randomized question.
- RCTs where the study population consisted of both pediatric and adult patients will be deemed eligible if adults were less than or equal to 25 years of age.
- Only the most recent RCT trial will be reported (i.e., in the event interim results are published).

Study exclusion criteria:
- RCTs that are long-term follow up studies.
- RCTs wherein the primary outcome are treatment complications or side effects, pharmacokinetic trials, toxicity trials, non-clinical interventions, or drug safety profile trials.
- RCTs which have a non-randomized component or a historical control.
- RCTs reported in a language other than English.

Exposure: Not applicable as this is a methodology systematic review.

Comparator: Not applicable as this is a methodology systematic review.

Outcome: Not applicable as this is a methodology systematic review.

Study type:
Randomized controlled trials

Search strategy:
A comprehensive literature review will be performed using the databases MEDLINE (Via Ovid), EMBASE (via OVID) and Cochrane Childhood Cancer Group Specialized Register (Via CENTRAL).

The reference lists / bibliographies of included studies will be searched. Databases will searched from their conception until the present day (July 2016) and limited to the English language.

Study Identification:
Two investigators will screen the title and abstracts based on the specified inclusion criteria. The full text will then be retrieved and reviewed if the title and abstract is insufficient to determine fulfillment of inclusion criteria. Subsequently, one investigator will conduct a full text review to assess all of the studies that passed through the first round of title and abstract screening for inclusion eligibility. The principal investigator will be available to resolve any discrepancies or disagreements encountered during study selection.

Study quality assessment checklist/assessment: Not applicable as this is a methodology systematic review.

Data extraction strategy: Data will be manually entered into a standard data extraction template for each study and then analyzed. The data extraction template will be initially piloted on a sample of 15 included studies to ensure that pertinent information is captured and will then be subsequently finalized based on the results of this pilot.

Synthesis of extracted data:
SAS Version 9.4 will be used perform the analysis of the extracted data.

Search Strategies

EMBASE

1. Randomized Controlled Trial.pt. or Pragmatic Clinical Trial.pt. or exp Randomized Controlled Trials as Topic/ or Randomized Controlled Trial (Topic) or Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double-Blind Procedure or Double-Blind Studies/ or Single-Blind Method/ or Single-Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kf,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. rr ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
2. leukemia or leukemi* or leukaemi* or (childhood ALL) or AML or lymphoma or lymphom* or hodgkin OR hodgkin* or T-cell or B-cell or non-hodgkin or sarcoma or sarcom* or sarcoma, Ewing's or Ewing* or osteosarcoma or osteosarcom* or wilms tumor or wilms* or nephroblastom* or neuroblastoma or neuroblastom* or rhabdomyosarcoma or rhabdomyosarcom* or teratoma or teratom* or hepatoma or hepatom* or hepatoblastoma or hepatoblastom* or PNET or medulloblastoma or medulloblastom* or PNET* or neuroectodermal tumors, primitive or retinoblastoma or retinoblastom* or meningioma or meningiom* or glioma or gliom* or pediatric oncology or paediatric oncology or childhood cancer or childhood tumor or childhood tumors or brain tumor* or brain tumour* or brain neoplasms or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumor* or central nervous system tumour* or brain cancer* or brain neoplasm* or intracranial neoplasm* or leukemia lymphocytic acute or acute lymphoblastic leukemia/
3. cancer or cancers or cancer* or oncology or oncolog* or neoplasm or neoplasms or neoplasm* or carcinoma or carcinom* or tumor or tumour or tumor* or tumour* or tumors or tumours or malignan* or malignant or hematooncological or hemato oncological or hemato-oncological or hematologic neoplasms or hematolo*

4. 1 AND 2 AND 3
5. Limit 4 to Human/ English Language
6. Limit 5 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")
7. Final filter: Limit 7 to NOT IN MEDLINE

MEDLINE

1. Randomized Controlled Trial.pt. or Pragmatic Clinical Trial.pt. or exp Randomized Controlled Trials as Topic/ or Randomized Controlled Trial (Topic) or Randomized Controlled Trial/ or Randomization/ or Random Allocation/ or Double-Blind Method/ or Double-Blind Procedure or Double-Blind Studies/ or Single-Blind Method/ or Single-Blind Procedure/ or Single-Blind Studies/ or Placebos/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kf,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. rr ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
2. leukemia or leukemi* or leukaemi* or (childhood ALL) or AML or lymphoma or lymphom* or hodgkin OR hodgkin* or T-cell or B-cell or non-hodgkin or sarcoma or sarcom* or sarcoma, Ewing's or Ewing* or osteosarcoma or osteosarcom* or wilms tumor or wilms* or nephroblastom* or neuroblastoma or neuroblastom* or rhabdomyosarcoma or rhabdomyosarcom* or teratoma or teratom* or hepatoma or hepatom* or hepatoblastoma or hepatoblastom* or PNET or medulloblastoma or medulloblastom* or PNET* or neuroectodermal tumors, primitive or retinoblastoma or retinoblastom* or meningioma or meningiom* or glioma or gliom* or pediatric oncology or paediatric oncology or childhood cancer or childhood tumor or childhood tumors or brain tumor* or brain tumour* or brain neoplasms or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumor* or central nervous system tumour* or brain cancer* or brain neoplasm* or intracranial neoplasm* or leukemia lymphocytic acute or acute lymphoblastic leukemia/
3. cancer or cancers or cancer* or oncology or oncolog* or neoplasm or neoplasms or neoplasm* or carcinoma or carcinom* or tumor or tumour or tumor* or tumour* or tumors or tumours or malignan* or malignant or hematooncological or hemato oncological or hemato-oncological or hematologic neoplasms or hematolo*
4. 1 AND 2 AND 3
5. Limit 4 to Human/ English Language
6. Limit 5 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")

CENTRAL (Wiley)

1. SR-CHILDCA

Appendix B – List of included and excluded studies

List of Included Studies:

1. Alexander S, Kraveka JM, Weitzman S, et al. Advanced stage anaplastic large cell lymphoma in children and adolescents: results of ANHL0131, a randomized phase III trial of APO versus a modified regimen with vinblastine: a report from the children's oncology group. Pediatric Blood & Cancer 2014;61(12):2236-42. doi: http://dx.doi.org/10.1002/pbc.25187

2. Balduzzi A, Valsecchi MG, Uderzo C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: Comparison by genetic randomisation in an international prospective study. Lancet 2005;366(9486):635-42.

3. Brandalise SR, Pinheiro VR, Aguiar SS, et al. Benefits of the intermittent use of 6-mercaptopurine and methotrexate in maintenance treatment for low-risk acute lymphoblastic leukemia in children: randomized trial from the Brazilian Childhood Cooperative Group--protocol ALL-99. Journal of Clinical Oncology 2010;28(11):1911-18. doi: http://dx.doi.org/10.1200/JCO.2009.25.6115

4. Buchanan GR, Rivera GK, Pollock BH, et al. Alternating drug pairs with or without periodic reinduction in children with acute lymphoblastic leukemia in second bone marrow remission: a Pediatric Oncology Group Study. Cancer 2000;88(5):1166-74.

5. Conter V, Valsecchi MG, Silvestri D, et al. Pulses of vincristine and dexamethasone in addition to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: a multicentre randomised trial. Lancet 2007;369(9556):123-31.

6. Creutzig U, Dworzak M, Zimmermann M, et al. Randomised introduction of 2-CDA as intensification during consolidation for children with high-risk AML - Results from study AML-BFM 2004. Klinische Padiatrie 2015;227(3):116-22.

7. Creutzig U, Ritter J, Zimmermann M, et al. Improved treatment results in high-risk pediatric acute myeloid leukemia patients after intensification with high-dose cytarabine and mitoxantrone: Results of study acute myeloid Leukemia-Berlin-Frankfurt-Munster 93. Journal of Clinical Oncology 2001;19(10):2705-13.

8. Creutzig U, Zimmermann M, Bourquin J-P, et al. Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from Study AML-BFM 2004. Blood 2013;122(1):37-43. doi: http://dx.doi.org/10.1182/blood-2013-02-484097

9. Creutzig U, Zimmermann M, Lehrnbecher T, et al. Less toxicity by optimizing chemotherapy, but not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid leukemia: Results of AML-BFM 98. Journal of Clinical Oncology 2006;24(27):4499-506.

10. Duval M, Suciu S, Ferster A, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. Blood 2002;99(8):2734-39.

11. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin lymphoma: a report from the Children's Oncology Group Study AHOD0031. Journal of Clinical Oncology 2014;32(32):3651-58. doi: http://dx.doi.org/10.1200/JCO.2013.52.5410

12. Gaynon PS, Harris RE, Altman AJ, et al. Bone marrow transplantation versus prolonged intensive chemotherapy for children with acute lymphoblastic leukemia and an initial bone marrow relapse within 12 months of the completion of primary therapy: Children's Oncology Group study CCG-1941. Journal of Clinical Oncology 2006;24(19):3150-56.

13. Hann I, Vora A, Richards S, et al. Benefit of intensified treatment for all children with acute lymphoblastic leukaemia: results from MRC UKALL XI and MRC ALL97 randomised trials. UK Medical Research Council's Working Party on Childhood Leukaemia. Leukemia 2000;14(3):356-63.

14. Harris MB, Shuster JJ, Pullen DJ, et al. Consolidation therapy with antimetabolite-based therapy in standard-risk acute lymphocytic leukemia of childhood: a Pediatric Oncology Group Study. Journal of Clinical Oncology 1998;16(8):2840-47.

15. Hill FGH, Richards S, Gibson B, et al. Successful treatment without cranial radiotherapy of children receiving intensified chemotherapy for acute lymphoblastic leukaemia: results of the risk-stratified randomized central nervous system treatment trial MRC UKALL XI (ISRC TN 16757172). British journal of haematology 2004;124(1):33-46.

16. Hvizdala EV, Berard C, Callihan T, et al. Lymphoblastic lymphoma in children--a randomized trial comparing LSA2-L2 with the A-COP+ therapeutic regimen: a Pediatric Oncology Group Study. Journal of Clinical Oncology 1988;6(1):26-33.

17. Kung FH, Schwartz CL, Ferree CR, et al. POG 8625: a randomized trial comparing chemotherapy with chemoradiotherapy for children and adolescents with Stages I, IIA, IIIA1 Hodgkin Disease: a report from the Children's Oncology Group. Journal of Pediatric Hematology/Oncology 2006;28(6):362-68.

18. Lange BJ, Blatt J, Sather HN, et al. Randomized comparison of moderate-dose methotrexate infusions to oral methotrexate in children with intermediate risk acute lymphoblastic leukemia: a Childrens Cancer Group study. Medical & Pediatric Oncology 1996;27(1):15-20.

19. Lange BJ, Yang RK, Gan J, et al. Soluble interleukin-2 receptor alpha activation in a Children's Oncology Group randomized trial of interleukin-2 therapy for pediatric acute myeloid leukemia. Pediatric Blood & Cancer 2011;57(3):398-405. doi: http://dx.doi.org/10.1002/pbc.22966

20. Lanino E, Rondelli R, Locatelli F, et al. Early (day -7) versus conventional (day -1) inception of cyclosporine-A for graft-versus-host disease prophylaxis after unrelated donor hematopoietic stem cell transplantation in children. Long-term results of an AIEOP prospective, randomized study. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2009;15(6):741-8. doi: 10.1016/j.bbmt.2009.03.004 [published Online First: 2009/05/20]

21. Lauer SJ, Shuster JJ, Mahoney Jr DH, et al. A comparison of early intensive methotrexate/mercaptopurine with early intensive alternating combination chemotherapy for high-risk B-precursor acute lymphoblastic leukemia: A Pediatric Oncology Group phase III randomized trial. Leukemia 2001;15(7):1038-45.

22. Laver JH, Kraveka JM, Hutchison RE, et al. Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. Journal of Clinical Oncology 2005;23(3):541-47.

23. Laver JH, Mahmoud H, Pick TE, et al. Results of a randomized phase III trial in children and adolescents with advanced stage diffuse large cell non-Hodgkin's lymphoma: a Pediatric Oncology Group study. Leukemia & lymphoma 2002;43(1):105-09.

24. Le Deley M-C, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. Journal of Clinical Oncology 2010;28(25):3987-93. doi: http://dx.doi.org/10.1200/JCO.2010.28.5999

25. Mahoney DH, Jr., Shuster J, Nitschke R, et al. Intermediate-dose intravenous methotrexate with intravenous mercaptopurine is superior to repetitive low-dose oral methotrexate with intravenous mercaptopurine for children with lower-risk B-lineage acute lymphoblastic leukemia: a Pediatric Oncology Group phase III trial. Journal of Clinical Oncology 1998;16(1):246-54.

26. Mahoney DH, Jr., Shuster JJ, Nitschke R, et al. Intensification with intermediate-dose intravenous methotrexate is effective therapy for children with lower-risk B-precursor acute lymphoblastic leukemia: A Pediatric Oncology Group study. Journal of Clinical Oncology 2000;18(6):1285-94.

27. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council ALL97 randomized trial. British journal of haematology 2005;129(6):734-45.

28. Mondelaers V, Suciu S, De Moerloose B, et al. Prolonged versus standard native E. coli asparaginase therapy in childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma: final results of the EORTC-CLG randomized phase III trial 58951. Haematologica 2017;102(10):1727-38. doi: https://dx.doi.org/10.3324/haematol.2017.165845

29. Moricke A, Zimmermann M, Valsecchi MG, et al. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. Blood 2016;127(17):2101-12. doi: https://dx.doi.org/10.1182/blood-2015-09-670729

30. Nachman J, Sather HN, Cherlow JM, et al. Response of children with high-risk acute lymphoblastic leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. Journal of Clinical Oncology 1998;16(3):920-30.

31. Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. New England Journal of Medicine 1998;338(23):1663-71.

32. Nachman JB, Sposto R, Herzog P, et al. Randomized comparison of low-dose involved-field radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to chemotherapy. Journal of Clinical Oncology 2002;20(18):3765-71.

33. Nagatoshi Y, Matsuzaki A, Suminoe A, et al. Randomized trial to compare LSA2L2-type maintenance therapy to daily 6-mercaptopurine and weekly methotrexate with vincristine and dexamethasone pulse for children with acute lymphoblastic leukemia. Pediatric Blood & Cancer 2010;55(2):239-47. doi: http://dx.doi.org/10.1002/pbc.22528

34. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. Lancet 2007;370(9583):240-50. doi: 10.1016/s0140-6736(07)61126-x [published Online First: 2007/07/31]

35. Ribera JM, Ortega JJ, Oriol A, et al. Comparison of intensive chemotherapy, allogeneic, or autologous stem-cell transplantation as postremission treatment for children with very high risk acute lymphoblastic leukemia: PETHEMA ALL-93 trial. Journal of Clinical Oncology 2007;25(1):16-24.

36. Sadowitz PD, Smith SD, Shuster J, et al. Treatment of late bone marrow relapse in children with acute lymphoblastic leukemia: a Pediatric Oncology Group study. Blood 1993;81(3):602-09.

37. Sposto R, Meadows AT, Chilcote RR, et al. Comparison of long-term outcome of children and adolescents with disseminated non-lymphoblastic non-hodgkin lymphoma treated with COMP or daunomycin-comp: A report from the children's cancer group. Medical and pediatric oncology 2001;37(5):432-41.

38. Sullivan MP, Fuller LM, Berard C, et al. Comparative effectiveness of two combined modality regimens in the treatment of surgical stage III Hodgkin's disease in children. An 8-year follow-up study by the Pediatric Oncology Group. American Journal of Pediatric Hematology/Oncology 1991;13(4):450-58.

39. van der Werff ten Bosch J, Suciu S, Thyss A, et al. Value of intravenous 6-mercaptopurine during continuation treatment in childhood acute lymphoblastic leukemia and non-Hodgkin's lymphoma: Final results of a randomized phase III trial (58881) of the EORTC CLG. Leukemia 2005;19(5):721-26.

40. Von Stackelberg A, Hartmann R, Buhrer C, et al. High-dose compared with intermediate-dose methotrexate in children with a first relapse of acute lymphoblastic leukemia. Blood 2008;111(5):2573-80.

41. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncology 2014;15(8):809-18. doi: http://dx.doi.org/10.1016/S1470-2045(14)70243-8

42. Wagner JE, Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for hematologic cancers. New England Journal of Medicine 2014;371(18):1685-94.

43. Woods WG, Kobrinsky N, Buckley JD, et al. Timed-sequential induction therapy improves postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group. Blood 1996;87(12):4979-89.

List of Excluded Studies:

1. Treatment of acute lymphoblastic leukaemia: effect of variation in length of treatment on duration of remission. Report to the Medical Research Council by the Working Party on Leukaemia in Childhood. *British medical journal* 1977;2(6085):495-97.

2. Randomized trial of adjuvant chemotherapy in osteogenic osteosarcoma: comparison of altering sequential administrations of high doses of adriamycin, methotrexate, and cyclophosphamide with a 6-month administration of high-dose adriamycin followed by a low-dose semicontinuous chemotherapy. EORTC Osteosarcoma Working Party Group. *Recent results in cancer researchFortschritte der KrebsforschungProgres dans les recherches sur le cancer* 1978;68:28-32.

3. The treatment of acute lymphoblastic leukaemia (ALL) in childhood, UKALL III: the effects of added cytosine arabinoside and/or asparaginase, and a comparison of continuous or discontinuous mercaptopurine in regimens for standard risk ALL. *Medical and pediatric oncology* 1982;10(5):501-10.

4. Duration of chemotherapy in childhood acute lymphoblastic leukaemia. The Medical Research Council's Working Party on Leukaemia in Childhood. *Medical & Pediatric Oncology* 1982;10(5):511-20.

5. Adamson PC, Matthay KK, O'Brien M, et al. A phase 2 trial of all-trans-retinoic acid in combination with interferon-alpha2a in children with recurrent neuroblastoma or wilms tumor: A pediatric oncology branch, NCI and children's oncology group study. *Pediatric Blood and Cancer* 2007;49(5):661-65.

6. Aly MMD, Hamza AF, Abdel Kader HM, et al. Therapeutic superiority of combined propranolol with short steroids course over propranolol monotherapy in infantile hemangioma. *European journal of pediatrics* 2015;174(11):1503-09.

7. Amadori S, Testi AM, Arico M, et al. Prospective comparative study of bone marrow transplantation and postremission chemotherapy for childhood acute myelogenous leukemia. The Associazione Italiana Ematologia ed Oncologia Pediatrica Cooperative Group. *Journal of Clinical Oncology* 1993;11(6):1046-54.

8. Amylon MD, Shuster J, Pullen J, et al. Intensive high-dose asparaginase consolidation improves survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic lymphoma: A Pediatric Oncology Group study. *Leukemia* 1999;13(3):335-42.

9. Anderson J, Krivit W, Chilcote R, et al. Comparison of the therapeutic response of patients with childhood acute lymphoblastic leukemia in relapse to vindesine versus vincristine in combination with prednisone and L-asparaginase: a phase III trial. *Cancer treatment reports* 1981;65(11-12):1015-19.

10. Anderson JR, Wilson JF, Jenkin DT, et al. Childhood non-Hodgkin's lymphoma. The results of a randomized therapeutic trial comparing a 4-drug regimen (COMP) with a 10-drug regimen (LSA2-L2). *New England Journal of Medicine* 1983;308(10):559-65.

11. Andre MPE, Girinsky T, Federico M, et al. Early Positron Emission Tomography Response-Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial. *Journal of Clinical Oncology* 2017;35(16):1786-94. doi: https://dx.doi.org/10.1200/JCO.2016.68.6394

12. Arico M, Valsecchi MG, Rizzari C, et al. Long-term results of the AIEOP-ALL-95 trial for childhood acute lymphoblastic leukemia: Insight on the prognostic value of DNA index in the framework of Berlin-Frankfurt-Muenster-based chemotherapy. *Journal of Clinical Oncology* 2008;26(2):283-89.

13. Arndt CAS, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group Study D9803. *Journal of Clinical Oncology* 2009;27(31):5182-88.

14. Asselin BL, Devidas M, Chen L, et al. Cardioprotection and Safety of Dexrazoxane in Patients Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric Oncology Group 9404. *Journal of Clinical Oncology* 2016;34(8):854-62. doi: https://dx.doi.org/10.1200/JCO.2015.60.8851

15. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). *Blood* 2011;118(4):874-83. doi: http://dx.doi.org/10.1182/blood-2010-06-292615

16. Asselin BL, Kreissman S, Coppola DJ, et al. Prognostic significance of early response to a single dose of asparaginase in childhood acute lymphoblastic leukemia. *Journal of Pediatric Hematology/Oncology* 1999;21(1):6-12.

17. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: A report from the Children's Oncology Group. *Journal of Clinical Oncology* 2012;30(21):2641-47.

18. Attarbaschi A, Panzer-Grumayer R, Mann G, et al. Minimal residual disease-based treatment is adequate for relapse-prone childhood acute lymphoblastic leukemia with an intrachromosomal amplification of chromosome 21: the experience of the ALL-BFM 2000 trial. *Klinische Padiatrie* 2014;226(6-7):338-43. doi: http://dx.doi.org/10.1055/s-0034-1387795

19. Aur RJ, Simone JV, Hustu HO, et al. A comparative study of central nervous system irradiation and intensive chemotherapy early in remission of childhood acute lymphocytic leukemia. *Cancer* 1972;29(2):381-91.

20. Aur RJ, Simone JV, Verzosa MS, et al. Childhood acute lymphocytic leukemia: study VIII. *Cancer* 1978;42(5):2123-34.

21. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood* 2002;99(6):1986-94.

22. Awada A, Colomer R, Inoue K, et al. Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical Trial. *JAMA Oncol* 2016;2(12):1557-64. doi: https://dx.doi.org/10.1001/jamaoncol.2016.0237

23. Bailey CC, Gnekow A, Wellek S, et al. Prospective randomised trial of chemotherapy given before radiotherapy in childhood medulloblastoma. International Society of Paediatric Oncology (SIOP) and the (German) Society of Paediatric Oncology (GPO): SIOP II. *Medical & Pediatric Oncology* 1995;25(3):166-78.

24. Balzarotti M, Brusamolino E, Angelucci E, et al. B-IGEV (bortezomib plus IGEV) versus IGEV before high-dose chemotherapy followed by autologous stem cell transplantation in relapsed or refractory

Hodgkin lymphoma: a randomized, phase II trial of the Fondazione Italiana Linfomi (FIL). *Leukemia & Lymphoma* 2016;57(10):2375-81. doi: https://dx.doi.org/10.3109/10428194.2016.1140161

25. Barry EV, Vrooman LM, Dahlberg SE, et al. Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *Journal of Clinical Oncology* 2008;26(7):1106-11. doi: http://dx.doi.org/10.1200/JCO.2007.12.2481

26. Batra V, Sands SA, Holmes E, et al. Long-term survival of children less than six years of age enrolled on the ccg-945 phase iii trial for newly-diagnosed high-grade glioma: A report from the children's oncology group. *Pediatric Blood and Cancer* 2014;61(1):151-57.

27. Baum E, Sather H, Nachman J. Relapse rates following cessation of chemotherapy during complete remission of acute lymphocytic leukemia. A report from Children's Cancer Study Group. *Medical and pediatric oncology* 1979;7(1):25-34.

28. Becton D, Dahl GV, Ravindranath Y, et al. Randomized use of cyclosporin A (CsA) to modulate P-glycoprotein in children with AML in remission: Pediatric Oncology Group Study 9421. *Blood* 2006;107(4):1315-24.

29. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group Phase II Study 9457--a report from the Children's Oncology Group. *Journal of Clinical Oncology* 2006;24(1):152-59.

30. Bertolone SJ, Yates AJ, Boyett JM, et al. Combined modality therapy for poorly differentiated gliomas of the posterior fossa in children: a Children's Cancer Group report. *Journal of neuro-oncology* 2003;63(1):49-54.

31. Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukemia after Ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the Children's Oncology Group. *Blood* 2007;109(1):46-51.

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Appendix C: Recommendation on how to calculate and assess the number needed to treat to inform decision-making

Step 1:

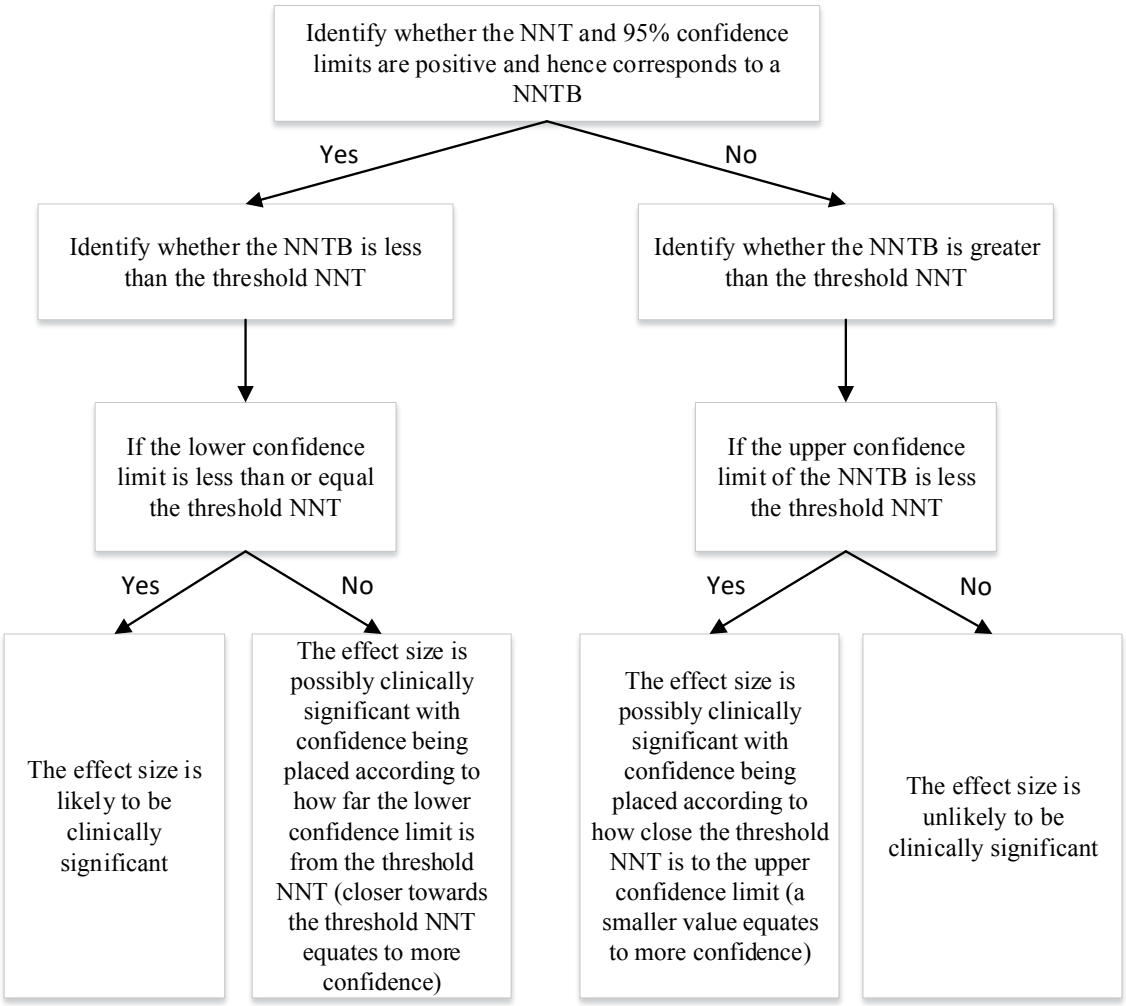
Identify the delta value reported in the sample size calculation and whether the authors reported on the way in which the delta value was chosen. A delta value informed by a previous trial or systematic review should be given more confidence in comparison to one from pilot data or clinical expertise. If no explanation is provided for the delta value, make the assumption that the delta value represents the absolute difference required that would result in a change in clinical practice, while exercising caution that the delta value may have been more influenced by feasibility than clinical evidence. The threshold NNT will correspond to the inverse of the absolute difference unless otherwise stated.

Step 2:

Identify the experimental and control estimates and calculate the ARR and NNT, along with 95% confidence limits as recommended by Altman & Anderson[19]. If the confidence limits, the standard error, or the number of patients at risk at specific time points (in the case of time to event outcomes), are not reported, then the 95% confidence limits of the NNT cannot be calculated.

Step 3:

Apply the following algorithm to determine the clinical significance of the NNT. Plot the ARR and NNT, along with 95% confidence limits and the threshold NNT using a forest plot.



Step 4:

In order to assess whether the NNTB arising from a RCT can be of significance, the following conditions should be satisfied in the population of interest:

- Baseline risk is comparable
- Outcome and time point are identical