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# BMJ Open

## The utility of the number needed to treat in pediatric hematological cancer randomized controlled treatment trials: A systematic review

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3 **1 The utility of the number needed to treat in pediatric hematological cancer randomized controlled**  
4 **2 treatment trials: A systematic review**  
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## Abstract

**Objectives:** The primary objective was to assess the utility of the number needed to treat (NNT) to inform decision-making in the context of pediatric oncology and to calculate the NNT in all superiority pediatric hematological cancer randomized controlled trials (RCTs), with a comparison to the threshold NNT as a measure of clinical significance.

**Design:** Systematic review

**Data sources:** MEDLINE, EMBASE and the Cochrane Childhood Cancer Group Specialized Register through CENTRAL from inception to July 2016.

**Eligibility criteria for selecting studies:** Superiority RCTs of hematological malignancy treatments in pediatric patients that assessed an outcome related to survival, relapse or remission; reported a sample size calculation with a delta value to allow for calculation of the threshold NNT, and that included parameters required to calculate the NNT and associated confidence intervals.

**Results:** A total of 50 RCTs were included, representing 68 randomized questions, of which none reported the NNT. Two RCTs were excluded in the NNT analysis due to an absolute risk reduction of 0 and hence an undefined NNT, resulting in a total of 65 randomized questions. Among acute lymphoblastic leukemia RCTs, 33% (13/40) of randomized questions were found to have a NNT corresponding to benefit, in comparison to acute myeloid leukemia RCTs with 63% (5/8), and none in lymphoma RCTs (0/15). Only 31% (4/13) and 20% (1/5) had a NNT that was less than the threshold NNT for acute lymphoblastic leukemia and acute myeloid leukemia, respectively. Of these, 75% (3/4) and 100% (1/1) were determined to be possibly clinically significant, respectively.

**Conclusions:** We recommend that decision-makers in pediatric oncology use the NNT and associated 95% confidence limits as a supportive tool to evaluate evidence from RCTs, while placing careful attention to the inherent limitation of this measure.

69 **Strengths and Limitations of this Study**

<b>Strengths</b>	<ul style="list-style-type: none"> <li>• We demonstrated the use of a validated methodological approach to assess the numbers needed to treat that involved calculating and comparing the numbers needed to treat to the threshold numbers needed to treat as a measure of clinical significance.</li> <li>• Our review provides a comprehensive analysis of the utility of the numbers needed to treat through an evaluation of all pediatric hematological randomized controlled trials assessing relapse, remission and survival from inception to 2016.</li> <li>• Our visualization, in the form of a forest plot, of the relationship between numbers needed to treat and threshold numbers needed to treat of all included studies, provides an example of a clinically relevant means of communicating complex information.</li> </ul>
<b>Limitations</b>	<ul style="list-style-type: none"> <li>• We excluded a number of trials due to reporting that precluded calculating the numbers needed to treat.</li> <li>• For each study, the delta value in the sample size calculation was assumed to be the absolute difference that would provide an effect size that would lead to a change in clinical practice, if not explicitly indicated, and a proxy for the threshold numbers needed to treat. This assumption, thus would lead to the possibility of effect sizes being chosen that might be more reflective of feasibility as opposed to clinical benefit.</li> </ul>

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## Introduction

84 Cancer in children is exceedingly rare and consists of less than 1% of all cancers diagnosed in Canada,  
85 with hematological cancers accounting for approximately 40% of cases<sup>1</sup>. Pediatric hematological cancer  
86 survival rates are currently upwards of 80%, largely as a result of treatment advances evaluated through  
87 randomized controlled trials (RCTs)<sup>2</sup>. Owing to the relative rarity of pediatric hematological cancers,  
88 multicenter international trials have been necessary to conduct adequately powered treatment  
89 investigations<sup>1,3</sup>. However, even with coordinated resource-intensive efforts, it can take five to seven  
90 years to complete a phase III RCT and another five years to publish outcomes with meaningful follow-  
91 up<sup>2</sup>. There is also an additional time lag before high-level evidence becomes the standard of care<sup>2</sup>.

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93 Given the lengthy timeline from research to practice, evaluating evidence arising from RCTs published in  
94 the pediatric oncology literature is critical for informing subsequent RCTs and standard of care. In other  
95 treatment contexts, the number needed to treat (NNT) has proven to be of value in assisting clinicians to  
96 assess therapeutic interventions and act as a supportive tool in benefit-risk assessments as well as  
97 formulary decision-making<sup>4-8</sup>. The NNT is an absolute effect measure coined almost 30 years ago,  
98 defined as the “*number of patients needed to be treated with one therapy versus another for one patient to*  
99 *encounter an additional outcome of interest within a defined period of time*”<sup>6,9,10</sup>. The NNT corresponds  
100 to the inverse of the absolute risk reduction (ARR), which is the absolute difference between the  
101 experimental and control estimates, for a specific time point. For example, a RCT comparing the effect of  
102 the medication strontium ranelate to a placebo on the incidence of vertebral fractures at three years in  
103 women with postmenopausal osteoporosis found that the event rate in the strontium ranelate group was  
104 20.9% compared to 32.8% in the placebo<sup>11</sup>. The inverse of the absolute difference in event rates between  
105 the experimental and control group corresponds to the NNT, such that in this study, “*9 patients would*  
106 *need to be treated for three years with strontium ranelate in order to prevent 1 patient from having a*  
107 *vertebral fracture (95 percent confidence interval, 6 to 14)*”<sup>11</sup>. The evaluation of evidence requires at a  
108 minimum, consideration of the absolute risk and relative benefits (and harms) related to a therapy in  
109 question, with the NNT being a supportive tool do so<sup>12</sup>. Despite the usefulness of the NNT and the  
110 Consolidated Standard of Reporting Trials (CONSORT) recommendation to report the NNT and ARR,  
111 recent research suggests that these measures are rarely reported in the literature<sup>6,13-16</sup>.

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113 At this time, the utility of the NNT to support evidence-based practice in pediatric oncology treatment  
114 trials remains unexamined, as does the degree to which the NNT has been reported in the pediatric  
115 oncology literature. We specifically aimed to assess the utility of the NNT with consideration of a

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3 116 threshold NNT, which is the point where the therapeutic benefit equals the therapeutic risk<sup>17</sup>. The  
4 117 threshold NNT should correspond to the inverse of the ARR that a RCT is designed to detect and a  
5 118 clinically significant effect size that would lead to a clinical practice change. Therefore, a decision to  
6 119 administer a therapeutic intervention over the standard of care should occur when the NNT is less than the  
7 120 threshold NNT<sup>17</sup>. The primary study objective was to assess the utility of the NNT in pediatric  
8 121 hematologic cancer, by calculating the NNT in all superiority RCTs assessing treatment related survival,  
9 122 relapse or remission, and comparing the NNT to the threshold NNT. A secondary study objective was to  
10 123 assess the proportion of published studies (specifically randomized questions) that reported the NNT.  
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### 19 126 **Methods**

20 127 This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-  
21 128 Analyses (PRISMA) statement (Supplementary File)<sup>18</sup>.  
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25 130 This review consisted of a subset of studies from a previous systematic review conducted by our research  
26 131 team. Methods describing the search strategy, eligibility criteria, study identification and data extraction  
27 132 for our previous systematic review have been detailed in the protocol (Supplementary File). The subset  
28 133 consisted of superiority, parallel group, RCTs in pediatric patients diagnosed with a hematological cancer  
29 134 that assessed an outcome related to survival, relapse or remission and those that reported either  
30 135 confidence intervals (CIs) or standard errors associated with both the experimental and control estimates,  
31 136 or numbers of patients at risk on a Kaplan Meier curve.  
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38 138 The number needed to treat to benefit (NNTB), which corresponds to a positive NNT, or number needed  
39 139 to treat to harm (NNTH), which corresponds to a negative NNT, and associated 95% confidence intervals  
40 140 were calculated for each randomized question as per the validated methodology described by Altman &  
41 141 Andersen<sup>19</sup>. The NNT was based on the primary outcome and time point as specified in the sample size  
42 142 calculation. In the event that the time point specified in the sample size calculation was not reported, the  
43 143 information was inferred if a Kaplan Meier curve with the number of patients at risk was reported<sup>19</sup>. If the  
44 144 aforementioned was not provided, the time point reported in the results was used, and thus, these trials  
45 145 were prone to selective reporting bias.  
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52 147 The ARR, NNT and delta value (i.e., threshold ARR and NNT), as reported in the sample size  
53 148 calculation, were visualized on a forest plot, grouped by disease (Acute Lymphoblastic Leukemia, Acute  
54 149 Myeloid Leukemia, Lymphoma and Mixed, which corresponds to the inclusion of multiple diseases), to  
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3 150 allow for identification of NNTB (defined as the NNT and 95% CI that only included positive numbers),  
4 151 NNTH (defined as the NNT and 95% CI that only included negative numbers) and inconclusive NNT  
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6 152 (defined as the NNT where the 95% CI included both a positive and a negative number). Descriptive  
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8 153 statistics were used to summarize the frequency and percentage of randomized questions reporting the  
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10 154 NNT, as well as the NNTB, NNTH, and inconclusive NNT by disease site.

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12 156 In order to ascertain whether the NNTB was clinically significant, we calculated the frequency and  
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14 157 percentage of randomized questions where the  $NNT < \text{threshold NNT}$ ,  $NNT > \text{threshold NNT}$  or  $NNT =$   
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16 158  $\text{threshold NNT}$ . The threshold NNT was considered to be the inverse of the ARR (i.e., delta value) as  
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18 159 specified in the sample size calculation and was assumed to correspond to a clinically significant effect  
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20 160 size that would lead to a change in clinical practice. The threshold NNT was compared to the treatment  
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22 161 NNT and classified as definitely clinically significant, possibly clinical significant, inconclusive clinical  
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24 162 significance and definitely not clinically significant as specified in Figure 1. These categories were  
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26 163 informed by methods described by Man-Son-Hing et al.<sup>20</sup>. RCTs where an ARR of zero occurred were  
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28 164 excluded from the analysis because the inverse corresponds to an undefined NNT. SAS (Statistical  
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30 165 Analysis Software) version 9.4 (SAS Institute, Cary, NC) was used to perform all analyses.

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## Results

### *Included studies*

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34 169 Our search identified 3,750 unique studies from MEDLINE, EMBASE and the Cochrane Childhood  
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36 170 Cancer Group Specialized Register accessed through CENTRAL. Following title and abstract screening,  
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38 171 406 studies were evaluated for eligibility based on full text review. Of these studies, 356 studies were  
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40 172 excluded and 50 studies (i.e., RCTs), representing 68 randomized questions, were included in the  
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42 173 systematic review (Figure 2) (Supplementary File).

42 174 Of the 50 studies, two were further excluded as the ARR was equal to 0, which left 48 studies inclusive of  
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44 175 65 randomized questions. The randomized questions corresponded to RCTs investigating treatments for  
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46 176 acute lymphoblastic leukemia (ALL) (62%), lymphoma (23%), acute myeloid leukemia (AML) (12%)  
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48 177 and mixed diagnoses (3%).

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### *Number needed to treat*

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54 180 The frequency and proportion of the NNTB, inconclusive NNT, and NNTH are summarized in Table 1.  
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56 181 Approximately 33% (13/40) of randomized questions in ALL RCTs were found to have a NNT



182 corresponding to a NNTB, in comparison to AML with 63% (5/8). There were no randomized questions  
183 in lymphoma (N = 15) trials with a NNTB.

#### 184 *Comparison of NNT and Threshold NNT*

185 A comparison of the NNT to the threshold NNT is summarized in Table 1 and visualized in Figure 3.  
186 Although, the NNTB was associated with a positive effect size, 31% (4/13) and 20% (1/5) had a NNT less  
187 than the threshold NNT for ALL and AML respectively. However, of these, 75% (3/4) and 100% (1/1)  
188 had a lower confidence limit that exceeded or equalled the threshold NNT for ALL and AML,  
189 respectively, and hence were possibly clinically significant. In contrast, 62% (8/13) and 80% (4/5) had a  
190 NNT that exceeded the threshold NNT; however, 63% (5/8) and 25% (1/4) of these had an upper  
191 confidence limit that was lower or equal to the threshold NNT for ALL and AML, respectively, and hence  
192 were possibly clinically significant.

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#### 194 **Discussion**

195 In this systematic review, we demonstrated that variation in the NNT exists among RCTs assessing  
196 outcomes related to remission, relapse, and survival in pediatric hematological cancers. A majority of  
197 randomized questions found to have a NNTB were not necessarily associated with a positive effect size  
198 when using the inverse of the delta value as specified in the sample size calculation as a proxy for the  
199 threshold NNT and a measure of what a clinically significant NNT should be. There were no randomized  
200 questions reporting the NNT, which highlights reporting deficits in the pediatric oncology RCT literature.

#### 201 *Strengths and weaknesses*

202 Our review provides a comprehensive analysis of the utility of the NNT through an evaluation of all  
203 pediatric hematological RCTs assessing relapse, remission and survival from inception to 2016.  
204 Furthermore, we provide the NNT and ARR with 95% CI along with the threshold NNT and ARR for  
205 these RCTs using a validated methodological approach, which will serve as a valuable tool for decision-  
206 makers, clinicians and researchers to assess treatment effects. A weakness of this study is the exclusion  
207 of a number of trials due to reporting that precluded calculating the NNT. However, as the exclusion is  
208 due to reporting deficits, this limitation is beyond our control and serves as an important finding that  
209 reporting quality is limited in the pediatric oncology RCT literature. An additional weakness is that the  
210 delta value in the sample size calculation was assumed to be the absolute difference that would provide an  
211 effect size that would lead to a change in clinical practice, if not explicitly indicated, and a proxy for the

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3 212 threshold ARR and NNT. This assumption, thus would lead to the possibility of effect sizes being chosen  
4 213 that might be more reflective of feasibility as opposed to clinical benefit.

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7 214 *Comparison with existing literature*

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9 215 Considerable published literature has evaluated the utility of the NNT. The overarching conclusion is that  
10 216 the NNT is a metric of value in clinical, health policy and formulary decision-making when interpreted  
11 217 correctly<sup>4-8</sup>. However, the NNT and ARR are rarely reported or poorly reported in the literature despite  
12 218 being recommended in the CONSORT statement and are often calculated using inappropriate methods<sup>6</sup>  
13 219<sup>12-16,21-26</sup>. Our findings corroborate the existing literature because no studies reported the NNT in our  
14 220 review. Previous studies have not highlighted the utility of the NNT specifically in the pediatric oncology  
15 221 literature or evaluated the clinical significance of the NNT using the approach described in our study and  
16 222 thus, our study is a novel and important addition to the literature.  
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25 224 *Study explanations and implications*

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27 225 Our study quantified the NNT as a means to better understand the utility of this tool to facilitate decision  
28 226 making in pediatric oncology. The NNT allows for an intuitive understanding of the absolute effect size  
29 227 in terms of patients and can help considerably when comparing one treatment to another, after ensuring  
30 228 baseline characteristics, the outcome and time point for the patient population of interest are  
31 229 comparable<sup>12</sup>. For instance, a RCT conducted by Creutzig et al.<sup>27</sup> in pediatric AML patients assessing 5-  
32 230 year event free survival, found a 6% (95% CI, 1%-10%) absolute increase associated with the  
33 231 experimental treatment compared to the control treatment. The associated NNT corresponded to 15 (33-  
34 232 10), meaning that it is estimated that by administering the experimental treatment, 1 extra patient would  
35 233 survive at 5 years for every 15 patients treated (95% CI, 33-10). Of note, this RCT was powered to detect  
36 234 an absolute increase in 5-year EFS of 13% (i.e., delta value), which would correspond to a NNTB of 8  
37 235 (i.e., threshold NNT). Although the NNTB is 15, the lower confidence limit is 33 and the upper  
38 236 confidence limit is 10 (a range that does not include 8), which, given the range, would lead one to believe  
39 237 that the effect size does not provide strong enough evidence to change clinical practice. In situations  
40 238 where the lower confidence limit of the NNTB is less than the threshold NNT, one can be more confident  
41 239 that the treatment confers a clinically improved outcome as compared to the control. On the other hand, if  
42 240 the NNTB is less than the threshold NNT and the lower confidence limit is greater than the threshold  
43 241 NNT, one should exercise greater caution in concluding that the effect size is clinically significant. As  
44 242 demonstrated in our study, a forest plot is a convenient method to visualize the relationship between the  
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3 243 NNT (and the associated 95% CI) evident in study results compared to the NNT that the study was  
4 244 designed to detect as a proxy for the threshold NNT and that would be considered clinically significant.  
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7 245 The aforementioned approach is recommended in light of smaller sample sizes that are often attained in  
8 246 pediatric oncology RCTs and rare disease trials in general. This was demonstrated in our study where the  
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10 247 majority of randomized questions found to have a NNTB had a NNT less than the specified threshold  
11 248 NNT, with the majority of those in ALL having an upper confidence limit exceeding the threshold NNT.  
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13  
14 249 The utility of the NNT, however, is inherently reliant on three major areas, baseline risk, the outcome and  
15 250 the time point<sup>12</sup>. In order for the NNT from an RCT demonstrating a NNTB to have utility, the patient  
16 251 population of interest should share a similar baseline risk because the desired treatment effect may be  
17 252 overestimated and thus the NNTB may be underestimated. Outcomes related to event-free survival often  
18 253 differ in what is considered an event and thus it is critical to ensure that the NNTB being applied to the  
19 254 population of interest is identical in terms of the outcome in question. Numerous studies have  
20 255 demonstrated how the NNT varies with time and thus, comparability in time points is critical to ensure  
21 256 accurate interpretation of the NNT to a population of interest<sup>4 12 22 23</sup>.

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### 29 258 *Recommendations*

31 259 We recommend that clinicians and decision-makers in pediatric oncology consider using the NNT as a  
32 260 supportive tool to evaluate evidence from RCTs, while placing careful attention to the inherent limitation  
33 261 of this measure. Figure 4 provides a summary of how the NNT can be calculated and assessed to inform  
34 262 decision-making<sup>19 20</sup>.

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## References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2017. Toronto, ON: Canadian Cancer Society; 2017. Available at: [cancer.ca/Canadian-CancerStatistics-2017-EN.pdf](http://cancer.ca/Canadian-CancerStatistics-2017-EN.pdf).
2. Saletta F, Seng MS, Lau LM. Advances in paediatric cancer treatment. *Translational pediatrics* 2014;3(2):156-82. doi: 10.3978/j.issn.2224-4336.2014.02.01 [published Online First: 2014/04/01]
3. Bond MC, Pritchard S. Understanding clinical trials in childhood cancer. *Paediatrics & child health* 2006;11(3):148-50. [published Online First: 2008/11/26]
4. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract* 2013;67 doi: 10.1111/ijcp.12142
5. Mendes D, Alves C, Batel MF. Testing the usefulness of the number needed to treat to be harmed (NNT<sub>H</sub>) in benefit-risk evaluations: case study with medicines withdrawn from the European market due to safety reasons. *Expert Opin Drug Saf* 2016;15 doi: 10.1080/14740338.2016.1217989
6. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. *BMC Medicine* 2017;15(1):112. doi: 10.1186/s12916-017-0875-8
7. Mendes D, Alves C, Batel-Marques F. Number needed to harm in the post-marketing safety evaluation: results for rosiglitazone and pioglitazone. *Pharmacoepidemiol Drug Saf* 2015;24 doi: 10.1002/pds.3874
8. Mendes D, Alves C, Batel-Marques F. Benefit-risk of therapies for relapsing-remitting multiple sclerosis: testing the number needed to treat to benefit (NNT<sub>B</sub>), number needed to treat to harm (NNT<sub>H</sub>) and the likelihood to be helped or harmed (LHH): a systematic review and meta-analysis. *CNS Drugs* 2016;30 doi: 10.1007/s40263-016-0377-9
9. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318 doi: 10.1056/nejm198806303182605
10. Cook D, Sackett D. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310 doi: 10.1136/bmj.310.6977.452
11. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350(5):459-68. doi: 10.1056/NEJMoa022436 [published Online First: 2004/01/30]
12. McAlister FA. The "number needed to treat" turns 20—and continues to be used and misused. *CMAJ* 2008;179 doi: 10.1503/cmaj.080484
13. Hildebrandt M, Vervölgyi E, Bender R. Calculation of NNTs in RCTs with time-to-event outcomes: a literature review. *BMC Med Res Methodol* 2009;9 doi: 10.1186/1471-2288-9-21
14. Nuovo J, Melnikow J, Chang D. Reporting number needed to treat and absolute risk reduction in randomized controlled trials. *JAMA* 2002;287 doi: 10.1001/jama.287.21.2813
15. Alonso-Coello P, Carrasco-Labra A, Brignardello-Petersen R. Systematic reviews experience major limitations in reporting absolute effects. *J Clin Epidemiol* 2016;72 doi: 10.1016/j.jclinepi.2015.11.002
16. Moher D, Hopewell S, Schulz KF. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340 doi: 10.1136/bmj.c869
17. Sinclair JC, Cook RJ, Guyatt GH, et al. When should an effective treatment be used? Derivation of the threshold number needed to treat and the minimum event rate for treatment. *J Clin Epidemiol* 2001;54(3):253-62. [published Online First: 2001/02/27]
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj* 2009;339:b2700. doi: 10.1136/bmj.b2700 [published Online First: 2009/07/23]
19. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319 doi: 10.1136/bmj.319.7223.1492

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2  
3 323 20. Man-Son-Hing M, Laupacis A, O'Rourke K, et al. Determination of the clinical importance of study  
4 324 results. *Journal of general internal medicine* 2002;17(6):469-76. [published Online First:  
5 325 2002/07/23]
- 6 326 21. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. *Thorax* 2013;68 doi:  
7 327 10.1136/thoraxjnl-2012-202709
- 8 328 22. Suissa S. The number needed to treat: 25 years of trials and tribulations in clinical research. *Rambam*  
9 329 *Maimonides Med J* 2015;30
- 10 330 23. Suissa D, Brassard P, Smiechowski B, et al. Number needed to treat is incorrect without proper time-  
11 331 related considerations. *J Clin Epidemiol* 2012;65 doi: 10.1016/j.jclinepi.2011.04.009
- 12 332 24. Stang A, Poole C, Bender R. Common problems related to the use of number needed to treat. *J Clin*  
13 333 *Epidemiol* 2010;63 doi: 10.1016/j.jclinepi.2009.08.006
- 14 334 25. Tramer MR, Walder B. Number needed to treat (or harm). *World journal of surgery* 2005;29(5):576-  
15 335 81. doi: 10.1007/s00268-005-7916-8 [published Online First: 2005/04/14]
- 16 336 26. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance  
17 337 employed in randomized controlled trials of drugs for dementia. *Journal of the American*  
18 338 *Geriatrics Society* 2009;57(3):536-46. doi: 10.1111/j.1532-5415.2008.02122.x [published Online  
19 339 First: 2009/02/04]
- 20 340 27. Creutzig U, Zimmermann M, Bourquin J-P, et al. Randomized trial comparing liposomal  
21 341 daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from  
22 342 Study AML-BFM 2004. *Blood* 2013;122(1):37-43. doi: [http://dx.doi.org/10.1182/blood-2013-02-](http://dx.doi.org/10.1182/blood-2013-02-484097)  
23 343 [484097](http://dx.doi.org/10.1182/blood-2013-02-484097)

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346 **Table 1:** Randomized questions corresponding to number needed to benefit, harm and inclusive relative  
 347 to threshold number needed to treat by hematological cancer type  
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NNT <sup>1</sup>	Hematological Cancer Randomized Questions (N = 65)			
	ALL (N = 40)	Lymphoma (N = 15)	AML (N = 8)	Mixed Diagnoses <sup>2</sup> (N = 2)
<b>NNTB (n, %)</b>	13 (32.5%)	0 (0.0%)	5 (62.5%)	1 (50.0%)
<b><i>NNT &lt; Threshold NNT</i></b>	4 (30.8%)	0 (0.0%)	1 (20.0%)	1 (100.0%)
<b><i>NNT Lower Confidence Limit ≥ Threshold NNT</i></b>	3 (75.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
<b><i>NNT &gt; Threshold</i></b>	8 (61.5%)	0 (0.0%)	4 (80.0%)	0 (0.0%)
<b><i>NNT Upper Confidence Limit ≤ Threshold NNT</i></b>	5 (62.5%)	0 (0.0%)	1 (25.0%)	0 (0.0%)
<b><i>NNT = Threshold NNT</i></b>	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Inconclusive NNT (n, %)</b>	21 (52.5%)	13 (86.7%)	3 (37.5%)	1 (50.0%)
<b>NNTH (n, %)</b>	6 (15.0%) <sup>3</sup>	2 (13.3%)	0 (0.0%)	0 (0.0%)

349 Note: Percentages due not sum to a 100% due to rounding and randomized questions with absolute risk reduction equal to zero  
 350 are excluded. Threshold NNT corresponds to the inverse of the absolute difference (i.e., delta value) as reported in the sample  
 351 size calculation.

352 Abbreviations: NNT, number needed to treat; NNTB, number needed to treat to benefit; NNTH, number needed to treat to harm;  
 353 ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; UCL, Upper confidence limit; LCL, Lower Confidence  
 354 Limit; ARR, absolute risk reduction

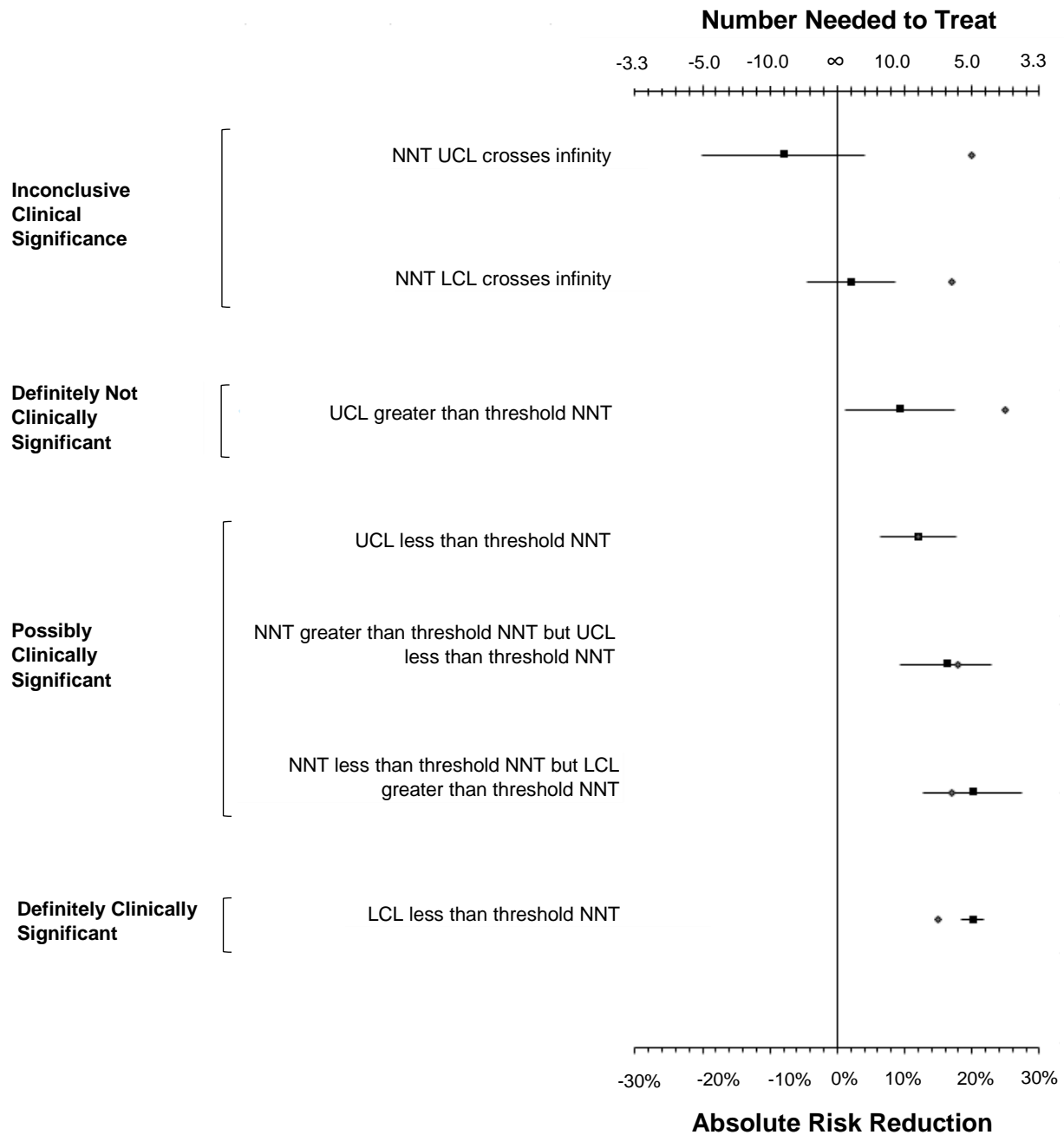
355 <sup>1</sup> Denominator for indented corresponds to above row

356 <sup>2</sup> Mixed diagnoses refer to RCTs where more than one hematological cancer was included

357 <sup>3</sup> One randomized question (Bostrom et al. 2003) was included where the outcome was related to a decrease in CNS relapse rate  
 358 and thus NNTH is actually beneficial

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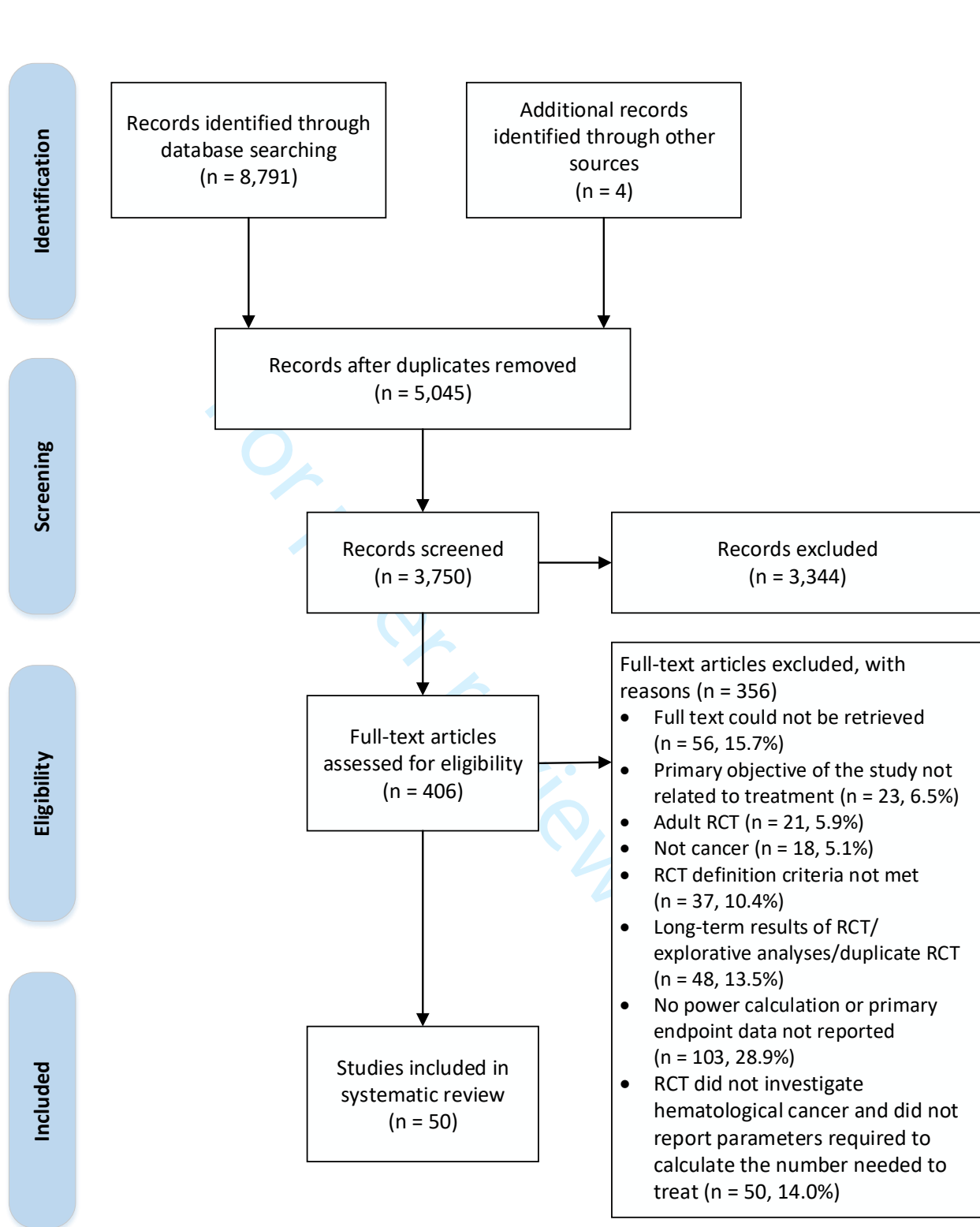
**Figure 1:** Guideline to assess level of clinical significance using numbers needed to treat

Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study ARR or NNT.

ARR corresponds to the absolute difference between the experimental and control estimates. The inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value the randomized control trial was designed to detect as determined in the sample size calculation. The inverse of the threshold ARR corresponds to the threshold NNT.

Abbreviations; NNT, number needed to treat; ARR, absolute risk reduction; UCL, upper confidence limit; LCL, lower confidence limit





**Figure 2:** Selection of randomized controlled trials in the systematic review



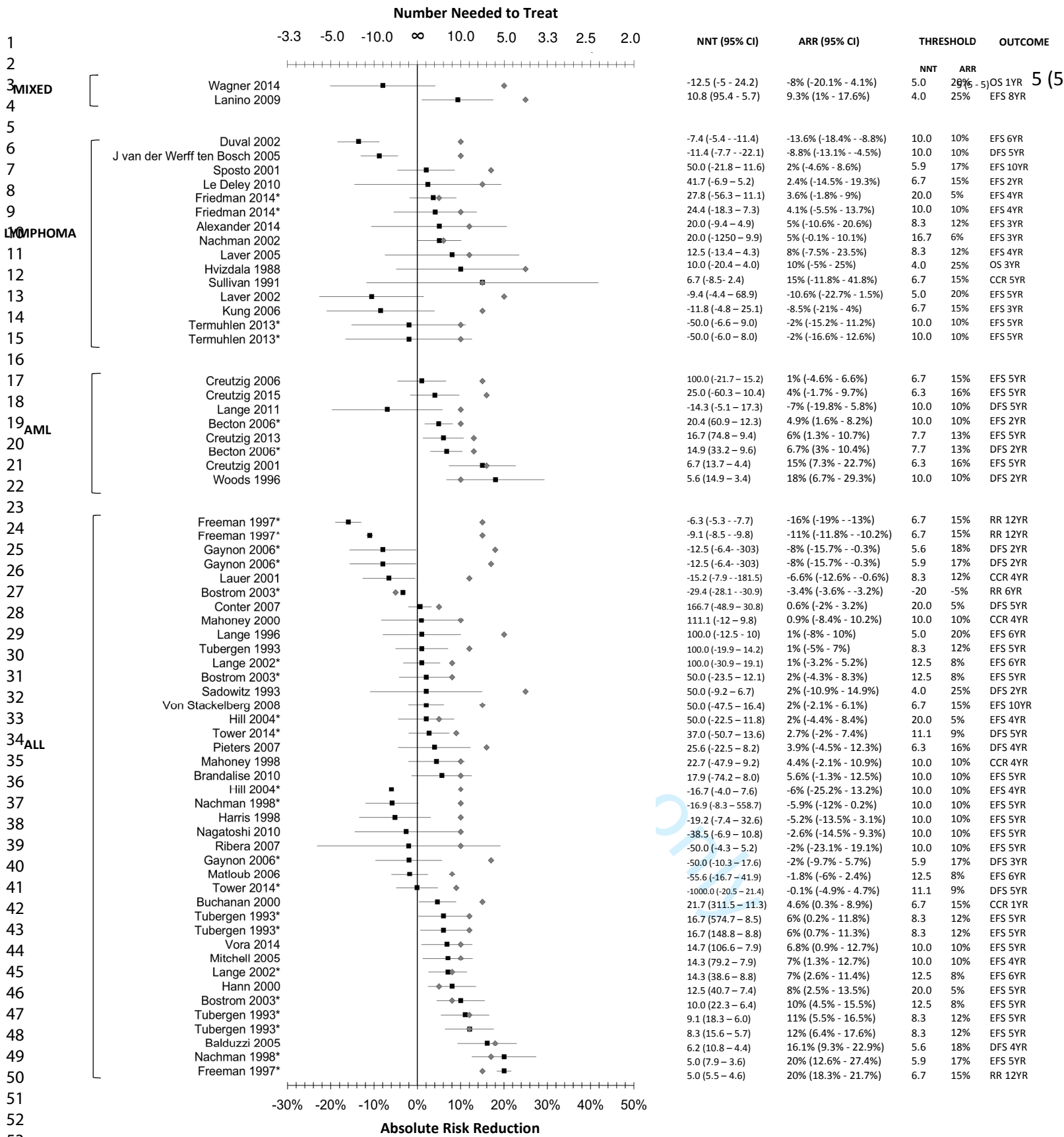


Figure 3: Forest plot summarizing randomized questions by the number needed to treat relative to the threshold number needed to treat according to hematological cancer type

1 \*Correspond to RCTs where more than one randomized question was investigated.

2 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study ARR or NNT.

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4 ARR corresponds to the absolute difference between the experimental and control estimates. The inverse of the ARR corresponds to the NNT. The threshold ARR  
5 corresponds to the delta value the randomized control trial was designed to detect as determined in the sample size calculation. The inverse of the threshold ARR  
6 corresponds to the threshold NNT.

7 Abbreviations: AML, acute myeloid leukemia; ALL, Acute lymphoblastic Leukemia; NNT, number needed to treat; ARR, absolute risk reduction; OS, overall survival;  
8 EFS, event-free survival; DFS, disease-free survival; CCR, complete cancer remission; RR, relapse rate; YR, year; CI, confidence interval

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**Step 1:**

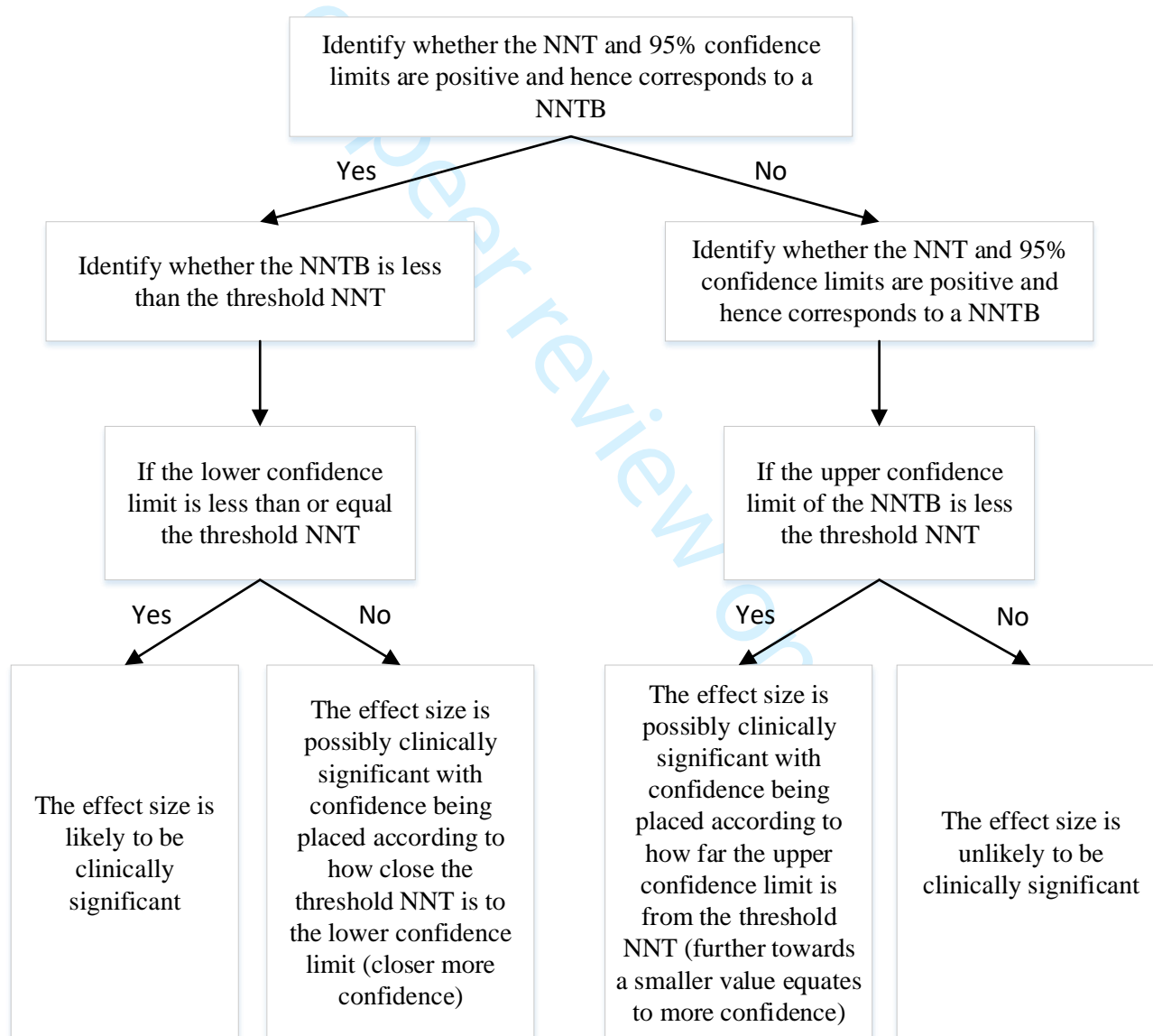
1 Identify the delta value reported in the sample size calculation and whether the authors reported on the way in which  
 2 the delta value was chosen. A delta value informed by a previous trial or systematic review should be given more  
 3 confidence in comparison to one from pilot data or clinical expertise. If no explanation is provided for the delta value,  
 4 make the assumption that the delta value represents the absolute difference required that would result in a change in  
 5 clinical practice, while exercising caution that the delta value may have been more influenced by feasibility than  
 6 clinical evidence. The threshold NNT will correspond to the inverse of the absolute difference.  
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**Step 2:**

10 Identify the experimental and control estimates and calculate the ARR and NNT, along with 95% confidence limits as  
 11 recommended by Altman & Anderson<sup>19</sup>. If the confidence limits, the standard error, or the number of patients at risk at  
 12 specific time points (in the case of time to event outcomes), are not reported, then the NNT cannot be calculated.  
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**Step 3:**

16 Apply the following algorithm to determine the clinical significance of the NNT. Plot the ARR and NNT, along with  
 17 95% confidence limits and the threshold NNT using a forest plot.  
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**Step 4:**

58 In order to assess whether the NNTB arising from a RCT can be of significance, the following conditions should be  
 59 satisfied in the population of interest:  
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- Baseline risk is comparable
- Outcome and time point are identical

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**Figure 4:** Recommendation on how to calculate and assess the numbers needed to treat to inform decision-making

## 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 be 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 to 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/
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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.
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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 Studies:

1. 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.
2. 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):450-458.
3. 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):602-609.
4. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Improved outcome with delayed intensification for children with acute lymphoblastic leukemia and intermediate presenting features: a Childrens Cancer Group phase III trial. *Journal of Clinical Oncology* 1993;11(3):527-537.
5. 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.
6. Ravindranath Y, Yeager AM, Chang MN, et al. Autologous bone marrow transplantation versus intensive consolidation chemotherapy for acute myeloid leukemia in childhood. *Pediatric Oncology Group. New England Journal of Medicine* 1996;334(22):1428-1434.
7. 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):4979-4989.
8. Freeman AI, Boyett JM, Glicksman AS, et al. Intermediate-dose methotrexate versus cranial irradiation in childhood acute lymphoblastic leukemia: a ten-year follow-up. *Medical & Pediatric Oncology* 1997;28(2):98-107.
9. 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):2840-2847.
10. 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):246-254.
11. 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):920-930.
12. 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):1663-1671.

13. 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):1166-1174.
14. 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):356-363.
15. 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):1285-1294.
16. 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):2705-2713.
17. 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):1038-1045.
18. Rizzari C, Valsecchi MG, Arico M, et al. Effect of protracted high-dose L-asparaginase given as a second exposure in a Berlin-Frankfurt-Munster-based treatment: Results of the randomized 9102 intermediate-risk childhood acute lymphoblastic leukemia study - A report from the Associazione Italiana Ematologia Oncologia Pediatrica. *Journal of Clinical Oncology* 2001;19(5):1297-1303.
19. 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):432-441.
20. Duval M, Suci 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):2734-2739.
21. Lange BJ, Bostrom BC, Cherlow JM, et al. Double-delayed intensification improves event-free survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood* 2002;99(3):825-833.
22. 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):105-109.
23. 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):3765-3771.
24. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood* 2003;101(10):3809-3817.



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3 25. Hill FGH, Richards S, Gibson B, et al. Successful treatment without cranial radiotherapy of  
4 children receiving intensified chemotherapy for acute lymphoblastic leukaemia: results of the risk-  
5 stratified randomized central nervous system treatment trial MRC UKALL XI (ISRC TN 16757172).  
6 British journal of haematology 2004;124(1):33-46.  
7
- 8 26. Balduzzi A, Valsecchi MG, Uderzo C, et al. Chemotherapy versus allogeneic transplantation for  
9 very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: Comparison by  
10 genetic randomisation in an international prospective study. Lancet 2005;366(9486):635-642.  
11
- 12 27. Laver JH, Kravaka JM, Hutchison RE, et al. Advanced-stage large-cell lymphoma in children and  
13 adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose  
14 cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial.  
15 Journal of Clinical Oncology 2005;23(3):541-547.  
16
- 17 28. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with  
18 prednisolone for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council  
19 ALL97 randomized trial. British journal of haematology 2005;129(6):734-745.  
20
- 21 29. van der Werff ten Bosch J, Suci S, Thyss A, et al. Value of intravenous 6-mercaptopurine during  
22 continuation treatment in childhood acute lymphoblastic leukemia and non-Hodgkin's lymphoma: Final  
23 results of a randomized phase III trial (58881) of the EORTC CLG. Leukemia 2005;19(5):721-726.  
24
- 25 30. Becton D, Dahl GV, Ravindranath Y, et al. Randomized use of cyclosporin A (CsA) to modulate  
26 P-glycoprotein in children with AML in remission: Pediatric Oncology Group Study 9421. Blood  
27 2006;107(4):1315-1324.  
28
- 29 31. Creutzig U, Zimmermann M, Lehrnbecher T, et al. Less toxicity by optimizing chemotherapy, but  
30 not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid  
31 leukemia: Results of AML-BFM 98. Journal of Clinical Oncology 2006;24(27):4499-4506.  
32
- 33 32. Gaynon PS, Harris RE, Altman AJ, et al. Bone marrow transplantation versus prolonged intensive  
34 chemotherapy for children with acute lymphoblastic leukemia and an initial bone marrow relapse within  
35 12 months of the completion of primary therapy: Children's Oncology Group study CCG-1941. Journal of  
36 Clinical Oncology 2006;24(19):3150-3156.  
37
- 38 33. Kung FH, Schwartz CL, Ferree CR, et al. POG 8625: a randomized trial comparing  
39 chemotherapy with chemoradiotherapy for children and adolescents with Stages I, IIA, IIIA1 Hodgkin  
40 Disease: a report from the Children's Oncology Group. Journal of Pediatric Hematology/Oncology  
41 2006;28(6):362-368.  
42
- 43 34. Matloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous  
44 system relapse but fails to improve event-free survival when compared with intrathecal methotrexate:  
45 results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia,  
46 reported by the Children's Oncology Group. Blood 2006;108(4):1165-1173.  
47
- 48 35. Conter V, Valsecchi MG, Silvestri D, et al. Pulses of vincristine and dexamethasone in addition  
49 to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: a  
50 multicentre randomised trial. Lancet 2007;369(9556):123-131.  
51
- 52 36. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year  
53 with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised  
54 trial. Lancet 2007;370(9583):240-50.  
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3 37. Ribera JM, Ortega JJ, Oriol A, et al. Comparison of intensive chemotherapy, allogeneic, or  
4 autologous stem-cell transplantation as postremission treatment for children with very high risk acute  
5 lymphoblastic leukemia: PETHEMA ALL-93 trial. *Journal of Clinical Oncology* 2007;25(1):16-24.  
6  
7 38. Von Stackelberg A, Hartmann R, Buhrer C, et al. High-dose compared with intermediate-dose  
8 methotrexate in children with a first relapse of acute lymphoblastic leukemia. *Blood* 2008;111(5):2573-  
9 2580.  
10  
11 39. Lanino E, Rondelli R, Locatelli F, et al. Early (day -7) versus conventional (day -1) inception of  
12 cyclosporine-A for graft-versus-host disease prophylaxis after unrelated donor hematopoietic stem cell  
13 transplantation in children. Long-term results of an AIEOP prospective, randomized study. *Biol Blood*  
14 *Marrow Transplant* 2009;15(6):741-8.  
15  
16 40. Brandalise SR, Pinheiro VR, Aguiar SS, et al. Benefits of the intermittent use of 6-  
17 mercaptopurine and methotrexate in maintenance treatment for low-risk acute lymphoblastic leukemia in  
18 children: randomized trial from the Brazilian Childhood Cooperative Group--protocol ALL-99. *Journal of*  
19 *Clinical Oncology* 2010;28(11):1911-1918.  
20  
21 41. Nagatoshi Y, Matsuzaki A, Suminoe A, et al. Randomized trial to compare LSA2L2-type  
22 maintenance therapy to daily 6-mercaptopurine and weekly methotrexate with vincristine and  
23 dexamethasone pulse for children with acute lymphoblastic leukemia. *Pediatric Blood & Cancer*  
24 2010;55(2):239-247.  
25  
26 42. Lange BJ, Yang RK, Gan J, et al. Soluble interleukin-2 receptor alpha activation in a Children's  
27 Oncology Group randomized trial of interleukin-2 therapy for pediatric acute myeloid leukemia. *Pediatric*  
28 *Blood & Cancer* 2011;57(3):398-405.  
29  
30 43. Creutzig U, Zimmermann M, Bourquin J-P, et al. Randomized trial comparing liposomal  
31 daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from Study AML-  
32 BFM 2004. *Blood* 2013;122(1):37-43.  
33  
34 44. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children  
35 and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. *British*  
36 *journal of haematology* 2013;162(6):792-801.  
37  
38 45. Alexander S, Kravaka JM, Weitzman S, et al. Advanced stage anaplastic large cell lymphoma in  
39 children and adolescents: results of ANHL0131, a randomized phase III trial of APO versus a modified  
40 regimen with vinblastine: a report from the children's oncology group. *Pediatric Blood & Cancer*  
41 2014;61(12):2236-2242.  
42  
43 46. Friedman DL, Chen L, Wolden S, et al. Dose-intensive response-based chemotherapy and  
44 radiation therapy for children and adolescents with newly diagnosed intermediate-risk hodgkin  
45 lymphoma: a report from the Children's Oncology Group Study AHOD0031. *Journal of Clinical*  
46 *Oncology* 2014;32(32):3651-3658.  
47  
48 47. Tower RL, Jones TL, Camitta BM, et al. Dose intensification of methotrexate and cytarabine  
49 during intensified continuation chemotherapy for high-risk B-precursor acute lymphoblastic leukemia:  
50 POG 9406: a report from the Children's Oncology Group. *Journal of Pediatric Hematology/Oncology*  
51 2014;36(5):353-361.  
52  
53 48. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual  
54 disease-defined high-risk subgroup of children and young people with clinical standard-risk and  
55  
56  
57  
58  
59  
60

intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. *Lancet Oncology* 2014;15(8):809-818.

49. 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):1685-1694.

50. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus intramuscular native *Escherichia coli* L-asparaginase in newly diagnosed childhood acute lymphoblastic leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. *Lancet Oncology* 2015;16(16):1677-1690.

### List of Excluded Studies:

1. Karon M, Freireich EJ, Frei E, et al. The role of vincristine in the treatment of childhood acute leukemia. *Clinical pharmacology and therapeutics* 1966;7(3):332-339.

2. Wolff JA, Newton WA, Jr., Krivit W, et al. Single versus multiple dose dactinomycin therapy of Wilms's tumor. A controlled co-operative study conducted by the Children's Cancer Study Group A (formerly Acute Leukemia Co-operative Chemotherapy Group A). *New England Journal of Medicine* 1968;279(6):290-294.

3. 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):381-391.

4. Wolff JA, D'Angio G, Hartmann J, et al. Long-term evaluation of single versus multiple courses of actinomycin D therapy of Wilm's tumor. *The New England journal of medicine* 1974;290(2):84-86.

5. Fernbach DJ, George SL, Sutow WW, et al. Long-term results of reinforcement therapy in children with acute leukemia. *Cancer* 1975;36(5):1552-1559.

6. Fujimoto T, Goya H, Nakagawa K. Comparison of high dose infusion of methotrexate (MTX) vs sequential complementary method for maintenance of remission in acute childhood leukemia. A cooperative study. *Proceedings of the American Association for Cancer Research* 1975;16(66):no.257.

7. Rivera G, Avery T, Pratt C. 4' Demethylepipodophyllotoxin 9 (4,6 O 2 thenylidene beta D glucopyranoside) (NSC 122819; VM 26) and 4' demethylepipodophyllotoxin 9 (4,6 O ethylidene beta D glucopyranoside) (NSC 141540; VP 16 213) in childhood cancer: preliminary observations. *CANCER CHEMOTHER.REP* 1975;59(4):743-749.

8. Evans AE, Albo V, D'Angio GJ. Cyclophosphamide treatment of patients with localized and regional neuroblastoma. A randomized study. *Cancer* 1976;38(2):655-659.

9. Lemerle J, Voute PA, Tournade MF, et al. Preoperative versus postoperative radiotherapy, single versus multiple courses of actinomycin D, in the treatment of Wilms' tumor. Preliminary results of a controlled clinical trial conducted by the International Society of Paediatric Oncology (S.I.O.P.). *Cancer* 1976;38(2):647-654.

10. 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):495-497.

11. 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 research. *Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer* 1978;68:28-32.
12. Aur RJ, Simone JV, Verzosa MS, et al. Childhood acute lymphocytic leukemia: study VIII. *Cancer* 1978;42(5):2123-2134.
13. Jones PHM, Pearson D, Johnson AL. Management of nephroblastoma in childhood. Clinical study of two forms of maintenance chemotherapy. *Archives of Disease in Childhood* 1978;53(2):112-119.
14. Rivera G, Murphy SB, Aur RJA. Recurrent childhood lymphocytic leukemia. Clinical and cytokinetic studies of cytosine arabinoside and methotrexate for maintenance of second hematologic remission. *Cancer* 1978;42(6):2521-2528.
15. 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.
16. Doering EJ, Nitschke R, Haggard ME. Phase II study demonstrating failure of both a five-drug continuous-therapy regimen and a two-drug pulse-therapy regimen in the treatment of metastatic neuroblastoma: Southwest Oncology Group Study 822. *Cancer treatment reports* 1979;63(8):1383-1384.
17. Ferrant A, Hulhoven R, Bosly A, et al. Clinical trials with daunorubicin-DNA and adriamycin-DNA in acute lymphoblastic leukemia of childhood, acute nonlymphoblastic leukemia, and bronchogenic carcinoma. *Cancer Chemotherapy & Pharmacology* 1979;2(1):67-71.
18. Rausen AR, Glidewell O, Cuttner J. Superiority of L-asparaginase combination chemotherapy in advanced acute lymphocytic leukemia of childhood. Randomized comparative trial of combination versus solo therapy. *Cancer clinical trials* 1979;2(2):137-144.
19. Camitta BM, Pinkel D, Thatcher LG. Failure of early intensive chemotherapy to improve prognosis in childhood acute lymphocytic leukemia. *Medical and pediatric oncology* 1980;8(4):383-389.
20. Ekert H, Waters KD, Matthews RN. A randomized study of intermittent chemotherapy with or without BCG inoculation in maintenance therapy of childhood ALL. *Medical and pediatric oncology* 1980;8(4):353-360.
21. Jacquillat C, Weil M, Auclerc MF. Application of the study of prognostic factors to the treatment of childhood (<20 years old) acute lymphoblastic leukemia. Protocol 08 LA 74. *Bulletin du cancer* 1980;67(4):458-469.
22. Murphy SB, Hustu HO. A randomized trial of combined modality therapy of childhood non-Hodgkin's lymphoma. *Cancer* 1980;45(4):630-637.
23. 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):1015-1019.
24. D'Angio GJ, Evans A, Breslow N. The treatment of Wilms' tumor: Results of the second National Wilms' Tumor Study. *Cancer* 1981;47(9):2302-2311.

- 1  
2  
3 25. D'Angio GJ, Littman P, Nesbit M. Evaluation of radiation therapy factors in prophylactic central  
4 nervous system irradiation for childhood leukemia: A report from the children's cancer study group.  
5 International Journal of Radiation Oncology Biology Physics 1981;7(8):1031-1038.  
6
- 7 26. Nesbit ME, Jr., Sather HN, Robison LL, et al. Presymptomatic central nervous system therapy in  
8 previously untreated childhood acute lymphoblastic leukaemia: comparison of 1800 rad and 2400 rad. A  
9 report for Children's Cancer Study Group. Lancet 1981;1(8218):461-466.  
10
- 11 27. Sackmann Muriel F, Morgenfeld M, Kvicala R. Hodgkin's disease in childhood. Therapy results  
12 in Argentina. American Journal of Pediatric Hematology/Oncology 1981;3(3):247-254.  
13
- 14 28. Sexauer CL, Vietti T, Humphrey GB. Combination chemotherapy study for remission  
15 maintenance in ALL: An evaluation of vincristine, cyclophosphamide and vincristine, cyclophosphamide,  
16 and BCNU. A Southwest oncology group phase II study. American Journal of Pediatric  
17 Hematology/Oncology 1981;3(3):255-257.  
18
- 19 29. Van Eys J, Chen T, Moore T. Adjuvant chemotherapy for medulloblastoma and ependymoma  
20 using Iv vincristine, intrathecal methotrexate, and intrathecal hydrocortisone: A southwest oncology  
21 group study. Cancer treatment reports 1981;65(7-8):681-684.  
22
- 23 30. The treatment of acute lymphoblastic leukaemia (ALL) in childhood, UKALL III: the effects of  
24 added cytosine arabinoside and/or asparaginase, and a comparison of continuous or discontinuous  
25 mercaptopurine in regimens for standard risk ALL. Medical and pediatric oncology 1982;10(5):501-510.  
26
- 27 31. Duration of chemotherapy in childhood acute lymphoblastic leukaemia. The Medical Research  
28 Council's Working Party on Leukaemia in Childhood. Medical & Pediatric Oncology 1982;10(5):511-  
29 520.  
30
- 31 32. Nesbit M, Sather H, Robison L. The duration of chemotherapy for childhood acute lymphoblastic  
32 leukemia (ALL): A randomized study of 316 patients. Proceedings of the American Society of Clinical  
33 Oncology. Vol 1982;1:480.  
34
- 35 33. Nesbit ME, Sather H, Robison LL, et al. Sanctuary therapy: a randomized trial of 724 children  
36 with previously untreated acute lymphoblastic leukemia: A Report from Children's Cancer Study Group.  
37 Cancer research 1982;42(2):674-680.  
38
- 39 34. Sullivan MP, Chen T, Dymont PG, et al. Equivalence of intrathecal chemotherapy and  
40 radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric  
41 oncology group study. Blood 1982;60(4):948-958.  
42
- 43 35. Sullivan MP, Fuller LM, Chen T. Intergroup Hodgkin's disease in children study of stages I and  
44 II: A preliminary report. Cancer treatment reports 1982;66(4):937-947.  
45
- 46 36. Anderson JR, Wilson JF, Jenkin DT, et al. Childhood non-Hodgkin's lymphoma. The results of a  
47 randomized therapeutic trial comparing a 4-drug regimen (COMP) with a 10-drug regimen (LSA2-L2).  
48 New England Journal of Medicine 1983;308(10):559-565.  
49
- 50 37. Freeman AI, Weinberg V, Brecher ML, et al. Comparison of intermediate-dose methotrexate with  
51 cranial irradiation for the post-induction treatment of acute lymphocytic leukemia in children. New  
52 England Journal of Medicine 1983;308(9):477-484.  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 38. Lemerle J, Voute PA, Tournade MF, et al. Effectiveness of preoperative chemotherapy in Wilms' tumor: results of an International Society of Paediatric Oncology (SIOP) clinical trial. *Journal of Clinical Oncology* 1983;1(10):604-609.
- 4  
5  
6  
7 39. Nesbit ME, Jr., Sather HN, Robison LL, et al. Randomized study of 3 years versus 5 years of chemotherapy in childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology* 1983;1(5):308-316.
- 8  
9  
10  
11 40. Sallan SE, Hitchcock Bryan S, Gelber R. Influence of intensive asparaginase in the treatment of childhood non-T-cell acute lymphoblastic leukemia. *Cancer research* 1983;43(11):5601-5607.
- 12  
13  
14 41. Cangir A, Ragab AH, Steuber P. Combination chemotherapy with vincristine (NSC-67574), procarbazine (NSC-77213), prednisone (NSC-10023) with or without nitrogen mustard (NSC-762)(MOPP vs OPP) in children with recurrent brain tumors. *Medical and pediatric oncology* 1984;12(1):1-3.
- 15  
16  
17  
18 42. Evans WE, Crom WR, Stewart CF, et al. Methotrexate systemic clearance influences probability of relapse in children with standard-risk acute lymphocytic leukaemia. *Lancet* 1984;1(8373):359-362.
- 19  
20  
21 43. Krischer J, Land VJ, Civin CI, et al. Evaluation of AMSA in children with acute leukemia. A Pediatric Oncology Group study. *Cancer* 1984;54(2):207-210.
- 22  
23  
24 44. Lilleyman JS, Campbell RHA. Vindesine in relapsed childhood ALL. A pilot study by the United Kingdom children's cancer study group. *European Paediatric Haematology and Oncology* 1984;1(1):37-38.
- 25  
26  
27  
28 45. Mott MG, Eden OB, Palmer MK. Adjuvant low dose radiation in childhood non-Hodgkin's lymphoma. (Report from the United Kingdom Childrens' Cancer Study Group - UKCCSG). *British journal of cancer* 1984;50(4):463-469.
- 29  
30  
31  
32 46. Movassaghi N, Higgins G, Pyesmany A. Evaluation of cycloctidine in reinduction and maintenance therapy of children with acute nonlymphocytic leukemia previously treated with cytosine arabinoside: A report from children's cancer study group. *Medical and pediatric oncology* 1984;12(5):352-356.
- 33  
34  
35  
36  
37 47. Pui CH, Aur RJA, Bowman WP. Failure of late intensification therapy to improve a poor result in childhood lymphoblastic leukemia. *Cancer research* 1984;44(8):3593-3598.
- 38  
39  
40  
41 48. Sackmann Muriel F, Svarech E, Pavlovsky S. Alternating pulses of vincristine-prednisone with cytarabine-cyclophosphamide versus vincristine-prednisone in the maintenance therapy of acute lymphoblastic leukemia. *Cancer treatment reports* 1984;68(4):581-586.
- 42  
43  
44  
45 49. Flamant F, Rodary C, Voute PA, et al. Primary chemotherapy in the treatment of rhabdomyosarcoma in children: Trial of the international society of pediatric oncology (SIOP) preliminary results. *Radiotherapy and Oncology* 1985;3(3):227-236.
- 46  
47  
48  
49 50. Land VJ, Thomas PR, Boyett JM, et al. Comparison of maintenance treatment regimens for first central nervous system relapse in children with acute lymphocytic leukemia. A Pediatric Oncology Group study. *Cancer* 1985;56(1):81-87.
- 50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 51. Mehta P, Gardner R, Graham-Pole J, et al. Methylprednisolone is effective in chemotherapy-  
4 induced emesis: Results of a double blind randomized trial in children. Proceedings of the American  
5 Association for Cancer Research. VOL 1985;26:No. 602.  
6
- 7 52. Brecher ML, Weinberg V, Boyett JM, et al. Intermediate dose methotrexate in childhood acute  
8 lymphoblastic leukemia resulting in decreased incidence of testicular relapse. Cancer 1986;58(5):1024-  
9 1028.  
10
- 11 53. Chessells JM, Durrant J, Hardy RM, et al. Medical Research Council leukaemia trial--UKALL V:  
12 an attempt to reduce the immunosuppressive effects of therapy in childhood acute lymphoblastic  
13 leukemia. Report to the Council by the Working Party on Leukaemia in Childhood. Journal of Clinical  
14 Oncology 1986;4(12):1758-1764.  
15
- 16 54. Link MP, Goorin AM, Miser AW. The effect of adjuvant chemotherapy on relapse-free survival  
17 in patients with osteosarcoma of the extremity. New England Journal of Medicine 1986;314(25):1600-  
18 1606.  
19
- 20 55. Ragab AH, Boyett JM, Frankel L, et al. Rubidazole in the treatment of recurrent acute leukemia  
21 in children. A Pediatric Oncology Group Study. Cancer 1986;57(8):1461-1463.  
22
- 23 56. Chan HSL, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer  
24 chemotherapy-induced emesis in children: A double-blind, crossover trial. Pediatrics 1987;79(6):946-952.  
25
- 26 57. Jenkin RD, Boesel C, Ertel I, et al. Brain-stem tumors in childhood: a prospective randomized  
27 trial of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Childrens  
28 Cancer Study Group. Journal of neurosurgery 1987;66(2):227-233.  
29
- 30 58. Krailo M, Ertel I, Makley J, et al. A randomized study comparing high-dose methotrexate with  
31 moderate-dose methotrexate as components of adjuvant chemotherapy in childhood nonmetastatic  
32 osteosarcoma: a report from the Childrens Cancer Study Group. Medical & Pediatric Oncology  
33 1987;15(2):69-77.  
34
- 35 59. Littman P, Coccia P, Bleyer WA, et al. Central nervous system (CNS) prophylaxis in children  
36 with low risk acute lymphoblastic leukemia (ALL). International journal of radiation oncology, biology,  
37 physics 1987;13(10):1443-1449.  
38
- 39 60. Ortega JJ, Javier G, Olive T. Treatment of standard- and high-risk childhood acute lymphoblastic  
40 leukaemia with two CNS prophylaxis regimens. Haematology & Blood Transfusion 1987;30:483-492.  
41
- 42 61. Zintl F, Plenert W, Malke H. Results of acute lymphoblastic leukemia therapy in childhood with a  
43 modified BFM protocol in a multicenter study in the German Democratic Republic. Haematology &  
44 Blood Transfusion 1987;30:471-479.  
45
- 46 62. Carli M, Pastore G, Perilongo G, et al. Tumor response and toxicity after single high-dose versus  
47 standard five-day divided-dose dactinomycin in childhood rhabdomyosarcoma. Journal of Clinical  
48 Oncology 1988;6(4):654-658.  
49
- 50 63. Gaynon PS, Steinherz PG, Bleyer WA, et al. Intensive therapy for children with acute  
51 lymphoblastic leukaemia and unfavourable presenting features. Early conclusions of study CCG-106 by  
52 the Childrens Cancer Study Group. Lancet 1988;2(8617):921-924.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 64. JankaSchaub GE, Winkler K, Gobel U, et al. Rapidly rotating combination chemotherapy in  
4 childhood acute lymphoblastic leukemia: Preliminary results of a randomized comparison with  
5 conventional treatment. *Leukemia* 1988;2(12 SUPPL):73s-78s.  
6
- 7 65. Koizumi S, Fujimoto T, Takeda T, et al. Comparison of intermittent or continuous methotrexate  
8 plus 6-mercaptopurine in regimens for standard-risk acute lymphoblastic leukemia in childhood  
9 (JCCLSG-S811). The Japanese Children's Cancer and Leukemia Study Group. *Cancer* 1988;61(7):1292-  
10 1300.  
11
- 12 66. Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study-I. A  
13 final report. *Cancer* 1988;61(2):209-220.  
14
- 15 67. Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: Results of a  
16 randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor  
17 response. *Journal of Clinical Oncology* 1988;6(2):329-337.  
18
- 19 68. Crist W, Boyett J, Jackson J, et al. Prognostic importance of the pre-B-cell immunophenotype and  
20 other presenting features in B-lineage childhood acute lymphoblastic leukemia: a Pediatric Oncology  
21 Group study. *Blood* 1989;74(4):1252-1259.  
22
- 23 69. Meadows AT, Sposto R, Jenkin RD, et al. Similar efficacy of 6 and 18 months of therapy with  
24 four drugs (COMP) for localized non-Hodgkin's lymphoma of children: a report from the Childrens  
25 Cancer Study Group. *Journal of Clinical Oncology* 1989;7(1):92-99.  
26
- 27 70. Miller DR, Coccia PF, Bleyer WA, et al. Early response to induction therapy as a predictor of  
28 disease-free survival and late recurrence of childhood acute lymphoblastic leukemia: a report from the  
29 Childrens Cancer Study Group. *Journal of Clinical Oncology* 1989;7(12):1807-1815.  
30
- 31 71. Miller DR, Leikin SL, Albo VC, et al. Three versus five years of maintenance therapy are  
32 equivalent in childhood acute lymphoblastic leukemia: a report from the Childrens Cancer Study Group.  
33 *Journal of Clinical Oncology* 1989;7(3):316-325.  
34
- 35 72. Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high  
36 grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study  
37 Group. *Journal of neuro-oncology* 1989;7(2):165-177.  
38
- 39 73. Van Eys J, Berry D, Crist W, et al. Treatment intensity and outcome for children with acute  
40 lymphocytic leukemia of standard risk. A Pediatric Oncology Group Study. *Cancer* 1989;63(8):1466-  
41 1471.  
42
- 43 74. Lampkin BC, Woods WG, Buckley JD, et al. Preliminary results of intensive therapy of children  
44 and adolescents with acute nonlymphocytic leukemia--a Childrens Cancer Study Group report.  
45 *Haematology and blood transfusion* 1990;33:210-214.  
46
- 47 75. Steuber CP, Culbert SJ, Ravindranath Y, et al. Therapy of childhood acute nonlymphocytic  
48 leukemia: the Pediatric Oncology Group experience (1977-1988). *Haematology and blood transfusion*  
49 1990;33:198-209.  
50
- 51 76. Tait DM, Thornton-Jones H, Bloom HJ, et al. Adjuvant chemotherapy for medulloblastoma: the  
52 first multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). *European*  
53 *journal of cancer* 1990;26(4):464-469.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 77. Bleyer WA, Sather HN, Nickerson HJ, et al. Monthly pulses of vincristine and prednisone  
4 prevent bone marrow and testicular relapse in low-risk childhood acute lymphoblastic leukemia: a report  
5 of the CCG-161 study by the Childrens Cancer Study Group. *Journal of Clinical Oncology*  
6 1991;9(6):1012-1021.  
7
- 8 78. Buchanan GR, Boyett JM, Pollock BH, et al. Improved treatment results in boys with overt  
9 testicular relapse during or shortly after initial therapy for acute lymphoblastic leukemia. A Pediatric  
10 Oncology group study. *Cancer* 1991;68(1):48-55.  
11
- 12 79. Castleberry RP, Kun LE, Shuster JJ, et al. Radiotherapy improves the outlook for patients older  
13 than 1 year with Pediatric Oncology Group stage C neuroblastoma. *Journal of Clinical Oncology*  
14 1991;9(5):789-795.  
15
- 16 80. Conner K, Sandler E, Weyman C, et al. Intravenous midazolam versus fentanyl as premedication  
17 for painful procedures in pediatric oncology patients. *Journal of Pediatric Oncology Nursing*  
18 1991;8(2):86-87.  
19
- 20 81. Culbert SJ, Shuster JJ, Land VJ, et al. Remission induction and continuation therapy in children  
21 with their first relapse of acute lymphoid leukemia. A Pediatric Oncology Group study. *Cancer*  
22 1991;67(1):37-42.  
23
- 24 82. De Camargo B, Franco EL. Single-dose versus fractionated-dose dactinomycin in the treatment of  
25 Wilms' tumor: Preliminary results of a clinical trial. *Cancer* 1991;67(12):2990-2996.  
26
- 27 83. Eden OB, Lilleyman JS, Richards S, et al. Results of Medical Research Council Childhood  
28 Leukaemia Trial UKALL VIII (report to the Medical Research Council on behalf of the Working Party on  
29 Leukaemia in Childhood). *British journal of haematology* 1991;78(2):187-196.  
30
- 31 84. Henze G, Fengler R, Hartmann R, et al. Six-year experience with a comprehensive approach to  
32 the treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85). A relapse study  
33 of the BFM group. *Blood* 1991;78(5):1166-1172.  
34
- 35 85. Krischer JP, Ragab AH, Kun L, et al. Nitrogen mustard, vincristine, procarbazine, and prednisone  
36 as adjuvant chemotherapy in the treatment of medulloblastoma. A Pediatric Oncology Group study.  
37 *Journal of neurosurgery* 1991;74(6):905-909.  
38
- 39 86. Patte C, Philip T, Rodary C, et al. High survival rate in advanced-stage B-cell lymphomas and  
40 leukemias without CNS involvement with a short intensive polychemotherapy: results from the French  
41 Pediatric Oncology Society of a randomized trial of 216 children. *Journal of Clinical Oncology*  
42 1991;9(1):123-132.  
43
- 44 87. Rivera GK, Raimondi SC, Hancock ML, et al. Improved outcome in childhood acute  
45 lymphoblastic leukaemia with reinforced early treatment and rotational combination chemotherapy.  
46 *Lancet* 1991;337(8733):61-66.  
47
- 48 88. Sullivan MP, Brecher M, Ramirez I, et al. High-dose cyclophosphamide-high-dose methotrexate  
49 with coordinated intrathecal therapy for advanced nonlymphoblastic lymphoma of childhood: results of a  
50 Pediatric Oncology Group study. *American Journal of Pediatric Hematology/Oncology* 1991;13(3):288-  
51 295.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 89. Tsuchida M, Akatsuka J, Bessho F, et al. Treatment of acute lymphoblastic leukemia in the  
4 Tokyo Children's Cancer Study Group--preliminary results of L84-11 protocol. *Acta Paediatrica Japonica*  
5 1991;33(4):522-532.  
6
- 7 90. Weiner MA, Leventhal BG, Marcus R, et al. Intensive chemotherapy and low-dose radiotherapy  
8 for the treatment of advanced-stage Hodgkin's disease in pediatric patients: A Pediatric Oncology Group  
9 study. *Journal of Clinical Oncology* 1991;9(9):1591-1598.  
10
- 11 91. Crist W, Shuster J, Look T, et al. Current results of studies of immunophenotype-, age- and  
12 leukocyte-based therapy for children with acute lymphoblastic leukemia. *Leukemia* 1992;6(SUPPL.  
13 2):162-166.  
14
- 15 92. Harris MB, Shuster JJ, Carroll A, et al. Trisomy of leukemic cell chromosomes 4 and 10  
16 identifies children with B- progenitor cell acute lymphoblastic leukemia with a very low risk of treatment  
17 failure: A Pediatric Oncology Group Study. *Blood* 1992;79(12):3316-3324.  
18
- 19 93. Miser JS, Roloff J, Blatt J, et al. Lack of significant activity of 2'-deoxycoformycin alone or in  
20 combination with adenine arabinoside in relapsed childhood acute lymphoblastic leukemia. A randomized  
21 phase II trial from the Childrens Cancer Study Group. *American Journal of Clinical Oncology*  
22 1992;15(6):490-493.  
23
- 24 94. Pui CH, Simone JV, Hancock ML, et al. Impact of three methods of treatment intensification on  
25 acute lymphoblastic leukemia in children: long-term results of St Jude total therapy study X. *Leukemia*  
26 1992;6(2):150-157.  
27
- 28 95. Amadori S, Testi AM, Arico M, et al. Prospective comparative study of bone marrow  
29 transplantation and postremission chemotherapy for childhood acute myelogenous leukemia. The  
30 Associazione Italiana Ematologia ed Oncologia Pediatrica Cooperative Group. *Journal of Clinical*  
31 *Oncology* 1993;11(6):1046-1054.  
32
- 33 96. Cherlow JM, Steinherz PG, Sather HN, et al. The role of radiation therapy in the treatment of  
34 acute lymphoblastic leukemia with lymphomatous presentation: a report from the Childrens Cancer  
35 Group. *International journal of radiation oncology, biology, physics* 1993;27(5):1001-1009.  
36
- 37 97. Creutzig U, Ritter J, Zimmermann M, et al. Does cranial irradiation reduce the risk for bone  
38 marrow relapse in acute myelogenous leukemia? Unexpected results of the Childhood Acute  
39 Myelogenous Leukemia Study BFM-87. *Journal of Clinical Oncology* 1993;11(2):279-286.  
40
- 41 98. Gaynon PS, Steinherz PG, Bleyer WA, et al. Improved therapy for children with acute  
42 lymphoblastic leukemia and unfavorable presenting features: a follow-up report of the Childrens Cancer  
43 Group Study CCG-106. *Journal of Clinical Oncology* 1993;11(11):2234-2242.  
44
- 45 99. Miser JS, Pritchard DJ, Rock MG, et al. Osteosarcoma in adolescents and young adults: new  
46 developments and controversies. The Mayo Clinic studies. *Cancer treatment and research* 1993;62:333-  
47 338.  
48
- 49 100. Tournade MF, Com-Nougue C, Voute PA, et al. Results of the Sixth International Society of  
50 Pediatric Oncology Wilms' Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms' tumor.  
51 *Journal of Clinical Oncology* 1993;11(6):1014-1023.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 101. Tsukada M, Komiyama A, Nakazawa S, et al. Treatment of standard risk acute lymphoblastic  
4 leukemia in children with the Tokyo Children Cancer Study Group (TCCSG) L84-11 protocol in Japan.  
5 International journal of hematology 1993;57(1):1-7.  
6
- 7 102. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Prevention of CNS disease in intermediate-risk  
8 acute lymphoblastic leukemia: comparison of cranial radiation and intrathecal methotrexate and the  
9 importance of systemic therapy: a Childrens Cancer Group report. Journal of Clinical Oncology  
10 1993;11(3):520-526.  
11
- 12 103. Winick NJ, Smith SD, Shuster J, et al. Treatment of CNS relapse in children with acute  
13 lymphoblastic leukemia: A Pediatric Oncology Group study. Journal of Clinical Oncology  
14 1993;11(2):271-278.  
15
- 16 104. Yang CP, Lin ST, Liang DC, et al. Treatment of childhood acute lymphoblastic leukemia with  
17 protocol TCL-842 in Taiwan: the Taiwan Children's Cancer Study Group. Journal of the Formosan  
18 Medical Association 1993;92(5):431-439.  
19
- 20 105. Castleberry RP, Cantor AB, Green AA, et al. Phase II investigational window using carboplatin,  
21 iproplatin, ifosfamide, and epirubicin in children with untreated disseminated neuroblastoma: a Pediatric  
22 Oncology Group study. Journal of Clinical Oncology 1994;12(8):1616-1620.  
23
- 24 106. Creutzig U, Ritter J, Zimmermann M, et al. Superior results by cranial irradiation in children with  
25 acute myelogenous leukemia: An update of study AML-BFM-87. Onkologie 1994;17(1):66-68.  
26
- 27 107. De Camargo B, Franco EL. A randomized clinical trial of single-dose versus fractionated-dose  
28 dactinomycin in the treatment of Wilms' tumor: Results after extended follow- up. Cancer  
29 1994;73(12):3081-3086.  
30
- 31 108. Elder JS. Results of the Sixth International Society of Pediatric Oncology Wilms' tumor trial and  
32 study: a risk-adapted therapeutic approach in Wilms' tumor. The Journal of urology 1994;152(1):271-272.  
33
- 34 109. Gilchrist GS, Tubergen DG, Sather HN, et al. Low numbers of CSF blasts at diagnosis do not  
35 predict for the development of CNS leukemia in children with intermediate-risk acute lymphoblastic  
36 leukemia: A Childrens Cancer Group report. Journal of Clinical Oncology 1994;12(12):2594-2600.  
37
- 38 110. Koizumi S, Fujimoto T. Improvement in treatment of childhood acute lymphoblastic leukemia: a  
39 10-year study by the Children's Cancer and Leukemia Study Group. International journal of hematology  
40 1994;59(2):99-112.  
41
- 42 111. Land VJ, Shuster JJ, Crist WM, et al. Comparison of two schedules of intermediate-dose  
43 methotrexate and cytarabine consolidation therapy for childhood B-precursor cell acute lymphoblastic  
44 leukemia: a Pediatric Oncology Group study. Journal of Clinical Oncology 1994;12(9):1939-1945.  
45
- 46 112. Nesbit ME, Jr., Buckley JD, Feig SA, et al. Chemotherapy for induction of remission of  
47 childhood acute myeloid leukemia followed by marrow transplantation or multiagent chemotherapy: a  
48 report from the Childrens Cancer Group. Journal of Clinical Oncology 1994;12(1):127-135.  
49
- 50 113. Sertoli MR, Santini G, Chisesi T, et al. MACOP-B versus ProMACE-MOPP in the treatment of  
51 advanced diffuse non- Hodgkin's lymphoma: Results of a prospective randomized trial by the Non-  
52 Hodgkin's Lymphoma Cooperative Study Group. Journal of Clinical Oncology 1994;12(7):1366-1374.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 114. Wells RJ, Woods WG, Buckley JD, et al. Treatment of newly diagnosed children and adolescents  
4 with acute myeloid leukemia: A Childrens Cancer Group study. *Journal of Clinical Oncology*  
5 1994;12(11):2367-2377.  
6
- 7 115. Bailey CC, Gnekow A, Wellek S, et al. Prospective randomised trial of chemotherapy given  
8 before radiotherapy in childhood medulloblastoma. *International Society of Paediatric Oncology (SIOP)*  
9 and the (German) Society of Paediatric Oncology (GPO): SIOP II. *Medical & Pediatric Oncology*  
10 1995;25(3):166-178.  
11
- 12 116. Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children  
13 with lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. *Medical*  
14 *Research Council Working Party on Childhood Leukaemia. Lancet* 1995;345(8943):143-148.  
15
- 16 117. Cohen BH, Zeltzer PM, Boyett JM, et al. Prognostic factors and treatment results for  
17 supratentorial primitive neuroectodermal tumors in children using radiation and chemotherapy: a  
18 Childrens Cancer Group randomized trial. *Journal of Clinical Oncology* 1995;13(7):1687-1696.  
19
- 20 118. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *Journal*  
21 *of Clinical Oncology* 1995;13(3):610-630.  
22
- 23 119. Donaldson SS, Asmar L, Breneman J, et al. Hyperfractionated radiation in children with  
24 rhabdomyosarcoma - Results of an intergroup rhabdomyosarcoma pilot study. *International Journal of*  
25 *Radiation Oncology Biology Physics* 1995;32(4):903-911.  
26
- 27 120. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade  
28 astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen.  
29 Childrens Cancer Group. *Journal of Clinical Oncology* 1995;13(1):112-123.  
30
- 31 121. McWilliams NB, Hayes FA, Green AA, et al. Cyclophosphamide/doxorubicin vs.  
32 cisplatin/teniposide in the treatment of children older than 12 months of age with disseminated  
33 neuroblastoma: a Pediatric Oncology Group Randomized Phase II study. *Medical & Pediatric Oncology*  
34 1995;24(3):176-180.  
35
- 36 122. Sebban C, Browman GP, Lepage E, et al. Prognostic value of early response to chemotherapy  
37 assessed by the day 15 bone marrow aspiration in adult acute lymphoblastic leukemia: A prospective  
38 analysis of 437 cases and its application for designing induction chemotherapy trials. *Leukemia research*  
39 1995;19(11):861-868.  
40
- 41 123. Tubergen DG, Krailo MD, Meadows AT, et al. Comparison of treatment regimens for pediatric  
42 lymphoblastic non-Hodgkin's lymphoma: a Childrens Cancer Group study. *Journal of Clinical Oncology*  
43 1995;13(6):1368-1376.  
44
- 45 124. Calandra T, Gaya H, Zinner SH, et al. Monotherapy with meropenem versus combination therapy  
46 with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer.  
47 *Antimicrobial Agents and Chemotherapy* 1996;40(5):1108-1115.  
48
- 49 125. Deutsch M, Thomas PR, Krischer J, et al. Results of a prospective randomized trial comparing  
50 standard dose neuraxis irradiation (3,600 cGy/20) with reduced neuraxis irradiation (2,340 cGy/13) in  
51 patients with low-stage medulloblastoma. A Combined Children's Cancer Group-Pediatric Oncology  
52 Group Study. *Pediatric neurosurgery* 1996;24(4):167-176.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 126. Evans AE, Anderson JR, Lefkowitz-Boudreaux IB, et al. Adjuvant chemotherapy of childhood  
4 posterior fossa ependymoma: cranio-spinal irradiation with or without adjuvant CCNU, vincristine, and  
5 prednisone: a Children's Cancer Group study. *Medical & Pediatric Oncology* 1996;27(1):8-14.  
6  
7 127. Feig SA, Ames MM, Sather HN, et al. Comparison of idarubicin to daunomycin in a randomized  
8 multidrug treatment of childhood acute lymphoblastic leukemia at first bone marrow relapse: a report  
9 from the Children's Cancer Group. *Medical & Pediatric Oncology* 1996;27(6):505-514.  
10  
11 128. Richards S, Gray R, Peto R, et al. Duration and intensity of maintenance chemotherapy in acute  
12 lymphoblastic leukaemia: Overview of 42 trials involving 12,000 randomised children. *Lancet*  
13 1996;347(9018):1783-1788.  
14  
15 129. Steuber CP, Krischer J, Holbrook T, et al. Therapy of refractory or recurrent childhood acute  
16 myeloid leukemia using amsacrine and etoposide with or without azacitidine: a Pediatric Oncology Group  
17 randomized phase II study. *Journal of Clinical Oncology* 1996;14(5):1521-1525.  
18  
19 130. Brecher ML, Schwenn MR, Coppes MJ, et al. Fractionated cyclophosphamide and back to back  
20 high dose methotrexate and cytosine arabinoside improves outcome in patients with stage III high grade  
21 small non-cleaved cell lymphomas (SNCCCL): a randomized trial of the Pediatric Oncology Group.  
22 *Medical & Pediatric Oncology* 1997;29(6):526-533.  
23  
24 131. Conter V, Schrappe M, Arico M, et al. Role of cranial radiotherapy for childhood T-cell acute  
25 lymphoblastic leukemia with high WBC count and good response to prednisone. *Journal of Clinical*  
26 *Oncology* 1997;15(8):2786-2791.  
27  
28 132. Coze C, Hartmann O, Michon J, et al. NB87 induction protocol for stage 4 neuroblastoma in  
29 children over 1 year of age: a report from the French Society of Pediatric Oncology. *Journal of Clinical*  
30 *Oncology* 1997;15(12):3433-3440.  
31  
32 133. Feig SA, Harris RE, Sather HN. Bone marrow transplantation versus chemotherapy for  
33 maintenance of second remission of childhood acute lymphoblastic leukemia: A study of the children's  
34 cancer group (CCG-1884). *Medical and pediatric oncology* 1997;29(6):534-540.  
35  
36 134. Koizumi S, Fujimoto T, Oka T, et al. Overview of clinical studies of childhood acute  
37 lymphoblastic leukemia for more than ten years by the Japanese Children's Cancer and Leukemia Study  
38 Group. *Pediatric hematology and oncology* 1997;14(1):17-28.  
39  
40 135. Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-  
41 stage non-hodgkin's lymphoma. *New England Journal of Medicine* 1997;337(18):1259-1266.  
42  
43 136. Sackmann-Muriel F, Zubizarreta P, Gallo G, et al. Hodgkin disease in children: results of a  
44 prospective randomized trial in a single institution in Argentina. *Medical & Pediatric Oncology*  
45 1997;29(6):544-552.  
46  
47 137. Souhami RL, Craft AW, Van Der Eijken JW, et al. Randomised trial of two regimens of  
48 chemotherapy in operable osteosarcoma: A study of the European Osteosarcoma Intergroup. *Lancet*  
49 1997;350(9082):911-917.  
50  
51 138. Weiner MA, Leventhal B, Brecher ML, et al. Randomized study of intensive MOPP-ABVD with  
52 or without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV  
53 Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. *Journal of Clinical Oncology*  
54 1997;15(8):2769-2779.  
55  
56  
57  
58  
59  
60



- 1  
2  
3 139. Donaldson SS, Torrey M, Link MP, et al. A multidisciplinary study investigating radiotherapy in  
4 Ewing's sarcoma: end results of POG #8346. Pediatric Oncology Group. International journal of radiation  
5 oncology, biology, physics 1998;42(1):125-135.  
6  
7 140. Green DM, Breslow NE, Beckwith JB, et al. Comparison between single-dose and divided-dose  
8 administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the  
9 National Wilms' Tumor Study Group. Journal of Clinical Oncology 1998;16(1):237-245.  
10  
11 141. Hutchinson RJ, Fryer CJ, Davis PC, et al. MOPP or radiation in addition to ABVD in the  
12 treatment of pathologically staged advanced Hodgkin's disease in children: results of the Children's  
13 Cancer Group Phase III Trial. Journal of Clinical Oncology 1998;16(3):897-906.  
14  
15 142. Kawano Y, Takaue Y, Mimaya J, et al. Marginal benefit/disadvantage of granulocyte colony-  
16 stimulating factor therapy after autologous blood stem cell transplantation in children: results of a  
17 prospective randomized trial. The Japanese Cooperative Study Group of PBSCT. Blood  
18 1998;92(11):4040-4046.  
19  
20 143. Kuhl J, Muller HL, Berthold F, et al. Preradiation chemotherapy of children and young adults  
21 with malignant brain tumors: results of the German pilot trial HIT'88/'89. Klinische Padiatrie  
22 1998;210(4):227-233.  
23  
24 144. Michon JM, Hartmann O, Bouffet E, et al. An open-label, multicentre, randomised phase 2 study  
25 of recombinant human granulocyte colony-stimulating factor (filgrastim) as an adjunct to combination  
26 chemotherapy in paediatric patients with metastatic neuroblastoma. European journal of cancer  
27 1998;34(7):1063-1069.  
28  
29 145. Pratt CB, Maurer HM, Gieser P, et al. Treatment of unresectable or metastatic pediatric soft tissue  
30 sarcomas with surgery, irradiation, and chemotherapy: a Pediatric Oncology Group study. Medical &  
31 Pediatric Oncology 1998;30(4):201-209.  
32  
33 146. Richards S, Burrett J, Hann I, et al. Improved survival with early intensification: Combined  
34 results from The Medical Research Council childhood ALL randomised trials, UKALL X and UKALL  
35 XI. Leukemia 1998;12(7):1031-1036.  
36  
37 147. Schrappe M, Reiter A, Henze G, et al. Prevention of CNS recurrence in childhood ALL: Results  
38 with reduced radiotherapy combined with CNS-directed chemotherapy in four consecutive ALL- BFM  
39 trials. Klinische Padiatrie 1998;210(4):192-199.  
40  
41 148. Steinherz PG, Gaynon PS, Breneman JC, et al. Treatment of patients with acute lymphoblastic  
42 leukemia with bulky extramedullary disease and T-cell phenotype or other poor prognostic features:  
43 randomized controlled trial from the Children's Cancer Group. Cancer 1998;82(3):600-612.  
44  
45 149. Amylon MD, Shuster J, Pullen J, et al. Intensive high-dose asparaginase consolidation improves  
46 survival for pediatric patients with T cell acute lymphoblastic leukemia and advanced stage lymphoblastic  
47 lymphoma: A Pediatric Oncology Group study. Leukemia 1999;13(3):335-342.  
48  
49 150. Asselin BL, Kreissman S, Coppola DJ, et al. Prognostic significance of early response to a single  
50 dose of asparaginase in childhood acute lymphoblastic leukemia. Journal of Pediatric  
51 Hematology/Oncology 1999;21(1):6-12.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 151. Kamps WA, Bokkerink JP, Hahlen K, et al. Intensive treatment of children with acute  
4 lymphoblastic leukemia according to ALL-BFM-86 without cranial radiotherapy: results of Dutch  
5 Childhood Leukemia Study Group Protocol ALL-7 (1988-1991). *Blood* 1999;94(4):1226-1236.  
6
- 7 152. Kobrinsky NL, Packer RJ, Boyett JM, et al. Etoposide with or without mannitol for the treatment  
8 of recurrent or primarily unresponsive brain tumors: a Children's Cancer Group Study, CCG-9881.  
9 *Journal of neuro-oncology* 1999;45(1):47-54.  
10
- 11 153. Liang DC, Hung IJ, Yang CP, et al. Unexpected mortality from the use of E. coli L-asparaginase  
12 during remission induction therapy for childhood acute lymphoblastic leukemia: a report from the Taiwan  
13 Pediatric Oncology Group. *Leukemia* 1999;13(2):155-160.  
14
- 15 154. Mandell LR, Kadota R, Freeman C, et al. There is no role for hyperfractionated radiotherapy in  
16 the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a  
17 Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy.  
18 *International journal of radiation oncology, biology, physics* 1999;43(5):959-964.  
19
- 20 155. Marina NM, Pappo AS, Parham DM, et al. Chemotherapy dose-intensification for pediatric  
21 patients with Ewing's family of tumors and desmoplastic small round-cell tumors: a feasibility study at St.  
22 Jude Children's Research Hospital. *Journal of Clinical Oncology* 1999;17(1):180-190.  
23
- 24 156. Matsuzaki A, Okamura J, Ishii E, et al. Treatment of standard-risk acute lymphoblastic leukemia  
25 in children: The results of protocol AL841 from the Kyushu-Yamaguchi Children's Cancer Study Group  
26 in Japan. *Pediatric hematology and oncology* 1999;16(3):187-199.  
27
- 28 157. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with  
29 intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid.  
30 *Children's Cancer Group. New England Journal of Medicine* 1999;341(16):1165-1173.  
31
- 32 158. Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically  
33 resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: A Pediatric Oncology Group Study.  
34 *Journal of Clinical Oncology* 1999;17(4):1219-1226.  
35
- 36 159. Suryanarayan K, Shuster JJ, Donaldson SS, et al. Treatment of localized primary non-Hodgkin's  
37 lymphoma of bone in children: A Pediatric Oncology Group Study. *Journal of Clinical Oncology*  
38 1999;17(2):456-459.  
39
- 40 160. Tsurusawa M, Katano N, Yamamoto Y, et al. Improvement in CNS protective treatment in non-  
41 high-risk childhood acute lymphoblastic leukemia: report from the Japanese Children's Cancer and  
42 Leukemia Study Group. *Medical & Pediatric Oncology* 1999;32(4):259-256.  
43
- 44 161. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor  
45 are prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group  
46 921 randomized phase III study. *Journal of Clinical Oncology* 1999;17(3):832-845.  
47
- 48 162. CoustanSmith E, Sancho J, Hancock ML, et al. Clinical importance of minimal residual disease in  
49 childhood acute lymphoblastic leukemia. *Blood* 2000;96(8):2691-2696.  
50
- 51 163. Dahl GV, Lacayo NJ, Brophy N, et al. Mitoxantrone, etoposide, and cyclospine therapy in  
52 pediatric patients with recurrent or refractory acute myeloid leukemia. *Journal of Clinical Oncology*  
53 2000;18(9):1867-1875.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 164. Freeman CR, Kepner J, Kun LE, et al. A detrimental effect of a combined chemotherapy-  
4 radiotherapy approach in children with diffuse intrinsic brain stem gliomas? *International Journal of*  
5 *Radiation Oncology Biology Physics* 2000;47(3):561-564.  
6
- 7 165. Harris MB, Shuster JJ, Pullen J, et al. Treatment of children with early pre-B and pre-B acute  
8 lymphocytic leukemia with antimetabolite-based intensification regimens: A pediatric oncology group  
9 study. *Leukemia* 2000;14(9):1570-1576.  
10
- 11 166. Kohler JA, Imeson J, Ellershaw C, et al. A randomized trial of 13-Cis retinoic acid in children  
12 with advanced neuroblastoma after high-dose therapy. *British journal of cancer* 2000;83(9):1124-1127.  
13
- 14 167. Kojima S, Hibi S, Kosaka Y, et al. Immunosuppressive therapy using antithymocyte globulin,  
15 cyclosporine, and danazol with or without human granulocyte colony-Stimulating factor in children with  
16 acquired aplastic anemia. *Blood* 2000;96(6):2049-2054.  
17
- 18 168. Kortmann RD, Kuhl J, Timmermann B, et al. Postoperative neoadjuvant chemotherapy before  
19 radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the  
20 treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91.  
21 *International journal of radiation oncology, biology, physics* 2000;46(2):269-279.  
22
- 23 169. Laver JH, Barredo JC, Amylon M, et al. Effects of cranial radiation in children with high risk T  
24 cell acute lymphoblastic leukemia: A Pediatric Oncology Group report. *Leukemia* 2000;14(3):369-373.  
25
- 26 170. Locatelli F, Zecca M, Rondelli R, et al. Graft versus host disease prophylaxis with low-dose  
27 cyclosporine-A reduces the risk of relapse in children with acute leukemia given HLA- identical sibling  
28 bone marrow transplantation: Results of a randomized trial. *Blood* 2000;95(5):1572-1579.  
29
- 30 171. Loning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-  
31 Munster therapy of acute lymphoblastic leukemia in childhood: Significantly lower risk without cranial  
32 radiotherapy. *Blood* 2000;95(9):2770-2775.  
33
- 34 172. Maris JM, Weiss MJ, Guo C, et al. Loss of heterozygosity at 1p36 independently predicts for  
35 disease progression but not decreased overall survival probability in neuroblastoma patients: A children's  
36 cancer group study. *Journal of Clinical Oncology* 2000;18(9):1888-1899.  
37
- 38 173. Michel G, Landman-Parker J, Auclerc MF, et al. Use of recombinant human granulocyte colony-  
39 stimulating factor to increase chemotherapy dose-intensity: a randomized trial in very high-risk childhood  
40 acute lymphoblastic leukemia. *Journal of Clinical Oncology* 2000;18(7):1517-1524.  
41
- 42 174. Ortega JA, Douglass EC, Feusner JH, et al. Randomized comparison of  
43 cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric  
44 hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *Journal of*  
45 *Clinical Oncology* 2000;18(14):2665-2675.  
46
- 47 175. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy  
48 provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: A BFM Group  
49 report. *Blood* 2000;95(2):416-421.  
50
- 51 176. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic  
52 leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90.  
53 German-Austrian-Swiss ALL-BFM Study Group. *Blood* 2000;95(11):3310-3322.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 177. Shamberger RC, Laquaglia MP, Krailo MD, et al. Ewing sarcoma of the rib: results of an  
4 intergroup study with analysis of outcome by timing of resection. *Journal of Thoracic & Cardiovascular*  
5 *Surgery* 2000;119(6):1154-1161.  
6
- 7 178. Sievers EL, Lange BJ, Sondel PM, et al. Children's cancer group trials of interleukin-2 therapy to  
8 prevent relapse of acute myelogenous leukemia. *The cancer journal from Scientific American*  
9 2000;6(Suppl 1):S39-44.  
10
- 11 179. Vilmer E, Suciu S, Ferster A, et al. Long-term results of three randomized trials (58831, 58832,  
12 58881) in childhood acute lymphoblastic leukemia: A CLCG-EORTC report. *Leukemia*  
13 2000;14(12):2257-2266.  
14
- 15 180. Wells RJ, Woods WG, Buckley JD, et al. Therapy for acute myeloid leukemia: intensive timing  
16 of induction chemotherapy. *Current oncology reports* 2000;2(6):524-528.  
17
- 18 181. Breitfeld PP, Lyden E, Raney RB, et al. Ifosfamide and etoposide are superior to vincristine and  
19 melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and  
20 combination chemotherapy: A report from the Intergroup Rhabdomyosarcoma Study Group. *Journal of*  
21 *Pediatric Hematology/Oncology* 2001;23(4):225-233.  
22
- 23 182. Creutzig U, Ritter J, Zimmermann M, et al. Idarubicin improves blast cell clearance during  
24 induction therapy in children with AML: Results of study AML-BFM 93. *Leukemia* 2001;15(3):348-354.  
25
- 26 183. Donaldson SS, Meza J, Breneman JC, et al. Results from the IRS-IV randomized trial of  
27 hyperfractionated radiotherapy in children with rhabdomyosarcoma--a report from the IRSG.  
28 *International journal of radiation oncology, biology, physics* 2001;51(3):718-728.  
29
- 30 184. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between  
31 rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*  
32 2001;97(10):2998-3003.  
33
- 34 185. Laver JH, Mahmoud H, Pick TE, et al. Results of a randomized phase III trial in children and  
35 adolescents with advanced stage diffuse large cell non Hodgkin's lymphoma: a Pediatric Oncology Group  
36 study. *Leukemia & lymphoma* 2001;42(3):399-405.  
37
- 38 186. Manabe A, Tsuchida M, Hanada R, et al. Delay of the diagnostic lumbar puncture and intrathecal  
39 chemotherapy in children with acute lymphoblastic leukemia who undergo routine corticosteroid testing:  
40 Tokyo Children's Cancer Study Group Study L89-12. *Journal of Clinical Oncology* 2001;19(13):3182-  
41 3187.  
42
- 43 187. Ortega JJ, Ribera JM, Oriol A, et al. Early and delayed consolidation chemotherapy significantly  
44 improves the outcome of children with intermediate-risk acute lymphoblastic leukemia. Final results of  
45 the prospective randomized PETHEMA ALL-89 TRIAL. *Haematologica* 2001;86(6):586-595.  
46
- 47 188. Rescorla F, Billmire D, Stolar C, et al. The effect of cisplatin dose and surgical resection in  
48 children with malignant germ cell tumors at the sacrococcygeal region: A pediatric intergroup trial (POG  
49 9049/CCG 8882). *Journal of pediatric surgery* 2001;36(1):12-17.  
50
- 51 189. Tournade MF, ComNougue C, De Kraker J, et al. Optimal duration of preoperative therapy in  
52 unilateral and nonmetastatic Wilms' tumor in children older than 6 months: Results of the Ninth  
53 International Society of Pediatric Oncology Wilms' Tumor Trial and Study. *Journal of Clinical Oncology*  
54 2001;19(2):488-500.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 190. Woods WG, Neudorf S, Gold S, et al. A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission: A report from the Children's Cancer Group. *Blood* 2001;97(1):56-62.
- 7 191. 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):1986-1994.
- 12 192. Chessells JM, Harrison G, Richards SM, et al. Failure of a new protocol to improve treatment results in paediatric lymphoblastic leukaemia: Lessons from the UK Medical Research Council trials UKALL X and UKALL XI. *British journal of haematology* 2002;118(2):445-455.
- 17 193. Couban S, Simpson DR, Barnett MJ, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. *Blood* 2002;100(5):1525-1531.
- 21 194. Jennings MT, Sposto R, Boyett JM, et al. Preradiation chemotherapy in primary high-risk brainstem tumors: phase II study CCG-9941 of the Children's Cancer Group. *Journal of Clinical Oncology* 2002;20(16):3431-3437.
- 25 195. Kamps WA, Bokkerink JPM, HakvoortCammel FG AJ, et al. BFM-oriented treatment for children with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk patients: Results of DCLSG protocol ALL-8 (1991-1996). *Leukemia* 2002;16(6):1099-1111.
- 29 196. Katzenstein HM, Krailo MD, Malogolowkin MH, et al. Hepatocellular carcinoma in children and adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup study. *Journal of Clinical Oncology* 2002;20(12):2789-2797.
- 33 197. Perel Y, Auvrignon A, Leblanc T, et al. Impact of addition of maintenance therapy to intensive induction and consolidation chemotherapy for childhood acute myeloblastic leukemia: Results of a prospective randomized trial, LAME 89/91. *Journal of Clinical Oncology* 2002;20(12):2774-2782.
- 37 198. Woods WG, Barnard DR, Alonzo TA, et al. Prospective study of 90 children requiring treatment for juvenile myelomonocytic leukemia or myelodysplastic syndrome: A report from the Children's Cancer Group. *Journal of Clinical Oncology* 2002;20(2):434-440.
- 41 199. 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.
- 45 200. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2003;21(5):774-780.
- 49 201. Bunin N, Aplenc R, Kamani N, et al. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: A pediatric blood and marrow transplant consortium study. *Bone marrow transplantation* 2003;32(6):543-548.

- 1  
2  
3 202. Cairo MS, Sposto R, HooverRegan M, et al. Childhood and adolescent large-cell lymphoma  
4 (LCL): A review of the Children's Cancer Group experience. *American Journal of Hematology*  
5 2003;72(1):53-63.  
6
- 7 203. Clarke M, Gaynon P, Hann I, et al. CNS-directed therapy for childhood acute lymphoblastic  
8 leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials. *Journal of clinical*  
9 *oncology : official journal of the American Society of Clinical Oncology* 2003;21(9):1798-1809.  
10
- 11 204. Goorin AM, Schwartzentruber DJ, Devidas M, et al. Presurgical chemotherapy compared with  
12 immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology  
13 Group Study POG-8651. *Journal of Clinical Oncology* 2003;21(8):1574-1580.  
14
- 15 205. Haas-Kogan DA, Swift PS, Selch M, et al. Impact of radiotherapy for high-risk neuroblastoma: a  
16 Children's Cancer Group study. *International journal of radiation oncology, biology, physics*  
17 2003;56(1):28-39.  
18
- 19 206. Heath JA, Steinherz PG, Altman A, et al. Human granulocyte colony-stimulating factor in  
20 children with high-risk acute lymphoblastic leukemia: a Children's Cancer Group Study. *Journal of*  
21 *Clinical Oncology* 2003;21(8):1612-1617.  
22
- 23 207. Hutchinson RJ, Gaynon PS, Sather H, et al. Intensification of therapy for children with lower-risk  
24 acute lymphoblastic leukemia: long-term follow-up of patients treated on Children's Cancer Group Trial  
25 1881. *Journal of Clinical Oncology* 2003;21(9):1790-1797.  
26
- 27 208. Katzenstein HM, Krailo MD, Malogolowkin MH, et al. Fibrolamellar hepatocellular carcinoma in  
28 children and adolescents. *Cancer* 2003;97(8):2006-2012.  
29
- 30 209. Schmiegelow K, Bjork O, Glomstein A, et al. Intensification of mercaptopurine/methotrexate  
31 maintenance chemotherapy may increase the risk of relapse for some children with acute lymphoblastic  
32 leukemia. *Journal of Clinical Oncology* 2003;21(7):1332-1339.  
33
- 34 210. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation  
35 chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of  
36 Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. *Journal of Clinical*  
37 *Oncology* 2003;21(8):1581-1591.  
38
- 39 211. Yetgin S, Tuncer MA, Cetin M, et al. Benefit of high-dose methylprednisolone in comparison  
40 with conventional-dose prednisolone during remission induction therapy in childhood acute  
41 lymphoblastic leukemia for long-term follow-up. *Leukemia* 2003;17(2):328-333.  
42
- 43 212. Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy  
44 with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents  
45 with high-risk malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049  
46 and Children's Cancer Group 8882. *Journal of Clinical Oncology* 2004;22(13):2691-2700.  
47
- 48 213. de Kraker J, Graf N, van Tinteren H, et al. Reduction of postoperative chemotherapy in children  
49 with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled  
50 trial. *Lancet* 2004;364(9441):1229-1235.  
51
- 52 214. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's  
53 disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is  
54 there a need? *J Clin Oncol* 2004;22(1):62-8.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 215. Lehrnbecher T, Varwig D, Kaiser J, et al. Infectious complications in pediatric acute myeloid  
4 leukemia: Analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukemia*  
5 2004;18(1):72-77.  
6  
7 216. LopezHernandez MA, Alvarado M, De Diego J, et al. A randomized trial of dexamethasone  
8 before remission induction, in de novo childhood acute lymphoblastic leukemia. *Haematologica*  
9 2004;89(3):365-366.  
10  
11 217. Milpied N, Deconinck E, Gaillard F, et al. Initial Treatment of Aggressive Lymphoma with High-  
12 Dose Chemotherapy and Autologous Stem-Cell Support. *New England Journal of Medicine*  
13 2004;350(13):1287-1295.  
14  
15 218. Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive  
16 neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer  
17 Group and Pediatric Oncology Group study. *Journal of Clinical Oncology* 2004;22(14):2873-2876.  
18  
19 219. Neudorf S, Sanders J, Kobrinsky N, et al. Allogeneic bone marrow transplantation for children  
20 with acute myelocytic leukemia in first remission demonstrates a role for graft versus leukemia in the  
21 maintenance of disease-free survival. *Blood* 2004;103(10):3655-3661.  
22  
23 220. Reinhard H, Semler O, Burger D, et al. Results of the SIOP 93-01/GPOH trial and study for the  
24 treatment of patients with unilateral nonmetastatic wilms tumor. *Klinische Padiatrie* 2004;216(3):132-  
25 140.  
26  
27 221. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of  
28 doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus  
29 ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood* 2004;104(12):3483-3489.  
30  
31 222. Suh C, Kim HJ, Kim SH, et al. Low-dose lenograstim to enhance engraftment after autologous  
32 stem cell transplantation: A prospective randomized evaluation of two different fixed doses. *Transfusion*  
33 2004;44(4):533-538.  
34  
35 223. Taylor RE, Bailey CC, Robinson KJ, et al. Impact of radiotherapy parameters on outcome in the  
36 International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3  
37 study of preradiotherapy chemotherapy for M0-M1 medulloblastoma. *International journal of radiation*  
38 *oncology, biology, physics* 2004;58(4):1184-1193.  
39  
40 224. Waber DP, Silverman LB, Catania L, et al. Outcomes of a randomized trial of hyperfractionated  
41 cranial radiation therapy for treatment of high-risk acute lymphoblastic leukemia: Therapeutic efficacy  
42 and neurotoxicity. *Journal of Clinical Oncology* 2004;22(13):2701-2707.  
43  
44 225. Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with  
45 relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse  
46 study of the Berlin-Frankfurt-Munster Group 87. *Journal of clinical oncology : official journal of the*  
47 *American Society of Clinical Oncology* 2005;23(31):7942-7950.  
48  
49 226. George RE, London WB, Cohn SL, et al. Hyperdiploidy plus nonamplified MYCN confers a  
50 favorable prognosis in children 12 to 18 months old with disseminated neuroblastoma: a Pediatric  
51 Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical*  
52 *Oncology* 2005;23(27):6466-6473.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 227. Geyer JR, Sposto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in  
4 infants with malignant brain tumors: a report from the Children's Cancer Group. *Journal of Clinical*  
5 *Oncology* 2005;23(30):7621-7631.  
6  
7 228. Gibson BES, Wheatley K, Hann IM, et al. Treatment strategy and long-term results in paediatric  
8 patients treated in consecutive UK AML trials. *Leukemia* 2005;19(12):2130-2138.  
9  
10 229. Igarashi S, Manabe A, Ohara A, et al. No advantage of dexamethasone over prednisolone for the  
11 outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in the Tokyo  
12 Children's Cancer Study Group L95-14 protocol. *Journal of Clinical Oncology* 2005;23(27):6489-6498.  
13  
14 230. MacDonald TJ, Arenson EB, Ater J, et al. Phase II study of high-dose chemotherapy before  
15 radiation in children with newly diagnosed high-grade astrocytoma: Final Analysis of Children's Cancer  
16 Group Study 9933. *Cancer* 2005;104(12):2862-2871.  
17  
18 231. Meyers PA, Schwartz CL, Krailo M, et al. Osteosarcoma: A randomized, prospective trial of the  
19 addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate.  
20 *Journal of Clinical Oncology* 2005;23(9):2004-2011.  
21  
22 232. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended  
23 use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. *Journal of*  
24 *Clinical Oncology* 2005;23(28):7161-7167.  
25  
26 233. Pritchard J, Cotterill SJ, Germond SM, et al. High dose melphalan in the treatment of advanced  
27 neuroblastoma: Results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group.  
28 *Pediatric Blood and Cancer* 2005;44(4):348-357.  
29  
30 234. Smith FO, Alonzo TA, Gerbing RB, et al. Long-term results of children with acute myeloid  
31 leukemia: a report of three consecutive Phase III trials by the Children's Cancer Group: CCG 251, CCG  
32 213 and CCG 2891. *Leukemia* 2005;19(12):2054-2062.  
33  
34 235. Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in  
35 childhood and adolescence: third study of the International Society of Paediatric Oncology--SIOP  
36 Malignant Mesenchymal Tumor 89. *Journal of clinical oncology : official journal of the American*  
37 *Society of Clinical Oncology* 2005;23(12):2618-2628.  
38  
39 236. Testi AM, Biondi A, Lo Coco F, et al. GIMEMA-AIEOP AIDA protocol for the treatment of  
40 newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005;106(2):447-453.  
41  
42 237. Tolar J, Bostrom BC, La MK, et al. Intravenous 6-mercaptopurine decreases salvage after relapse  
43 in childhood acute lymphoblastic leukemia: a report from the Children's Cancer Group study CCG 1922.  
44 *Pediatric Blood & Cancer* 2005;45(1):5-9.  
45  
46 238. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration  
47 schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the  
48 BFM Group Study NHL-BFM95. *Blood* 2005;105(3):948-958.  
49  
50 239. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for  
51 patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group  
52 Phase II Study 9457--a report from the Children's Oncology Group. *Journal of Clinical Oncology*  
53 2006;24(1):152-159.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 240. Mahoney Jr DH, Camitta BM, Devidas M. Does intravenous 6-mercaptopurine decrease salvage  
4 after relapse in childhood acute lymphoblastic leukemia? [3]. *Pediatric Blood and Cancer*  
5 2006;46(5):660-661.  
6
- 7 241. Malogolowkin MH, Katzenstein H, Krailo MD, et al. Intensified platinum therapy is an  
8 ineffective strategy for improving outcome in pediatric patients with advanced hepatoblastoma. *Journal of*  
9 *Clinical Oncology* 2006;24(18):2879-2884.  
10
- 11 242. Mitchell C, Pritchard-Jones K, Shannon R, et al. Immediate nephrectomy versus preoperative  
12 chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3)  
13 by the UK Children's Cancer Study Group. *European journal of cancer* 2006;42(15):2554-2562.  
14
- 15 243. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed  
16 by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *Journal of Clinical*  
17 *Oncology* 2006;24(25):4202-4208.  
18
- 19 244. Pollack IF, Hamilton RL, Sobol RW, et al. O6-Methylguanine-DNA methyltransferase  
20 expression strongly correlates with outcome in childhood malignant gliomas: Results from the CCG-945  
21 cohort. *Journal of Clinical Oncology* 2006;24(21):3431-3437.  
22
- 23 245. Adamson PC, Matthay KK, O'Brien M, et al. A phase 2 trial of all-trans-retinoic acid in  
24 combination with interferon-alpha2a in children with recurrent neuroblastoma or wilms tumor: A  
25 pediatric oncology branch, NCI and children's oncology group study. *Pediatric Blood and Cancer*  
26 2007;49(5):661-665.  
27
- 28 246. Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukemia  
29 after Ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the Children's  
30 Oncology Group. *Blood* 2007;109(1):46-51.  
31
- 32 247. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk  
33 central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and  
34 adolescents. *Blood* 2007;109(7):2736-2743.  
35
- 36 248. Dinndorf PA, Gootenberg J, Cohen MH, et al. FDA drug approval summary: Pegaspargase  
37 (Oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). *Oncologist*  
38 2007;12(8):991-998.  
39
- 40 249. Le Deley MC, Guinebretiere JM, Gentet JC, et al. SFOP OS94: A randomised trial comparing  
41 preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and  
42 ifosfamide in osteosarcoma patients. *European journal of cancer* 2007;43(4):752-761.  
43
- 44 250. Lehrnbecher T, Zimmermann M, Reinhardt D, et al. Prophylactic human granulocyte colony-  
45 stimulating factor after induction therapy in pediatric acute myeloid leukemia. *Blood* 2007;109(3):936-  
46 943.  
47
- 48 251. Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic response but not survival in  
49 osteosarcoma patients treated with intensified chemotherapy: A randomized phase III trial of the european  
50 osteosarcoma intergroup. *Journal of the National Cancer Institute* 2007;99(2):112-128.  
51
- 52 252. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL  
53 Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood* 2007;109(3):896-904.  
54  
55  
56  
57  
58  
59



- 1  
2  
3 253. Neudorf S, Sanders J, Kobrinsky N, et al. Autologous bone marrow transplantation for children  
4 with AML in first remission. *Bone marrow transplantation* 2007;40(4):313-318.  
5
- 6 254. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial  
7 for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce  
8 treatment for the early responding patients. *Blood* 2007;109(7):2773-2780.  
9
- 10 255. Rutkowski S, von Bueren A, von Hoff K, et al. Prognostic relevance of clinical and biological  
11 risk factors in childhood medulloblastoma: results of patients treated in the prospective multicenter trial  
12 HIT'91. *Clinical Cancer Research* 2007;13(9):2651-2657.  
13
- 14 256. Skapek SX, Ferguson WS, Granowetter L, et al. Vinblastine and methotrexate for desmoid  
15 fibromatosis in children: Results of a Pediatric Oncology Group phase II trial. *Journal of Clinical  
16 Oncology* 2007;25(5):501-506.  
17
- 18 257. Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid  
19 leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease.  
20 *Journal of Clinical Oncology* 2007;25(5):493-500.  
21
- 22 258. Arico M, Valsecchi MG, Rizzari C, et al. Long-term results of the AIEOP-ALL-95 trial for  
23 childhood acute lymphoblastic leukemia: Insight on the prognostic value of DNA index in the framework  
24 of Berlin-Frankfurt-Muenster-based chemotherapy. *Journal of Clinical Oncology* 2008;26(2):283-289.  
25
- 26 259. Barry EV, Vrooman LM, Dahlberg SE, et al. Absence of secondary malignant neoplasms in  
27 children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *Journal of Clinical  
28 Oncology* 2008;26(7):1106-1111.  
29
- 30 260. Bhatla D, Gerbing RB, Alonzo TA, et al. DNA repair polymorphisms and outcome of  
31 chemotherapy for acute myelogenous leukemia: A report from the Children's Oncology Group. *Leukemia*  
32 2008;22(2):265-272.  
33
- 34 261. Bond M, Bernstein ML, Pappo A, et al. A phase II study of imatinib mesylate in children with  
35 refractory or relapsed solid tumors: A children's oncology group study. *Pediatric Blood and Cancer*  
36 2008;50(2):254-258.  
37
- 38 262. Bradley KA, Pollack IF, Reid JM, et al. Motexafin gadolinium and involved field radiation  
39 therapy for intrinsic pontine glioma of childhood: A Children's Oncology Group phase i study. *Neuro-  
40 oncology* 2008;10(5):752-758.  
41
- 42 263. Gadner H, Grois N, Potschger U, et al. Improved outcome in multisystem Langerhans cell  
43 histiocytosis is associated with therapy intensification. *Blood* 2008;111(5):2556-62.  
44
- 45 264. Gangopadhyay AN, Rajeev R, Sharma SP, et al. Anterior intratumoural chemotherapy: a newer  
46 modality of treatment in advanced solid tumours in children. *Asian Journal of Surgery* 2008;31(4):225-  
47 229.  
48
- 49 265. Karachunskiy A, Herold R, von Stackelberg A, et al. Results of the first randomized multicentre  
50 trial on childhood acute lymphoblastic leukaemia in Russia. *Leukemia* 2008;22(6):1144-1153.  
51
- 52 266. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG-2961, a children's oncology group phase  
53 3 trial for untreated pediatric acute myeloid leukemia: a report from the children's oncology group. *Blood*  
54 2008;111(3):1044-1053.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 267. Meyers PA, Schwartz CL, Krailo MD, et al. Osteosarcoma: the addition of muramyl tripeptide to  
4 chemotherapy improves overall survival--a report from the Children's Oncology Group. *Journal of*  
5 *Clinical Oncology* 2008;26(4):633-638.  
6
- 7 268. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic  
8 leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected  
9 pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 2008;111(9):4477-4489.  
10
- 11 269. Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 study: Two randomized trials  
12 of Ewing's sarcoma treatment - Cyclophosphamide compared with ifosfamide in standard-risk patients  
13 and assessment of benefit of etoposide added to standard treatment in high-risk patients. *Journal of*  
14 *Clinical Oncology* 2008;26(27):4385-4393.  
15
- 16 270. Pearson ADJ, Pinkerton CR, Lewis IJ, et al. High-dose rapid and standard induction  
17 chemotherapy for patients aged over 1 year with stage 4 neuroblastoma: a randomised trial. *Lancet*  
18 *Oncology* 2008;9(3):247-256.  
19
- 20 271. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves  
21 survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the  
22 Children's Oncology Group. *Blood* 2008;111(5):2548-2555.  
23
- 24 272. Arndt CAS, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide  
25 compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan,  
26 and cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group Study  
27 D9803. *Journal of Clinical Oncology* 2009;27(31):5182-5188.  
28
- 29 273. Bhatla D, Gerbing RB, Alonzo TA, et al. Cytidine deaminase genotype and toxicity of cytosine  
30 arabinoside therapy in children with acute myeloid leukemia. *British journal of haematology*  
31 2009;144(3):388-394.  
32
- 33 274. Brugieres L, Le Deley M-C, Rosolen A, et al. Impact of the methotrexate administration dose on  
34 the need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results  
35 of a randomized trial of the EICNHL Group. *Journal of Clinical Oncology* 2009;27(6):897-903.  
36
- 37 275. Chou AJ, Kleinerman ES, Krailo MD, et al. Addition of muramyl tripeptide to chemotherapy for  
38 patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group.  
39 *Cancer* 2009;115(22):5339-5348.  
40
- 41 276. Granowetter L, Womer R, Devidas M, et al. Dose-intensified compared with standard  
42 chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study.  
43 *Journal of Clinical Oncology* 2009;27(15):2536-2541.  
44
- 45 277. Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk  
46 neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a  
47 children's oncology group study. *Journal of Clinical Oncology* 2009;27(7):1007-1013.  
48
- 49 278. Nachman JB, La MK, Hunger SP, et al. Young adults with acute lymphoblastic leukemia have an  
50 excellent outcome with chemotherapy alone and benefit from intensive postinduction treatment: a report  
51 from the children's oncology group. *Journal of Clinical Oncology* 2009;27(31):5189-5194.  
52
- 53 279. Rubnitz JE, Crews KR, Pounds S, et al. Combination of cladribine and cytarabine is effective for  
54 childhood acute myeloid leukemia: Results of the St Jude AML97 trial. *Leukemia* 2009;23(8):1410-1416.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 280. von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in  
4 children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91. *European*  
5 *journal of cancer* 2009;45(7):1209-1217.  
6
- 7 281. De Moerloose B, Suciú S, Bertrand Y, et al. Improved outcome with pulses of vincristine and  
8 corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL)  
9 and lymphoblastic non-Hodgkin lymphoma (NHL): report of the EORTC randomized phase 3 trial  
10 58951. *Blood* 2010;116(1):36-44.  
11
- 12 282. Ehlers S, Herbst C, Zimmermann M, et al. Granulocyte colony-stimulating factor (G-CSF)  
13 treatment of childhood acute myeloid leukemias that overexpress the differentiation-defective G-CSF  
14 receptor isoform IV is associated with a higher incidence of relapse. *Journal of Clinical Oncology*  
15 2010;28(15):2591-2597.  
16
- 17 283. Johnson PWM, Sydes MR, Hancock BW, et al. Consolidation radiotherapy in patients with  
18 advanced Hodgkin's lymphoma: Survival data from the UKLG LY09 randomized controlled trial  
19 (ISRCTN97144519). *Journal of Clinical Oncology* 2010;28(20):3352-3359.  
20
- 21 284. Le Deley M-C, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with  
22 high-risk anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *Journal of*  
23 *Clinical Oncology* 2010;28(25):3987-3993.  
24
- 25 285. Liang DC, Yang CP, Lin DT, et al. Long-term results of Taiwan Pediatric Oncology Group  
26 studies 1997 and 2002 for childhood acute lymphoblastic leukemia. *Leukemia* 2010;24(2):397-405.  
27
- 28 286. London WB, Frantz CN, Campbell LA, et al. Phase II randomized comparison of topotecan plus  
29 cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a  
30 Children's Oncology Group study. *Journal of Clinical Oncology* 2010;28(24):3808-3815.  
31
- 32 287. Mascarenhas L, Lyden ER, Breitfeld PP, et al. Randomized phase II window trial of two  
33 schedules of irinotecan with vincristine in patients with first relapse or progression of  
34 rhabdomyosarcoma: a report from the Children's Oncology Group. *Journal of Clinical Oncology*  
35 2010;28(30):4658-4663.  
36
- 37 288. Moorman AV, Ensor HM, Richards SM, et al. Prognostic effect of chromosomal abnormalities in  
38 childhood B-cell precursor acute lymphoblastic leukaemia: Results from the UK Medical Research  
39 Council ALL97/99 randomised trial. *The Lancet Oncology* 2010;11(5):429-438.  
40
- 41 289. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first  
42 relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet*  
43 2010;376(9757):2009-2017.  
44
- 45 290. Stork LC, Matloub Y, Broxson E, et al. Oral 6-mercaptopurine versus oral 6-thioguanine and  
46 veno-occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the  
47 Children's Oncology Group CCG-1952 clinical trial. *Blood* 2010;115(14):2740-2748.  
48
- 49 291. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute  
50 lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course  
51 multidrug chemotherapy: Results of trial ALL-REZ BFM 90. *Journal of Clinical Oncology*  
52 2010;28(14):2339-2347.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 292. Tsuchida M, Ohara A, Manabe A, et al. Long-term results of Tokyo children's cancer study group  
4 trials for childhood acute lymphoblastic leukemia, 1984-1999. *Leukemia* 2010;24(2):383-396.  
5
- 6 293. Vora AJ, Mitchell C, Goulden N, et al. UKALL 2003, a randomised trial investigating treatment  
7 reduction for children and young adults with minimal residual disease defined low risk acute  
8 lymphoblastic leukaemia. 52nd Annual Meeting of the American Society of Hematology, ASH 2010  
9 Orlando, FL United States 2010;116 (21) (no pagination).  
10
- 11 294. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and  
12 isotretinoin for neuroblastoma. *N Engl J Med* 2010;363(14):1324-34.  
13
- 14 295. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell  
15 lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the  
16 Children's Oncology Group (POG 9404). *Blood* 2011;118(4):874-883.  
17
- 18 296. Freyer DR, Devidas M, La M, et al. Postrelapse survival in childhood acute lymphoblastic  
19 leukemia is independent of initial treatment intensity: A report from the Children's Oncology Group.  
20 *Blood* 2011;117(11):3010-3015.  
21
- 22 297. Gibson BES, Webb DKH, Howman AJ, et al. Results of a randomized trial in children with Acute  
23 Myeloid Leukaemia: Medical Research Council AML12 trial. *British journal of haematology*  
24 2011;155(3):366-376.  
25
- 26 298. Horstmann M, Escherich G. Treatment of acute lymphoblastic leucemia of childhood: Interim  
27 report CoALL 08-09. 78. Wissenschaftlichen Halbjahrestagung der Gesellschaft fur Padiatrische  
28 Onkologie und Hamatologie, GPOH Frankfurt Germany 2011;159(10):1006-1007.  
29
- 30 299. Kramm C, Roth D, Wolff JEA. First results of the randomized clinical trial HIT-GBM-D for  
31 treatment of children and adolescents with high grade glioma. 78. Wissenschaftlichen Halbjahrestagung  
32 der Gesellschaft fur Padiatrische Onkologie und Hamatologie, GPOH Frankfurt Germany  
33 2011;159(10):1005.  
34
- 35 300. Kurtzberg J, Asselin B, Bernstein M, et al. Polyethylene Glycol-conjugated L-asparaginase  
36 versus native L-asparaginase in combination with standard agents for children with acute lymphoblastic  
37 leukemia in second bone marrow relapse: a Children's Oncology Group Study (POG 8866). *Journal of*  
38 *Pediatric Hematology/Oncology* 2011;33(8):610-616.  
39
- 40 301. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-  
41 free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's  
42 Oncology Group. *Blood* 2011;118(2):243-251.  
43
- 44 302. Von Bueren AO, Von Hoff K, Pietsch T, et al. Treatment of young children with localized  
45 medulloblastoma by chemotherapy alone: Results of the prospective, multicenter trial HIT 2000  
46 confirming the prognostic impact of histology. *Neuro-oncology* 2011;13(6):669-679.  
47
- 48 303. Vrooman LM, Neuberg DS, Stevenson KE, et al. The low incidence of secondary acute  
49 myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic  
50 leukaemia: a report from the Dana-Farber Cancer Institute ALL Consortium. *European journal of cancer*  
51 2011;47(9):1373-1379.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 304. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment  
4 of low-grade glioma in young children: A report from the Children's Oncology Group. *Journal of Clinical*  
5 *Oncology* 2012;30(21):2641-2647.  
6  
7 305. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and  
8 adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a  
9 randomised, open-label, intergroup study. *Lancet Oncology* 2012;13(9):936-945.  
10  
11 306. Hasle H, Abrahamsson J, Forestier E, et al. Gemtuzumab ozogamicin as postconsolidation  
12 therapy does not prevent relapse in children with AML: Results from NOPHO-AML 2004. *Blood*  
13 2012;120(5):978-984.  
14  
15 307. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy  
16 followed by chemotherapy in standard-risk medulloblastoma: Results from the randomized multicenter  
17 HIT-SIOP PNET 4 trial. *Journal of Clinical Oncology* 2012;30(26):3187-3193.  
18  
19 308. Lipshultz SE, Miller TL, Lipsitz SR, et al. Continuous Versus Bolus Infusion of Doxorubicin in  
20 Children With ALL: Long-term Cardiac Outcomes. *Pediatrics* 2012;130(6):1003-1011.  
21  
22 309. Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug  
23 versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other  
24 chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society  
25 of Pediatric Oncology MMT95 study. *Journal of Clinical Oncology* 2012;30(20):2457-2465.  
26  
27 310. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in  
28 lower risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's  
29 Oncology Group. *Pediatric Blood & Cancer* 2012;59(7):1259-1265.  
30  
31 311. Vu K, Busaidy N, Cabanillas ME, et al. A randomized controlled trial of an intensive insulin  
32 regimen in patients with hyperglycemic acute lymphoblastic leukemia. *Clinical Lymphoma, Myeloma*  
33 *and Leukemia* 2012;12(5):355-362.  
34  
35 312. Wolden SL, Chen L, Kelly KM, et al. Long-term results of CCG 5942: a randomized comparison  
36 of chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma--a report from the  
37 Children's Oncology Group. *Journal of Clinical Oncology* 2012;30(26):3174-3180.  
38  
39 313. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed  
40 chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology  
41 Group. *Journal of Clinical Oncology* 2012;30(33):4148-4154.  
42  
43 314. Escherich G, Zimmermann M, Janka-Schaub G. Doxorubicin or daunorubicin given upfront in a  
44 therapeutic window are equally effective in children with newly diagnosed acute lymphoblastic leukemia.  
45 A randomized comparison in trial CoALL 07-03. *Pediatric Blood and Cancer* 2013;60(2):254-257.  
46  
47 315. Fouladi M, Stewart CF, Blaney SM, et al. A molecular biology and phase II trial of lapatinib in  
48 children with refractory CNS malignancies: a pediatric brain tumor consortium study. *Journal of neuro-*  
49 *oncology* 2013;114(2):173-179.  
50  
51 316. Heerema NA, Carroll AJ, Devidas M, et al. Intrachromosomal amplification of chromosome 21 is  
52 associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary  
53 standard-risk children's oncology group studies: a report from the children's oncology group. *Journal of*  
54 *clinical oncology* : official journal of the American Society of Clinical Oncology 2013;31(27):3397-3402.  
55  
56  
57  
58  
59  
60



- 1  
2  
3 317. Kaspers GJL, Zimmermann M, Reinhardt D, et al. Improved outcome in pediatric relapsed acute  
4 myeloid leukemia: Results of a randomized trial on liposomal daunorubicin by the international BFM  
5 study group. *Journal of Clinical Oncology* 2013;31(5):599-607.  
6
- 7 318. Packer RJ, Zhou T, Holmes E, et al. Survival and secondary tumors in children with  
8 medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology  
9 Group trial A9961. *Neuro-oncology* 2013;15(1):97-103.  
10
- 11 319. Tarbell NJ, Friedman H, Polkinghorn WR, et al. High-risk medulloblastoma: a pediatric oncology  
12 group randomized trial of chemotherapy before or after radiation therapy (POG 9031). *Journal of Clinical  
13 Oncology* 2013;31(23):2936-2941.  
14
- 15 320. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-  
16 risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised  
17 controlled trial. *Lancet Oncology* 2013;14(3):199-209.  
18
- 19 321. Vose JM, Carter S, Burns LJ, et al. Phase III randomized study of rituximab/carmustine,  
20 etoposide, cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with  
21 autologous hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the  
22 BMT CTN 0401 trial. *Journal of clinical oncology : official journal of the American Society of Clinical  
23 Oncology* 2013;31(13):1662-1668.  
24
- 25 322. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized  
26 dosing of *Escherichia Coli* L-asparaginase each improve outcome of children and adolescents with newly  
27 diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute  
28 ALL Consortium Protocol 00-01. *Journal of Clinical Oncology* 2013;31(9):1202-1210.  
29
- 30 323. Attarbaschi A, Panzer-Grumayer R, Mann G, et al. Minimal residual disease-based treatment is  
31 adequate for relapse-prone childhood acute lymphoblastic leukemia with an intrachromosomal  
32 amplification of chromosome 21: the experience of the ALL-BFM 2000 trial. *Klinische Padiatrie*  
33 2014;226(6-7):338-343.  
34
- 35 324. Batra V, Sands SA, Holmes E, et al. Long-term survival of children less than six years of age  
36 enrolled on the ccg-945 phase iii trial for newly-diagnosed high-grade glioma: A report from the  
37 children's oncology group. *Pediatric Blood and Cancer* 2014;61(1):151-157.  
38
- 39 325. Chagaluka G, Stanley C, Banda K, et al. Kaposi's sarcoma in children: an open randomised trial  
40 of vincristine, oral etoposide and a combination of vincristine and bleomycin. *European journal of cancer*  
41 2014;50(8):1472-1481.  
42
- 43 326. Creutzig U, Semmler J, Kaspers GL, et al. Re-induction with L-DNR/FLAG improves response  
44 after AML relapse, but not long-term survival. *Klinische Padiatrie* 2014;226(6-7):323-331.  
45
- 46 327. Flaherty LE, Othus M, Atkins MB, et al. Southwest Oncology Group S0008: a phase III trial of  
47 high-dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and  
48 interferon in patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B,  
49 Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group.  
50 *Journal of Clinical Oncology* 2014;32(33):3771-3778.  
51
- 52 328. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents  
53 with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from  
54  
55  
56  
57  
58  
59  
60



1  
2  
3 the randomized phase III Children's Oncology Group trial AAML0531. *Journal of Clinical Oncology*  
4 2014;32(27):3021-3032.  
5

6 329. Kato M, Koh K, Manabe A, et al. No impact of high-dose cytarabine and asparaginase as early  
7 intensification with intermediate-risk paediatric acute lymphoblastic leukaemia: results of randomized  
8 trial TCCSG study L99-15. *British journal of haematology* 2014;164(3):376-383.  
9

10 330. Mo XD, Zhao XY, Liu DH, et al. Umbilical cord blood transplantation and unmanipulated  
11 haploidentical hematopoietic SCT for pediatric hematologic malignances. *Bone marrow transplantation*  
12 2014;49(8):1070-1075.  
13

14 331. Mori T, Fukano R, Saito A, et al. Analysis of Japanese registration from the randomized  
15 international trial for childhood anaplastic large cell lymphoma (ALCL99-R1). [Rinsho ketsueki] *The*  
16 *Japanese journal of clinical hematology* 2014;55(5):526-533.  
17

18 332. Pulsipher MA, Langholz B, Wall DA, et al. The addition of sirolimus to tacrolimus/methotrexate  
19 GVHD prophylaxis in children with ALL: a phase 3 Children's Oncology Group/Pediatric Blood and  
20 Marrow Transplant Consortium trial. *Blood* 2014;123(13):2017-2025.  
21

22 333. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission  
23 tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse:  
24 Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial.  
25 *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*  
26 2014;32(12):1188-1194.  
27

28 334. Roos DE, Smith JG. Randomized trial on radiotherapy for paediatric diffuse intrinsic pontine  
29 glioma (DIPG). *Radiotherapy & Oncology* 2014;113(3):425.  
30

31 335. Shinagawa K, Yanada M, Sakura T, et al. Tamibarotene as maintenance therapy for acute  
32 promyelocytic leukemia: Results from a randomized controlled trial. *Journal of Clinical Oncology*  
33 2014;32(33):3729-3735.  
34

35 336. Stary J, Zimmermann M, Campbell M, et al. Intensive chemotherapy for childhood acute  
36 lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. *Journal of*  
37 *Clinical Oncology* 2014;32(3):174-184.  
38

39 337. Strother DR, Lafay-Cousin L, Boyett JM, et al. Benefit from prolonged dose-intensive  
40 chemotherapy for infants with malignant brain tumors is restricted to patients with ependymoma: a report  
41 of the Pediatric Oncology Group randomized controlled trial 9233/34. *Neuro-oncology* 2014;16(3):457-  
42 465.  
43

44 338. Zaghoul MS, Eldebawy E, Ahmed S, et al. Hypofractionated conformal radiotherapy for  
45 pediatric diffuse intrinsic pontine glioma (DIPG): a randomized controlled trial. *Radiotherapy &*  
46 *Oncology* 2014;111(1):35-40.  
47

48 339. Aly MMD, Hamza AF, Abdel Kader HM, et al. Therapeutic superiority of combined propranolol  
49 with short steroids course over propranolol monotherapy in infantile hemangioma. *European journal of*  
50 *pediatrics* 2015;174(11):1503-1509.  
51

52 340. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in  
53 high risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* 2015;126(8):964-  
54 971.  
55  
56

- 1  
2  
3 341. Chow EJ, Asselin BL, Schwartz CL, et al. Late Mortality After Dexrazoxane Treatment: A  
4 Report From the Children's Oncology Group. *Journal of Clinical Oncology* 2015;33(24):2639-2645.  
5
- 6 342. Creutzig U, Dworzak M, Zimmermann M, et al. Randomised introduction of 2-CDA as  
7 intensification during consolidation for children with high-risk AML - Results from study AML-BFM  
8 2004. *Klinische Padiatrie* 2015;227(3):116-122.  
9
- 10 343. Dharmarajan KV, Friedman DL, Schwartz CL, et al. Patterns of relapse from a phase 3 Study of  
11 response-based therapy for intermediate-risk Hodgkin lymphoma (AHOD0031): a report from the  
12 Children's Oncology Group. *International journal of radiation oncology, biology, physics* 2015;92(1):60-  
13 66.  
14
- 15 344. Junjun J, Xuelian Z, Dhruba K, et al. Efficacy of preoperative chemotherapy in treatment of  
16 children with wilms' tumor: A meta-analysis. *Iranian Journal of Pediatrics* 2015;25(2) (pagination):Arte  
17 Number: e366. *ate of Pubaton*: 2015.  
18
- 19 345. Karol SE, CoustanSmith E, Cao X, et al. Prognostic factors in children with acute myeloid  
20 leukaemia and excellent response to remission induction therapy. *British journal of haematology*  
21 2015;168(1):94-101.  
22
- 23 346. Ko RH, Jones TL, Radvinsky D, et al. Allergic reactions and anti-asparaginase antibodies in  
24 children with high-risk acute lymphoblastic leukemia: A children's oncology group report. *Cancer*  
25 2015;121(23):4205-4211.  
26
- 27 347. O'Connor D, Bartram J, Enshaei A, et al. Integration of minimal residual disease with other  
28 patient risk factors identifies a population with very poor overall survival in pediatric ALL: Results from  
29 the UKALL 2003 trial. 57th Annual Meeting of the American Society of Hematology, ASH 2015 San  
30 Diego, CA United States 2015;126(23):1412.  
31
- 32 348. Pritchard-Jones K, Bergeron C, de Camargo B, et al. Omission of doxorubicin from the treatment  
33 of stage II-III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority,  
34 randomised controlled trial. *Lancet* 2015;386(9999):1156-1164.  
35
- 36 349. Rodeberg DA, Wharam MD, Lyden ER, et al. Delayed primary excision with subsequent  
37 modification of radiotherapy dose for intermediate-risk rhabdomyosarcoma: A report from the Children's  
38 Oncology Group Soft Tissue Sarcoma Committee. *International Journal of Cancer* 2015;137(1):204-211.  
39
- 40 350. Sellar RS, Rowntree C, Vora AJ, et al. Relapse in teenage and young adult (TYA) patients treated  
41 on a pediatric minimal residual disease (MRD) stratified protocol is associated with a poor outcome:  
42 Results from UKALL2003. 57th Annual Meeting of the American Society of Hematology, ASH 2015  
43 San Diego, CA United States 2015;126(23):2493.  
44
- 45 351. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive  
46 chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group  
47 Study AALL0434. *Pediatric Blood & Cancer* 2015;62(7):1176-1183.  
48
- 49 352. Wolden SL, Lyden ER, Arndt CA, et al. Local Control for Intermediate-Risk  
50 Rhabdomyosarcoma: Results From D9803 According to Histology, Group, Site, and Size: A Report From  
51 the Children's Oncology Group. *International journal of radiation oncology, biology, physics*  
52 2015;93(5):1071-1076.  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 353. Asselin BL, Devidas M, Chen L, et al. Cardioprotection and safety of dexrazoxane in patients  
4 treated for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-  
5 Hodgkin lymphoma: A report of the Children's Oncology Group randomized trial Pediatric Oncology  
6 Group 9404. *Journal of Clinical Oncology* 2016;34(8):854-862.  
7

8 354. Falsini B, Chiaretti A, Rizzo D, et al. Nerve growth factor improves visual loss in childhood optic  
9 gliomas: A randomized, double-blind, phase II clinical trial. *Brain* 2016;139(2):404-414.  
10

11 355. Lucchese A, Matarese G, Manuelli M, et al. Reliability and efficacy of palifermin in prevention  
12 and management of oral mucositis in patients with acute lymphoblastic leukemia: A randomized, double-  
13 blind controlled clinical trial. *Minerva stomatologica* 2016;65(1):43-53.  
14

15 356. Pollard JA, Loken M, Gerbing RB, et al. CD33 expression and its association with gemtuzumab  
16 ozogamicin response: Results from the randomized phase III children's oncology group trial AAML0531.  
17 *Journal of Clinical Oncology* 2016;34(7):747-755.  
18  
19  
20  
21  
22  
23  
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26  
27  
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**PRISMA 2009 Checklist**

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Objectives stated on page 5; however, as this is a systematic review on research methods the PICOS format is not appropriate
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Developed but not published. Included as Appendix A in Supplementary File.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 and Appendix A in Supplementary File
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Appendix A in Supplementary File
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A in Supplementary File
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Appendix A in Supplementary File

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Appendix A in Supplementary File
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A since we were assessing research methods rather than results
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	5-6

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A since we were assessing methodology and reporting rather than results
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-6
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 and Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Figure 3 and Appendix B in Supplementary File
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A



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Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 1 and 6-7
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-9
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

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# BMJ Open

## The utility of the number needed to treat in pediatric hematological cancer randomized controlled treatment trials: A systematic review

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3 **1 The utility of the number needed to treat in pediatric hematological cancer randomized controlled**  
4 **2 treatment trials: A systematic review**  
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3 **Abstract**  
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7 **Objectives:** The primary objective was to assess the utility of the number needed to treat (NNT) to  
8 inform decision-making in the context of pediatric oncology and to calculate the NNT in all superiority  
9 parallel pediatric hematological cancer randomized controlled trials (RCTs), with a comparison to the  
10 threshold NNT as a measure of clinical significance.  
11

12 **Design:** Systematic review  
13

14 **Data sources:** MEDLINE, EMBASE and the Cochrane Childhood Cancer Group Specialized Register  
15 through CENTRAL from inception to August 2018.  
16

17 **Eligibility criteria for selecting studies:** Superiority parallel RCTs of hematological malignancy  
18 treatments in pediatric patients that assessed an outcome related to survival, relapse or remission; reported  
19 a sample size calculation with a delta value to allow for calculation of the threshold NNT, and that  
20 included parameters required to calculate the NNT and associated confidence interval.  
21

22 **Results:** A total of 43 RCTs were included, representing 45 randomized questions, of which none  
23 reported the NNT. Among acute lymphoblastic leukemia RCTs, 29.2% (7/24) of randomized questions  
24 were found to have a NNT corresponding to benefit, in comparison to acute myeloid leukemia RCTs with  
25 50% (3/6), and none in lymphoma RCTs (0/13). Only 28.6% (2/7) and 33.3% (1/3) had a NNT that was  
26 less than the threshold NNT for acute lymphoblastic leukemia and acute myeloid leukemia, respectively.  
27 Of these, 100% (2/2 acute lymphoblastic leukemia and 1/1 acute myeloid leukemia) were determined to  
28 be possibly clinically significant.  
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30 **Conclusions:** We recommend that decision-makers in pediatric oncology use the NNT and associated  
31 confidence limits as a supportive tool to evaluate evidence from RCTs, while placing careful attention to  
32 the inherent limitations of this measure.  
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69 **Strengths and Limitations of this Study**

<b>Strengths</b>	<ul style="list-style-type: none"> <li>• The use of the number of needed to treat (NNT) to assess clinical significance relative to a threshold NNT is a supportive tool to inform evidence-based decision making.</li> <li>• Comparing the threshold NNT to the NNT and its confidence interval is an effective method to assess the level of clinical significance.</li> <li>• Visualization, in the form of a forest plot, of the relationship between NNT with associated confidence intervals and the threshold NNT is a clinically relevant means of communicating complex information.</li> </ul>
<b>Limitations</b>	<ul style="list-style-type: none"> <li>• The delta value in the sample size calculation was assumed to be the absolute difference that would provide an effect size that would lead to a change in clinical practice, if not explicitly indicated, and a proxy for the threshold number needed to treat. This assumption, thus would lead to the possibility of effect sizes being chosen that might be more reflective of feasibility as opposed to clinical benefit and therefore limits generalisability, as this is not a universally recognized approach.</li> <li>• The proposed method implies that that the threshold NNT is equivalent to the threshold absolute risk reduction even though the NNT results in a transformation of scale and is expressed using a unit measured in patients. Therefore, a threshold absolute risk reduction may not correspond to a minimal clinically important difference in terms of the NNT.</li> </ul>

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**Introduction**

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3 79 Cancer in children is exceedingly rare and consists of less than 1% of all cancers diagnosed in Canada,  
4 80 with hematological cancers accounting for approximately 40% of cases<sup>1</sup>. Pediatric hematological cancer  
5 81 survival rates are currently upwards of 80%, largely as a result of treatment advances evaluated through  
6 82 randomized controlled trials (RCTs)<sup>2</sup>. Owing to the relative rarity of pediatric hematological cancers,  
7 83 multicenter international trials have been necessary to conduct adequately powered treatment  
8 84 investigations<sup>1,3</sup>. However, even with coordinated resource-intensive efforts, it can take five to seven  
9 85 years to complete a phase III RCT and another five years to publish outcomes with meaningful follow-  
10 86 up<sup>2</sup>. There is also an additional time lag before high-level evidence becomes the standard of care<sup>2</sup>.

16 87  
17 88 Given the lengthy timeline from research to practice, evaluating evidence arising from RCTs published in  
18 89 the pediatric oncology literature is critical for informing subsequent RCTs and standard of care. In other  
19 90 treatment contexts, the number needed to treat (NNT) has proven to be of value in assisting clinicians to  
20 91 assess therapeutic interventions and act as a supportive tool in benefit-risk assessments as well as  
21 92 formulary decision-making<sup>4-8</sup>. The NNT is an absolute effect measure coined almost 30 years ago,  
22 93 defined as the “*number of patients needed to be treated with one therapy versus another for one patient to*  
23 94 *encounter an additional outcome of interest within a defined period of time*”<sup>6,9,10</sup>. The NNT corresponds  
24 95 to the inverse of the absolute risk reduction (ARR), which is the absolute difference between the  
25 96 experimental and control estimates, for a specific time point. For example, a RCT comparing the effect of  
26 97 the medication strontium ranelate to a placebo on the incidence of vertebral fractures at three years in  
27 98 women with postmenopausal osteoporosis found that the event rate in the strontium ranelate group was  
28 99 20.9% compared to 32.8% in the placebo<sup>11</sup>. The inverse of the absolute difference in event rates between  
29 100 the experimental and control group corresponds to the NNT, such that in this study, “*9 patients would*  
30 101 *need to be treated for three years with strontium ranelate in order to prevent 1 patient from having a*  
31 102 *vertebral fracture (95 percent confidence interval, 6 to 14)*”<sup>11</sup>. The evaluation of evidence requires at a  
32 103 minimum, consideration of the absolute risk and relative benefits (and harms) related to a therapy in  
33 104 question, with the NNT being a supportive tool do so<sup>12</sup>. Despite the usefulness of the NNT and the  
34 105 Consolidated Standard of Reporting Trials (CONSORT) statement, which considers the NNT as a helpful  
35 106 tool, recent research suggests that these measures are rarely reported in the literature<sup>6,13-16</sup>.

36 107  
37 108 At this time, the utility of the NNT to support evidence-based practice in pediatric oncology treatment  
38 109 trials remains unexamined, as does the degree to which the NNT has been reported in the pediatric  
39 110 oncology literature. We specifically aimed to assess the utility of the NNT with consideration of a  
40 111 threshold NNT, which is the point where the therapeutic benefit equals the therapeutic risk<sup>17</sup>. The  
41 112 threshold NNT should correspond to the inverse of the ARR that a RCT is designed to detect and a



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3 113 clinically significant effect size that would lead to a clinical practice change. Therefore, a decision to  
4 114 administer a therapeutic intervention over the standard of care should occur when the NNT is less than the  
5 115 threshold NNT<sup>17</sup>. The primary study objective was to assess the utility of the NNT in pediatric  
6 116 hematologic cancer, by calculating the NNT in all superiority parallel RCTs assessing treatment related  
7 117 survival, relapse or remission, and comparing the NNT to the threshold NNT. A secondary study  
8 118 objective was to assess the proportion of published studies (specifically randomized questions) that  
9 119 reported the NNT.  
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## 16 121 **Methods**

17 122 This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-  
18 123 Analyses (PRISMA) statement (Supplementary File)<sup>18</sup>. This review consisted of a subset of studies from  
19 124 a previous systematic review conducted by our research team, which was conducted from inception of the  
20 125 databases searched to July 2016. The search strategy used in that systematic review was re-run to capture  
21 126 studies published from July 2016 to August 2018. Methods describing the search strategy, eligibility  
22 127 criteria, study identification and data extraction for our previous systematic review have been detailed in  
23 128 the protocol (Supplementary File – Appendix A).  
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### 30 130 *Search Strategy and Study Inclusion*

31 131 A comprehensive literature review was performed using the databases MEDLINE (Via Ovid), EMBASE  
32 132 (via OVID) and Cochrane Childhood Cancer Group Specialized Register (Via CENTRAL) from  
33 133 inception to August 2018 to identify all superiority, parallel group, RCTs in pediatric patients diagnosed  
34 134 with a hematological cancer that assessed an outcome related to survival, relapse or remission and those  
35 135 that reported either confidence intervals (CI) or standard errors associated with both the experimental and  
36 136 control estimates, or numbers of patients at risk on a Kaplan Meier curve. The reference lists of included  
37 137 studies during the full-text review stage were hand-searched to identify any additional studies. The search  
38 138 was restricted to studies published in English and therefore prone to language bias.  
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### 46 140 *Study Identification and Data Extraction*

47 141 Two investigators (HH and KN) screened the titles and abstracts non-independently to identify studies  
48 142 that fulfilled the study inclusion criteria. Discrepancies were settled by discussion and consensus, with the  
49 143 principal investigator (AFH) available as an adjudicator. Studies that fulfilled the inclusion criterion at the  
50 144 title and abstract screening stage were selected for full-text review by one investigator (HH) to confirm  
51 145 study eligibility. A data extraction template was developed and piloted with 15 included studies to ensure  
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3 146 all pertinent data was captured. One investigator (HH) then extracted all of the data, of which a random  
4 147 sample was selected and verified by the principal investigator (AFH) as a quality assurance measure.

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8 149 *Analysis*

9 150 The number needed to treat to benefit (NNTB), which corresponds to a positive NNT, or number needed  
10 151 to treat to harm (NNTH), which corresponds to a negative NNT, and associated 95% CI were calculated  
11 152 for each randomized question as per the validated methodology described by Altman & Andersen<sup>19</sup>. A  
12 153 randomized question is defined as an intervention comparison assessing a primary outcome for which a  
13 154 sample size calculation is reported. The NNT was based on the primary outcome and time point as  
14 155 specified in the sample size calculation. In the event that the time point specified in the sample size  
15 156 calculation was not reported, the information was inferred if a Kaplan Meier curve with the number of  
16 157 patients at risk was reported<sup>19</sup>. If the aforementioned was not provided, the time point reported in the  
17 158 results was used, and thus, these trials were prone to selective reporting bias. All analyses were conducted  
18 159 based on randomized questions to account for the possibility that a RCT could have more than one  
19 160 parallel group.

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21 161  
22 162 The ARR, NNT and delta value (i.e., threshold ARR and NNT), as reported in the sample size  
23 163 calculation, were visualized on a forest plot, grouped by disease (Acute Lymphoblastic Leukemia, Acute  
24 164 Myeloid Leukemia, Lymphoma and Mixed, which corresponds to the inclusion of multiple diseases), to  
25 165 allow for identification of NNTB (defined as the NNT and 95% CI that only included positive numbers),  
26 166 NNTH (defined as the NNT and 95% CI that only included negative numbers) and inconclusive NNT  
27 167 (defined as the NNT where the 95% CI included both a positive and a negative number). Descriptive  
28 168 statistics were used to summarize the frequency and percentage of randomized questions reporting the  
29 169 NNT, as well as the NNTB, NNTH, and inconclusive NNT by disease site.

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32 171 In order to ascertain whether the NNTB was clinically significant, we calculated the frequency and  
33 172 percentage of randomized questions where the  $NNT < \text{threshold NNT}$ ,  $NNT > \text{threshold NNT}$  or  $NNT =$   
34 173  $\text{threshold NNT}$ . The threshold NNT was considered to be the inverse of the ARR (i.e., delta value) as  
35 174 specified in the sample size calculation and was assumed to correspond to a clinically significant effect  
36 175 size that would lead to a change in clinical practice. The threshold NNT was compared to the treatment  
37 176 NNT and classified as definitely clinically significant, possibly clinical significant, inconclusive clinical  
38 177 significance and definitely not clinically significant as specified in Figure 1. These categories, as well as  
39 178 the overall method, were informed by methods described by Man-Son-Hing et al.<sup>20</sup> and Guyatt et al.<sup>21</sup>  
40 179 Randomized controlled trials where an ARR of zero occurred were excluded from the analysis because

180 the inverse corresponds to an undefined NNT. SAS (Statistical Analysis Software) version 9.4 (SAS  
181 Institute, Cary, NC) was used to perform all analyses.

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### 183 *Patient and Public Involvement*

184 Given this is a research methods systematic review, there was no patient or public involvement.

185

## 186 **Results**

### 187 *Included studies*

188 Our search identified 4,151 unique studies from MEDLINE, EMBASE and the Cochrane Childhood  
189 Cancer Group Specialized Register accessed through CENTRAL. Following title and abstract screening,  
190 432 studies were evaluated for eligibility based on full-text review. Of these studies, 387 studies were  
191 excluded and 43 studies (i.e., RCTs), representing 45 randomized questions, were included in the  
192 systematic review (Figure 2) (Supplementary File – Appendix B). The randomized questions  
193 corresponded to RCTs investigating treatments for acute lymphoblastic leukemia (ALL) (N = 24; 53.3%),  
194 lymphoma (N = 13; 28.9%), acute myeloid leukemia (AML) (N = 6; 13.3%) and mixed diagnoses (N = 2;  
195 4.4%).

### 196 *Number needed to treat*

197 The frequency and proportion of the NNTB, inconclusive NNT, and NNTH are summarized in Table 1.  
198 Approximately 29.2% (7/24) of randomized questions in ALL RCTs were found to have a NNT  
199 corresponding to a NNTB, in comparison to AML with 50.0% (3/6). There were no randomized questions  
200 in lymphoma (N = 15) trials with a NNTB.

### 201 *Comparison of NNT and Threshold NNT*

202 A comparison of the NNT to the threshold NNT is summarized in Table 1 and visualized in Figure 3. For  
203 randomized questions corresponding to NNTB, the NNT was less than the threshold NNT in 28.6% (2/7)  
204 ALL and 33.3% (1/3) AML comparisons. However, of these, 100% (2/2 and 1/1) had a lower confidence  
205 limit that was greater or equal to the threshold NNT for ALL and AML, respectively, and hence were  
206 possibly clinically significant. In contrast, 71.4% (5/7) and 66.7% (2/6) had a NNT greater than the  
207 threshold NNT; however, 80.0% (4/5) and 50.0% (1/2) of these had an upper confidence limit that was  
208 less than or equal to the threshold NNT for ALL and AML, respectively, and hence were possibly  
209 clinically significant.

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3 2114  
5 212 *Reporting of NNT*6  
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8 213 There were no randomized questions that reported the NNT to support the reporting of the primary  
9 214 outcome of the study.10  
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14 216 **Discussion**15 217 In this systematic review, we demonstrated that variation in the NNT exists among RCTs assessing  
16 218 outcomes related to remission, relapse, and survival in pediatric hematological cancers. A majority of  
17 219 randomized questions found to have a NNTB were not necessarily associated with a positive effect size  
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20 220 when using the inverse of the delta value as specified in the sample size calculation as a proxy for the  
21 221 threshold NNT and a measure of what a clinically significant NNT should be. There were no randomized  
22 222 questions reporting the NNT, which highlights reporting deficits in the pediatric hematological cancer  
23 223 RCT literature.24  
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26  
27 224 *Strengths and weaknesses*28  
29 225 Our review provides a comprehensive analysis of the utility of the NNT through an evaluation of all  
30 226 superiority parallel group pediatric hematological RCTs assessing relapse, remission and survival from  
31 227 inception to August 2018. We provide the NNT and ARR with its 95% CI along with the threshold NNT  
32 228 and ARR for these RCTs using a validated methodological approach, which will serve as a valuable tool  
33  
34 229 for decision-makers, clinicians and researchers to assess treatment effects. A weakness of this study is the  
35 230 exclusion of a number of RCTs due to reporting that precluded calculating the NNT. However, as the  
36 231 exclusion is due to reporting deficits, this limitation is beyond our control and serves as an important  
37 232 finding that reporting quality is limited in the pediatric hematological cancer RCT literature. An  
38 233 additional weakness is that the delta value in the sample size calculation was assumed to be the absolute  
39 234 difference that would provide an effect size that would lead to a change in clinical practice (i.e., minimal  
40 235 clinically important difference), if not explicitly indicated, and a proxy for the threshold ARR and NNT.  
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42 236 This assumption, thus, would lead to the possibility of effect sizes being chosen that might be more  
43 237 reflective of study feasibility as opposed to clinical benefit. This approach may be limited in terms of  
44 238 generalisability given that this is not a universally recognized approach. Additionally, this assumption  
45 239 implies that the threshold NNT is equivalent to the threshold ARR even though the NNT results in a  
46 240 transformation of scale and is expressed using a unit measured in patients. Therefore, a threshold ARR  
47 241 may not correspond to a minimal clinically important difference in terms of NNT. However, as there were

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3 242 no studies that reported a threshold NNT, our approach represents a feasible method to apply in the  
4 243 absence of a reported threshold NNT. This method is nonetheless not validated and further studies will  
5 244 need to be undertaken to compare whether researchers would equate the minimal clinical important  
6 245 difference in terms of ARR to the NNT.  
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### 11 247 *Comparison with existing literature*

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14 248 Considerable published literature has evaluated the utility of the NNT. The overarching conclusion is that  
15 249 the NNT is a metric of value in clinical, health policy and formulary decision-making when interpreted  
16 250 correctly<sup>4-8</sup>. However, the NNT and ARR are rarely reported or poorly reported in the literature despite  
17 251 being recommended as a helpful tool in the CONSORT statement and are often calculated using  
18 252 inappropriate methods<sup>6 12-16 22-27</sup>. Our findings corroborate the existing literature because no studies  
19 253 reported the NNT in our review. Previous studies have not highlighted the utility of the NNT specifically  
20 254 in the pediatric oncology literature or evaluated the clinical significance of the NNT using the approach  
21 255 described in our study and thus, our study is a novel and important addition to the literature.  
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### 29 257 *Study explanations and implications*

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32 258 Our study quantified the NNT as a means to better understand the utility of this tool to facilitate decision-  
33 259 making in pediatric oncology. The NNT allows for an intuitive understanding of the absolute effect size  
34 260 in terms of patients and can help considerably when comparing one treatment to another, after ensuring  
35 261 baseline characteristics, the outcome and time point for the patient population of interest are  
36 262 comparable<sup>12</sup>. For instance, a RCT conducted by Creutzig et al.<sup>28</sup> in pediatric AML patients assessing 5-  
37 263 year event free survival found a 6.0% (95% CI, 1.3%-10.7%) absolute increase associated with the  
38 264 experimental treatment (liposomal daunorubic induction) compared to the control treatment (idarubicin  
39 265 induction). The associated NNT corresponded to 17 (95% CI; 75-9), or NNTB 17 (95% CI, NNTB 75 to  
40 266 NNTB 9), meaning that it is estimated that by administering the experimental treatment, 1 extra patient  
41 267 would survive at 5 years for every 17 patients treated (95% CI, NNTB 75 to NNTB 9). Of note, this RCT  
42 268 was powered to detect an absolute increase in 5-year event free survival of 13% (i.e., delta value), which  
43 269 would correspond to a NNTB of 8 (i.e., threshold NNT). Although the NNTB is 17, the lower confidence  
44 270 limit is 75 and the upper confidence limit is 9 (a range that does not include 8), which, given the range,  
45 271 would lead one to believe that the effect size does not provide strong enough evidence to change clinical  
46 272 practice. In situations where the lower confidence limit of the NNTB is less than the threshold NNT, one  
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3 273 can be more confident that the treatment confers a clinically improved outcome as compared to the  
4 274 control. On the other hand, if the NNTB is less than the threshold NNT and the lower confidence limit is  
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6 275 greater than the threshold NNT, one should exercise greater caution in concluding that the effect size is  
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8 276 clinically significant (refer to Figure 1 for visual). As demonstrated in our study, a forest plot is a  
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10 277 convenient method to visualize the relationship between the NNT (and the associated 95% CI) evident in  
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12 278 study results compared to the NNT that the study was designed to detect as a proxy for the threshold NNT  
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14 279 and that would be considered clinically significant.

15 280 The aforementioned approach is recommended in light of smaller sample sizes that are often attained in  
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17 281 pediatric oncology RCTs and rare disease trials in general, as it allows for assessment of the precision of  
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19 282 the treatment effect as well as clinical and statistical significance. This was demonstrated in our study  
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21 283 where the majority of randomized questions found to have a NNTB had a NNT greater than the threshold  
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23 284 NNT, of which the upper confidence limit was less than or equal to the threshold NNT. If these RCTs  
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25 285 were designed with higher power it is possible that definite clinical significance may have been obtained.  
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27 286 On the other hand, based on statistical significance these findings would be considered not significant.  
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29 287 Since statistical significance does not provide an indication on the size of the treatment effect, one would  
30  
31 288 not be able to discern whether the findings could have possible clinical significance. An assessment of  
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33 289 clinical significance, therefore requires a summary measure be presented with a CI. By presenting a CI, an  
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35 290 assessment can be made of both statistical and clinical significance, which can inform clinical decision-  
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37 291 making. Interpreting results from RCTs based solely on statistical significance, without taking into  
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39 292 consideration clinical significance, can result in misappraisal of evidence. Using the results of our study  
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41 293 as an example, we demonstrated that all randomized questions, for which the NNTB was less than  
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43 294 threshold NNT, had a lower confidence limit that was equal to, or greater than, the threshold NNT.  
44  
45 295 Although these results were statistically significant, none had definite clinical significance and were only  
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47 296 possibly clinically significant. These findings have clinical implications because clinicians often have to  
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49 297 make decisions about administering treatments that are not standard of care, and rely on an accurate  
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51 298 appraisal of evidence to inform these decisions. Inconclusive evidence, however, does not necessarily  
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53 299 infer an ineffective intervention. Rather, inconclusive evidence (when the CI of the NNT crosses infinity  
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55 300 as a result of the CI of the ARR crossing 0) infers that the level of clinical significance cannot be  
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57 301 determined from the study results. The use of the NNT and the method we describe can be one more tool  
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59 302 to support clinical decision-making within this context.

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62 303 Scenarios where the NNT results in inconclusive evidence is a limitation in the utility of NNT, as  
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64 304 discussed by Altman<sup>29</sup>. To illustrate, Lange et al.<sup>30</sup> assessed 5-year disease free survival in pediatric AML  
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66 305 patients in first remission after intensive chemotherapy, and found a 7.0% (95% CI, -19.8% to 5.8%)



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3 306 absolute decrease associated with the experimental treatment (interleukin-2 infused on days 0-3 and 8-17)  
4 307 compared to the control treatment (no further therapy). The study was powered to detect a 10% difference  
5 308 in 5-year disease free survival, which was assumed to be the minimal clinical importance difference, and  
6 309 hence, corresponds to a threshold NNTB of 10. The resulting NNT of the RCT was -14 (95% CI, -5 to 17)  
7 310 or a NNTH 14 (95% CI, NNTH 5 to NNTB 17). At first glance, it appears as though the point estimate  
8 311 does not fall within the 95% CI, given the disjointed confidence limits. In other studies wherein the CI  
9 312 traverses both harm and benefit the NNT is reported without the CI<sup>31</sup>. In reality, the CI encompasses  
10 313 values from a NNTH of 5 to  $\infty$  and NNTB of 17 to  $\infty$ . Plotting the NNT and CI on a forest plot (Figure 3)  
11 314 demonstrates that a NNTH of 14 does fall within the interval range and in fact, the interval is continuous.  
12 315 Altman, therefore, recommended presenting the CI of the NNT as the following to emphasize continuity  
13 316 (using results from Lange et al. as an example): NNTH 14 (NNTH 5 to  $\infty$  to NNTB 17).

14 317 We strongly encourage plotting the ARR and the NNT on a forest plot simultaneously because the NNT  
15 318 is simply a method of re-expressing the ARR and supports the interpretation of the ARR. As the NNT is a  
16 319 relative measure it should always be accompanied by the absolute measure, the ARR<sup>16</sup>. Additionally, the  
17 320 utility of the NNT is inherently reliant on three major areas: baseline risk, the outcome and the time  
18 321 point<sup>12</sup>. In order for the NNT from an RCT demonstrating a NNTB to have utility, the patient population  
19 322 of interest should share a similar baseline risk because the desired treatment effect may be overestimated  
20 323 and thus the NNTB may be underestimated. Outcomes related to event free survival often differ in what is  
21 324 considered an event and thus it is critical to ensure that the NNTB being applied to the population of  
22 325 interest is identical in terms of the outcome in question. Numerous studies have demonstrated how the  
23 326 NNT varies with time and thus, comparability in time points is critical to ensure accurate interpretation of  
24 327 the NNT to a population of interest<sup>4 12 23 24</sup>. Lastly, criticisms of the statistical properties of the NNT have  
25 328 been highlighted by Hutton et al.<sup>32 33</sup> and Katz et al.<sup>34</sup> We agree with Altman & Deeks<sup>32</sup> response to these  
26 329 criticisms in that the NNT was designed for translation of research results and, therefore, arguments  
27 330 related to computation and its distribution properties are of less relevance. The NNT is simply a metric to  
28 331 re-express the ARR and, therefore, should be viewed as a measure to support the interpretation of the  
29 332 ARR.

### 30 333 *Recommendations*

31 334 We recommend that clinicians and decision-makers in pediatric oncology consider using the NNT as a  
32 335 supportive tool to evaluate evidence from RCTs, while paying careful attention to the inherent limitation  
33 336 of this measure. Additionally, we recommend that researchers report the NNT and associated CI to  
34 337 support the interpretation and generalisability of the trial results. Given the inherent limitations of the  
35 338 NNT, we emphasize that the NNT should be considered a supportive tool to inform evidence-based

339 decision making and not a replacement. Supplementary file Appendix C provides a summary of how the  
 340 NNT can be calculated and assessed to inform decision-making<sup>19,20</sup>.

### 341 **Figure Legends**

342 **Figure 1:** Guideline to assess level of clinical significance using number needed to treat

343 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to  
 344 the study ARR or NNT.

345 ARR corresponds to the absolute difference between the experimental and control estimates. The  
 346 inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value  
 347 the randomized control trial was designed to detect as determined in the sample size calculation.  
 348 The inverse of the threshold ARR corresponds to the threshold NNT.

349 Abbreviations; NNT, number needed to treat; ARR, absolute risk reduction; UCL, upper  
 350 confidence limit; LCL, lower confidence limit

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352 **Figure 2:** Selection of randomized controlled trials in the systematic review

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354 **Figure 3:** Forest plot summarizing randomized questions by the number needed to treat relative to the  
 355 threshold number needed to treat according to hematological cancer type

356 \*Correspond to RCT where more than one randomized question was investigated.

357 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to  
 358 the study ARR or NNT.

359 ARR corresponds to the absolute difference between the experimental and control estimates. The  
 360 inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value  
 361 the randomized control trial was designed to detect as determined in the sample size calculation.  
 362 The inverse of the threshold ARR corresponds to the threshold NNT.

363 Abbreviations: AML, acute myeloid leukemia; ALL, Acute lymphoblastic Leukemia; NNT,  
 364 numbers needed to treat; NNTB, number needed to benefit; NNTH, number needed to harm;  
 365 ARR, absolute risk reduction; OS, overall survival; EFS, event-free survival; DFS, disease-free  
 366 survival; CCR, complete cancer remission; RR, relapse rate; YR, year; CI, confidence interval

367 **Contributorship Statement:** AFH, KG and HH conceived and designed the study. HH collected and  
 analyzed the data. AFH and HH wrote the first drafts of the manuscript, and all authors contributed to  
 subsequent drafts. All authors had full access to all of the data in the review and take responsibility for the  
 integrity of the data and the accuracy of the data analysis.

**Competing Interests:** There are no competing interests for any author.

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2  
3 368 **Role of Funding Source:** Funding support was provided by the University of British Columbia School of  
4  
5 369 Nursing to conduct this systematic review. The funder played no role in study design, collection, analysis,  
6  
7 370 interpretation of data, writing of the report, or in the decision to submit the paper for publication. They  
8  
9 371 accept no responsibility for the contents.

10 372 **Data Sharing Statement:** Unpublished data will be made available upon request to the corresponding  
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12 373 author.

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## References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2017. Toronto, ON: Canadian Cancer Society; 2017. Available at: [cancer.ca/Canadian-CancerStatistics-2017-EN.pdf](http://cancer.ca/Canadian-CancerStatistics-2017-EN.pdf).
2. Saletta F, Seng MS, Lau LM. Advances in paediatric cancer treatment. *Translational pediatrics* 2014;3(2):156-82. doi: 10.3978/j.issn.2224-4336.2014.02.01 [published Online First: 2014/04/01]
3. Bond MC, Pritchard S. Understanding clinical trials in childhood cancer. *Paediatrics & child health* 2006;11(3):148-50. [published Online First: 2008/11/26]
4. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract* 2013;67 doi: 10.1111/ijcp.12142
5. Mendes D, Alves C, Batel MF. Testing the usefulness of the number needed to treat to be harmed (NNT<sub>H</sub>) in benefit-risk evaluations: case study with medicines withdrawn from the European market due to safety reasons. *Expert Opin Drug Saf* 2016;15 doi: 10.1080/14740338.2016.1217989
6. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. *BMC Medicine* 2017;15(1):112. doi: 10.1186/s12916-017-0875-8
7. Mendes D, Alves C, Batel-Marques F. Number needed to harm in the post-marketing safety evaluation: results for rosiglitazone and pioglitazone. *Pharmacoepidemiol Drug Saf* 2015;24 doi: 10.1002/pds.3874
8. Mendes D, Alves C, Batel-Marques F. Benefit-risk of therapies for relapsing-remitting multiple sclerosis: testing the number needed to treat to benefit (NNT<sub>B</sub>), number needed to treat to harm (NNT<sub>H</sub>) and the likelihood to be helped or harmed (LHH): a systematic review and meta-analysis. *CNS Drugs* 2016;30 doi: 10.1007/s40263-016-0377-9
9. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318 doi: 10.1056/nejm198806303182605
10. Cook D, Sackett D. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310 doi: 10.1136/bmj.310.6977.452
11. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350(5):459-68. doi: 10.1056/NEJMoa022436 [published Online First: 2004/01/30]
12. McAlister FA. The "number needed to treat" turns 20—and continues to be used and misused. *CMAJ* 2008;179 doi: 10.1503/cmaj.080484
13. Hildebrandt M, Vervölgyi E, Bender R. Calculation of NNTs in RCTs with time-to-event outcomes: a literature review. *BMC Med Res Methodol* 2009;9 doi: 10.1186/1471-2288-9-21
14. Nuovo J, Melnikow J, Chang D. Reporting number needed to treat and absolute risk reduction in randomized controlled trials. *JAMA* 2002;287 doi: 10.1001/jama.287.21.2813
15. Alonso-Coello P, Carrasco-Labra A, Brignardello-Petersen R. Systematic reviews experience major limitations in reporting absolute effects. *J Clin Epidemiol* 2016;72 doi: 10.1016/j.jclinepi.2015.11.002
16. Moher D, Hopewell S, Schulz KF. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340 doi: 10.1136/bmj.c869
17. Sinclair JC, Cook RJ, Guyatt GH, et al. When should an effective treatment be used? Derivation of the threshold number needed to treat and the minimum event rate for treatment. *J Clin Epidemiol* 2001;54(3):253-62. [published Online First: 2001/02/27]
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj* 2009;339:b2700. doi: 10.1136/bmj.b2700 [published Online First: 2009/07/23]
19. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319 doi: 10.1136/bmj.319.7223.1492

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3 424 20. Man-Son-Hing M, Laupacis A, O'Rourke K, et al. Determination of the clinical importance of study  
4 425 results. *Journal of general internal medicine* 2002;17(6):469-76. [published Online First:  
5 426 2002/07/23]
- 6 427 21. Guyatt GH, Sackett DL, Sinclair JC, et al. Users' guides to the medical literature. IX. A method for  
7 428 grading health care recommendations. Evidence-Based Medicine Working Group. *Jama*  
8 429 1995;274(22):1800-4. [published Online First: 1995/12/13]
- 9 430 22. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. *Thorax* 2013;68 doi:  
10 431 10.1136/thoraxjnl-2012-202709
- 11 432 23. Suissa S. The number needed to treat: 25 years of trials and tribulations in clinical research. *Rambam*  
12 433 *Maimonides Med J* 2015;30
- 13 434 24. Suissa D, Brassard P, Smiechowski B, et al. Number needed to treat is incorrect without proper time-  
14 435 related considerations. *J Clin Epidemiol* 2012;65 doi: 10.1016/j.jclinepi.2011.04.009
- 15 436 25. Stang A, Poole C, Bender R. Common problems related to the use of number needed to treat. *J Clin*  
16 437 *Epidemiol* 2010;63 doi: 10.1016/j.jclinepi.2009.08.006
- 17 438 26. Tramer MR, Walder B. Number needed to treat (or harm). *World journal of surgery* 2005;29(5):576-  
18 439 81. doi: 10.1007/s00268-005-7916-8 [published Online First: 2005/04/14]
- 19 440 27. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance  
20 441 employed in randomized controlled trials of drugs for dementia. *Journal of the American*  
21 442 *Geriatrics Society* 2009;57(3):536-46. doi: 10.1111/j.1532-5415.2008.02122.x [published Online  
22 443 First: 2009/02/04]
- 23 444 28. Creutzig U, Zimmermann M, Bourquin J-P, et al. Randomized trial comparing liposomal  
24 445 daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from  
25 446 Study AML-BFM 2004. *Blood* 2013;122(1):37-43. doi: [http://dx.doi.org/10.1182/blood-2013-02-](http://dx.doi.org/10.1182/blood-2013-02-484097)  
26 447 [484097](http://dx.doi.org/10.1182/blood-2013-02-484097)
- 27 448 29. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317 doi:  
28 449 10.1136/bmj.317.7168.1309
- 29 450 30. Lange BJ, Yang RK, Gan J, et al. Soluble interleukin-2 receptor alpha activation in a Children's  
30 451 Oncology Group randomized trial of interleukin-2 therapy for pediatric acute myeloid leukemia.  
31 452 *Pediatric blood & cancer* 2011;57(3):398-405. doi: 10.1002/pbc.22966 [published Online First:  
32 453 2011/06/18]
- 33 454 31. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Annals*  
34 455 *of internal medicine* 1997;126(9):712-20. [published Online First: 1997/05/01]
- 35 456 32. Hutton JL. Number needed to treat: properties and problems. *J R Stat Soc A Stat Soc* 2000;163 doi:  
36 457 10.1111/1467-985x.00175
- 37 458 33. Hutton JL. Number needed to treat and number needed to harm are not the best way to report and  
38 459 assess the results of randomised clinical trials. *British journal of haematology* 2009;146(1):27-30.  
39 460 doi: 10.1111/j.1365-2141.2009.07707.x [published Online First: 2009/05/15]
- 40 461 34. Katz N, Paillard FC, Van Inwegen R. A review of the use of the number needed to treat to evaluate  
41 462 the efficacy of analgesics. *The journal of pain : official journal of the American Pain Society*  
42 463 2015;16(2):116-23. doi: 10.1016/j.jpain.2014.08.005 [published Online First: 2014/11/25]

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466 **Table 1:** Randomized questions corresponding to number needed to benefit, harm and inconclusive  
 467 relative to threshold number needed to treat by hematological cancer type

NNT <sup>1</sup>	Hematological Cancer Randomized Questions (N = 45)			
	ALL (N = 24)	Lymphoma (N = 13)	AML (N = 6)	Mixed Diagnoses <sup>2</sup> (N = 2)
<b>NNTB (n, %)</b>	7 (29.2%)	0 (0.0%)	3 (50.0%)	1 (50.0%)
<i>NNTB &lt; Threshold NNT</i>	2 (28.6%)	0 (0.0%)	1 (33.3%)	1 (100.0%)
<i>NNTB Lower Confidence Limit ≥ Threshold NNT</i>	2 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
<i>NNTB &gt; Threshold</i>	5 (71.4%)	0 (0.0%)	2 (66.7%)	0 (0.0%)
<i>NNTB Upper Confidence Limit ≤ Threshold NNT</i>	4 (80.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
<i>NNTB = Threshold NNT</i>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Inconclusive NNT (n, %)</b>	16 (66.7%)	11 (84.6%)	3 (50.0%)	1 (50.0%)
<b>NNTH (n, %)</b>	1 (4.2%)	2 (15.4%)	0 (0.0%)	0 (0.0%)

468 Note: Threshold NNT corresponds to the inverse of the absolute difference (i.e., delta value) as reported in the sample size  
 469 calculation.

470 Abbreviations: NNT, number needed to treat; NNTB, number needed to treat to benefit; NNTH, number needed to treat to harm;  
 471 ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; UCL, Upper confidence limit; LCL, Lower Confidence  
 472 Limit; ARR, absolute risk reduction

473 <sup>1</sup> Denominator for indented corresponds to above row

474 <sup>2</sup> Mixed diagnoses refer to RCTs where more than one hematological cancer was included

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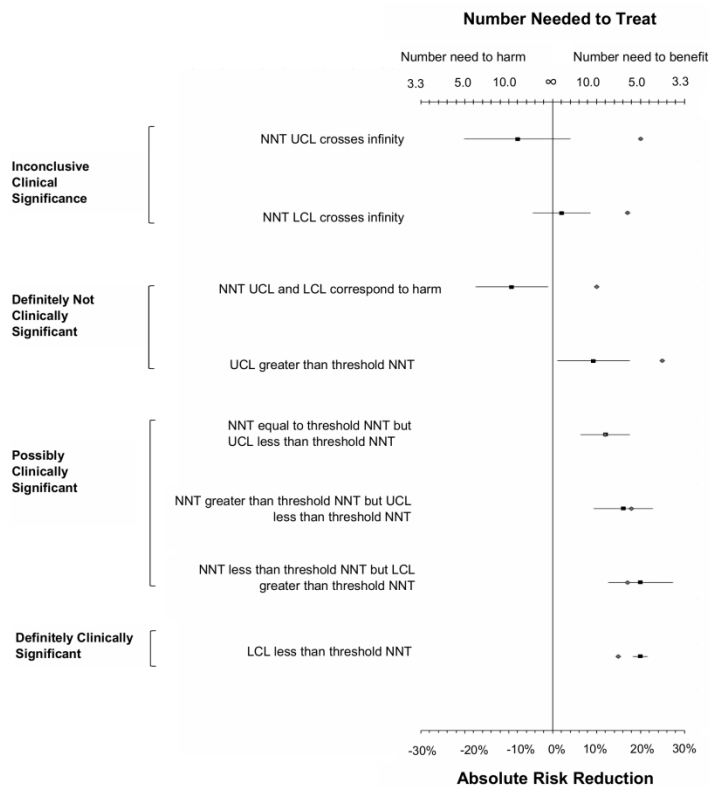


Figure 1: Guideline to assess level of clinical significance using numbers needed to treat  
 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study  
 ARR or NNT.

ARR corresponds to the absolute difference between the experimental and control estimates. The inverse of  
 the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value the randomized control  
 trial was designed to detect as determined in the sample size calculation. The inverse of the threshold ARR  
 corresponds to the threshold NNT.

Abbreviations; NNT, number needed to treat; ARR, absolute risk reduction; UCL, upper confidence limit;  
 LCL, lower confidence limit

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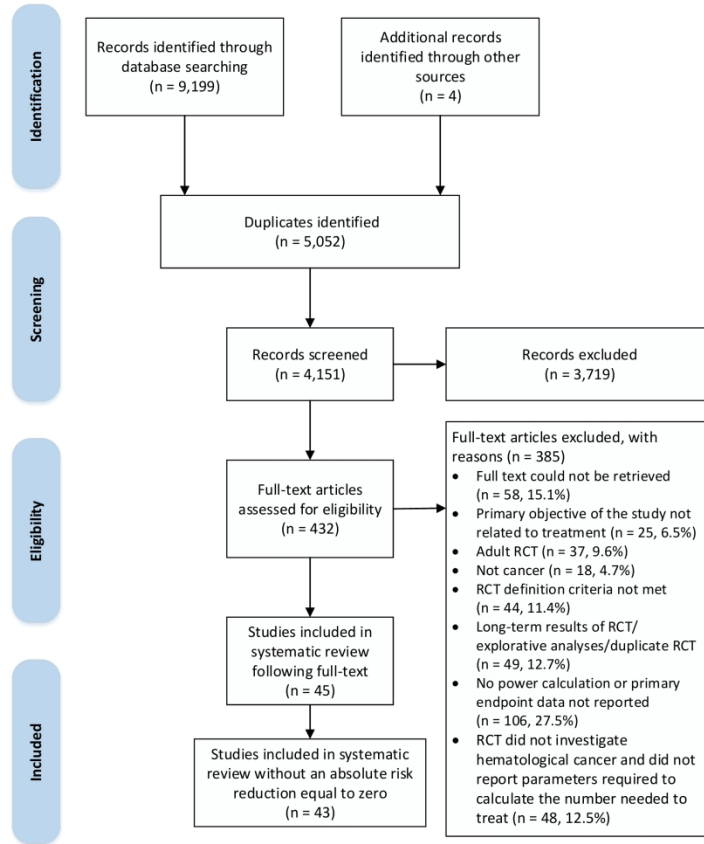


Figure 2: Selection of randomized controlled trials in the systematic review

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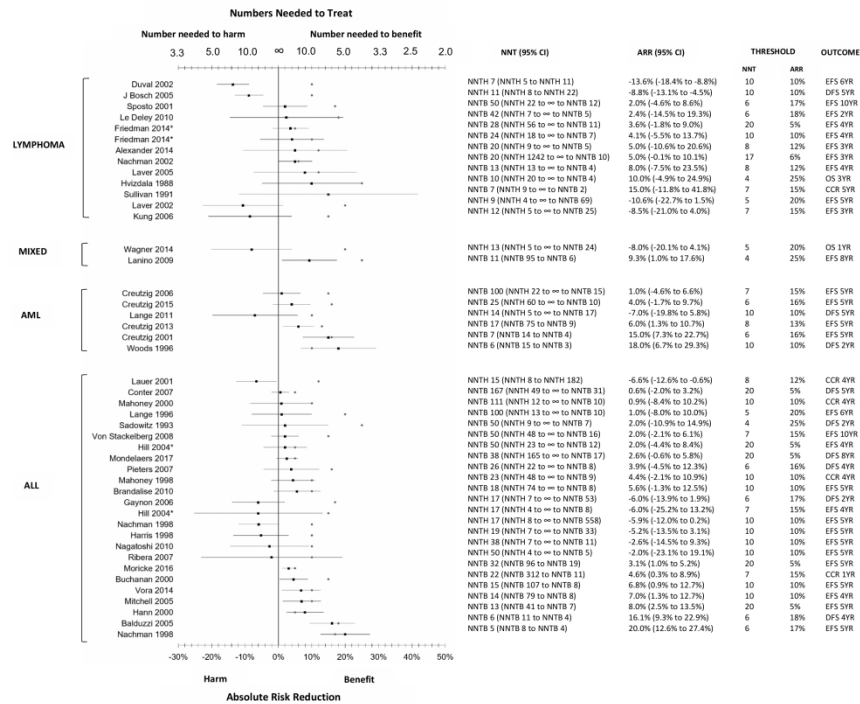


Figure 3: Forest plot summarizing randomized questions by the number needed to treat relative to the threshold number needed to treat according to hematological cancer type  
 \*Correspond to RCT where more than one randomized question was investigated.  
 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study ARR or NNT.

ARR corresponds to the absolute difference between the experimental and control estimates. The inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value the randomized control trial was designed to detect as determined in the sample size calculation. The inverse of the threshold ARR corresponds to the threshold NNT.

Abbreviations: AML, acute myeloid leukemia; ALL, Acute lymphoblastic Leukemia; NNT, numbers needed to treat; NNTB, number needed to benefit; NNTH, number needed to harm; ARR, absolute risk reduction; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; CCR, complete cancer remission; RR, relapse rate; YR, year; CI, confidence interval

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## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Objectives stated on page 5; however, as this is a systematic review on research methods the PICOS format is not appropriate
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix A in Supplementary File I
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 and Appendix A in Supplementary File I
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and Appendix A in Supplementary File I
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A in Supplementary File
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 and Appendix A in Supplementary File I

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Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and Appendix A in Supplementary File I
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A since we were assessing research methods rather than results
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	6

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A since we were assessing methodology and reporting rather than results
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 and Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Figure 3 and Appendix B in Supplementary File I
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 1 and 7-8
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-12
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).



## 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 be 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 to 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, Kravka 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, Suci 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 Children's 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, Kravaka 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.



- 1  
2  
3 23. Laver JH, Mahmoud H, Pick TE, et al. Results of a randomized phase III trial in children and  
4 adolescents with advanced stage diffuse large cell non-Hodgkin's lymphoma: a Pediatric Oncology Group  
5 study. *Leukemia & lymphoma* 2002;43(1):105-09.  
6
- 7 24. Le Deley M-C, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with high-risk  
8 anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *Journal of Clinical  
9 Oncology* 2010;28(25):3987-93. doi: <http://dx.doi.org/10.1200/JCO.2010.28.5999>  
10
- 11 25. Mahoney DH, Jr., Shuster J, Nitschke R, et al. Intermediate-dose intravenous methotrexate with  
12 intravenous mercaptopurine is superior to repetitive low-dose oral methotrexate with intravenous  
13 mercaptopurine for children with lower-risk B-lineage acute lymphoblastic leukemia: a Pediatric  
14 Oncology Group phase III trial. *Journal of Clinical Oncology* 1998;16(1):246-54.  
15
- 16 26. Mahoney DH, Jr., Shuster JJ, Nitschke R, et al. Intensification with intermediate-dose intravenous  
17 methotrexate is effective therapy for children with lower-risk B-precursor acute lymphoblastic leukemia:  
18 A Pediatric Oncology Group study. *Journal of Clinical Oncology* 2000;18(6):1285-94.  
19
- 20 27. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone  
21 for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council ALL97  
22 randomized trial. *British journal of haematology* 2005;129(6):734-45.  
23
- 24 28. Mondelaers V, Suci S, De Moerloose B, et al. Prolonged versus standard native E. coli asparaginase  
25 therapy in childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma: final results of the  
26 EORTC-CLG randomized phase III trial 58951. *Haematologica* 2017;102(10):1727-38. doi:  
27 <https://dx.doi.org/10.3324/haematol.2017.165845>  
28
- 29 29. Moricke A, Zimmermann M, Valsecchi MG, et al. Dexamethasone vs prednisone in induction  
30 treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. *Blood*  
31 2016;127(17):2101-12. doi: <https://dx.doi.org/10.1182/blood-2015-09-670729>  
32
- 33 30. Nachman J, Sather HN, Cherlow JM, et al. Response of children with high-risk acute lymphoblastic  
34 leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. *Journal  
35 of Clinical Oncology* 1998;16(3):920-30.  
36
- 37 31. Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-  
38 risk acute lymphoblastic leukemia and a slow response to initial therapy. *New England Journal of  
39 Medicine* 1998;338(23):1663-71.  
40
- 41 32. Nachman JB, Sposto R, Herzog P, et al. Randomized comparison of low-dose involved-field  
42 radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to  
43 chemotherapy. *Journal of Clinical Oncology* 2002;20(18):3765-71.  
44
- 45 33. Nagatoshi Y, Matsuzaki A, Suminoe A, et al. Randomized trial to compare LSA2L2-type  
46 maintenance therapy to daily 6-mercaptopurine and weekly methotrexate with vincristine and  
47 dexamethasone pulse for children with acute lymphoblastic leukemia. *Pediatric Blood & Cancer*  
48 2010;55(2):239-47. doi: <http://dx.doi.org/10.1002/pbc.22528>  
49
- 50 34. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with  
51 acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial.  
52 *Lancet* 2007;370(9583):240-50. doi: 10.1016/s0140-6736(07)61126-x [published Online First:  
53 2007/07/31]  
54  
55  
56  
57  
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2  
3 35. Ribera JM, Ortega JJ, Oriol A, et al. Comparison of intensive chemotherapy, allogeneic, or autologous  
4 stem-cell transplantation as postremission treatment for children with very high risk acute lymphoblastic  
5 leukemia: PETHEMA ALL-93 trial. *Journal of Clinical Oncology* 2007;25(1):16-24.  
6  
7 36. Sadowitz PD, Smith SD, Shuster J, et al. Treatment of late bone marrow relapse in children with acute  
8 lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 1993;81(3):602-09.  
9  
10 37. Sposto R, Meadows AT, Chilcote RR, et al. Comparison of long-term outcome of children and  
11 adolescents with disseminated non-lymphoblastic non-hodgkin lymphoma treated with COMP or  
12 daunomycin-comp: A report from the children's cancer group. *Medical and pediatric oncology*  
13 2001;37(5):432-41.  
14  
15 38. Sullivan MP, Fuller LM, Berard C, et al. Comparative effectiveness of two combined modality  
16 regimens in the treatment of surgical stage III Hodgkin's disease in children. An 8-year follow-up study  
17 by the Pediatric Oncology Group. *American Journal of Pediatric Hematology/Oncology* 1991;13(4):450-  
18 58.  
19  
20 39. van der Werff ten Bosch J, Suci S, Thyss A, et al. Value of intravenous 6-mercaptopurine during  
21 continuation treatment in childhood acute lymphoblastic leukemia and non-Hodgkin's lymphoma: Final  
22 results of a randomized phase III trial (58881) of the EORTC CLG. *Leukemia* 2005;19(5):721-26.  
23  
24 40. Von Stackelberg A, Hartmann R, Buhner C, et al. High-dose compared with intermediate-dose  
25 methotrexate in children with a first relapse of acute lymphoblastic leukemia. *Blood* 2008;111(5):2573-  
26 80.  
27  
28 41. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual  
29 disease-defined high-risk subgroup of children and young people with clinical standard-risk and  
30 intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. *Lancet*  
31 *Oncology* 2014;15(8):809-18. doi: [http://dx.doi.org/10.1016/S1470-2045\(14\)70243-8](http://dx.doi.org/10.1016/S1470-2045(14)70243-8)  
32  
33 42. Wagner JE, Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for  
34 hematologic cancers. *New England Journal of Medicine* 2014;371(18):1685-94.  
35  
36 43. Woods WG, Kobrinsky N, Buckley JD, et al. Timed-sequential induction therapy improves  
37 postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group. *Blood*  
38 1996;87(12):4979-89.  
39  
40  
41  
42  
43  
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49  
50  
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### 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 research/Fortschritte der Krebsforschung/Progres 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.

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2  
3 13. Arndt CAS, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared  
4 with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and  
5 cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group Study D9803.  
6 *Journal of Clinical Oncology* 2009;27(31):5182-88.  
7
- 8 14. Asselin BL, Devidas M, Chen L, et al. Cardioprotection and Safety of Dexrazoxane in Patients  
9 Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic  
10 Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric  
11 Oncology Group 9404. *Journal of Clinical Oncology* 2016;34(8):854-62. doi:  
12 <https://dx.doi.org/10.1200/JCO.2015.60.8851>  
13
- 14 15. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell  
15 lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the  
16 Children's Oncology Group (POG 9404). *Blood* 2011;118(4):874-83. doi:  
17 <http://dx.doi.org/10.1182/blood-2010-06-292615>  
18
- 19 16. Asselin BL, Kreissman S, Coppola DJ, et al. Prognostic significance of early response to a single dose  
20 of asparaginase in childhood acute lymphoblastic leukemia. *Journal of Pediatric Hematology/Oncology*  
21 1999;21(1):6-12.  
22
- 23 17. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of  
24 low-grade glioma in young children: A report from the Children's Oncology Group. *Journal of Clinical*  
25 *Oncology* 2012;30(21):2641-47.  
26
- 27 18. Attarbaschi A, Panzer-Grumayer R, Mann G, et al. Minimal residual disease-based treatment is  
28 adequate for relapse-prone childhood acute lymphoblastic leukemia with an intrachromosomal  
29 amplification of chromosome 21: the experience of the ALL-BFM 2000 trial. *Klinische Padiatrie*  
30 2014;226(6-7):338-43. doi: <http://dx.doi.org/10.1055/s-0034-1387795>  
31
- 32 19. Aur RJ, Simone JV, Hustu HO, et al. A comparative study of central nervous system irradiation and  
33 intensive chemotherapy early in remission of childhood acute lymphocytic leukemia. *Cancer*  
34 1972;29(2):381-91.  
35
- 36 20. Aur RJ, Simone JV, Verzosa MS, et al. Childhood acute lymphocytic leukemia: study VIII. *Cancer*  
37 1978;42(5):2123-34.  
38
- 39 21. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native *Escherichia coli*  
40 asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly  
41 diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood*  
42 2002;99(6):1986-94.  
43
- 44 22. Awada A, Colomer R, Inoue K, et al. Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in  
45 Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical  
46 Trial. *JAMA Oncol* 2016;2(12):1557-64. doi: <https://dx.doi.org/10.1001/jamaoncol.2016.0237>  
47
- 48 23. Bailey CC, Gnekow A, Wellek S, et al. Prospective randomised trial of chemotherapy given before  
49 radiotherapy in childhood medulloblastoma. International Society of Paediatric Oncology (SIOP) and the  
50 (German) Society of Paediatric Oncology (GPO): SIOP II. *Medical & Pediatric Oncology*  
51 1995;25(3):166-78.  
52
- 53 24. Balzarotti M, Brusamolino E, Angelucci E, et al. B-IGEV (bortezomib plus IGEV) versus IGEV  
54 before high-dose chemotherapy followed by autologous stem cell transplantation in relapsed or refractory  
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2  
3 Hodgkin lymphoma: a randomized, phase II trial of the Fondazione Italiana Linfomi (FIL). *Leukemia &*  
4 *Lymphoma* 2016;57(10):2375-81. doi: <https://dx.doi.org/10.3109/10428194.2016.1140161>  
5  
6 25. Barry EV, Vrooman LM, Dahlberg SE, et al. Absence of secondary malignant neoplasms in children  
7 with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *Journal of Clinical Oncology*  
8 2008;26(7):1106-11. doi: <http://dx.doi.org/10.1200/JCO.2007.12.2481>  
9  
10 26. Batra V, Sands SA, Holmes E, et al. Long-term survival of children less than six years of age enrolled  
11 on the ccg-945 phase iii trial for newly-diagnosed high-grade glioma: A report from the children's  
12 oncology group. *Pediatric Blood and Cancer* 2014;61(1):151-57.  
13  
14 27. Baum E, Sather H, Nachman J. Relapse rates following cessation of chemotherapy during complete  
15 remission of acute lymphocytic leukemia. A report from Children's Cancer Study Group. *Medical and*  
16 *pediatric oncology* 1979;7(1):25-34.  
17  
18 28. Becton D, Dahl GV, Ravindranath Y, et al. Randomized use of cyclosporin A (CsA) to modulate P-  
19 glycoprotein in children with AML in remission: Pediatric Oncology Group Study 9421. *Blood*  
20 2006;107(4):1315-24.  
21  
22 29. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for  
23 patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group  
24 Phase II Study 9457--a report from the Children's Oncology Group. *Journal of Clinical Oncology*  
25 2006;24(1):152-59.  
26  
27 30. Bertolone SJ, Yates AJ, Boyett JM, et al. Combined modality therapy for poorly differentiated  
28 gliomas of the posterior fossa in children: a Children's Cancer Group report. *Journal of neuro-oncology*  
29 2003;63(1):49-54.  
30  
31 31. Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukemia after  
32 Ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the Children's Oncology  
33 Group. *Blood* 2007;109(1):46-51.  
34  
35 32. Bhatla D, Gerbing RB, Alonzo TA, et al. Cytidine deaminase genotype and toxicity of cytosine  
36 arabinoside therapy in children with acute myeloid leukemia. *British journal of haematology*  
37 2009;144(3):388-94.  
38  
39 33. Bhatla D, Gerbing RB, Alonzo TA, et al. DNA repair polymorphisms and outcome of chemotherapy  
40 for acute myelogenous leukemia: A report from the Children's Oncology Group. *Leukemia*  
41 2008;22(2):265-72.  
42  
43 34. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and  
44 adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a  
45 randomised, open-label, intergroup study. *Lancet Oncology* 2012;13(9):936-45. doi:  
46 [http://dx.doi.org/10.1016/S1470-2045\(12\)70377-7](http://dx.doi.org/10.1016/S1470-2045(12)70377-7)  
47  
48 35. Bleyer WA, Sather HN, Nickerson HJ, et al. Monthly pulses of vincristine and prednisone prevent  
49 bone marrow and testicular relapse in low-risk childhood acute lymphoblastic leukemia: a report of the  
50 CCG-161 study by the Children's Cancer Study Group. *Journal of Clinical Oncology* 1991;9(6):1012-21.  
51  
52 36. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be  
53 treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*  
4 2003;21(5):774-80.  
5

6 37. Bond M, Bernstein ML, Pappo A, et al. A phase II study of imatinib mesylate in children with  
7 refractory or relapsed solid tumors: A children's oncology group study. *Pediatric Blood and Cancer*  
8 2008;50(2):254-58.  
9

10 38. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high  
11 risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* 2015;126(8):964-71. doi:  
12 <http://dx.doi.org/10.1182/blood-2015-03-633685>  
13

14 39. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus  
15 weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report  
16 from the Children's Cancer Group. *Blood* 2003;101(10):3809-17.  
17

18 40. Bradley KA, Pollack IF, Reid JM, et al. Motexafin gadolinium and involved field radiation therapy  
19 for intrinsic pontine glioma of childhood: A Children's Oncology Group phase i study. *Neuro-oncology*  
20 2008;10(5):752-58.  
21

22 41. Brecher ML, Schwenn MR, Coppes MJ, et al. Fractionated cylophosphamide and back to back high  
23 dose methotrexate and cytosine arabinoside improves outcome in patients with stage III high grade small  
24 non-cleaved cell lymphomas (SNCCCL): a randomized trial of the Pediatric Oncology Group. *Medical &*  
25 *Pediatric Oncology* 1997;29(6):526-33.  
26

27 42. Brecher ML, Weinberg V, Boyett JM, et al. Intermediate dose methotrexate in childhood acute  
28 lymphoblastic leukemia resulting in decreased incidence of testicular relapse. *Cancer* 1986;58(5):1024-  
29 28.  
30

31 43. Breitfeld PP, Lyden E, Raney RB, et al. Ifosfamide and etoposide are superior to vincristine and  
32 melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and  
33 combination chemotherapy: A report from the Intergroup Rhabdomyosarcoma Study Group. *Journal of*  
34 *Pediatric Hematology/Oncology* 2001;23(4):225-33.  
35  
36

37 44. Brugieres L, Le Deley M-C, Rosolen A, et al. Impact of the methotrexate administration dose on the  
38 need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of  
39 a randomized trial of the EICNHL Group. *Journal of Clinical Oncology* 2009;27(6):897-903. doi:  
40 <http://dx.doi.org/10.1200/JCO.2008.18.1487>  
41

42 45. Buchanan GR, Boyett JM, Pollock BH, et al. Improved treatment results in boys with overt testicular  
43 relapse during or shortly after initial therapy for acute lymphoblastic leukemia. A Pediatric Oncology  
44 group study. *Cancer* 1991;68(1):48-55.  
45

46 46. Bunin N, Aplenc R, Kamani N, et al. Randomized trial of busulfan vs total body irradiation containing  
47 conditioning regimens for children with acute lymphoblastic leukemia: A pediatric blood and marrow  
48 transplant consortium study. *Bone marrow transplantation* 2003;32(6):543-48.  
49

50 47. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central  
51 nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and  
52 adolescents. *Blood* 2007;109(7):2736-43.  
53

54 48. Cairo MS, Sposto R, HooverRegan M, et al. Childhood and adolescent large-cell lymphoma (LCL): A  
55 review of the Children's Cancer Group experience. *American Journal of Hematology* 2003;72(1):53-63.  
56  
57  
58  
59



- 1  
2  
3 49. Calandra T, Gaya H, Zinner SH, et al. Monotherapy with meropenem versus combination therapy  
4 with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer.  
5 *Antimicrobial Agents and Chemotherapy* 1996;40(5):1108-15.  
6
- 7 50. Camitta BM, Pinkel D, Thatcher LG. Failure of early intensive chemotherapy to improve prognosis in  
8 childhood acute lymphocytic leukemia. *Medical and pediatric oncology* 1980;8(4):383-89.  
9
- 10 51. Cangir A, Ragab AH, Steuber P. Combination chemotherapy with vincristine (NSC-67574),  
11 procarbazine (NSC-77213), prednisone (NSC-10023) with or without nitrogen mustard (NSC-  
12 762)(MOPP vs OPP) in children with recurrent brain tumors. *Medical and pediatric oncology*  
13 1984;12(1):1-3.  
14
- 15 52. Carli M, Pastore G, Perilongo G, et al. Tumor response and toxicity after single high-dose versus  
16 standard five-day divided-dose dactinomycin in childhood rhabdomyosarcoma. *Journal of Clinical*  
17 *Oncology* 1988;6(4):654-58.  
18
- 19 53. Castleberry RP, Cantor AB, Green AA, et al. Phase II investigational window using carboplatin,  
20 iproplatin, ifosfamide, and epirubicin in children with untreated disseminated neuroblastoma: a Pediatric  
21 Oncology Group study. *Journal of Clinical Oncology* 1994;12(8):1616-20.  
22
- 23 54. Castleberry RP, Kun LE, Shuster JJ, et al. Radiotherapy improves the outlook for patients older than 1  
24 year with Pediatric Oncology Group stage C neuroblastoma. *Journal of Clinical Oncology* 1991;9(5):789-  
25 95.  
26
- 27 55. Chagaluka G, Stanley C, Banda K, et al. Kaposi's sarcoma in children: an open randomised trial of  
28 vincristine, oral etoposide and a combination of vincristine and bleomycin. *European journal of cancer*  
29 2014;50(8):1472-81. doi: <http://dx.doi.org/10.1016/j.ejca.2014.02.019>  
30
- 31 56. Chan HSL, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer  
32 chemotherapy-induced emesis in children: A double-blind, crossover trial. *Pediatrics* 1987;79(6):946-52.  
33
- 34 57. Chen RW, Li H, Bernstein SH, et al. RB but not R-HCVAD is a feasible induction regimen prior to  
35 auto-HCT in frontline MCL: results of SWOG Study S1106. *British Journal of Haematology*  
36 2017;176(5):759-69. doi: <https://dx.doi.org/10.1111/bjh.14480>  
37
- 38 58. Cherlow JM, Steinherz PG, Sather HN, et al. The role of radiation therapy in the treatment of acute  
39 lymphoblastic leukemia with lymphomatous presentation: a report from the Childrens Cancer Group.  
40 *International journal of radiation oncology, biology, physics* 1993;27(5):1001-09.  
41
- 42 59. Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children with  
43 lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. Medical Research  
44 Council Working Party on Childhood Leukaemia. *Lancet* 1995;345(8943):143-48.  
45
- 46 60. Chessells JM, Durrant J, Hardy RM, et al. Medical Research Council leukaemia trial--UKALL V: an  
47 attempt to reduce the immunosuppressive effects of therapy in childhood acute lymphoblastic leukemia.  
48 Report to the Council by the Working Party on Leukaemia in Childhood. *Journal of Clinical Oncology*  
49 1986;4(12):1758-64.  
50
- 51 61. Chessells JM, Harrison G, Richards SM, et al. Failure of a new protocol to improve treatment results  
52 in paediatric lymphoblastic leukaemia: Lessons from the UK Medical Research Council trials UKALL X  
53 and UKALL XI. *British journal of haematology* 2002;118(2):445-55.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 62. Chou AJ, Kleinerman ES, Krailo MD, et al. Addition of muramyl tripeptide to chemotherapy for  
4 patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group.  
5 *Cancer* 2009;115(22):5339-48. doi: <http://dx.doi.org/10.1002/cncr.24566>  
6
- 7 63. Chow EJ, Asselin BL, Schwartz CL, et al. Late Mortality After Dexrazoxane Treatment: A Report  
8 From the Children's Oncology Group. *Journal of Clinical Oncology* 2015;33(24):2639-45. doi:  
9 <http://dx.doi.org/10.1200/JCO.2014.59.4473>  
10
- 11 64. Clarke M, Gaynon P, Hann I, et al. CNS-directed therapy for childhood acute lymphoblastic  
12 leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials. *Journal of clinical*  
13 *oncology : official journal of the American Society of Clinical Oncology* 2003;21(9):1798-809.  
14
- 15 65. Cohen BH, Zeltzer PM, Boyett JM, et al. Prognostic factors and treatment results for supratentorial  
16 primitive neuroectodermal tumors in children using radiation and chemotherapy: a Childrens Cancer  
17 Group randomized trial. *Journal of Clinical Oncology* 1995;13(7):1687-96.  
18
- 19 66. Conner K, Sandler E, Weyman C, et al. Intravenous midazolam versus fentanyl as premedication for  
20 painful procedures in pediatric oncology patients. *Journal of Pediatric Oncology Nursing* 1991;8(2):86-  
21 87.  
22
- 23 67. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or  
24 IV Hodgkin's Lymphoma.[Erratum appears in N Engl J Med. 2018 Mar 1;378(9):878; PMID: 29490175].  
25 *New England Journal of Medicine* 2018;378(4):331-44. doi: <https://dx.doi.org/10.1056/NEJMoa1708984>  
26
- 27 68. Conter V, Schrappe M, Arico M, et al. Role of cranial radiotherapy for childhood T-cell acute  
28 lymphoblastic leukemia with high WBC count and good response to prednisone. *Journal of Clinical*  
29 *Oncology* 1997;15(8):2786-91.  
30
- 31 69. Cortelazzo S, Tarella C, Gianni AM, et al. Randomized Trial Comparing R-CHOP Versus High-Dose  
32 Sequential Chemotherapy in High-Risk Patients With Diffuse Large B-Cell Lymphomas. *Journal of*  
33 *Clinical Oncology* 2016;34(33):4015-22. doi: <https://dx.doi.org/10.1200/JCO.2016.67.2980>  
34
- 35 70. Couban S, Simpson DR, Barnett MJ, et al. A randomized multicenter comparison of bone marrow and  
36 peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. *Blood*  
37 2002;100(5):1525-31.  
38
- 39 71. CoustanSmith E, Sancho J, Hancock ML, et al. Clinical importance of minimal residual disease in  
40 childhood acute lymphoblastic leukemia. *Blood* 2000;96(8):2691-96.  
41
- 42 72. Coze C, Hartmann O, Michon J, et al. NB87 induction protocol for stage 4 neuroblastoma in children  
43 over 1 year of age: a report from the French Society of Pediatric Oncology. *Journal of Clinical Oncology*  
44 1997;15(12):3433-40.  
45
- 46 73. Creutzig U, Ritter J, Zimmermann M, et al. Idarubicin improves blast cell clearance during induction  
47 therapy in children with AML: Results of study AML-BFM 93. *Leukemia* 2001;15(3):348-54.  
48
- 49 74. Creutzig U, Ritter J, Zimmermann M, et al. Does cranial irradiation reduce the risk for bone marrow  
50 relapse in acute myelogenous leukemia? Unexpected results of the Childhood Acute Myelogenous  
51 Leukemia Study BFM-87. *Journal of Clinical Oncology* 1993;11(2):279-86.  
52
- 53 75. Creutzig U, Ritter J, Zimmermann M, et al. Superior results by cranial irradiation in children with  
54 acute myelogenous leukemia: An update of study AML-BFM-87. *Onkologie* 1994;17(1):66-68.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 76. Creutzig U, Semmler J, Kaspers GL, et al. Re-induction with L-DNR/FLAG improves response after  
4 AML relapse, but not long-term survival. *Klinische Padiatrie* 2014;226(6-7):323-31. doi:  
5 <http://dx.doi.org/10.1055/s-0034-1385918>  
6
- 7 77. Crist W, Boyett J, Jackson J, et al. Prognostic importance of the pre-B-cell immunophenotype and  
8 other presenting features in B-lineage childhood acute lymphoblastic leukemia: a Pediatric Oncology  
9 Group study. *Blood* 1989;74(4):1252-59.  
10
- 11 78. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *Journal of*  
12 *Clinical Oncology* 1995;13(3):610-30.  
13
- 14 79. Crist W, Shuster J, Look T, et al. Current results of studies of immunophenotype-, age- and leukocyte-  
15 based therapy for children with acute lymphoblastic leukemia. *Leukemia* 1992;6(SUPPL. 2):162-66.  
16
- 17 80. Culbert SJ, Shuster JJ, Land VJ, et al. Remission induction and continuation therapy in children with  
18 their first relapse of acute lymphoid leukemia. A Pediatric Oncology Group study. *Cancer* 1991;67(1):37-  
19 42.  
20
- 21 81. Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with  
22 etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with  
23 high-risk malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049 and  
24 Children's Cancer Group 8882. *Journal of Clinical Oncology* 2004;22(13):2691-700.  
25
- 26 82. Dahl GV, Lacayo NJ, Brophy N, et al. Mitoxantrone, etoposide, and cyclospine therapy in pediatric  
27 patients with recurrent or refractory acute myeloid leukemia. *Journal of Clinical Oncology*  
28 2000;18(9):1867-75.  
29
- 30 83. D'Angio GJ, Evans A, Breslow N. The treatment of Wilms' tumor: Results of the second National  
31 Wilms' Tumor Study. *Cancer* 1981;47(9):2302-11.  
32
- 33 84. D'Angio GJ, Littman P, Nesbit M. Evaluation of radiation therapy factors in prophylactic central  
34 nervous system irradiation for childhood leukemia: A report from the children's cancer study group.  
35 *International Journal of Radiation Oncology Biology Physics* 1981;7(8):1031-38.  
36
- 37 85. De Camargo B, Franco EL. Single-dose versus fractionated-dose dactinomycin in the treatment of  
38 Wilms' tumor: Preliminary results of a clinical trial. *Cancer* 1991;67(12):2990-96.  
39
- 40 86. De Camargo B, Franco EL. A randomized clinical trial of single-dose versus fractionated-dose  
41 dactinomycin in the treatment of Wilms' tumor: Results after extended follow- up. *Cancer*  
42 1994;73(12):3081-86.  
43
- 44 87. de Kraker J, Graf N, van Tinteren H, et al. Reduction of postoperative chemotherapy in children with  
45 stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial.  
46 *Lancet* 2004;364(9441):1229-35.  
47
- 48 88. De Moerloose B, Suciu S, Bertrand Y, et al. Improved outcome with pulses of vincristine and  
49 corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL)  
50 and lymphoblastic non-Hodgkin lymphoma (NHL): report of the EORTC randomized phase 3 trial 58951.  
51 *Blood* 2010;116(1):36-44. doi: <http://dx.doi.org/10.1182/blood-2009-10-247965>  
52  
53
- 54 89. Deutsch M, Thomas PR, Krischer J, et al. Results of a prospective randomized trial comparing  
55 standard dose neuraxis irradiation (3,600 cGy/20) with reduced neuraxis irradiation (2,340 cGy/13) in  
56  
57  
58  
59

- 1  
2  
3 patients with low-stage medulloblastoma. A Combined Children's Cancer Group-Pediatric Oncology  
4 Group Study. *Pediatric neurosurgery* 1996;24(4):167-76.  
5
- 6 90. Dharmarajan KV, Friedman DL, Schwartz CL, et al. Patterns of relapse from a phase 3 Study of  
7 response-based therapy for intermediate-risk Hodgkin lymphoma (AHOD0031): a report from the  
8 Children's Oncology Group. *International journal of radiation oncology, biology, physics* 2015;92(1):60-  
9 66. doi: <http://dx.doi.org/10.1016/j.ijrobp.2014.10.042>  
10
- 11 91. Dinndorf PA, Gootenberg J, Cohen MH, et al. FDA drug approval summary: Pegaspargase  
12 (Oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). *Oncologist*  
13 2007;12(8):991-98.  
14
- 15 92. Doering EJ, Nitschke R, Haggard ME. Phase II study demonstrating failure of both a five-drug  
16 continuous-therapy regimen and a two-drug pulse-therapy regimen in the treatment of metastatic  
17 neuroblastoma: Southwest Oncology Group Study 822. *Cancer treatment reports* 1979;63(8):1383-84.  
18
- 19 93. Donaldson SS, Asmar L, Breneman J, et al. Hyperfractionated radiation in children with  
20 rhabdomyosarcoma - Results of an intergroup rhabdomyosarcoma pilot study. *International Journal of*  
21 *Radiation Oncology Biology Physics* 1995;32(4):903-11.  
22
- 23 94. Donaldson SS, Meza J, Breneman JC, et al. Results from the IRS-IV randomized trial of  
24 hyperfractionated radiotherapy in children with rhabdomyosarcoma--a report from the IRSG.  
25 *International journal of radiation oncology, biology, physics* 2001;51(3):718-28.  
26
- 27 95. Donaldson SS, Torrey M, Link MP, et al. A multidisciplinary study investigating radiotherapy in  
28 Ewing's sarcoma: end results of POG #8346. Pediatric Oncology Group. *International journal of*  
29 *radiation oncology, biology, physics* 1998;42(1):125-35.  
30
- 31 96. Eden OB, Lilleyman JS, Richards S, et al. Results of Medical Research Council Childhood  
32 Leukaemia Trial UKALL VIII (report to the Medical Research Council on behalf of the Working Party on  
33 Leukaemia in Childhood). *British journal of haematology* 1991;78(2):187-96.  
34
- 35 97. Ehlers S, Herbst C, Zimmermann M, et al. Granulocyte colony-stimulating factor (G-CSF) treatment  
36 of childhood acute myeloid leukemias that overexpress the differentiation-defective G-CSF receptor  
37 isoform IV is associated with a higher incidence of relapse. *Journal of Clinical Oncology*  
38 2010;28(15):2591-97.  
39
- 40 98. Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with relapsed  
41 ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the  
42 Berlin-Frankfurt-Munster Group 87. *Journal of clinical oncology : official journal of the American*  
43 *Society of Clinical Oncology* 2005;23(31):7942-50.  
44
- 45 99. Ekert H, Waters KD, Matthews RN. A randomized study of intermittent chemotherapy with or  
46 without BCG inoculation in maintenance therapy of childhood ALL. *Medical and pediatric oncology*  
47 1980;8(4):353-60.  
48
- 49 100. Elder JS. Results of the Sixth International Society of Pediatric Oncology Wilms' tumor trial and  
50 study: a risk-adapted therapeutic approach in Wilms' tumor. *The Journal of urology* 1994;152(1):271-72.  
51
- 52 101. Escherich G, Zimmermann M, Janka-Schaub G. Doxorubicin or daunorubicin given upfront in a  
53 therapeutic window are equally effective in children with newly diagnosed acute lymphoblastic leukemia.  
54 A randomized comparison in trial CoALL 07-03. *Pediatric Blood and Cancer* 2013;60(2):254-57.  
55  
56  
57  
58  
59

- 1  
2  
3 102. Evans AE, Albo V, D'Angio GJ. Cyclophosphamide treatment of patients with localized and  
4 regional neuroblastoma. A randomized study. *Cancer* 1976;38(2):655-59.  
5  
6 103. Evans AE, Anderson JR, Lefkowitz-Boudreaux IB, et al. Adjuvant chemotherapy of childhood  
7 posterior fossa ependymoma: cranio-spinal irradiation with or without adjuvant CCNU, vincristine, and  
8 prednisone: a Childrens Cancer Group study. *Medical & Pediatric Oncology* 1996;27(1):8-14.  
9  
10 104. Evans WE, Crom WR, Stewart CF, et al. Methotrexate systemic clearance influences probability of  
11 relapse in children with standard-risk acute lymphocytic leukaemia. *Lancet* 1984;1(8373):359-62.  
12  
13 105. Falsini B, Chiaretti A, Rizzo D, et al. Nerve growth factor improves visual loss in childhood optic  
14 gliomas: A randomized, double-blind, phase II clinical trial. *Brain* 2016;139(2):404-14.  
15  
16 106. Feig SA, Ames MM, Sather HN, et al. Comparison of idarubicin to daunomycin in a randomized  
17 multidrug treatment of childhood acute lymphoblastic leukemia at first bone marrow relapse: a report  
18 from the Children's Cancer Group. *Medical & Pediatric Oncology* 1996;27(6):505-14.  
19  
20 107. Feig SA, Harris RE, Sather HN. Bone marrow transplantation versus chemotherapy for maintenance  
21 of second remission of childhood acute lymphoblastic leukemia: A study of the children's cancer group  
22 (CCG-1884). *Medical and pediatric oncology* 1997;29(6):534-40.  
23  
24 108. Fernbach DJ, George SL, Sutow WW, et al. Long-term results of reinforcement therapy in children  
25 with acute leukemia. *Cancer* 1975;36(5):1552-59.  
26  
27 109. Ferrant A, Hulhoven R, Bosly A, et al. Clinical trials with daunorubicin-DNA and adriamycin-DNA  
28 in acute lymphoblastic leukemia of childhood, acute nonlymphoblastic leukemia, and bronchogenic  
29 carcinoma. *Cancer Chemotherapy & Pharmacology* 1979;2(1):67-71.  
30  
31 110. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade  
32 astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen.  
33 Childrens Cancer Group. *Journal of Clinical Oncology* 1995;13(1):112-23.  
34  
35 111. Flaherty LE, Othus M, Atkins MB, et al. Southwest Oncology Group S0008: a phase III trial of high-  
36 dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in  
37 patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B, Children's  
38 Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Journal of*  
39 *Clinical Oncology* 2014;32(33):3771-78. doi: <http://dx.doi.org/10.1200/JCO.2013.53.1590>  
40  
41 112. Flamant F, Rodary C, Voute PA, et al. Primary chemotherapy in the treatment of rhabdomyosarcoma  
42 in children: Trial of the international society of pediatric oncology (SIOP) preliminary results.  
43 *Radiotherapy and Oncology* 1985;3(3):227-36.  
44  
45 113. Fouladi M, Stewart CF, Blaney SM, et al. A molecular biology and phase II trial of lapatinib in  
46 children with refractory CNS malignancies: a pediatric brain tumor consortium study. *Journal of neuro-*  
47 *oncology* 2013;114(2):173-79.  
48  
49 114. Freeman AI, Boyett JM, Glicksman AS, et al. Intermediate-dose methotrexate versus cranial  
50 irradiation in childhood acute lymphoblastic leukemia: a ten-year follow-up. *Medical & Pediatric*  
51 *Oncology* 1997;28(2):98-107.  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 115. Freeman AI, Weinberg V, Brecher ML, et al. Comparison of intermediate-dose methotrexate with  
4 cranial irradiation for the post-induction treatment of acute lymphocytic leukemia in children. *New*  
5 *England Journal of Medicine* 1983;308(9):477-84.  
6
- 7 116. Freeman CR, Kepner J, Kun LE, et al. A detrimental effect of a combined chemotherapy-  
8 radiotherapy approach in children with diffuse intrinsic brain stem gliomas? *International Journal of*  
9 *Radiation Oncology Biology Physics* 2000;47(3):561-64.  
10
- 11 117. Freyer DR, Devidas M, La M, et al. Postrelapse survival in childhood acute lymphoblastic leukemia  
12 is independent of initial treatment intensity: A report from the Children's Oncology Group. *Blood*  
13 2011;117(11):3010-15.  
14
- 15 118. Fujimoto T, Goya H, Nakagawa K. Comparison of high dose infusion of methotrexate (MTX) vs  
16 sequential complementary method for maintenance of remission in acute childhood leukemia. A  
17 cooperative study. *Proceedings of the American Association for Cancer Research* 1975;16(66):no.257.  
18
- 19 119. Gardner H, Grois N, Potschger U, et al. Improved outcome in multisystem Langerhans cell  
20 histiocytosis is associated with therapy intensification. *Blood* 2008;111(5):2556-62. doi: 10.1182/blood-  
21 2007-08-106211 [published Online First: 2007/12/20]  
22
- 23 120. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents  
24 with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from  
25 the randomized phase III Children's Oncology Group trial AAML0531. *Journal of Clinical Oncology*  
26 2014;32(27):3021-32.  
27
- 28 121. Gangopadhyay AN, Rajeev R, Sharma SP, et al. Anterior intratumoural chemotherapy: a newer  
29 modality of treatment in advanced solid tumours in children. *Asian Journal of Surgery* 2008;31(4):225-  
30 29. doi: [http://dx.doi.org/10.1016/S1015-9584\(08\)60092-5](http://dx.doi.org/10.1016/S1015-9584(08)60092-5)  
31
- 32 122. Gautam A, Zhu Y, Ma E, et al. Brentuximab vedotin consolidation post-autologous stem cell  
33 transplant in Hodgkin lymphoma patients at risk of residual disease: number needed to treat. *Leukemia &*  
34 *Lymphoma* 2018;59(1):69-76. doi: <https://dx.doi.org/10.1080/10428194.2017.1324160>  
35
- 36 123. Gaynon PS, Steinherz PG, Bleyer WA, et al. Intensive therapy for children with acute lymphoblastic  
37 leukaemia and unfavourable presenting features. Early conclusions of study CCG-106 by the Childrens  
38 Cancer Study Group. *Lancet* 1988;2(8617):921-24.  
39
- 40 124. Gaynon PS, Steinherz PG, Bleyer WA, et al. Improved therapy for children with acute lymphoblastic  
41 leukemia and unfavorable presenting features: a follow-up report of the Childrens Cancer Group Study  
42 CCG-106. *Journal of Clinical Oncology* 1993;11(11):2234-42.  
43
- 44 125. George RE, London WB, Cohn SL, et al. Hyperdiploidy plus nonamplified MYCN confers a  
45 favorable prognosis in children 12 to 18 months old with disseminated neuroblastoma: a Pediatric  
46 Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical*  
47 *Oncology* 2005;23(27):6466-73.  
48
- 49 126. Geyer JR, Sposto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in  
50 infants with malignant brain tumors: a report from the Children's Cancer Group. *Journal of Clinical*  
51 *Oncology* 2005;23(30):7621-31.  
52  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 127. Gibson BES, Webb DKH, Howman AJ, et al. Results of a randomized trial in children with Acute  
4 Myeloid Leukaemia: Medical Research Council AML12 trial. *British journal of haematology*  
5 2011;155(3):366-76.  
6
- 7 128. Gibson BES, Wheatley K, Hann IM, et al. Treatment strategy and long-term results in paediatric  
8 patients treated in consecutive UK AML trials. *Leukemia* 2005;19(12):2130-38.  
9
- 10 129. Gilchrist GS, Tubergen DG, Sather HN, et al. Low numbers of CSF blasts at diagnosis do not predict  
11 for the development of CNS leukemia in children with intermediate-risk acute lymphoblastic leukemia: A  
12 Childrens Cancer Group report. *Journal of Clinical Oncology* 1994;12(12):2594-600.  
13
- 14 130. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase  
15 and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*  
16 2001;97(10):2998-3003.  
17
- 18 131. Goorin AM, Schwartzentruber DJ, Devidas M, et al. Presurgical chemotherapy compared with  
19 immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology  
20 Group Study POG-8651. *Journal of Clinical Oncology* 2003;21(8):1574-80.  
21
- 22 132. Granowetter L, Womer R, Devidas M, et al. Dose-intensified compared with standard chemotherapy  
23 for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. *Journal of*  
24 *Clinical Oncology* 2009;27(15):2536-41. doi: <http://dx.doi.org/10.1200/JCO.2008.19.1478>  
25
- 26 133. Green DM, Breslow NE, Beckwith JB, et al. Comparison between single-dose and divided-dose  
27 administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the  
28 National Wilms' Tumor Study Group. *Journal of Clinical Oncology* 1998;16(1):237-45.  
29
- 30 134. Haas-Kogan DA, Swift PS, Selch M, et al. Impact of radiotherapy for high-risk neuroblastoma: a  
31 Children's Cancer Group study. *International journal of radiation oncology, biology, physics*  
32 2003;56(1):28-39.  
33
- 34 135. Harris MB, Shuster JJ, Carroll A, et al. Trisomy of leukemic cell chromosomes 4 and 10 identifies  
35 children with B- progenitor cell acute lymphoblastic leukemia with a very low risk of treatment failure: A  
36 Pediatric Oncology Group Study. *Blood* 1992;79(12):3316-24.  
37
- 38 136. Harris MB, Shuster JJ, Pullen J, et al. Treatment of children with early pre-B and pre-B acute  
39 lymphocytic leukemia with antimetabolite-based intensification regimens: A pediatric oncology group  
40 study. *Leukemia* 2000;14(9):1570-76.  
41
- 42 137. Hasle H, Abrahamsson J, Forestier E, et al. Gemtuzumab ozogamicin as postconsolidation therapy  
43 does not prevent relapse in children with AML: Results from NOPHO-AML 2004. *Blood*  
44 2012;120(5):978-84.  
45
- 46 138. Heath JA, Steinherz PG, Altman A, et al. Human granulocyte colony-stimulating factor in children  
47 with high-risk acute lymphoblastic leukemia: a Children's Cancer Group Study. *Journal of Clinical*  
48 *Oncology* 2003;21(8):1612-17.  
49
- 50 139. Heerema NA, Carroll AJ, Devidas M, et al. Intrachromosomal amplification of chromosome 21 is  
51 associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary  
52 standard-risk children's oncology group studies: a report from the children's oncology group. *Journal of*  
53 *clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31(27):3397-402.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 140. Henze G, Fengler R, Hartmann R, et al. Six-year experience with a comprehensive approach to the  
4 treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85). A relapse study of  
5 the BFM group. *Blood* 1991;78(5):1166-72.  
6
- 7 141. Horstmann M, Escherich G. Treatment of acute lymphoblastic leucemia of childhood: Interim report  
8 CoALL 08-09. *78 Wissenschaftlichen Halbjahrestagung der Gesellschaft fur Padiatrische Onkologie und*  
9 *Hamatologie, GPOH Frankfurt Germany* 2011;159(10):1006-07. doi: [http://dx.doi.org/10.1007/s00112-](http://dx.doi.org/10.1007/s00112-011-2482-7)  
10 [011-2482-7](http://dx.doi.org/10.1007/s00112-011-2482-7)  
11
- 12 142. Hough R, Rowntree C, Goulden N, et al. Efficacy and toxicity of a paediatric protocol in teenagers  
13 and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from  
14 UKALL 2003. *British Journal of Haematology* 2016;172(3):439-51. doi:  
15 <https://dx.doi.org/10.1111/bjh.13847>  
16
- 17 143. Hutchinson RJ, Fryer CJ, Davis PC, et al. MOPP or radiation in addition to ABVD in the treatment  
18 of pathologically staged advanced Hodgkin's disease in children: results of the Children's Cancer Group  
19 Phase III Trial. *Journal of Clinical Oncology* 1998;16(3):897-906.  
20
- 21 144. Hutchinson RJ, Gaynon PS, Sather H, et al. Intensification of therapy for children with lower-risk  
22 acute lymphoblastic leukemia: long-term follow-up of patients treated on Children's Cancer Group Trial  
23 1881. *Journal of Clinical Oncology* 2003;21(9):1790-97.  
24
- 25 145. Igarashi S, Manabe A, Ohara A, et al. No advantage of dexamethasone over prednisolone for the  
26 outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in the Tokyo  
27 Children's Cancer Study Group L95-14 protocol. *Journal of Clinical Oncology* 2005;23(27):6489-98.  
28
- 29 146. Jabbour E, Short NJ, Ravandi F, et al. A randomized phase 2 study of idarubicin and cytarabine with  
30 clofarabine or fludarabine in patients with newly diagnosed acute myeloid leukemia. *Cancer*  
31 2017;123(22):4430-39. doi: <https://dx.doi.org/10.1002/ncr.30883>  
32
- 33 147. Jacquillat C, Weil M, Auclerc MF. Application of the study of prognostic factors to the treatment of  
34 childhood (<20 years old) acute lymphoblastic leukemia. Protocol 08 LA 74. *Bulletin du cancer*  
35 1980;67(4):458-69.  
36
- 37 148. JankaSchaub GE, Winkler K, Gobel U, et al. Rapidly rotating combination chemotherapy in  
38 childhood acute lymphoblastic leukemia: Preliminary results of a randomized comparison with  
39 conventional treatment. *Leukemia* 1988;2(12 SUPPL):73s-78s.  
40
- 41 149. Jaramillo S, Benner A, Krauter J, et al. Condensed versus standard schedule of high-dose cytarabine  
42 consolidation therapy with pegfilgrastim growth factor support in acute myeloid leukemia. *Blood Cancer*  
43 *J* 2017;7(5):e564. doi: <https://dx.doi.org/10.1038/bcj.2017.45>  
44
- 45 150. Jenkin RD, Boesel C, Ertel I, et al. Brain-stem tumors in childhood: a prospective randomized trial  
46 of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Children's Cancer  
47 Study Group. *Journal of neurosurgery* 1987;66(2):227-33.  
48
- 49 151. Jennings MT, Sposto R, Boyett JM, et al. Preradiation chemotherapy in primary high-risk brainstem  
50 tumors: phase II study CCG-9941 of the Children's Cancer Group. *Journal of Clinical Oncology*  
51 2002;20(16):3431-37.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 152. Johnson P, Federico M, Kirkwood A, et al. Adapted Treatment Guided by Interim PET-CT Scan in  
4 Advanced Hodgkin's Lymphoma. *New England Journal of Medicine* 2016;374(25):2419-29. doi:  
5 <https://dx.doi.org/10.1056/NEJMoa1510093>  
6
- 7 153. Johnson PWM, Sydes MR, Hancock BW, et al. Consolidation radiotherapy in patients with  
8 advanced Hodgkin's lymphoma: Survival data from the UKLG LY09 randomized controlled trial  
9 (ISRCTN97144519). *Journal of Clinical Oncology* 2010;28(20):3352-59.  
10
- 11 154. Jones PHM, Pearson D, Johnson AL. Management of nephroblastoma in childhood. Clinical study of  
12 two forms of maintenance chemotherapy. *Archives of Disease in Childhood* 1978;53(2):112-19.  
13
- 14 155. Junjun J, Xuelian Z, Dhruva K, et al. Efficacy of preoperative chemotherapy in treatment of children  
15 with wilms' tumor: A meta-analysis. *Iranian Journal of Pediatrics* 2015;25(2) (pagination):Arte Number:  
16 e366. ate of Pubaton: 2015. doi: <http://dx.doi.org/10.5812/ijp.366>  
17
- 18 156. Kamps WA, Bokkerink JP, Hahlen K, et al. Intensive treatment of children with acute lymphoblastic  
19 leukemia according to ALL-BFM-86 without cranial radiotherapy: results of Dutch Childhood Leukemia  
20 Study Group Protocol ALL-7 (1988-1991). *Blood* 1999;94(4):1226-36.  
21
- 22 157. Kamps WA, Bokkerink JPM, HakvoortCammel FG AJ, et al. BFM-oriented treatment for children  
23 with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk  
24 patients: Results of DCLSG protocol ALL-8 (1991-1996). *Leukemia* 2002;16(6):1099-111.  
25
- 26 158. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy  
27 for Acute Lymphoblastic Leukemia. *New England Journal of Medicine* 2016;375(8):740-53. doi:  
28 <https://dx.doi.org/10.1056/NEJMoa1509277>  
29
- 30 159. Karachunskiy A, Herold R, von Stackelberg A, et al. Results of the first randomized multicentre trial  
31 on childhood acute lymphoblastic leukaemia in Russia. *Leukemia* 2008;22(6):1144-53.  
32
- 33 160. Karol SE, CoustanSmith E, Cao X, et al. Prognostic factors in children with acute myeloid  
34 leukaemia and excellent response to remission induction therapy. *British journal of haematology*  
35 2015;168(1):94-101.  
36
- 37 161. Karon M, Freireich EJ, Frei E, et al. The role of vincristine in the treatment of childhood acute  
38 leukemia. *Clinical pharmacology and therapeutics* 1966;7(3):332-39.  
39
- 40 162. Kaspers GJL, Zimmermann M, Reinhardt D, et al. Improved outcome in pediatric relapsed acute  
41 myeloid leukemia: Results of a randomized trial on liposomal daunorubicin by the international BFM  
42 study group. *Journal of Clinical Oncology* 2013;31(5):599-607.  
43
- 44 163. Kato M, Koh K, Manabe A, et al. No impact of high-dose cytarabine and asparaginase as early  
45 intensification with intermediate-risk paediatric acute lymphoblastic leukaemia: results of randomized  
46 trial TCCSG study L99-15. *British journal of haematology* 2014;164(3):376-83. doi:  
47 <http://dx.doi.org/10.1111/bjh.12632>  
48
- 49 164. Katzenstein HM, Krailo MD, Malogolowkin MH, et al. Hepatocellular carcinoma in children and  
50 adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup  
51 study. *Journal of Clinical Oncology* 2002;20(12):2789-97.  
52
- 53 165. Katzenstein HM, Krailo MD, Malogolowkin MH, et al. Fibrolamellar hepatocellular carcinoma in  
54 children and adolescents. *Cancer* 2003;97(8):2006-12.  
55  
56  
57  
58  
59

- 1  
2  
3 166. Kawano Y, Takaue Y, Mimaya J, et al. Marginal benefit/disadvantage of granulocyte colony-stimulating factor therapy after autologous blood stem cell transplantation in children: results of a  
4 prospective randomized trial. The Japanese Cooperative Study Group of PBSCT. *Blood*  
5 1998;92(11):4040-46.  
6  
7  
8 167. Ko RH, Jones TL, Radvinsky D, et al. Allergic reactions and anti-asparaginase antibodies in children  
9 with high-risk acute lymphoblastic leukemia: A children's oncology group report. *Cancer*  
10 2015;121(23):4205-11.  
11  
12 168. Kobrinsky NL, Packer RJ, Boyett JM, et al. Etoposide with or without mannitol for the treatment of  
13 recurrent or primarily unresponsive brain tumors: a Children's Cancer Group Study, CCG-9881. *Journal*  
14 *of neuro-oncology* 1999;45(1):47-54.  
15  
16 169. Kohler JA, Imeson J, Ellershaw C, et al. A randomized trial of 13-Cis retinoic acid in children with  
17 advanced neuroblastoma after high-dose therapy. *British journal of cancer* 2000;83(9):1124-27.  
18  
19 170. Koizumi S, Fujimoto T. Improvement in treatment of childhood acute lymphoblastic leukemia: a 10-  
20 year study by the Children's Cancer and Leukemia Study Group. *International journal of hematology*  
21 1994;59(2):99-112.  
22  
23 171. Koizumi S, Fujimoto T, Oka T, et al. Overview of clinical studies of childhood acute lymphoblastic  
24 leukemia for more than ten years by the Japanese Children's Cancer and Leukemia Study Group.  
25 *Pediatric hematology and oncology* 1997;14(1):17-28.  
26  
27 172. Koizumi S, Fujimoto T, Takeda T, et al. Comparison of intermittent or continuous methotrexate plus  
28 6-mercaptopurine in regimens for standard-risk acute lymphoblastic leukemia in childhood (JCCLSG-  
29 S811). The Japanese Children's Cancer and Leukemia Study Group. *Cancer* 1988;61(7):1292-300.  
30  
31 173. Kojima S, Hibi S, Kosaka Y, et al. Immunosuppressive therapy using antithymocyte globulin,  
32 cyclosporine, and danazol with or without human granulocyte colony-stimulating factor in children with  
33 acquired aplastic anemia. *Blood* 2000;96(6):2049-54.  
34  
35 174. Kortmann RD, Kuhl J, Timmermann B, et al. Postoperative neoadjuvant chemotherapy before  
36 radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the  
37 treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91.  
38 *International journal of radiation oncology, biology, physics* 2000;46(2):269-79.  
39  
40 175. Krailo M, Ertel I, Makley J, et al. A randomized study comparing high-dose methotrexate with  
41 moderate-dose methotrexate as components of adjuvant chemotherapy in childhood nonmetastatic  
42 osteosarcoma: a report from the Children's Cancer Study Group. *Medical & Pediatric Oncology*  
43 1987;15(2):69-77.  
44  
45 176. Kramm C, Roth D, Wolff JEA. First results of the randomized clinical trial HIT-GBM-D for  
46 treatment of children and adolescents with high grade glioma. *78 Wissenschaftlichen Halbjahrestagung*  
47 *der Gesellschaft für Pädiatrische Onkologie und Hamatologie, GPOH Frankfurt Germany*  
48 2011;159(10):1005. doi: <http://dx.doi.org/10.1007/s00112-011-2482-7>  
49  
50 177. Krischer J, Land VJ, Civin CI, et al. Evaluation of AMSA in children with acute leukemia. A  
51 Pediatric Oncology Group study. *Cancer* 1984;54(2):207-10.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 178. Krischer JP, Ragab AH, Kun L, et al. Nitrogen mustard, vincristine, procarbazine, and prednisone as  
4 adjuvant chemotherapy in the treatment of medulloblastoma. A Pediatric Oncology Group study. *Journal*  
5 *of neurosurgery* 1991;74(6):905-09.  
6  
7 179. Kuhl J, Muller HL, Berthold F, et al. Preradiation chemotherapy of children and young adults with  
8 malignant brain tumors: results of the German pilot trial HIT'88/'89. *Klinische Padiatrie*  
9 1998;210(4):227-33.  
10  
11 180. Kurtzberg J, Asselin B, Bernstein M, et al. Polyethylene Glycol-conjugated L-asparaginase versus  
12 native L-asparaginase in combination with standard agents for children with acute lymphoblastic  
13 leukemia in second bone marrow relapse: a Children's Oncology Group Study (POG 8866). *Journal of*  
14 *Pediatric Hematology/Oncology* 2011;33(8):610-16. doi:  
15 <http://dx.doi.org/10.1097/MPH.0b013e31822d4d4e>  
16  
17 181. Lampkin BC, Woods WG, Buckley JD, et al. Preliminary results of intensive therapy of children and  
18 adolescents with acute nonlymphocytic leukemia--a Children's Cancer Study Group report. *Haematology*  
19 *and blood transfusion* 1990;33:210-14.  
20  
21 182. Land VJ, Shuster JJ, Crist WM, et al. Comparison of two schedules of intermediate-dose  
22 methotrexate and cytarabine consolidation therapy for childhood B-precursor cell acute lymphoblastic  
23 leukemia: a Pediatric Oncology Group study. *Journal of Clinical Oncology* 1994;12(9):1939-45.  
24  
25 183. Land VJ, Thomas PR, Boyett JM, et al. Comparison of maintenance treatment regimens for first  
26 central nervous system relapse in children with acute lymphocytic leukemia. A Pediatric Oncology Group  
27 study. *Cancer* 1985;56(1):81-87.  
28  
29 184. Landmann E, Burkhardt B, Zimmermann M, et al. Results and conclusions of the European  
30 Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma. *Haematologica*  
31 2017;102(12):2086-96. doi: <https://dx.doi.org/10.3324/haematol.2015.139162>  
32  
33 185. Lange BJ, Bostrom BC, Cherlow JM, et al. Double-delayed intensification improves event-free  
34 survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's  
35 Cancer Group. *Blood* 2002;99(3):825-33.  
36  
37 186. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG-2961, a children's oncology group phase 3  
38 trial for untreated pediatric acute myeloid leukemia: a report from the children's oncology group. *Blood*  
39 2008;111(3):1044-53.  
40  
41 187. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy  
42 followed by chemotherapy in standard-risk medulloblastoma: Results from the randomized multicenter  
43 HIT-SIOP PNET 4 trial. *Journal of Clinical Oncology* 2012;30(26):3187-93.  
44  
45 188. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and High-Dose Methotrexate Improve  
46 Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report  
47 From Children's Oncology Group Study AALL0232. *Journal of Clinical Oncology* 2016;34(20):2380-8.  
48 doi: <https://dx.doi.org/10.1200/JCO.2015.62.4544>  
49  
50 189. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's  
51 disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is  
52 there a need? *J Clin Oncol* 2004;22(1):62-8. doi: 10.1200/jco.2004.01.021 [published Online First:  
53 2003/12/06]  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 190. Laver JH, Barredo JC, Amylon M, et al. Effects of cranial radiation in children with high risk T cell  
4 acute lymphoblastic leukemia: A Pediatric Oncology Group report. *Leukemia* 2000;14(3):369-73.  
5
- 6 191. Laver JH, Mahmoud H, Pick TE, et al. Results of a randomized phase III trial in children and  
7 adolescents with advanced stage diffuse large cell non Hodgkin's lymphoma: a Pediatric Oncology Group  
8 study. *Leukemia & lymphoma* 2001;42(3):399-405.  
9
- 10 192. Le Deley MC, Guinebretiere JM, Gentet JC, et al. SFOP OS94: A randomised trial comparing  
11 preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and  
12 ifosfamide in osteosarcoma patients. *European journal of cancer* 2007;43(4):752-61.  
13
- 14 193. Lehrnbecher T, Varwig D, Kaiser J, et al. Infectious complications in pediatric acute myeloid  
15 leukemia: Analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukemia*  
16 2004;18(1):72-77.  
17
- 18 194. Lehrnbecher T, Zimmermann M, Reinhardt D, et al. Prophylactic human granulocyte colony-  
19 stimulating factor after induction therapy in pediatric acute myeloid leukemia. *Blood* 2007;109(3):936-43.  
20
- 21 195. Lemerle J, Voute PA, Tournade MF, et al. Preoperative versus postoperative radiotherapy, single  
22 versus multiple courses of actinomycin D, in the treatment of Wilms' tumor. Preliminary results of a  
23 controlled clinical trial conducted by the International Society of Paediatric Oncology (S.I.O.P.). *Cancer*  
24 1976;38(2):647-54.  
25
- 26 196. Lemerle J, Voute PA, Tournade MF, et al. Effectiveness of preoperative chemotherapy in Wilms'  
27 tumor: results of an International Society of Paediatric Oncology (SIOP) clinical trial. *Journal of Clinical*  
28 *Oncology* 1983;1(10):604-09.  
29
- 30 197. Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic response but not survival in  
31 osteosarcoma patients treated with intensified chemotherapy: A randomized phase III trial of the european  
32 osteosarcoma intergroup. *Journal of the National Cancer Institute* 2007;99(2):112-28.  
33
- 34 198. Li X, Cui Y, Sun Z, et al. DDGP versus SMILE in Newly Diagnosed Advanced Natural Killer/T-  
35 Cell Lymphoma: A Randomized Controlled, Multicenter, Open-label Study in China. *Clinical Cancer*  
36 *Research* 2016;22(21):5223-28.  
37
- 38 199. Liang DC, Hung IJ, Yang CP, et al. Unexpected mortality from the use of E. coli L-asparaginase  
39 during remission induction therapy for childhood acute lymphoblastic leukemia: a report from the Taiwan  
40 Pediatric Oncology Group. *Leukemia* 1999;13(2):155-60.  
41
- 42 200. Liang DC, Yang CP, Lin DT, et al. Long-term results of Taiwan Pediatric Oncology Group studies  
43 1997 and 2002 for childhood acute lymphoblastic leukemia. *Leukemia* 2010;24(2):397-405. doi:  
44 <http://dx.doi.org/10.1038/leu.2009.248>  
45
- 46 201. Lilleyman JS, Campbell RHA. Vindesine in relapsed childhood ALL. A pilot study by the United  
47 Kingdom children's cancer study group. *European Paediatric Haematology and Oncology* 1984;1(1):37-  
48 38.  
49
- 50 202. Link MP, Goorin AM, Miser AW. The effect of adjuvant chemotherapy on relapse-free survival in  
51 patients with osteosarcoma of the extremity. *New England Journal of Medicine* 1986;314(25):1600-06.  
52
- 53 203. Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-stage  
54 non-hodgkin's lymphoma. *New England Journal of Medicine* 1997;337(18):1259-66.  
55  
56  
57  
58  
59  
60



- 1  
2  
3 204. Lipshultz SE, Miller TL, Lipsitz SR, et al. Continuous Versus Bolus Infusion of Doxorubicin in  
4 Children With ALL: Long-term Cardiac Outcomes. *Pediatrics* 2012;130(6):1003-11. doi:  
5 <http://dx.doi.org/10.1542/peds.2012-0727>  
6
- 7 205. Lipton JH, Chuah C, Guerci-Bresler A, et al. Ponatinib versus imatinib for newly diagnosed chronic  
8 myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncology*  
9 2016;17(5):612-21. doi: [https://dx.doi.org/10.1016/S1470-2045\(16\)00080-2](https://dx.doi.org/10.1016/S1470-2045(16)00080-2)  
10
- 11 206. Littman P, Coccia P, Bleyer WA, et al. Central nervous system (CNS) prophylaxis in children with  
12 low risk acute lymphoblastic leukemia (ALL). *International journal of radiation oncology, biology,*  
13 *physics* 1987;13(10):1443-49.  
14
- 15 207. Locatelli F, Zecca M, Rondelli R, et al. Graft versus host disease prophylaxis with low-dose  
16 cyclosporine-A reduces the risk of relapse in children with acute leukemia given HLA- identical sibling  
17 bone marrow transplantation: Results of a randomized trial. *Blood* 2000;95(5):1572-79.  
18
- 19 208. London WB, Frantz CN, Campbell LA, et al. Phase II randomized comparison of topotecan plus  
20 cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a  
21 Children's Oncology Group study. *Journal of Clinical Oncology* 2010;28(24):3808-15. doi:  
22 <http://dx.doi.org/10.1200/JCO.2009.27.5016>  
23
- 24 209. Loning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-  
25 Munster therapy of acute lymphoblastic leukemia in childhood: Significantly lower risk without cranial  
26 radiotherapy. *Blood* 2000;95(9):2770-75.  
27
- 28 210. LopezHernandez MA, Alvarado M, De Diego J, et al. A randomized trial of dexamethasone before  
29 remission induction, in de novo childhood acute lymphoblastic leukemia. *Haematologica* 2004;89(3):365-  
30 66.  
31
- 32 211. Lucchese A, Matarese G, Manuelli M, et al. Reliability and efficacy of palifermin in prevention and  
33 management of oral mucositis in patients with acute lymphoblastic leukemia: A randomized, double-blind  
34 controlled clinical trial. *Minerva stomatologica* 2016;65(1):43-53.  
35
- 36 212. MacDonald TJ, Arenson EB, Ater J, et al. Phase II study of high-dose chemotherapy before radiation  
37 in children with newly diagnosed high-grade astrocytoma: Final Analysis of Children's Cancer Group  
38 Study 9933. *Cancer* 2005;104(12):2862-71.  
39
- 40 213. Mahoney Jr DH, Camitta BM, Devidas M. Does intravenous 6-mercaptopurine decrease salvage  
41 after relapse in childhood acute lymphoblastic leukemia? [3]. *Pediatric Blood and Cancer*  
42 2006;46(5):660-61.  
43
- 44 214. Malogolowkin MH, Katzenstein H, Krailo MD, et al. Intensified platinum therapy is an ineffective  
45 strategy for improving outcome in pediatric patients with advanced hepatoblastoma. *Journal of Clinical*  
46 *Oncology* 2006;24(18):2879-84.  
47
- 48 215. Manabe A, Tsuchida M, Hanada R, et al. Delay of the diagnostic lumbar puncture and intrathecal  
49 chemotherapy in children with acute lymphoblastic leukemia who undergo routine corticosteroid testing:  
50 Tokyo Children's Cancer Study Group Study L89-12. *Journal of Clinical Oncology* 2001;19(13):3182-87.  
51
- 52 216. Mandell LR, Kadota R, Freeman C, et al. There is no role for hyperfractionated radiotherapy in the  
53 management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric  
54  
55  
56  
57  
58  
59



Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. *International journal of radiation oncology, biology, physics* 1999;43(5):959-64.

217. Marina NM, Pappo AS, Parham DM, et al. Chemotherapy dose-intensification for pediatric patients with Ewing's family of tumors and desmoplastic small round-cell tumors: a feasibility study at St. Jude Children's Research Hospital. *Journal of Clinical Oncology* 1999;17(1):180-90.

218. Maris JM, Weiss MJ, Guo C, et al. Loss of heterozygosity at 1p36 independently predicts for disease progression but not decreased overall survival probability in neuroblastoma patients: A children's cancer group study. *Journal of Clinical Oncology* 2000;18(9):1888-99.

219. Mascarenhas L, Lyden ER, Breitfeld PP, et al. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. *Journal of Clinical Oncology* 2010;28(30):4658-63. doi: <http://dx.doi.org/10.1200/JCO.2010.29.7390>

220. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood* 2011;118(2):243-51. doi: <http://dx.doi.org/10.1182/blood-2010-12-322909>

221. Matloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. *Blood* 2006;108(4):1165-73.

222. Matsuzaki A, Okamura J, Ishii E, et al. Treatment of standard-risk acute lymphoblastic leukemia in children: The results of protocol AL841 from the Kyushu-Yamaguchi Children's Cancer Study Group in Japan. *Pediatric hematology and oncology* 1999;16(3):187-99.

223. Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *Journal of Clinical Oncology* 2009;27(7):1007-13. doi: <http://dx.doi.org/10.1200/JCO.2007.13.8925>

224. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *New England Journal of Medicine* 1999;341(16):1165-73.

225. Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer* 1988;61(2):209-20.

226. McWilliams NB, Hayes FA, Green AA, et al. Cyclophosphamide/doxorubicin vs. cisplatin/teniposide in the treatment of children older than 12 months of age with disseminated neuroblastoma: a Pediatric Oncology Group Randomized Phase II study. *Medical & Pediatric Oncology* 1995;24(3):176-80.

227. Meadows AT, Sposto R, Jenkin RD, et al. Similar efficacy of 6 and 18 months of therapy with four drugs (COMP) for localized non-Hodgkin's lymphoma of children: a report from the Children's Cancer Study Group. *Journal of Clinical Oncology* 1989;7(1):92-99.

- 1  
2  
3 228. Mehta P, Gardner R, Graham-Pole J, et al. Methylprednisolone is effective in chemotherapy-induced  
4 emesis: Results of a double blind randomized trial in children. *Proceedings of the American Association*  
5 *for Cancer Research* 1985;26:No. 602.  
6
- 7 229. Meyers PA, Schwartz CL, Krailo M, et al. Osteosarcoma: A randomized, prospective trial of the  
8 addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate.  
9 *Journal of Clinical Oncology* 2005;23(9):2004-11.  
10
- 11 230. Meyers PA, Schwartz CL, Krailo MD, et al. Osteosarcoma: the addition of muramyl tripeptide to  
12 chemotherapy improves overall survival--a report from the Children's Oncology Group. *Journal of*  
13 *Clinical Oncology* 2008;26(4):633-38. doi: <http://dx.doi.org/10.1200/JCO.2008.14.0095>  
14
- 15 231. Michel G, Landman-Parker J, Auclerc MF, et al. Use of recombinant human granulocyte colony-  
16 stimulating factor to increase chemotherapy dose-intensity: a randomized trial in very high-risk childhood  
17 acute lymphoblastic leukemia. *Journal of Clinical Oncology* 2000;18(7):1517-24.  
18
- 19 232. Michon JM, Hartmann O, Bouffet E, et al. An open-label, multicentre, randomised phase 2 study of  
20 recombinant human granulocyte colony-stimulating factor (filgrastim) as an adjunct to combination  
21 chemotherapy in paediatric patients with metastatic neuroblastoma. *European journal of cancer*  
22 1998;34(7):1063-69.  
23
- 24 233. Miller DR, Coccia PF, Bleyer WA, et al. Early response to induction therapy as a predictor of  
25 disease-free survival and late recurrence of childhood acute lymphoblastic leukemia: a report from the  
26 Children's Cancer Study Group. *Journal of Clinical Oncology* 1989;7(12):1807-15.  
27
- 28 234. Miller DR, Leikin SL, Albo VC, et al. Three versus five years of maintenance therapy are equivalent  
29 in childhood acute lymphoblastic leukemia: a report from the Children's Cancer Study Group. *Journal of*  
30 *Clinical Oncology* 1989;7(3):316-25.  
31
- 32 235. Milpied N, Deconinck E, Gaillard F, et al. Initial Treatment of Aggressive Lymphoma with High-  
33 Dose Chemotherapy and Autologous Stem-Cell Support. *New England Journal of Medicine*  
34 2004;350(13):1287-95.  
35
- 36 236. Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive  
37 neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer  
38 Group and Pediatric Oncology Group study. *Journal of Clinical Oncology* 2004;22(14):2873-76.  
39
- 40 237. Miser JS, Pritchard DJ, Rock MG, et al. Osteosarcoma in adolescents and young adults: new  
41 developments and controversies. The Mayo Clinic studies. *Cancer treatment and research* 1993;62:333-  
42 38.  
43
- 44 238. Miser JS, Roloff J, Blatt J, et al. Lack of significant activity of 2'-deoxycoformycin alone or in  
45 combination with adenine arabinoside in relapsed childhood acute lymphoblastic leukemia. A randomized  
46 phase II trial from the Children's Cancer Study Group. *American Journal of Clinical Oncology*  
47 1992;15(6):490-93.  
48
- 49 239. Mitchell C, Pritchard-Jones K, Shannon R, et al. Immediate nephrectomy versus preoperative  
50 chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3)  
51 by the UK Children's Cancer Study Group. *European journal of cancer* 2006;42(15):2554-62.  
52
- 53 240. Mo XD, Zhang XH, Xu LP, et al. Comparison of outcomes after donor lymphocyte infusion with or  
54 without prior chemotherapy for minimal residual disease in acute leukemia/myelodysplastic syndrome  
55  
56  
57  
58  
59

- 1  
2  
3 after allogeneic hematopoietic stem cell transplantation. *Ann Hematol* 2017;96(5):829-38. doi:  
4 <https://dx.doi.org/10.1007/s00277-017-2960-7>  
5
- 6 241. Mo XD, Zhao XY, Liu DH, et al. Umbilical cord blood transplantation and unmanipulated  
7 haploidentical hematopoietic SCT for pediatric hematologic malignances. *Bone marrow transplantation*  
8 2014;49(8):1070-75.  
9
- 10 242. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL  
11 Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood* 2007;109(3):896-904.  
12
- 13 243. Moorman AV, Ensor HM, Richards SM, et al. Prognostic effect of chromosomal abnormalities in  
14 childhood B-cell precursor acute lymphoblastic leukaemia: Results from the UK Medical Research  
15 Council ALL97/99 randomised trial. *The Lancet Oncology* 2010;11(5):429-38.  
16
- 17 244. Mori T, Fukano R, Saito A, et al. Analysis of Japanese registration from the randomized  
18 international trial for childhood anaplastic large cell lymphoma (ALCL99-R1). [*Rinsho ketsueki*] *The*  
19 *Japanese journal of clinical hematology* 2014;55(5):526-33.  
20
- 21 245. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia  
22 can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and  
23 adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 2008;111(9):4477-89. doi:  
24 <http://dx.doi.org/10.1182/blood-2007-09-112920>  
25
- 26 246. Mott MG, Eden OB, Palmer MK. Adjuvant low dose radiation in childhood non-Hodgkin's  
27 lymphoma. (Report from the United Kingdom Childrens' Cancer Study Group - UKCCSG). *British*  
28 *journal of cancer* 1984;50(4):463-69.  
29
- 30 247. Movassaghi N, Higgins G, Pyesmany A. Evaluation of cycloctidine in reinduction and maintenance  
31 therapy of children with acute nonlymphocytic leukemia previously treated with cytosine arabinoside: A  
32 report from children's cancer study group. *Medical and pediatric oncology* 1984;12(5):352-56.  
33
- 34 248. Murphy SB, Hustu HO. A randomized trial of combined modality therapy of childhood non-  
35 Hodgkin's lymphoma. *Cancer* 1980;45(4):630-37.  
36
- 37 249. Nachman JB, La MK, Hunger SP, et al. Young adults with acute lymphoblastic leukemia have an  
38 excellent outcome with chemotherapy alone and benefit from intensive postinduction treatment: a report  
39 from the children's oncology group. *Journal of Clinical Oncology* 2009;27(31):5189-94. doi:  
40 <http://dx.doi.org/10.1200/JCO.2008.20.8959>  
41
- 42 250. Nesbit M, Sather H, Robison L. The duration of chemotherapy for childhood acute lymphoblastic  
43 leukemia (ALL): A randomized study of 316 patients. *Proceedings of the American Society of Clinical*  
44 *Oncology* Vol 1982;1:480.  
45
- 46 251. Nesbit ME, Jr., Buckley JD, Feig SA, et al. Chemotherapy for induction of remission of childhood  
47 acute myeloid leukemia followed by marrow transplantation or multiagent chemotherapy: a report from  
48 the Childrens Cancer Group. *Journal of Clinical Oncology* 1994;12(1):127-35.  
49
- 50 252. Nesbit ME, Sather H, Robison LL, et al. Sanctuary therapy: a randomized trial of 724 children with  
51 previously untreated acute lymphoblastic leukemia: A Report from Children's Cancer Study Group.  
52 *Cancer research* 1982;42(2):674-80.  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 253. Nesbit ME, Jr., Sather HN, Robison LL, et al. Presymptomatic central nervous system therapy in  
4 previously untreated childhood acute lymphoblastic leukaemia: comparison of 1800 rad and 2400 rad. A  
5 report for Children's Cancer Study Group. *Lancet* 1981;1(8218):461-66.  
6
- 7 254. Nesbit ME, Jr., Sather HN, Robison LL, et al. Randomized study of 3 years versus 5 years of  
8 chemotherapy in childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology* 1983;1(5):308-  
9 16.  
10
- 11 255. Neudorf S, Sanders J, Kobrinsky N, et al. Autologous bone marrow transplantation for children with  
12 AML in first remission. *Bone marrow transplantation* 2007;40(4):313-18.  
13
- 14 256. Neudorf S, Sanders J, Kobrinsky N, et al. Allogeneic bone marrow transplantation for children with  
15 acute myelocytic leukemia in first remission demonstrates a role for graft versus leukemia in the  
16 maintenance of disease-free survival. *Blood* 2004;103(10):3655-61.  
17
- 18 257. Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug versus  
19 standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other  
20 chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society  
21 of Pediatric Oncology MMT95 study. *Journal of Clinical Oncology* 2012;30(20):2457-65. doi:  
22 <http://dx.doi.org/10.1200/JCO.2011.40.3287>  
23
- 24 258. O'Connor D, Bartram J, Enshaei A, et al. Integration of minimal residual disease with other patient  
25 risk factors identifies a population with very poor overall survival in pediatric ALL: Results from the  
26 UKALL 2003 trial. *57th Annual Meeting of the American Society of Hematology, ASH 2015 San Diego,*  
27 *CA United States* 2015;126(23):1412.  
28
- 29 259. Ortega JA, Douglass EC, Feusner JH, et al. Randomized comparison of  
30 cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric  
31 hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *Journal*  
32 *of Clinical Oncology* 2000;18(14):2665-75.  
33
- 34 260. Ortega JJ, Javier G, Olive T. Treatment of standard- and high-risk childhood acute lymphoblastic  
35 leukaemia with two CNS prophylaxis regimens. *Haematology & Blood Transfusion* 1987;30:483-92.  
36
- 37 261. Ortega JJ, Ribera JM, Oriol A, et al. Early and delayed consolidation chemotherapy significantly  
38 improves the outcome of children with intermediate-risk acute lymphoblastic leukemia. Final results of  
39 the prospective randomized PETHEMA ALL-89 TRIAL. *Haematologica* 2001;86(6):586-95.  
40
- 41 262. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by  
42 adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *Journal of Clinical Oncology*  
43 2006;24(25):4202-08.  
44
- 45 263. Packer RJ, Zhou T, Holmes E, et al. Survival and secondary tumors in children with  
46 medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology  
47 Group trial A9961. *Neuro-oncology* 2013;15(1):97-103. doi: <http://dx.doi.org/10.1093/neuonc/nos267>  
48
- 49 264. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first  
50 relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet*  
51 2010;376(9757):2009-17. doi: [http://dx.doi.org/10.1016/S0140-6736\(10\)62002-8](http://dx.doi.org/10.1016/S0140-6736(10)62002-8)  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 265. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for  
4 intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce  
5 treatment for the early responding patients. *Blood* 2007;109(7):2773-80.  
6
- 7 266. Patte C, Philip T, Rodary C, et al. High survival rate in advanced-stage B-cell lymphomas and  
8 leukemias without CNS involvement with a short intensive polychemotherapy: results from the French  
9 Pediatric Oncology Society of a randomized trial of 216 children. *Journal of Clinical Oncology*  
10 1991;9(1):123-32.  
11
- 12 267. Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 study: Two randomized trials of  
13 Ewing's sarcoma treatment - Cyclophosphamide compared with ifosfamide in standard-risk patients and  
14 assessment of benefit of etoposide added to standard treatment in high-risk patients. *Journal of Clinical*  
15 *Oncology* 2008;26(27):4385-93.  
16
- 17 268. Payandeh M, Najafi S, Shojaiyan FZ, et al. Phase III of Study of R-CHOP-21 vs R-CHOP-14 for  
18 Untreated Stage III and IV B-cell Non-Hodgkin's Lymphoma: a Report from Iran. *Asian Pac J Cancer*  
19 *Prev* 2016;17(3):1513-7.  
20
- 21 269. Pearson ADJ, Pinkerton CR, Lewis IJ, et al. High-dose rapid and standard induction chemotherapy  
22 for patients aged over 1 year with stage 4 neuroblastoma: a randomised trial. *Lancet Oncology*  
23 2008;9(3):247-56. doi: [http://dx.doi.org/10.1016/S1470-2045\(08\)70069-X](http://dx.doi.org/10.1016/S1470-2045(08)70069-X)  
24
- 25 270. Perel Y, Auvrignon A, Leblanc T, et al. Impact of addition of maintenance therapy to intensive  
26 induction and consolidation chemotherapy for childhood acute myeloblastic leukemia: Results of a  
27 prospective randomized trial, LAME 89/91. *Journal of Clinical Oncology* 2002;20(12):2774-82.  
28
- 29 271. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended use  
30 of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. *Journal of*  
31 *Clinical Oncology* 2005;23(28):7161-67.  
32
- 33 272. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus  
34 intramuscular native *Escherichia coli* L-asparaginase in newly diagnosed childhood acute lymphoblastic  
35 leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. *Lancet Oncology* 2015;16(16):1677-90.  
36 doi: [http://dx.doi.org/10.1016/S1470-2045\(15\)00363-0](http://dx.doi.org/10.1016/S1470-2045(15)00363-0)  
37
- 38 273. Pollack IF, Hamilton RL, Sobol RW, et al. O6-Methylguanine-DNA methyltransferase expression  
39 strongly correlates with outcome in childhood malignant gliomas: Results from the CCG-945 cohort.  
40 *Journal of Clinical Oncology* 2006;24(21):3431-37.  
41
- 42 274. Pollard JA, Loken M, Gerbing RB, et al. CD33 expression and its association with gemtuzumab  
43 ozogamicin response: Results from the randomized phase III children's oncology group trial AAML0531.  
44 *Journal of Clinical Oncology* 2016;34(7):747-55.  
45
- 46 275. Pratt CB, Maurer HM, Gieser P, et al. Treatment of unresectable or metastatic pediatric soft tissue  
47 sarcomas with surgery, irradiation, and chemotherapy: a Pediatric Oncology Group study. *Medical &*  
48 *Pediatric Oncology* 1998;30(4):201-09.  
49
- 50 276. Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically  
51 resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: A Pediatric Oncology Group Study.  
52 *Journal of Clinical Oncology* 1999;17(4):1219-26.  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 277. Pritchard J, Cotterill SJ, Germond SM, et al. High dose melphalan in the treatment of advanced  
4 neuroblastoma: Results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group.  
5 *Pediatric Blood and Cancer* 2005;44(4):348-57.  
6
- 7 278. Pritchard-Jones K, Bergeron C, de Camargo B, et al. Omission of doxorubicin from the treatment of  
8 stage II-III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised  
9 controlled trial. *Lancet* 2015;386(9999):1156-64. doi: [http://dx.doi.org/10.1016/S0140-6736\(14\)62395-3](http://dx.doi.org/10.1016/S0140-6736(14)62395-3)  
10
- 11 279. Pui CH, Aur RJA, Bowman WP. Failure of late intensification therapy to improve a poor result in  
12 childhood lymphoblastic leukemia. *Cancer research* 1984;44(8):3593-98.  
13
- 14 280. Pui CH, Simone JV, Hancock ML, et al. Impact of three methods of treatment intensification on  
15 acute lymphoblastic leukemia in children: long-term results of St Jude total therapy study X. *Leukemia*  
16 1992;6(2):150-57.  
17
- 18 281. Pulsipher MA, Langholz B, Wall DA, et al. The addition of sirolimus to tacrolimus/methotrexate  
19 GVHD prophylaxis in children with ALL: a phase 3 Children's Oncology Group/Pediatric Blood and  
20 Marrow Transplant Consortium trial. *Blood* 2014;123(13):2017-25. doi: [http://dx.doi.org/10.1182/blood-](http://dx.doi.org/10.1182/blood-2013-10-534297)  
21 2013-10-534297  
22
- 23 282. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission  
24 tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse:  
25 Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial.  
26 *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*  
27 2014;32(12):1188-94.  
28
- 29 283. Ragab AH, Boyett JM, Frankel L, et al. Rubidazone in the treatment of recurrent acute leukemia in  
30 children. A Pediatric Oncology Group Study. *Cancer* 1986;57(8):1461-63.  
31
- 32 284. Rausen AR, Glidewell O, Cuttner J. Superiority of L-asparaginase combination chemotherapy in  
33 advanced acute lymphocytic leukemia of childhood. Randomized comparative trial of combination versus  
34 solo therapy. *Cancer clinical trials* 1979;2(2):137-44.  
35
- 36 285. Ravindranath Y, Yeager AM, Chang MN, et al. Autologous bone marrow transplantation versus  
37 intensive consolidation chemotherapy for acute myeloid leukemia in childhood. Pediatric Oncology  
38 Group. *New England Journal of Medicine* 1996;334(22):1428-34.  
39
- 40 286. Reinhard H, Semler O, Burger D, et al. Results of the SIOP 93-01/GPOH trial and study for the  
41 treatment of patients with unilateral nonmetastatic wilms tumor. *Klinische Padiatrie* 2004;216(3):132-40.  
42
- 43 287. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy  
44 provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: A BFM Group  
45 report. *Blood* 2000;95(2):416-21.  
46
- 47 288. Rescorla F, Billmire D, Stolar C, et al. The effect of cisplatin dose and surgical resection in children  
48 with malignant germ cell tumors at the sacrococcygeal region: A pediatric intergroup trial (POG  
49 9049/CCG 8882). *Journal of pediatric surgery* 2001;36(1):12-17.  
50
- 51 289. Richards S, Burrett J, Hann I, et al. Improved survival with early intensification: Combined results  
52 from The Medical Research Council childhood ALL randomised trials, UKALL X and UKALL XI.  
53 *Leukemia* 1998;12(7):1031-36.  
54  
55  
56  
57  
58  
59



- 1  
2  
3 290. Richards S, Gray R, Peto R, et al. Duration and intensity of maintenance chemotherapy in acute  
4 lymphoblastic leukaemia: Overview of 42 trials involving 12,000 randomised children. *Lancet*  
5 1996;347(9018):1783-88.  
6
- 7 291. Rivera G, Avery T, Pratt C. 4' Demethylepipodophyllotoxin 9 (4,6 O 2 thenylidene beta D  
8 glucopyranoside) (NSC 122819; VM 26) and 4' demethylepipodophyllotoxin 9 (4,6 O ethylidene beta D  
9 glucopyranoside) (NSC 141540; VP 16 213) in childhood cancer: preliminary observations. *CANCER*  
10 *CHEMOTHERREP* 1975;59(4):743-49.  
11
- 12 292. Rivera G, Murphy SB, Aur RJA. Recurrent childhood lymphocytic leukemia. Clinical and  
13 cytokinetic studies of cytosine arabinoside and methotrexate for maintenance of second hematologic  
14 remission. *Cancer* 1978;42(6):2521-28.  
15
- 16 293. Rivera GK, Raimondi SC, Hancock ML, et al. Improved outcome in childhood acute lymphoblastic  
17 leukaemia with reinforced early treatment and rotational combination chemotherapy. *Lancet*  
18 1991;337(8733):61-66.  
19
- 20 294. Rizzari C, Valsecchi MG, Arico M, et al. Effect of protracted high-dose L-asparaginase given as a  
21 second exposure in a Berlin-Frankfurt-Munster-based treatment: Results of the randomized 9102  
22 intermediate-risk childhood acute lymphoblastic leukemia study - A report from the Associazione Italiana  
23 Ematologia Oncologia Pediatrica. *Journal of Clinical Oncology* 2001;19(5):1297-303.  
24
- 25 295. Rodeberg DA, Wharam MD, Lyden ER, et al. Delayed primary excision with subsequent  
26 modification of radiotherapy dose for intermediate-risk rhabdomyosarcoma: A report from the Children's  
27 Oncology Group Soft Tissue Sarcoma Committee. *International Journal of Cancer* 2015;137(1):204-11.  
28
- 29 296. Roos DE, Smith JG. Randomized trial on radiotherapy for paediatric diffuse intrinsic pontine glioma  
30 (DIPG). *Radiotherapy & Oncology* 2014;113(3):425. doi: <http://dx.doi.org/10.1016/j.radonc.2014.08.041>  
31  
32
- 33 297. Rubnitz JE, Crews KR, Pounds S, et al. Combination of cladribine and cytarabine is effective for  
34 childhood acute myeloid leukemia: Results of the St Jude AML97 trial. *Leukemia* 2009;23(8):1410-16.  
35
- 36 298. Rutkowski S, von Bueren A, von Hoff K, et al. Prognostic relevance of clinical and biological risk  
37 factors in childhood medulloblastoma: results of patients treated in the prospective multicenter trial  
38 HIT'91. *Clinical Cancer Research* 2007;13(9):2651-57.  
39
- 40 299. Sackmann Muriel F, Svarch E, Pavlovsky S. Alternating pulses of vincristine-prednisone with  
41 cytarabine-cyclophosphamide versus vincristine-prednisone in the maintenance therapy of acute  
42 lymphoblastic leukemia. *Cancer treatment reports* 1984;68(4):581-86.  
43
- 44 300. Sackmann Muriel F, Morgenfeld M, Kvicala R. Hodgkin's disease in childhood. Therapy results in  
45 Argentina. *American Journal of Pediatric Hematology/Oncology* 1981;3(3):247-54.  
46
- 47 301. Sackmann-Muriel F, Zubizarreta P, Gallo G, et al. Hodgkin disease in children: results of a  
48 prospective randomized trial in a single institution in Argentina. *Medical & Pediatric Oncology*  
49 1997;29(6):544-52.  
50
- 51 302. Sallan SE, Hitchcock Bryan S, Gelber R. Influence of intensive asparaginase in the treatment of  
52 childhood non-T-cell acute lymphoblastic leukemia. *Cancer research* 1983;43(11):5601-07.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 303. Schmiegelow K, Bjork O, Glomstein A, et al. Intensification of mercaptopurine/methotrexate  
4 maintenance chemotherapy may increase the risk of relapse for some children with acute lymphoblastic  
5 leukemia. *Journal of Clinical Oncology* 2003;21(7):1332-39.  
6
- 7 304. Schrappe M, Reiter A, Henze G, et al. Prevention of CNS recurrence in childhood ALL: Results with  
8 reduced radiotherapy combined with CNS-directed chemotherapy in four consecutive ALL- BFM trials.  
9 *Klinische Padiatrie* 1998;210(4):192-99.  
10
- 11 305. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic  
12 leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90.  
13 German-Austrian-Swiss ALL-BFM Study Group. *Blood* 2000;95(11):3310-22.  
14
- 15 306. Sebban C, Browman GP, Lepage E, et al. Prognostic value of early response to chemotherapy  
16 assessed by the day 15 bone marrow aspiration in adult acute lymphoblastic leukemia: A prospective  
17 analysis of 437 cases and its application for designing induction chemotherapy trials. *Leukemia research*  
18 1995;19(11):861-68.  
19
- 20 307. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves  
21 survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the  
22 Children's Oncology Group. *Blood* 2008;111(5):2548-55.  
23
- 24 308. Sellar RS, Rowntree C, Vora AJ, et al. Relapse in teenage and young adult (TYA) patients treated on  
25 a pediatric minimal residual disease (MRD) stratified protocol is associated with a poor outcome: Results  
26 from UKALL2003. *57th Annual Meeting of the American Society of Hematology, ASH 2015 San Diego,*  
27 *CA United States* 2015;126(23):2493.  
28
- 29 309. Sertoli MR, Santini G, Chisesi T, et al. MACOP-B versus ProMACE-MOPP in the treatment of  
30 advanced diffuse non- Hodgkin's lymphoma: Results of a prospective randomized trial by the Non-  
31 Hodgkin's Lymphoma Cooperative Study Group. *Journal of Clinical Oncology* 1994;12(7):1366-74.  
32  
33
- 34 310. Sexauer CL, Vietti T, Humphrey GB. Combination chemotherapy study for remission maintenance  
35 in ALL: An evaluation of vincristine, cyclophosphamide and vincristine, cyclophosphamide, and BCNU.  
36 A Southwest oncology group phase II study. *American Journal of Pediatric Hematology/Oncology*  
37 1981;3(3):255-57.  
38
- 39 311. Shamberger RC, Laquaglia MP, Krailo MD, et al. Ewing sarcoma of the rib: results of an intergroup  
40 study with analysis of outcome by timing of resection. *Journal of Thoracic & Cardiovascular Surgery*  
41 2000;119(6):1154-61.  
42
- 43 312. Shinagawa K, Yanada M, Sakura T, et al. Tamibarotene as maintenance therapy for acute  
44 promyelocytic leukemia: Results from a randomized controlled trial. *Journal of Clinical Oncology*  
45 2014;32(33):3729-35.  
46
- 47 313. Sievers EL, Lange BJ, Sondel PM, et al. Children's cancer group trials of interleukin-2 therapy to  
48 prevent relapse of acute myelogenous leukemia. *The cancer journal from Scientific American*  
49 2000;6(Suppl 1):S39-44.  
50
- 51 314. Skapek SX, Ferguson WS, Granowetter L, et al. Vinblastine and methotrexate for desmoid  
52 fibromatosis in children: Results of a Pediatric Oncology Group phase II trial. *Journal of Clinical*  
53 *Oncology* 2007;25(5):501-06.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 315. Smith FO, Alonzo TA, Gerbing RB, et al. Long-term results of children with acute myeloid  
4 leukemia: a report of three consecutive Phase III trials by the Children's Cancer Group: CCG 251, CCG  
5 213 and CCG 2891. *Leukemia* 2005;19(12):2054-62.  
6  
7 316. Souhami RL, Craft AW, Van Der Eijken JW, et al. Randomised trial of two regimens of  
8 chemotherapy in operable osteosarcoma: A study of the European Osteosarcoma Intergroup. *Lancet*  
9 1997;350(9082):911-17.  
10  
11 317. Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high grade  
12 astrocytoma in children: results of a randomized trial. A report from the Children's Cancer Study Group.  
13 *Journal of neuro-oncology* 1989;7(2):165-77.  
14  
15 318. Sary J, Zimmermann M, Campbell M, et al. Intensive chemotherapy for childhood acute  
16 lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. *Journal of*  
17 *Clinical Oncology* 2014;32(3):174-84. doi: <http://dx.doi.org/10.1200/JCO.2013.48.6522>  
18  
19 319. Steinherz PG, Gaynon PS, Breneman JC, et al. Treatment of patients with acute lymphoblastic  
20 leukemia with bulky extramedullary disease and T-cell phenotype or other poor prognostic features:  
21 randomized controlled trial from the Children's Cancer Group. *Cancer* 1998;82(3):600-12.  
22  
23 320. Steuber CP, Culbert SJ, Ravindranath Y, et al. Therapy of childhood acute nonlymphocytic  
24 leukemia: the Pediatric Oncology Group experience (1977-1988). *Haematology and blood transfusion*  
25 1990;33:198-209.  
26  
27 321. Steuber CP, Krischer J, Holbrook T, et al. Therapy of refractory or recurrent childhood acute  
28 myeloid leukemia using amsacrine and etoposide with or without azacitidine: a Pediatric Oncology Group  
29 randomized phase II study. *Journal of Clinical Oncology* 1996;14(5):1521-25.  
30  
31 322. Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood  
32 and adolescence: third study of the International Society of Paediatric Oncology--SIOP Malignant  
33 Mesenchymal Tumor 89. *Journal of clinical oncology : official journal of the American Society of*  
34 *Clinical Oncology* 2005;23(12):2618-28.  
35  
36 323. Stork LC, Matloub Y, Broxson E, et al. Oral 6-mercaptopurine versus oral 6-thioguanine and veno-  
37 occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the Children's  
38 Oncology Group CCG-1952 clinical trial. *Blood* 2010;115(14):2740-48. doi:  
39 <http://dx.doi.org/10.1182/blood-2009-07-230656>  
40  
41 324. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of  
42 doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus  
43 ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood* 2004;104(12):3483-89.  
44  
45 325. Strother DR, Lafay-Cousin L, Boyett JM, et al. Benefit from prolonged dose-intensive chemotherapy  
46 for infants with malignant brain tumors is restricted to patients with ependymoma: a report of the  
47 Pediatric Oncology Group randomized controlled trial 9233/34. *Neuro-oncology* 2014;16(3):457-65. doi:  
48 <http://dx.doi.org/10.1093/neuonc/not163>  
49  
50 326. Suh C, Kim HJ, Kim SH, et al. Low-dose lenograstim to enhance engraftment after autologous stem  
51 cell transplantation: A prospective randomized evaluation of two different fixed doses. *Transfusion*  
52 2004;44(4):533-38.  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 327. Sullivan MP, Brecher M, Ramirez I, et al. High-dose cyclophosphamide-high-dose methotrexate  
4 with coordinated intrathecal therapy for advanced nonlymphoblastic lymphoma of childhood: results of a  
5 Pediatric Oncology Group study. *American Journal of Pediatric Hematology/Oncology* 1991;13(3):288-  
6 95.  
7  
8 328. Sullivan MP, Chen T, Dymment PG, et al. Equivalence of intrathecal chemotherapy and radiotherapy  
9 as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric oncology  
10 group study. *Blood* 1982;60(4):948-58.  
11  
12 329. Sullivan MP, Fuller LM, Chen T. Intergroup Hodgkin's disease in children study of stages I and II: A  
13 preliminary report. *Cancer treatment reports* 1982;66(4):937-47.  
14  
15 330. Suryanarayan K, Shuster JJ, Donaldson SS, et al. Treatment of localized primary non-Hodgkin's  
16 lymphoma of bone in children: A Pediatric Oncology Group Study. *Journal of Clinical Oncology*  
17 1999;17(2):456-59.  
18  
19 331. Tait DM, Thornton-Jones H, Bloom HJ, et al. Adjuvant chemotherapy for medulloblastoma: the first  
20 multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). *European journal*  
21 *of cancer* 1990;26(4):464-69.  
22  
23 332. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic  
24 leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug  
25 chemotherapy: Results of trial ALL-REZ BFM 90. *Journal of Clinical Oncology* 2010;28(14):2339-47.  
26  
27 333. Tarbell NJ, Friedman H, Polkinghorn WR, et al. High-risk medulloblastoma: a pediatric oncology  
28 group randomized trial of chemotherapy before or after radiation therapy (POG 9031). *Journal of Clinical*  
29 *Oncology* 2013;31(23):2936-41. doi: <http://dx.doi.org/10.1200/JCO.2012.43.9984>  
30  
31 334. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation  
32 chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of  
33 Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. *Journal of Clinical*  
34 *Oncology* 2003;21(8):1581-91.  
35  
36 335. Taylor RE, Bailey CC, Robinson KJ, et al. Impact of radiotherapy parameters on outcome in the  
37 International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3  
38 study of preradiotherapy chemotherapy for M0-M1 medulloblastoma. *International journal of radiation*  
39 *oncology, biology, physics* 2004;58(4):1184-93.  
40  
41 336. Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid  
42 leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease.  
43 *Journal of Clinical Oncology* 2007;25(5):493-500.  
44  
45 337. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower  
46 risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's  
47 Oncology Group. *Pediatric Blood & Cancer* 2012;59(7):1259-65. doi:  
48 <http://dx.doi.org/10.1002/pbc.24279>  
49  
50 338. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children  
51 and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. *British*  
52 *journal of haematology* 2013;162(6):792-801. doi: <http://dx.doi.org/10.1111/bjh.12460>  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 339. Testi AM, Biondi A, Lo Coco F, et al. GIMEMA-AIEOP AIDA protocol for the treatment of newly  
4 diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005;106(2):447-53.  
5  
6 340. Tolar J, Bostrom BC, La MK, et al. Intravenous 6-mercaptopurine decreases salvage after relapse in  
7 childhood acute lymphoblastic leukemia: a report from the Children's Cancer Group study CCG 1922.  
8 *Pediatric Blood & Cancer* 2005;45(1):5-9.  
9  
10 341. Tournade MF, ComNougue C, De Kraker J, et al. Optimal duration of preoperative therapy in  
11 unilateral and nonmetastatic Wilms' tumor in children older than 6 months: Results of the Ninth  
12 International Society of Pediatric Oncology Wilms' Tumor Trial and Study. *Journal of Clinical Oncology*  
13 2001;19(2):488-500.  
14  
15 342. Tournade MF, Com-Nougue C, Voute PA, et al. Results of the Sixth International Society of  
16 Pediatric Oncology Wilms' Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms' tumor.  
17 *Journal of Clinical Oncology* 1993;11(6):1014-23.  
18  
19 343. Tower RL, Jones TL, Camitta BM, et al. Dose intensification of methotrexate and cytarabine during  
20 intensified continuation chemotherapy for high-risk B-precursor acute lymphoblastic leukemia: POG  
21 9406: a report from the Children's Oncology Group. *Journal of Pediatric Hematology/Oncology*  
22 2014;36(5):353-61. doi: <http://dx.doi.org/10.1097/MPH.0000000000000131>  
23  
24 344. Tsuchida M, Akatsuka J, Bessho F, et al. Treatment of acute lymphoblastic leukemia in the Tokyo  
25 Children's Cancer Study Group--preliminary results of L84-11 protocol. *Acta Paediatrica Japonica*  
26 1991;33(4):522-32.  
27  
28 345. Tsuchida M, Ohara A, Manabe A, et al. Long-term results of Tokyo children's cancer study group  
29 trials for childhood acute lymphoblastic leukemia, 1984-1999. *Leukemia* 2010;24(2):383-96.  
30  
31 346. Tsukada M, Komiyama A, Nakazawa S, et al. Treatment of standard risk acute lymphoblastic  
32 leukemia in children with the Tokyo Children Cancer Study Group (TCCSG) L84-11 protocol in Japan.  
33 *International journal of hematology* 1993;57(1):1-7.  
34  
35 347. Tsurusawa M, Katano N, Yamamoto Y, et al. Improvement in CNS protective treatment in non-high-  
36 risk childhood acute lymphoblastic leukemia: report from the Japanese Children's Cancer and Leukemia  
37 Study Group. *Medical & Pediatric Oncology* 1999;32(4):259-56.  
38  
39 348. Tsurusawa M, Watanabe T, Gosho M, et al. Randomized study of granulocyte colony stimulating  
40 factor for childhood B-cell non-Hodgkin lymphoma: a report from the Japanese pediatric  
41 leukemia/lymphoma study group B-NHL03 study. *Leukemia & Lymphoma* 2016;57(7):1657-64. doi:  
42 <https://dx.doi.org/10.3109/10428194.2015.1106534>  
43  
44 349. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Prevention of CNS disease in intermediate-risk acute  
45 lymphoblastic leukemia: comparison of cranial radiation and intrathecal methotrexate and the importance  
46 of systemic therapy: a Childrens Cancer Group report. *Journal of Clinical Oncology* 1993;11(3):520-26.  
47  
48 350. Tubergen DG, Krailo MD, Meadows AT, et al. Comparison of treatment regimens for pediatric  
49 lymphoblastic non-Hodgkin's lymphoma: a Childrens Cancer Group study. *Journal of Clinical Oncology*  
50 1995;13(6):1368-76.  
51  
52 351. Tulstrup M, Frandsen TL, Abrahamsson J, et al. Individualized 6-mercaptopurine increments in  
53 consolidation treatment of childhood acute lymphoblastic leukemia: A NOPHO randomized controlled  
54 trial. *Eur J Haematol* 2018;100(1):53-60. doi: <https://dx.doi.org/10.1111/ejh.12979>  
55  
56  
57  
58  
59



- 1  
2  
3 352. Van Eys J, Berry D, Crist W, et al. Treatment intensity and outcome for children with acute  
4 lymphocytic leukemia of standard risk. A Pediatric Oncology Group Study. *Cancer* 1989;63(8):1466-71.  
5
- 6 353. Van Eys J, Chen T, Moore T. Adjuvant chemotherapy for medulloblastoma and ependymoma using  
7 Iv vincristine, intrathecal methotrexate, and intrathecal hydrocortisone: A southwest oncology group  
8 study. *Cancer treatment reports* 1981;65(7-8):681-84.  
9
- 10 354. Vilmer E, Suci S, Ferster A, et al. Long-term results of three randomized trials (58831, 58832,  
11 58881) in childhood acute lymphoblastic leukemia: A CLCG-EORTC report. *Leukemia*  
12 2000;14(12):2257-66.  
13
- 14 355. Vitolo U, Trneny M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide,  
15 Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma.  
16 *Journal of Clinical Oncology* 2017;35(31):3529-37. doi: <https://dx.doi.org/10.1200/JCO.2017.73.3402>  
17
- 18 356. Von Bueren AO, Von Hoff K, Pietsch T, et al. Treatment of young children with localized  
19 medulloblastoma by chemotherapy alone: Results of the prospective, multicenter trial HIT 2000  
20 confirming the prognostic impact of histology. *Neuro-oncology* 2011;13(6):669-79.  
21
- 22 357. von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in  
23 children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91. *European*  
24 *journal of cancer* 2009;45(7):1209-17. doi: <http://dx.doi.org/10.1016/j.ejca.2009.01.015>  
25
- 26 358. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk  
27 acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised  
28 controlled trial. *Lancet Oncology* 2013;14(3):199-209. doi: [http://dx.doi.org/10.1016/S1470-  
29 2045\(12\)70600-9](http://dx.doi.org/10.1016/S1470-2045(12)70600-9)  
30
- 31 359. Vora AJ, Mitchell C, Goulden N, et al. UKALL 2003, a randomised trial investigating treatment  
32 reduction for children and young adults with minimal residual disease defined low risk acute  
33 lymphoblastic leukaemia. *52nd Annual Meeting of the American Society of Hematology, ASH 2010*  
34 *Orlando, FL United States* 2010;116 (21) (no pagination)  
35
- 36 360. Vose JM, Carter S, Burns LJ, et al. Phase III randomized study of rituximab/carmustine, etoposide,  
37 cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous  
38 hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN  
39 0401 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*  
40 2013;31(13):1662-68.  
41
- 42 361. Vrooman LM, Neuberg DS, Stevenson KE, et al. The low incidence of secondary acute  
43 myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic  
44 leukaemia: a report from the Dana-Farber Cancer Institute ALL Consortium. *European journal of cancer*  
45 2011;47(9):1373-79. doi: <http://dx.doi.org/10.1016/j.ejca.2011.03.022>  
46
- 47 362. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized  
48 dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly  
49 diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute  
50 ALL Consortium Protocol 00-01. *Journal of Clinical Oncology* 2013;31(9):1202-10. doi:  
51 <http://dx.doi.org/10.1200/JCO.2012.43.2070>  
52  
53  
54  
55  
56  
57  
58  
59



- 1  
2  
3 363. Vu K, Busaidy N, Cabanillas ME, et al. A randomized controlled trial of an intensive insulin  
4 regimen in patients with hyperglycemic acute lymphoblastic leukemia. *Clinical Lymphoma, Myeloma and*  
5 *Leukemia* 2012;12(5):355-62.  
6
- 7 364. Waber DP, Silverman LB, Catania L, et al. Outcomes of a randomized trial of hyperfractionated  
8 cranial radiation therapy for treatment of high-risk acute lymphoblastic leukemia: Therapeutic efficacy  
9 and neurotoxicity. *Journal of Clinical Oncology* 2004;22(13):2701-07.  
10
- 11 365. Weiner MA, Leventhal B, Brecher ML, et al. Randomized study of intensive MOPP-ABVD with or  
12 without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV  
13 Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. *Journal of Clinical Oncology*  
14 1997;15(8):2769-79.  
15
- 16 366. Weiner MA, Leventhal BG, Marcus R, et al. Intensive chemotherapy and low-dose radiotherapy for  
17 the treatment of advanced-stage Hodgkin's disease in pediatric patients: A Pediatric Oncology Group  
18 study. *Journal of Clinical Oncology* 1991;9(9):1591-98.  
19
- 20 367. Wells RJ, Woods WG, Buckley JD, et al. Therapy for acute myeloid leukemia: intensive timing of  
21 induction chemotherapy. *Current oncology reports* 2000;2(6):524-28.  
22
- 23 368. Wells RJ, Woods WG, Buckley JD, et al. Treatment of newly diagnosed children and adolescents  
24 with acute myeloid leukemia: A Childrens Cancer Group study. *Journal of Clinical Oncology*  
25 1994;12(11):2367-77.  
26
- 27 369. Winick NJ, Smith SD, Shuster J, et al. Treatment of CNS relapse in children with acute  
28 lymphoblastic leukemia: A Pediatric Oncology Group study. *Journal of Clinical Oncology*  
29 1993;11(2):271-78.  
30
- 31 370. Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: Results of a  
32 randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor  
33 response. *Journal of Clinical Oncology* 1988;6(2):329-37.  
34
- 35 371. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive  
36 chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group  
37 Study AALL0434. *Pediatric Blood & Cancer* 2015;62(7):1176-83. doi:  
38 <http://dx.doi.org/10.1002/psc.25470>  
39  
40
- 41 372. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration  
42 schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the  
43 BFM Group Study NHL-BFM95. *Blood* 2005;105(3):948-58.  
44
- 45 373. Wolden SL, Chen L, Kelly KM, et al. Long-term results of CCG 5942: a randomized comparison of  
46 chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma--a report from the  
47 Children's Oncology Group. *Journal of Clinical Oncology* 2012;30(26):3174-80. doi:  
48 <http://dx.doi.org/10.1200/JCO.2011.41.1819>  
49
- 50 374. Wolden SL, Lyden ER, Arndt CA, et al. Local Control for Intermediate-Risk Rhabdomyosarcoma:  
51 Results From D9803 According to Histology, Group, Site, and Size: A Report From the Children's  
52 Oncology Group. *International journal of radiation oncology, biology, physics* 2015;93(5):1071-76. doi:  
53 <http://dx.doi.org/10.1016/j.ijrobp.2015.08.040>  
54  
55  
56  
57  
58  
59

- 1  
2  
3 375. Wolff JA, D'Angio G, Hartmann J, et al. Long-term evaluation of single versus multiple courses of  
4 actinomycin D therapy of Wilm's tumor. *The New England journal of medicine* 1974;290(2):84-86.  
5
- 6 376. Wolff JA, Newton WA, Jr., Krivit W, et al. Single versus multiple dose dactinomycin therapy of  
7 Wilms's tumor. A controlled co-operative study conducted by the Children's Cancer Study Group A  
8 (formerly Acute Leukemia Co-operative Chemotherapy Group A). *New England Journal of Medicine*  
9 1968;279(6):290-94.  
10
- 11 377. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed  
12 chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology  
13 Group. *Journal of Clinical Oncology* 2012;30(33):4148-54. doi:  
14 <http://dx.doi.org/10.1200/JCO.2011.41.5703>  
15
- 16 378. Woods WG, Barnard DR, Alonzo TA, et al. Prospective study of 90 children requiring treatment for  
17 juvenile myelomonocytic leukemia or myelodysplastic syndrome: A report from the Children's Cancer  
18 Group. *Journal of Clinical Oncology* 2002;20(2):434-40.  
19
- 20 379. Woods WG, Neudorf S, Gold S, et al. A comparison of allogeneic bone marrow transplantation,  
21 autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid  
22 leukemia in remission: A report from the Children's Cancer Group. *Blood* 2001;97(1):56-62.  
23
- 24 380. Wu J, Song Y, Su L, et al. Rituximab plus chemotherapy as first-line treatment in Chinese patients  
25 with diffuse large B-cell lymphoma in routine practice: a prospective, multicentre, non-interventional  
26 study. *BMC Cancer* 2016;16:537. doi: <https://dx.doi.org/10.1186/s12885-016-2523-7>  
27
- 28 381. Yang CP, Lin ST, Liang DC, et al. Treatment of childhood acute lymphoblastic leukemia with  
29 protocol TCL-842 in Taiwan: the Taiwan Children's Cancer Study Group. *Journal of the Formosan*  
30 *Medical Association* 1993;92(5):431-39.  
31
- 32 382. Yetgin S, Tuncer MA, Cetin M, et al. Benefit of high-dose methylprednisolone in comparison with  
33 conventional-dose prednisolone during remission induction therapy in childhood acute lymphoblastic  
34 leukemia for long-term follow-up. *Leukemia* 2003;17(2):328-33.  
35
- 36 383. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and  
37 isotretinoin for neuroblastoma. *N Engl J Med* 2010;363(14):1324-34. doi: 10.1056/NEJMoa0911123  
38 [published Online First: 2010/10/01]  
39
- 40 384. Zaghoul MS, Eldebawy E, Ahmed S, et al. Hypofractionated conformal radiotherapy for pediatric  
41 diffuse intrinsic pontine glioma (DIPG): a randomized controlled trial. *Radiotherapy & Oncology*  
42 2014;111(1):35-40. doi: <http://dx.doi.org/10.1016/j.radonc.2014.01.013>  
43
- 44 385. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are  
45 prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921  
46 randomized phase III study. *Journal of Clinical Oncology* 1999;17(3):832-45.  
47
- 48 386. Zhang L, Jia S, Ma Y, et al. Efficacy and safety of cisplatin, dexamethasone, gemcitabine and  
49 pegaspargase (DDGP) regimen in newly diagnosed, advanced-stage extranodal natural killer/T-cell  
50 lymphoma: Interim analysis of a phase 4 study NCT01501149. *Oncotarget* 2016;7(34):55721-31. doi:  
51 <http://dx.doi.org/10.18632/oncotarget.10124>  
52  
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3 387. Zintl F, Plenert W, Malke H. Results of acute lymphoblastic leukemia therapy in childhood with a  
4 modified BFM protocol in a multicenter study in the German Democratic Republic. *Haematology &*  
5 *Blood Transfusion* 1987;30:471-79.  
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For peer review only

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

**Step 1:**

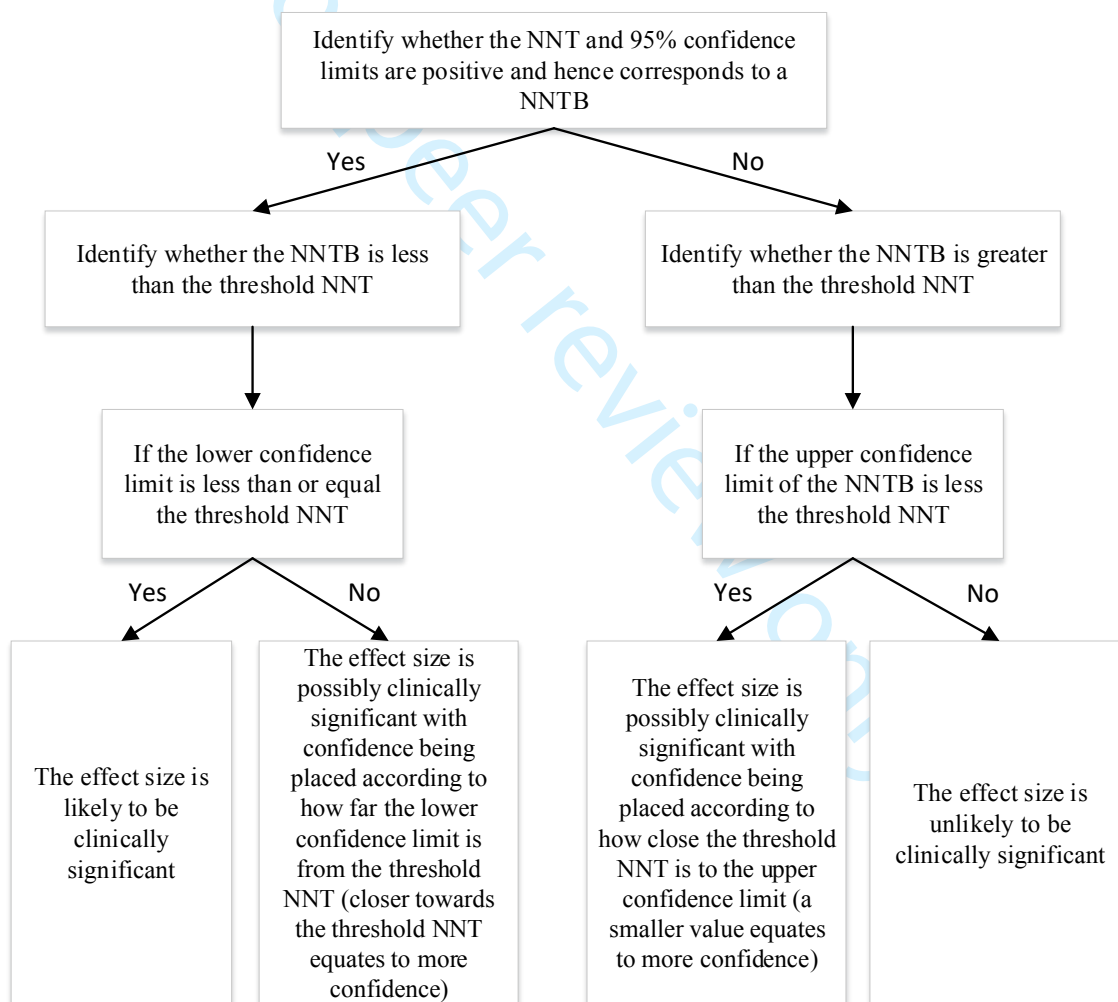
Identify the delta value reported in the sample size calculation and whether the authors reported on the way in which the delta value was chosen. A delta value informed by a previous trial or systematic review should be given more confidence in comparison to one from pilot data or clinical expertise. 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<sup>19</sup>. 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

# BMJ Open

## The utility of the number needed to treat in pediatric hematological cancer randomized controlled treatment trials: A systematic review

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Secondary Subject Heading:	Evidence based practice, Research methods
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Manuscripts

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3 **1 The utility of the number needed to treat in pediatric hematological cancer randomized controlled**  
4 **2 treatment trials: A systematic review**  
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7 3

8 4 Haroon Hasan<sup>1,2</sup>, Karen Goddard<sup>2</sup>, A. Fuchsia Howard<sup>3</sup>

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3 **Abstract**  
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7 **Objectives:** The primary objective was to assess the utility of the number needed to treat (NNT) to  
8 inform decision-making in the context of pediatric oncology and to calculate the NNT in all superiority,  
9 parallel, pediatric hematological cancer, randomized controlled trials (RCTs), with a comparison to the  
10 threshold NNT as a measure of clinical significance.  
11

12 **Design:** Systematic review  
13

14 **Data sources:** MEDLINE, EMBASE and the Cochrane Childhood Cancer Group Specialized Register  
15 through CENTRAL from inception to August 2018.  
16

17 **Eligibility criteria for selecting studies:** Superiority, parallel RCTs of hematological malignancy  
18 treatments in pediatric patients that assessed an outcome related to survival, relapse, or remission;  
19 reported a sample size calculation with a delta value to allow for calculation of the threshold NNT, and  
20 that included parameters required to calculate the NNT and associated confidence interval.  
21

22 **Results:** A total of 43 RCTs were included, representing 45 randomized questions, of which none  
23 reported the NNT. Among acute lymphoblastic leukemia RCTs, 29.2% (7/24) of randomized questions  
24 were found to have a NNT corresponding to benefit, in comparison to acute myeloid leukemia RCTs with  
25 50% (3/6), and none in lymphoma RCTs (0/13). Only 28.6% (2/7) and 33.3% (1/3) had a NNT that was  
26 less than the threshold NNT for acute lymphoblastic leukemia and acute myeloid leukemia, respectively.  
27 Of these, 100% (2/2 acute lymphoblastic leukemia and 1/1 acute myeloid leukemia) were determined to  
28 be possibly clinically significant.  
29

30 **Conclusions:** We recommend that decision-makers in pediatric oncology use the NNT and associated  
31 confidence limits as a supportive tool to evaluate evidence from RCTs, while placing careful attention to  
32 the inherent limitations of this measure.  
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69 **Strengths and Limitations of this Study**

<b>Strengths</b>	<ul style="list-style-type: none"> <li>• The utility of the NNT was evaluated in all superiority, parallel group, pediatric hematological RCTs published from inception to August 2018, wherein relapse, remission or survival was assessed.</li> <li>• The visualization, in the form of a forest plot, of the relationship between NNT, confidence intervals and the threshold NNT of all included studies provides a clinically relevant example of communicating complex information.</li> </ul>
<b>Limitations</b>	<ul style="list-style-type: none"> <li>• A number of RCTs were excluded from this review due to reporting that precluded calculating the NNT.</li> <li>• The delta value in the sample size calculation was assumed to be the absolute difference that would provide a clinically significant effect size and a proxy for the threshold NNT. This assumption, thus would lead to the possibility of effect sizes being chosen that might be more reflective of feasibility than clinical benefit and, therefore, limits generalisability, as this is not a universally recognized approach.</li> <li>• The proposed method implies that the threshold NNT is equivalent to the threshold absolute risk reduction even though the NNT results in a transformation of scale and is expressed using a unit measured in patients. Therefore, a threshold absolute risk reduction may not correspond to a minimal clinically important difference in terms of the NNT.</li> </ul>

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## 79 Introduction

80 Cancer in children is exceedingly rare and consists of less than 1% of all cancers diagnosed in Canada,  
81 with hematological cancers accounting for approximately 40% of cases<sup>1</sup>. Pediatric hematological cancer  
82 survival rates are currently upwards of 80%, largely as a result of treatment advances evaluated through  
83 randomized controlled trials (RCTs)<sup>2</sup>. Owing to the relative rarity of pediatric hematological cancers,  
84 multicenter international trials have been necessary to conduct adequately powered treatment  
85 investigations<sup>1,3</sup>. However, even with coordinated resource-intensive efforts, it can take five to seven  
86 years to complete a phase III RCT, and another five years to publish outcomes with meaningful follow-  
87 up<sup>2</sup>. There is also an additional time lag before high-level evidence becomes the standard of care<sup>2</sup>.

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89 Given the lengthy timeline from research to practice, evaluating evidence arising from RCTs published in  
90 the pediatric oncology literature is critical for informing subsequent RCTs and standard of care. In other  
91 treatment contexts, the number needed to treat (NNT) has proven to be of value in assisting clinicians to  
92 assess therapeutic interventions and act as a supportive tool in benefit-risk assessments as well as  
93 formulary decision-making<sup>4-8</sup>. The NNT is an absolute effect measure coined almost 30 years ago,  
94 defined as the “*number of patients needed to be treated with one therapy versus another for one patient to*  
95 *encounter an additional outcome of interest within a defined period of time*”<sup>6,9,10</sup>. The NNT corresponds  
96 to the inverse of the absolute risk reduction (ARR), which is the absolute difference between the  
97 experimental and control estimates, for a specific time point. For example, a RCT comparing the effect of  
98 the medication strontium ranelate to a placebo on the incidence of vertebral fractures at three years in  
99 women with postmenopausal osteoporosis found that the event rate in the strontium ranelate group was  
100 20.9% compared to 32.8% in the placebo<sup>11</sup>. The inverse of the absolute difference in event rates between  
101 the experimental and control group corresponds to the NNT, such that in this study, “*9 patients would*  
102 *need to be treated for three years with strontium ranelate in order to prevent 1 patient from having a*  
103 *vertebral fracture (95 percent confidence interval, 6 to 14)*”<sup>11</sup>. The evaluation of evidence requires, at a  
104 minimum, consideration of the absolute risk and relative benefits (and harms) related to a therapy in  
105 question, with the NNT being a supportive tool do so<sup>12</sup>. Despite the usefulness of the NNT and the  
106 Consolidated Standard of Reporting Trials (CONSORT) statement, which considers the NNT as a helpful  
107 tool, recent research suggests that these measures are rarely reported in the literature<sup>6,13-16</sup>.

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109 At this time, the utility of the NNT to support evidence-based practice in pediatric oncology treatment  
110 trials remains unexamined, as does the degree to which the NNT has been reported in the pediatric  
111 oncology literature. We specifically aimed to assess the utility of the NNT with consideration of a  
112 threshold NNT, which is the point where the therapeutic benefit equals the therapeutic risk<sup>17</sup>. The

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3 113 threshold NNT should correspond to the inverse of the ARR that a RCT is designed to detect and a  
4 114 clinically significant effect size that would lead to a clinical practice change. Therefore, a decision to  
5 115 administer a therapeutic intervention over the standard of care should occur when the NNT is less than the  
6 116 threshold NNT<sup>17</sup>. The primary study objective was to assess the utility of the NNT in pediatric  
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8 117 hematologic cancer, by calculating the NNT in all superiority parallel RCTs assessing treatment related  
9 118 survival, relapse or remission, and comparing the NNT to the threshold NNT. A secondary study  
10 119 objective was to assess the proportion of published studies (specifically randomized questions) that  
11 120 reported the NNT.  
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## 16 121

### 17 122 **Methods**

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19 123 This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-  
20 124 Analyses (PRISMA) statement (Supplementary File)<sup>18</sup>. This review consisted of a subset of studies from a  
21 125 previous systematic review conducted by our research team, which was conducted from inception of the  
22 126 databases searched to July 2016. The search strategy used in that systematic review was re-run to capture  
23 127 studies published from July 2016 to August 2018. Methods describing the search strategy, eligibility  
24 128 criteria, study identification and data extraction for our previous systematic review have been detailed in  
25 129 the protocol (Supplementary File – Appendix A).  
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#### 31 131 *Search Strategy and Study Inclusion*

32 132 A comprehensive literature review was performed using the databases MEDLINE (Via Ovid), EMBASE  
33 133 (via OVID) and Cochrane Childhood Cancer Group Specialized Register (Via CENTRAL) from  
34 134 inception to August 2018 to identify all superiority, parallel group, RCTs in pediatric patients diagnosed  
35 135 with a hematological cancer that assessed an outcome related to survival, relapse or remission and those  
36 136 that reported either confidence intervals (CI) or standard errors associated with both the experimental and  
37 137 control estimates, or numbers of patients at risk on a Kaplan Meier curve. The reference lists of included  
38 138 studies during the full-text review stage were hand-searched to identify any additional studies. The search  
39 139 was restricted to studies published in English and therefore prone to language bias.  
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#### 47 141 *Study Identification and Data Extraction*

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49 142 Two investigators (HH and KN) screened the titles and abstracts non-independently to identify studies  
50 143 that fulfilled the study inclusion criteria. Discrepancies were settled by discussion and consensus, with the  
51 144 principal investigator (AFH) available as an adjudicator. Studies that fulfilled the inclusion criterion at the  
52 145 title and abstract screening stage were selected for full-text review by one investigator (HH) to confirm  
53 146 study eligibility. A data extraction template was developed and piloted with 15 included studies to ensure  
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3 147 all pertinent data was captured. One investigator (HH) then extracted all of the data, of which a random  
4 148 sample was selected and verified by the principal investigator (AFH) as a quality assurance measure.

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### 7 8 150 *Analysis*

9 151 The number needed to treat to benefit (NNTB), which corresponds to a positive NNT, or number needed  
10 152 to treat to harm (NNTH), which corresponds to a negative NNT, and associated 95% CI were calculated  
11 153 for each randomized question as per the validated methodology described by Altman & Andersen<sup>19</sup>. A  
12 154 randomized question is defined as an intervention comparison assessing a primary outcome for which a  
13 155 sample size calculation is reported. The NNT was based on the primary outcome and time point as  
14 156 specified in the sample size calculation. In the event that the time point specified in the sample size  
15 157 calculation was not reported, the information was inferred if a Kaplan Meier curve with the number of  
16 158 patients at risk was reported<sup>19</sup>. If the aforementioned was not provided, the time point reported in the  
17 159 results was used, and thus, these trials were prone to selective reporting bias. All analyses were conducted  
18 160 based on randomized questions to account for the possibility that a RCT could have more than one  
19 161 parallel group.

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22 163 The ARR, NNT and delta value (i.e., threshold ARR and NNT), as reported in the sample size  
23 164 calculation, were visualized on a forest plot, grouped by disease (Acute Lymphoblastic Leukemia, Acute  
24 165 Myeloid Leukemia, Lymphoma and Mixed, which corresponds to the inclusion of multiple diseases), to  
25 166 allow for identification of NNTB (defined as the NNT and 95% CI that only included positive numbers),  
26 167 NNTH (defined as the NNT and 95% CI that only included negative numbers) and inconclusive NNT  
27 168 (defined as the NNT where the 95% CI included both a positive and a negative number). Descriptive  
28 169 statistics were used to summarize the frequency and percentage of randomized questions reporting the  
29 170 NNT, as well as the NNTB, NNTH, and inconclusive NNT by disease site.

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31 171

32 172 In order to ascertain whether the NNTB was clinically significant, we calculated the frequency and  
33 173 percentage of randomized questions where the  $NNT < \text{threshold NNT}$ ,  $NNT > \text{threshold NNT}$ , or  $NNT =$   
34 174  $\text{threshold NNT}$ . The threshold NNT was considered to be the inverse of the ARR (i.e., delta value), as  
35 175 specified in the sample size calculation, and was assumed to correspond to a clinically significant effect  
36 176 size that would lead to a change in clinical practice. The threshold NNT was compared to the treatment  
37 177 NNT and classified as definitely clinically significant, possibly clinical significant, inconclusive clinical  
38 178 significance, and definitely not clinically significant as specified in Figure 1. These categories, as well as  
39 179 the overall method, were informed by methods described by Man-Son-Hing et al.<sup>20</sup> and Guyatt et al.<sup>21</sup>  
40 180 Randomized controlled trials where an ARR of zero occurred were excluded from the analysis because

181 the inverse corresponds to an undefined NNT. SAS (Statistical Analysis Software) version 9.4 (SAS  
182 Institute, Cary, NC) was used to perform all analyses.

183

#### 184 *Patient and Public Involvement*

185 Given this is a research methods systematic review, there was no patient or public involvement.

186

### 187 **Results**

#### 188 *Included studies*

189 Our search identified 4,151 unique studies from MEDLINE, EMBASE, and the Cochrane Childhood  
190 Cancer Group Specialized Register accessed through CENTRAL. Following title and abstract screening,  
191 432 studies were evaluated for eligibility based on full-text review. Of these studies, 387 studies were  
192 excluded and 43 studies (i.e., RCTs), representing 45 randomized questions, were included in the  
193 systematic review (Figure 2) (Supplementary File – Appendix B). The randomized questions  
194 corresponded to RCTs investigating treatments for acute lymphoblastic leukemia (ALL) (N = 24; 53.3%),  
195 lymphoma (N = 13; 28.9%), acute myeloid leukemia (AML) (N = 6; 13.3%), and mixed diagnoses (N =  
196 2; 4.4%).

#### 197 *Number needed to treat*

198 The frequency and proportion of the NNTB, inconclusive NNT, and NNTH are summarized in Table 1.  
199 Approximately 29.2% (7/24) of randomized questions in ALL RCTs were found to have a NNT  
200 corresponding to a NNTB, in comparison to AML with 50.0% (3/6). There were no randomized questions  
201 in lymphoma (N = 15) trials with a NNTB.

#### 202 *Comparison of NNT and Threshold NNT*

203 A comparison of the NNT to the threshold NNT is summarized in Table 1 and visualized in Figure 3. For  
204 randomized questions corresponding to NNTB, the NNT was less than the threshold NNT in 28.6% (2/7)  
205 ALL and 33.3% (1/3) AML comparisons. However, of these, 100% (2/2 and 1/1) had a lower confidence  
206 limit that was greater or equal to the threshold NNT for ALL and AML, respectively, and hence were  
207 possibly clinically significant. In contrast, 71.4% (5/7) and 66.7% (2/6) had a NNT greater than the  
208 threshold NNT; however, 80.0% (4/5) and 50.0% (1/2) of these had an upper confidence limit that was  
209 less than or equal to the threshold NNT for ALL and AML, respectively, and hence were possibly  
210 clinically significant.

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5 213 *Reporting of NNT*6  
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8 214 There were no randomized questions that reported the NNT to support the reporting of the primary  
9 215 outcome of the study.10  
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14 217 **Discussion**15 218 In this systematic review, we demonstrated that variation in the NNT exists among RCTs assessing  
16 219 outcomes related to remission, relapse, and survival in pediatric hematological cancers. A majority of  
17 220 randomized questions found to have a NNTB were not necessarily associated with a positive effect size  
18 221 when using the inverse of the delta value as specified in the sample size calculation as a proxy for the  
19 222 threshold NNT and a measure of what a clinically significant NNT should be. There were no randomized  
20 223 questions reporting the NNT, which highlights reporting deficits in the pediatric hematological cancer  
21 224 RCT literature.22  
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27 225 *Strengths and weaknesses*28  
29 226 Our review provides a comprehensive analysis of the utility of the NNT through an evaluation of all  
30 227 superiority parallel group pediatric hematological RCTs assessing relapse, remission and survival from  
31 228 inception to August 2018. We provide the NNT and ARR with its 95% CI along with the threshold NNT  
32 229 and ARR for these RCTs using a validated methodological approach, which will serve as a valuable tool  
33 230 for decision-makers, clinicians and researchers to assess treatment effects. A weakness of this study is the  
34 231 exclusion of a number of RCTs due to reporting that precluded calculating the NNT. However, as the  
35 232 exclusion is due to reporting deficits, this limitation is beyond our control and serves as an important  
36 233 finding that reporting quality is limited in the pediatric hematological cancer RCT literature. An  
37 234 additional weakness is that the delta value in the sample size calculation was assumed to be the absolute  
38 235 difference that would provide an effect size that would lead to a change in clinical practice (i.e., minimal  
39 236 clinically important difference), if not explicitly indicated, and a proxy for the threshold ARR and NNT.  
40 237 This assumption, thus, would lead to the possibility of effect sizes being chosen that might be more  
41 238 reflective of study feasibility as opposed to clinical benefit. This approach may be limited in terms of  
42 239 generalisability given that this is not a universally recognized approach. Additionally, this assumption  
43 240 implies that the threshold NNT is equivalent to the threshold ARR even though the NNT results in a  
44 241 transformation of scale and is expressed using a unit measured in patients. Therefore, a threshold ARR  
45 242 may not correspond to a minimal clinically important difference in terms of NNT. However, as there were

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3 243 no studies that reported a threshold NNT, our approach represents a feasible method to apply in the  
4 244 absence of a reported threshold NNT. This method is nonetheless not validated and further studies will  
5 245 need to be undertaken to compare whether researchers would equate the minimal clinical important  
6 246 difference in terms of ARR to the NNT.  
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### 11 12 248 *Comparison with existing literature*

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14 249 Considerable published literature has evaluated the utility of the NNT. The overarching conclusion is that  
15 250 the NNT is a metric of value in clinical, health policy and formulary decision-making when interpreted  
16 251 correctly<sup>4-8</sup>. However, the NNT and ARR are rarely reported or poorly reported in the literature despite  
17 252 being recommended as a helpful tool in the CONSORT statement and are often calculated using  
18 253 inappropriate methods<sup>6 12-16 22-27</sup>. Our findings corroborate the existing literature because no studies  
19 254 reported the NNT in our review. Previous studies have not highlighted the utility of the NNT specifically  
20 255 in the pediatric oncology literature or evaluated the clinical significance of the NNT using the approach  
21 256 described in our study and thus, our study is a novel and important addition to the literature.  
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### 29 30 258 *Study explanations and implications*

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32 259 Our study quantified the NNT as a means to better understand the utility of this tool to facilitate decision-  
33 260 making in pediatric oncology. The NNT allows for an intuitive understanding of the absolute effect size  
34 261 in terms of patients and can help considerably when comparing one treatment to another, after ensuring  
35 262 baseline characteristics, the outcome and time point for the patient population of interest are  
36 263 comparable<sup>12</sup>. For instance, a RCT conducted by Creutzig et al.<sup>28</sup> in pediatric AML patients assessing 5-  
37 264 year event free survival found a 6.0% (95% CI, 1.3%-10.7%) absolute increase associated with the  
38 265 experimental treatment (liposomal daunorubic induction) compared to the control treatment (idarubicin  
39 266 induction). The associated NNT corresponded to 17 (95% CI; 75-9), or NNTB 17 (95% CI, NNTB 75 to  
40 267 NNTB 9), meaning that it is estimated that by administering the experimental treatment, 1 extra patient  
41 268 would survive at 5 years for every 17 patients treated (95% CI, NNTB 75 to NNTB 9). Of note, this RCT  
42 269 was powered to detect an absolute increase in 5-year event free survival of 13% (i.e., delta value), which  
43 270 would correspond to a NNTB of 8 (i.e., threshold NNT). Although the NNTB is 17, the lower confidence  
44 271 limit is 75 and the upper confidence limit is 9 (a range that does not include 8), which, given the range,  
45 272 would lead one to believe that the effect size does not provide strong enough evidence to change clinical  
46 273 practice. In situations where the lower confidence limit of the NNTB is less than the threshold NNT, one  
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3 274 can be more confident that the treatment confers a clinically improved outcome as compared to the  
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5 275 control. On the other hand, if the NNTB is less than the threshold NNT and the lower confidence limit is  
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7 276 greater than the threshold NNT, one should exercise greater caution in concluding that the effect size is  
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9 277 clinically significant (refer to Figure 1 for visual). As demonstrated in our study, a forest plot is a  
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11 278 convenient method to visualize the relationship between the NNT (and the associated 95% CI) evident in  
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13 279 study results compared to the NNT that the study was designed to detect as a proxy for the threshold NNT  
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15 280 and that would be considered clinically significant.

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17 281 The aforementioned approach is recommended in light of smaller sample sizes that are often attained in  
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19 282 pediatric oncology RCTs and rare disease trials in general, as it allows for assessment of the precision of  
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21 283 the treatment effect as well as clinical and statistical significance. This was demonstrated in our study  
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23 284 where the majority of randomized questions found to have a NNTB had a NNT greater than the threshold  
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25 285 NNT, of which the upper confidence limit was less than or equal to the threshold NNT. If these RCTs  
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27 286 were designed with higher power, it is possible that definite clinical significance may have been obtained.  
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29 287 On the other hand, these findings would not be considered significant based on statistical significance.  
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31 288 Since statistical significance does not provide an indication of the size of the treatment effect, one would  
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33 289 not be able to discern whether the findings could have possible clinical significance. An assessment of  
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35 290 clinical significance, therefore, requires a summary measure be presented with a CI. By presenting a CI,  
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37 291 an assessment can be made of both statistical and clinical significance, which can inform clinical  
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39 292 decision-making. Interpreting results from RCTs based solely on statistical significance, without taking  
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41 293 into consideration clinical significance, can result in misappraisal of evidence. Using the results of our  
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43 294 study as an example, we demonstrated that all randomized questions, for which the NNTB was less than  
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45 295 threshold NNT, had a lower confidence limit that was equal to, or greater than, the threshold NNT.  
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47 296 Although these results were statistically significant, none had definite clinical significance and were only  
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49 297 possibly clinically significant. These findings have clinical implications because clinicians often have to  
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51 298 make decisions about administering treatments that are not standard of care, and rely on an accurate  
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53 299 appraisal of evidence to inform these decisions. Inconclusive evidence, however, does not necessarily  
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55 300 infer an ineffective intervention. Rather, inconclusive evidence (when the CI of the NNT crosses infinity  
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57 301 as a result of the CI of the ARR crossing 0) infers that the level of clinical significance cannot be  
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59 302 determined from the study results. The use of the NNT and the method we describe can be one more tool  
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303 to support clinical decision-making within this context.

304  
305 Scenarios where the NNT results in inconclusive evidence is a limitation in the utility of NNT, as  
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discussed by Altman<sup>29</sup>. To illustrate, Lange et al.<sup>30</sup> assessed 5-year disease free survival in pediatric AML patients in first remission after intensive chemotherapy, and found a 7.0% (95% CI, -19.8% to 5.8%)

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3 307 absolute decrease associated with the experimental treatment (interleukin-2 infused on days 0-3 and 8-17)  
4 308 compared to the control treatment (no further therapy). The study was powered to detect a 10% difference  
5 309 in 5-year disease free survival, which was assumed to be the minimal clinical importance difference, and  
6 310 hence, corresponds to a threshold NNTB of 10. The resulting NNT of the RCT was -14 (95% CI, -5 to 17)  
7 311 or a NNTH 14 (95% CI, NNTH 5 to NNTB 17). At first glance, it appears as though the point estimate  
8 312 does not fall within the 95% CI, given the disjointed confidence limits. In other studies wherein the CI  
9 313 traverses both harm and benefit the NNT is reported without the CI<sup>31</sup>. In reality, the CI encompasses  
10 314 values from a NNTH of 5 to  $\infty$  and NNTB of 17 to  $\infty$ . Plotting the NNT and CI on a forest plot (Figure 3)  
11 315 demonstrates that a NNTH of 14 does fall within the interval range and in fact, the interval is continuous.  
12 316 Altman, therefore, recommended presenting the CI of the NNT as the following to emphasize continuity  
13 317 (using results from Lange et al. as an example): NNTH 14 (NNTH 5 to  $\infty$  to NNTB 17).

14 318 We strongly encourage plotting the ARR and the NNT on a forest plot simultaneously because the NNT  
15 319 is simply a method of re-expressing the ARR and supports the interpretation of the ARR. As the NNT is a  
16 320 relative measure it should always be accompanied by the absolute measure, the ARR<sup>16</sup>. Additionally, the  
17 321 utility of the NNT is inherently reliant on three major areas: baseline risk, the outcome and the time  
18 322 point<sup>12</sup>. In order for the NNT from an RCT demonstrating a NNTB to have utility, the patient population  
19 323 of interest should share a similar baseline risk because the desired treatment effect may be overestimated  
20 324 and thus the NNTB may be underestimated. Outcomes related to event free survival often differ in what is  
21 325 considered an event and thus it is critical to ensure that the NNTB being applied to the population of  
22 326 interest is identical in terms of the outcome in question. Numerous studies have demonstrated how the  
23 327 NNT varies with time and thus, comparability in time points is critical to ensure accurate interpretation of  
24 328 the NNT to a population of interest<sup>4 12 23 24</sup>. Lastly, criticisms of the statistical properties of the NNT have  
25 329 been highlighted by Hutton et al.<sup>32 33</sup> and Katz et al.<sup>34</sup> We agree with Altman & Deeks<sup>32</sup> response to these  
26 330 criticisms in that the NNT was designed for translation of research results and, therefore, arguments  
27 331 related to computation and its distribution properties are of less relevance. The NNT is simply a metric to  
28 332 re-express the ARR and, therefore, should be viewed as a measure to support the interpretation of the  
29 333 ARR.

### 334 *Recommendations*

335 We recommend that clinicians and decision-makers in pediatric oncology consider using the NNT as a  
336 supportive tool to evaluate evidence from RCTs, while paying careful attention to the inherent limitation  
337 of this measure. Additionally, we recommend that researchers report the NNT and associated CI to  
338 support the interpretation and generalisability of the trial results. Given the inherent limitations of the  
339 NNT, we emphasize that the NNT should be considered a supportive tool to inform evidence-based

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3 340 decision making and not a replacement. Supplementary file Appendix C provides a summary of how the  
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5 341 NNT can be calculated and assessed to inform decision-making<sup>19,20</sup>.

### 6 7 342 **Figure Legends**

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9 343 **Figure 1:** Guideline to assess level of clinical significance using number needed to treat

10 344 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to  
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12 345 the study ARR or NNT.

13 346 ARR corresponds to the absolute difference between the experimental and control estimates. The  
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15 347 inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value  
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17 348 the randomized control trial was designed to detect as determined in the sample size calculation.

18 349 The inverse of the threshold ARR corresponds to the threshold NNT.

19 350 Abbreviations; NNT, number needed to treat; ARR, absolute risk reduction; UCL, upper  
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21 351 confidence limit; LCL, lower confidence limit

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24 353 **Figure 2:** Selection of randomized controlled trials in the systematic review

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27 355 **Figure 3:** Forest plot summarizing randomized questions by the number needed to treat relative to the  
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29 356 threshold number needed to treat according to hematological cancer type

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31 357 \*Correspond to RCT where more than one randomized question was investigated.

32 358 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to  
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34 359 the study ARR or NNT.

35 360 ARR corresponds to the absolute difference between the experimental and control estimates. The  
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37 361 inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value  
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39 362 the randomized control trial was designed to detect as determined in the sample size calculation.

40 363 The inverse of the threshold ARR corresponds to the threshold NNT.

41 364 Abbreviations: AML, acute myeloid leukemia; ALL, Acute lymphoblastic Leukemia; NNT,  
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43 365 numbers needed to treat; NNTB, number needed to benefit; NNTH, number needed to harm;  
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45 366 ARR, absolute risk reduction; OS, overall survival; EFS, event-free survival; DFS, disease-free  
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47 367 survival; CCR, complete cancer remission; RR, relapse rate; YR, year; CI, confidence interval

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49 **Contributorship Statement:** AFH, KG and HH conceived and designed the study. HH collected and  
50  
51 analyzed the data. AFH and HH wrote the first drafts of the manuscript, and all authors contributed to  
52  
53 subsequent drafts. All authors had full access to all of the data in the review and take responsibility for the  
54  
55 integrity of the data and the accuracy of the data analysis.

56 368 **Competing Interests:** There are no competing interests for any author.

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3 369 **Role of Funding Source:** Funding support was provided by the University of British Columbia School of  
4  
5 370 Nursing to conduct this systematic review. The funder played no role in study design, collection, analysis,  
6  
7 371 interpretation of data, writing of the report, or in the decision to submit the paper for publication. They  
8  
9 372 accept no responsibility for the contents.

10 373 **Data Sharing Statement:** Unpublished data will be made available upon request to the corresponding  
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12 374 author.

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## References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2017. Toronto, ON: Canadian Cancer Society; 2017. Available at: [cancer.ca/Canadian-CancerStatistics-2017-EN.pdf](http://cancer.ca/Canadian-CancerStatistics-2017-EN.pdf).
2. Saletta F, Seng MS, Lau LM. Advances in paediatric cancer treatment. *Translational pediatrics* 2014;3(2):156-82. doi: 10.3978/j.issn.2224-4336.2014.02.01 [published Online First: 2014/04/01]
3. Bond MC, Pritchard S. Understanding clinical trials in childhood cancer. *Paediatrics & child health* 2006;11(3):148-50. [published Online First: 2008/11/26]
4. Citrome L, Ketter TA. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. *Int J Clin Pract* 2013;67 doi: 10.1111/ijcp.12142
5. Mendes D, Alves C, Batel MF. Testing the usefulness of the number needed to treat to be harmed (NNT<sub>H</sub>) in benefit-risk evaluations: case study with medicines withdrawn from the European market due to safety reasons. *Expert Opin Drug Saf* 2016;15 doi: 10.1080/14740338.2016.1217989
6. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. *BMC Medicine* 2017;15(1):112. doi: 10.1186/s12916-017-0875-8
7. Mendes D, Alves C, Batel-Marques F. Number needed to harm in the post-marketing safety evaluation: results for rosiglitazone and pioglitazone. *Pharmacoepidemiol Drug Saf* 2015;24 doi: 10.1002/pds.3874
8. Mendes D, Alves C, Batel-Marques F. Benefit-risk of therapies for relapsing-remitting multiple sclerosis: testing the number needed to treat to benefit (NNT<sub>B</sub>), number needed to treat to harm (NNT<sub>H</sub>) and the likelihood to be helped or harmed (LHH): a systematic review and meta-analysis. *CNS Drugs* 2016;30 doi: 10.1007/s40263-016-0377-9
9. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318 doi: 10.1056/nejm198806303182605
10. Cook D, Sackett D. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;310 doi: 10.1136/bmj.310.6977.452
11. Meunier PJ, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350(5):459-68. doi: 10.1056/NEJMoa022436 [published Online First: 2004/01/30]
12. McAlister FA. The "number needed to treat" turns 20—and continues to be used and misused. *CMAJ* 2008;179 doi: 10.1503/cmaj.080484
13. Hildebrandt M, Vervölgyi E, Bender R. Calculation of NNTs in RCTs with time-to-event outcomes: a literature review. *BMC Med Res Methodol* 2009;9 doi: 10.1186/1471-2288-9-21
14. Nuovo J, Melnikow J, Chang D. Reporting number needed to treat and absolute risk reduction in randomized controlled trials. *JAMA* 2002;287 doi: 10.1001/jama.287.21.2813
15. Alonso-Coello P, Carrasco-Labra A, Brignardello-Petersen R. Systematic reviews experience major limitations in reporting absolute effects. *J Clin Epidemiol* 2016;72 doi: 10.1016/j.jclinepi.2015.11.002
16. Moher D, Hopewell S, Schulz KF. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340 doi: 10.1136/bmj.c869
17. Sinclair JC, Cook RJ, Guyatt GH, et al. When should an effective treatment be used? Derivation of the threshold number needed to treat and the minimum event rate for treatment. *J Clin Epidemiol* 2001;54(3):253-62. [published Online First: 2001/02/27]
18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj* 2009;339:b2700. doi: 10.1136/bmj.b2700 [published Online First: 2009/07/23]
19. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;319 doi: 10.1136/bmj.319.7223.1492

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3 425 20. Man-Son-Hing M, Laupacis A, O'Rourke K, et al. Determination of the clinical importance of study  
4 426 results. *Journal of general internal medicine* 2002;17(6):469-76. [published Online First:  
5 427 2002/07/23]
- 6 428 21. Guyatt GH, Sackett DL, Sinclair JC, et al. Users' guides to the medical literature. IX. A method for  
7 429 grading health care recommendations. Evidence-Based Medicine Working Group. *Jama*  
8 430 1995;274(22):1800-4. [published Online First: 1995/12/13]
- 9 431 22. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. *Thorax* 2013;68 doi:  
10 432 10.1136/thoraxjnl-2012-202709
- 11 433 23. Suissa S. The number needed to treat: 25 years of trials and tribulations in clinical research. *Rambam*  
12 434 *Maimonides Med J* 2015;30
- 13 435 24. Suissa D, Brassard P, Smiechowski B, et al. Number needed to treat is incorrect without proper time-  
14 436 related considerations. *J Clin Epidemiol* 2012;65 doi: 10.1016/j.jclinepi.2011.04.009
- 15 437 25. Stang A, Poole C, Bender R. Common problems related to the use of number needed to treat. *J Clin*  
16 438 *Epidemiol* 2010;63 doi: 10.1016/j.jclinepi.2009.08.006
- 17 439 26. Tramer MR, Walder B. Number needed to treat (or harm). *World journal of surgery* 2005;29(5):576-  
18 440 81. doi: 10.1007/s00268-005-7916-8 [published Online First: 2005/04/14]
- 19 441 27. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance  
20 442 employed in randomized controlled trials of drugs for dementia. *Journal of the American*  
21 443 *Geriatrics Society* 2009;57(3):536-46. doi: 10.1111/j.1532-5415.2008.02122.x [published Online  
22 444 First: 2009/02/04]
- 23 445 28. Creutzig U, Zimmermann M, Bourquin J-P, et al. Randomized trial comparing liposomal  
24 446 daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from  
25 447 Study AML-BFM 2004. *Blood* 2013;122(1):37-43. doi: [http://dx.doi.org/10.1182/blood-2013-02-](http://dx.doi.org/10.1182/blood-2013-02-484097)  
26 448 [484097](http://dx.doi.org/10.1182/blood-2013-02-484097)
- 27 449 29. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317 doi:  
28 450 10.1136/bmj.317.7168.1309
- 29 451 30. Lange BJ, Yang RK, Gan J, et al. Soluble interleukin-2 receptor alpha activation in a Children's  
30 452 Oncology Group randomized trial of interleukin-2 therapy for pediatric acute myeloid leukemia.  
31 453 *Pediatric blood & cancer* 2011;57(3):398-405. doi: 10.1002/pbc.22966 [published Online First:  
32 454 2011/06/18]
- 33 455 31. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Annals*  
34 456 *of internal medicine* 1997;126(9):712-20. [published Online First: 1997/05/01]
- 35 457 32. Hutton JL. Number needed to treat: properties and problems. *J R Stat Soc A Stat Soc* 2000;163 doi:  
36 458 10.1111/1467-985x.00175
- 37 459 33. Hutton JL. Number needed to treat and number needed to harm are not the best way to report and  
38 460 assess the results of randomised clinical trials. *British journal of haematology* 2009;146(1):27-30.  
39 461 doi: 10.1111/j.1365-2141.2009.07707.x [published Online First: 2009/05/15]
- 40 462 34. Katz N, Paillard FC, Van Inwegen R. A review of the use of the number needed to treat to evaluate  
41 463 the efficacy of analgesics. *The journal of pain : official journal of the American Pain Society*  
42 464 2015;16(2):116-23. doi: 10.1016/j.jpain.2014.08.005 [published Online First: 2014/11/25]

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467 **Table 1:** Randomized questions corresponding to number needed to benefit, harm and inconclusive  
 468 relative to threshold number needed to treat by hematological cancer type

NNT <sup>1</sup>	Hematological Cancer Randomized Questions (N = 45)			
	ALL (N = 24)	Lymphoma (N = 13)	AML (N = 6)	Mixed Diagnoses <sup>2</sup> (N = 2)
<b>NNTB (n, %)</b>	7 (29.2%)	0 (0.0%)	3 (50.0%)	1 (50.0%)
<i>NNTB &lt; Threshold NNT</i>	2 (28.6%)	0 (0.0%)	1 (33.3%)	1 (100.0%)
<i>NNTB Lower Confidence Limit ≥ Threshold NNT</i>	2 (100.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
<i>NNTB &gt; Threshold</i>	5 (71.4%)	0 (0.0%)	2 (66.7%)	0 (0.0%)
<i>NNTB Upper Confidence Limit ≤ Threshold NNT</i>	4 (80.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
<i>NNTB = Threshold NNT</i>	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Inconclusive NNT (n, %)</b>	16 (66.7%)	11 (84.6%)	3 (50.0%)	1 (50.0%)
<b>NNTH (n, %)</b>	1 (4.2%)	2 (15.4%)	0 (0.0%)	0 (0.0%)

469 Note: Threshold NNT corresponds to the inverse of the absolute difference (i.e., delta value) as reported in the sample size  
 470 calculation.

471 Abbreviations: NNT, number needed to treat; NNTB, number needed to treat to benefit; NNTH, number needed to treat to harm;  
 472 ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; UCL, Upper confidence limit; LCL, Lower Confidence  
 473 Limit; ARR, absolute risk reduction

474 <sup>1</sup> Denominator for indented corresponds to above row

475 <sup>2</sup> Mixed diagnoses refer to RCTs where more than one hematological cancer was included

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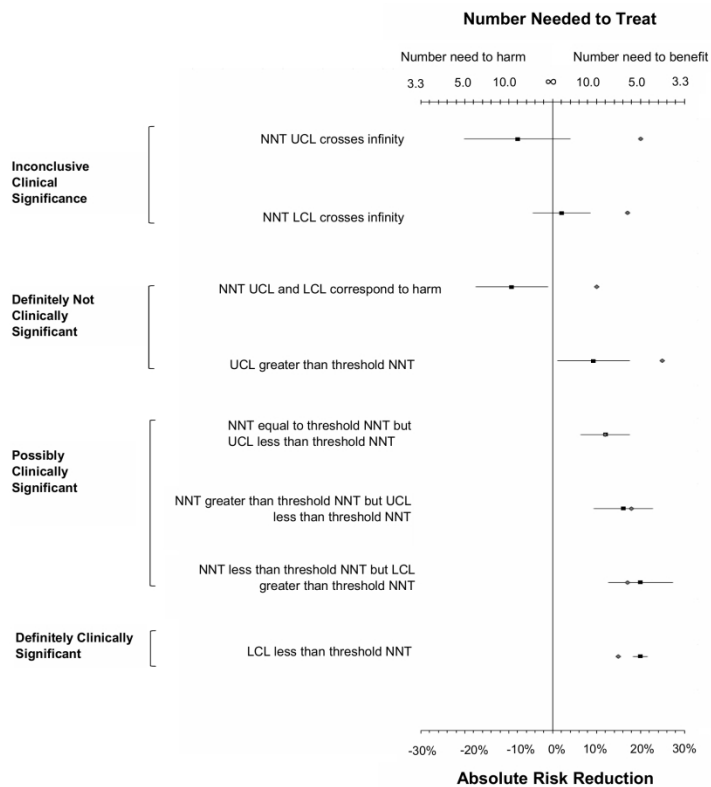


Figure 1: Guideline to assess level of clinical significance using numbers needed to treat  
 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study ARR or NNT.

ARR corresponds to the absolute difference between the experimental and control estimates. The inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value the randomized control trial was designed to detect as determined in the sample size calculation. The inverse of the threshold ARR corresponds to the threshold NNT.

Abbreviations; NNT, number needed to treat; ARR, absolute risk reduction; UCL, upper confidence limit; LCL, lower confidence limit

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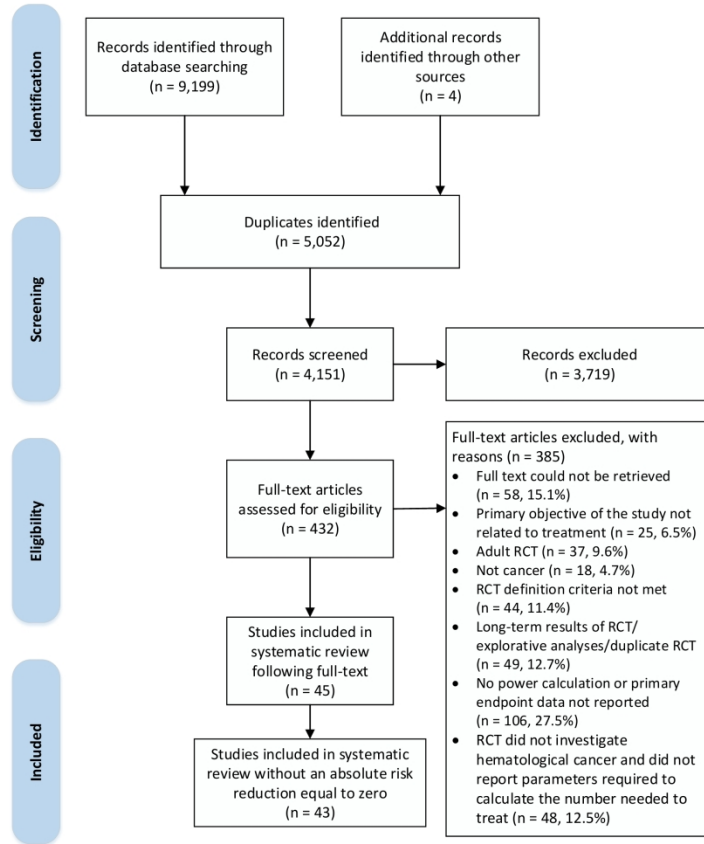


Figure 2: Selection of randomized controlled trials in the systematic review

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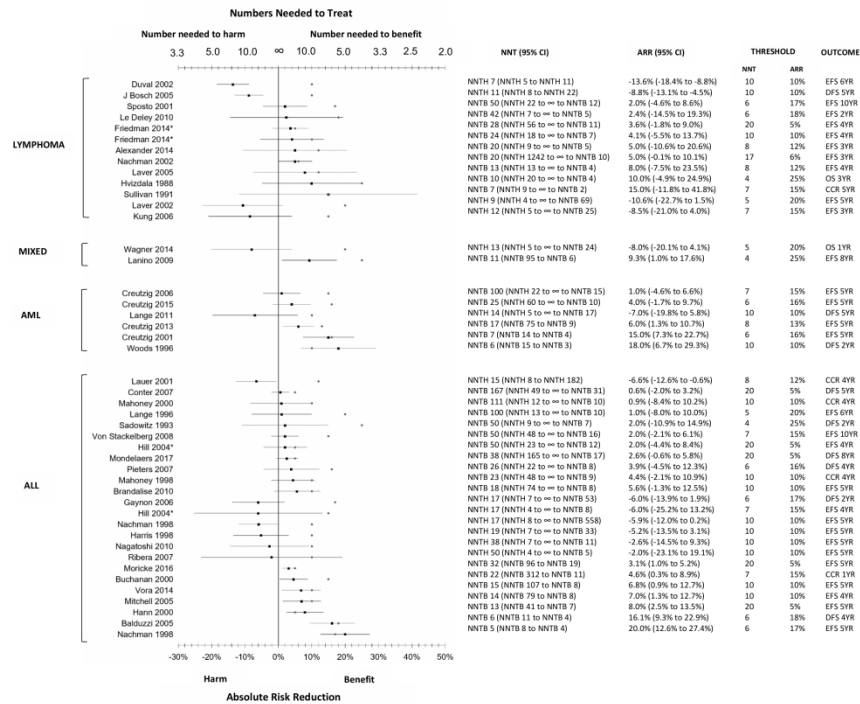


Figure 3: Forest plot summarizing randomized questions by the number needed to treat relative to the threshold number needed to treat according to hematological cancer type  
 \*Correspond to RCT where more than one randomized question was investigated.  
 Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study ARR or NNT.

ARR corresponds to the absolute difference between the experimental and control estimates. The inverse of the ARR corresponds to the NNT. The threshold ARR corresponds to the delta value the randomized control trial was designed to detect as determined in the sample size calculation. The inverse of the threshold ARR corresponds to the threshold NNT.

Abbreviations: AML, acute myeloid leukemia; ALL, Acute lymphoblastic Leukemia; NNT, numbers needed to treat; NNTB, number needed to benefit; NNTH, number needed to harm; ARR, absolute risk reduction; OS, overall survival; EFS, event-free survival; DFS, disease-free survival; CCR, complete cancer remission; RR, relapse rate; YR, year; CI, confidence interval

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## PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Objectives stated on page 5; however, as this is a systematic review on research methods the PICOS format is not appropriate
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix A in Supplementary File I
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 and Appendix A in Supplementary File I
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 and Appendix A in Supplementary File I
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A in Supplementary File
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 and Appendix A in Supplementary File I

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Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5 and Appendix A in Supplementary File I
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A since we were assessing research methods rather than results
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I <sup>2</sup> ) for each meta-analysis.	6

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A since we were assessing methodology and reporting rather than results
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 and Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Figure 3 and Appendix B in Supplementary File I
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 1 and 7-8
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-12
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

## 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 be 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 to 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, Kravka 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, Suci 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 Children's 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, Kravaka 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.

- 1  
2  
3 23. Laver JH, Mahmoud H, Pick TE, et al. Results of a randomized phase III trial in children and  
4 adolescents with advanced stage diffuse large cell non-Hodgkin's lymphoma: a Pediatric Oncology Group  
5 study. *Leukemia & lymphoma* 2002;43(1):105-09.  
6
- 7 24. Le Deley M-C, Rosolen A, Williams DM, et al. Vinblastine in children and adolescents with high-risk  
8 anaplastic large-cell lymphoma: results of the randomized ALCL99-vinblastine trial. *Journal of Clinical  
9 Oncology* 2010;28(25):3987-93. doi: <http://dx.doi.org/10.1200/JCO.2010.28.5999>  
10
- 11 25. Mahoney DH, Jr., Shuster J, Nitschke R, et al. Intermediate-dose intravenous methotrexate with  
12 intravenous mercaptopurine is superior to repetitive low-dose oral methotrexate with intravenous  
13 mercaptopurine for children with lower-risk B-lineage acute lymphoblastic leukemia: a Pediatric  
14 Oncology Group phase III trial. *Journal of Clinical Oncology* 1998;16(1):246-54.  
15
- 16 26. Mahoney DH, Jr., Shuster JJ, Nitschke R, et al. Intensification with intermediate-dose intravenous  
17 methotrexate is effective therapy for children with lower-risk B-precursor acute lymphoblastic leukemia:  
18 A Pediatric Oncology Group study. *Journal of Clinical Oncology* 2000;18(6):1285-94.  
19
- 20 27. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone  
21 for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council ALL97  
22 randomized trial. *British journal of haematology* 2005;129(6):734-45.  
23
- 24 28. Mondelaers V, Suci S, De Moerloose B, et al. Prolonged versus standard native *E. coli* asparaginase  
25 therapy in childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma: final results of the  
26 EORTC-CLG randomized phase III trial 58951. *Haematologica* 2017;102(10):1727-38. doi:  
27 <https://dx.doi.org/10.3324/haematol.2017.165845>  
28
- 29 29. Moricke A, Zimmermann M, Valsecchi MG, et al. Dexamethasone vs prednisone in induction  
30 treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. *Blood*  
31 2016;127(17):2101-12. doi: <https://dx.doi.org/10.1182/blood-2015-09-670729>  
32
- 33 30. Nachman J, Sather HN, Cherlow JM, et al. Response of children with high-risk acute lymphoblastic  
34 leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. *Journal  
35 of Clinical Oncology* 1998;16(3):920-30.  
36
- 37 31. Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-  
38 risk acute lymphoblastic leukemia and a slow response to initial therapy. *New England Journal of  
39 Medicine* 1998;338(23):1663-71.  
40
- 41 32. Nachman JB, Sposto R, Herzog P, et al. Randomized comparison of low-dose involved-field  
42 radiotherapy and no radiotherapy for children with Hodgkin's disease who achieve a complete response to  
43 chemotherapy. *Journal of Clinical Oncology* 2002;20(18):3765-71.  
44
- 45 33. Nagatoshi Y, Matsuzaki A, Suminoe A, et al. Randomized trial to compare LSA2L2-type  
46 maintenance therapy to daily 6-mercaptopurine and weekly methotrexate with vincristine and  
47 dexamethasone pulse for children with acute lymphoblastic leukemia. *Pediatric Blood & Cancer*  
48 2010;55(2):239-47. doi: <http://dx.doi.org/10.1002/pbc.22528>  
49
- 50 34. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with  
51 acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial.  
52 *Lancet* 2007;370(9583):240-50. doi: 10.1016/s0140-6736(07)61126-x [published Online First:  
53 2007/07/31]  
54  
55  
56  
57  
58  
59

- 1  
2  
3 35. Ribera JM, Ortega JJ, Oriol A, et al. Comparison of intensive chemotherapy, allogeneic, or autologous  
4 stem-cell transplantation as postremission treatment for children with very high risk acute lymphoblastic  
5 leukemia: PETHEMA ALL-93 trial. *Journal of Clinical Oncology* 2007;25(1):16-24.  
6  
7 36. Sadowitz PD, Smith SD, Shuster J, et al. Treatment of late bone marrow relapse in children with acute  
8 lymphoblastic leukemia: a Pediatric Oncology Group study. *Blood* 1993;81(3):602-09.  
9  
10 37. Sposto R, Meadows AT, Chilcote RR, et al. Comparison of long-term outcome of children and  
11 adolescents with disseminated non-lymphoblastic non-hodgkin lymphoma treated with COMP or  
12 daunomycin-comp: A report from the children's cancer group. *Medical and pediatric oncology*  
13 2001;37(5):432-41.  
14  
15 38. Sullivan MP, Fuller LM, Berard C, et al. Comparative effectiveness of two combined modality  
16 regimens in the treatment of surgical stage III Hodgkin's disease in children. An 8-year follow-up study  
17 by the Pediatric Oncology Group. *American Journal of Pediatric Hematology/Oncology* 1991;13(4):450-  
18 58.  
19  
20 39. van der Werff ten Bosch J, Suci S, Thyss A, et al. Value of intravenous 6-mercaptopurine during  
21 continuation treatment in childhood acute lymphoblastic leukemia and non-Hodgkin's lymphoma: Final  
22 results of a randomized phase III trial (58881) of the EORTC CLG. *Leukemia* 2005;19(5):721-26.  
23  
24 40. Von Stackelberg A, Hartmann R, Buhner C, et al. High-dose compared with intermediate-dose  
25 methotrexate in children with a first relapse of acute lymphoblastic leukemia. *Blood* 2008;111(5):2573-  
26 80.  
27  
28 41. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual  
29 disease-defined high-risk subgroup of children and young people with clinical standard-risk and  
30 intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. *Lancet*  
31 *Oncology* 2014;15(8):809-18. doi: [http://dx.doi.org/10.1016/S1470-2045\(14\)70243-8](http://dx.doi.org/10.1016/S1470-2045(14)70243-8)  
32  
33 42. Wagner JE, Eapen M, Carter S, et al. One-unit versus two-unit cord-blood transplantation for  
34 hematologic cancers. *New England Journal of Medicine* 2014;371(18):1685-94.  
35  
36 43. Woods WG, Kobrinsky N, Buckley JD, et al. Timed-sequential induction therapy improves  
37 postremission outcome in acute myeloid leukemia: a report from the Children's Cancer Group. *Blood*  
38 1996;87(12):4979-89.  
39  
40  
41  
42  
43  
44  
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49  
50  
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**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 research/Fortschritte der Krebsforschung/Progres 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.



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2  
3 13. Arndt CAS, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared  
4 with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and  
5 cyclophosphamide for intermediate-risk rhabdomyosarcoma: Children's Oncology Group Study D9803.  
6 *Journal of Clinical Oncology* 2009;27(31):5182-88.  
7
- 8 14. Asselin BL, Devidas M, Chen L, et al. Cardioprotection and Safety of Dexrazoxane in Patients  
9 Treated for Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia or Advanced-Stage Lymphoblastic  
10 Non-Hodgkin Lymphoma: A Report of the Children's Oncology Group Randomized Trial Pediatric  
11 Oncology Group 9404. *Journal of Clinical Oncology* 2016;34(8):854-62. doi:  
12 <https://dx.doi.org/10.1200/JCO.2015.60.8851>  
13
- 14 15. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell  
15 lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the  
16 Children's Oncology Group (POG 9404). *Blood* 2011;118(4):874-83. doi:  
17 <http://dx.doi.org/10.1182/blood-2010-06-292615>  
18
- 19 16. Asselin BL, Kreissman S, Coppola DJ, et al. Prognostic significance of early response to a single dose  
20 of asparaginase in childhood acute lymphoblastic leukemia. *Journal of Pediatric Hematology/Oncology*  
21 1999;21(1):6-12.  
22
- 23 17. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of  
24 low-grade glioma in young children: A report from the Children's Oncology Group. *Journal of Clinical*  
25 *Oncology* 2012;30(21):2641-47.  
26
- 27 18. Attarbaschi A, Panzer-Grumayer R, Mann G, et al. Minimal residual disease-based treatment is  
28 adequate for relapse-prone childhood acute lymphoblastic leukemia with an intrachromosomal  
29 amplification of chromosome 21: the experience of the ALL-BFM 2000 trial. *Klinische Padiatrie*  
30 2014;226(6-7):338-43. doi: <http://dx.doi.org/10.1055/s-0034-1387795>  
31
- 32 19. Aur RJ, Simone JV, Hustu HO, et al. A comparative study of central nervous system irradiation and  
33 intensive chemotherapy early in remission of childhood acute lymphocytic leukemia. *Cancer*  
34 1972;29(2):381-91.  
35
- 36 20. Aur RJ, Simone JV, Verzosa MS, et al. Childhood acute lymphocytic leukemia: study VIII. *Cancer*  
37 1978;42(5):2123-34.  
38
- 39 21. Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native Escherichia coli  
40 asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly  
41 diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study. *Blood*  
42 2002;99(6):1986-94.  
43
- 44 22. Awada A, Colomer R, Inoue K, et al. Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in  
45 Previously Untreated Metastatic ERBB2-Positive Breast Cancer: The NEfERT-T Randomized Clinical  
46 Trial. *JAMA Oncol* 2016;2(12):1557-64. doi: <https://dx.doi.org/10.1001/jamaoncol.2016.0237>  
47
- 48 23. Bailey CC, Gnekow A, Wellek S, et al. Prospective randomised trial of chemotherapy given before  
49 radiotherapy in childhood medulloblastoma. International Society of Paediatric Oncology (SIOP) and the  
50 (German) Society of Paediatric Oncology (GPO): SIOP II. *Medical & Pediatric Oncology*  
51 1995;25(3):166-78.  
52
- 53 24. Balzarotti M, Brusamolino E, Angelucci E, et al. B-IGEV (bortezomib plus IGEV) versus IGEV  
54 before high-dose chemotherapy followed by autologous stem cell transplantation in relapsed or refractory  
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59



- 1  
2  
3 Hodgkin lymphoma: a randomized, phase II trial of the Fondazione Italiana Linfomi (FIL). *Leukemia &*  
4 *Lymphoma* 2016;57(10):2375-81. doi: <https://dx.doi.org/10.3109/10428194.2016.1140161>  
5  
6 25. Barry EV, Vrooman LM, Dahlberg SE, et al. Absence of secondary malignant neoplasms in children  
7 with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *Journal of Clinical Oncology*  
8 2008;26(7):1106-11. doi: <http://dx.doi.org/10.1200/JCO.2007.12.2481>  
9  
10 26. Batra V, Sands SA, Holmes E, et al. Long-term survival of children less than six years of age enrolled  
11 on the ccg-945 phase iii trial for newly-diagnosed high-grade glioma: A report from the children's  
12 oncology group. *Pediatric Blood and Cancer* 2014;61(1):151-57.  
13  
14 27. Baum E, Sather H, Nachman J. Relapse rates following cessation of chemotherapy during complete  
15 remission of acute lymphocytic leukemia. A report from Children's Cancer Study Group. *Medical and*  
16 *pediatric oncology* 1979;7(1):25-34.  
17  
18 28. Becton D, Dahl GV, Ravindranath Y, et al. Randomized use of cyclosporin A (CsA) to modulate P-  
19 glycoprotein in children with AML in remission: Pediatric Oncology Group Study 9421. *Blood*  
20 2006;107(4):1315-24.  
21  
22 29. Bernstein ML, Devidas M, Lafreniere D, et al. Intensive therapy with growth factor support for  
23 patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group  
24 Phase II Study 9457--a report from the Children's Oncology Group. *Journal of Clinical Oncology*  
25 2006;24(1):152-59.  
26  
27 30. Bertolone SJ, Yates AJ, Boyett JM, et al. Combined modality therapy for poorly differentiated  
28 gliomas of the posterior fossa in children: a Children's Cancer Group report. *Journal of neuro-oncology*  
29 2003;63(1):49-54.  
30  
31 31. Bhatia S, Krailo MD, Chen Z, et al. Therapy-related myelodysplasia and acute myeloid leukemia after  
32 Ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the Children's Oncology  
33 Group. *Blood* 2007;109(1):46-51.  
34  
35 32. Bhatla D, Gerbing RB, Alonzo TA, et al. Cytidine deaminase genotype and toxicity of cytosine  
36 arabinoside therapy in children with acute myeloid leukemia. *British journal of haematology*  
37 2009;144(3):388-94.  
38  
39 33. Bhatla D, Gerbing RB, Alonzo TA, et al. DNA repair polymorphisms and outcome of chemotherapy  
40 for acute myelogenous leukemia: A report from the Children's Oncology Group. *Leukemia*  
41 2008;22(2):265-72.  
42  
43 34. Biondi A, Schrappe M, De Lorenzo P, et al. Imatinib after induction for treatment of children and  
44 adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a  
45 randomised, open-label, intergroup study. *Lancet Oncology* 2012;13(9):936-45. doi:  
46 [http://dx.doi.org/10.1016/S1470-2045\(12\)70377-7](http://dx.doi.org/10.1016/S1470-2045(12)70377-7)  
47  
48 35. Bleyer WA, Sather HN, Nickerson HJ, et al. Monthly pulses of vincristine and prednisone prevent  
49 bone marrow and testicular relapse in low-risk childhood acute lymphoblastic leukemia: a report of the  
50 CCG-161 study by the Children's Cancer Study Group. *Journal of Clinical Oncology* 1991;9(6):1012-21.  
51  
52 36. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be  
53 treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials.  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*  
4 2003;21(5):774-80.  
5

6 37. Bond M, Bernstein ML, Pappo A, et al. A phase II study of imatinib mesylate in children with  
7 refractory or relapsed solid tumors: A children's oncology group study. *Pediatric Blood and Cancer*  
8 2008;50(2):254-58.  
9

10 38. Borowitz MJ, Wood BL, Devidas M, et al. Prognostic significance of minimal residual disease in high  
11 risk B-ALL: a report from Children's Oncology Group study AALL0232. *Blood* 2015;126(8):964-71. doi:  
12 <http://dx.doi.org/10.1182/blood-2015-03-633685>  
13

14 39. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus  
15 weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report  
16 from the Children's Cancer Group. *Blood* 2003;101(10):3809-17.  
17

18 40. Bradley KA, Pollack IF, Reid JM, et al. Motexafin gadolinium and involved field radiation therapy  
19 for intrinsic pontine glioma of childhood: A Children's Oncology Group phase i study. *Neuro-oncology*  
20 2008;10(5):752-58.  
21

22 41. Brecher ML, Schwenn MR, Coppes MJ, et al. Fractionated cylophosphamide and back to back high  
23 dose methotrexate and cytosine arabinoside improves outcome in patients with stage III high grade small  
24 non-cleaved cell lymphomas (SNCCCL): a randomized trial of the Pediatric Oncology Group. *Medical &*  
25 *Pediatric Oncology* 1997;29(6):526-33.  
26

27 42. Brecher ML, Weinberg V, Boyett JM, et al. Intermediate dose methotrexate in childhood acute  
28 lymphoblastic leukemia resulting in decreased incidence of testicular relapse. *Cancer* 1986;58(5):1024-  
29 28.  
30

31 43. Breitfeld PP, Lyden E, Raney RB, et al. Ifosfamide and etoposide are superior to vincristine and  
32 melphalan for pediatric metastatic rhabdomyosarcoma when administered with irradiation and  
33 combination chemotherapy: A report from the Intergroup Rhabdomyosarcoma Study Group. *Journal of*  
34 *Pediatric Hematology/Oncology* 2001;23(4):225-33.  
35  
36

37 44. Brugieres L, Le Deley M-C, Rosolen A, et al. Impact of the methotrexate administration dose on the  
38 need for intrathecal treatment in children and adolescents with anaplastic large-cell lymphoma: results of  
39 a randomized trial of the EICNHL Group. *Journal of Clinical Oncology* 2009;27(6):897-903. doi:  
40 <http://dx.doi.org/10.1200/JCO.2008.18.1487>  
41

42 45. Buchanan GR, Boyett JM, Pollock BH, et al. Improved treatment results in boys with overt testicular  
43 relapse during or shortly after initial therapy for acute lymphoblastic leukemia. A Pediatric Oncology  
44 group study. *Cancer* 1991;68(1):48-55.  
45

46 46. Bunin N, Aplenc R, Kamani N, et al. Randomized trial of busulfan vs total body irradiation containing  
47 conditioning regimens for children with acute lymphoblastic leukemia: A pediatric blood and marrow  
48 transplant consortium study. *Bone marrow transplantation* 2003;32(6):543-48.  
49

50 47. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high-risk central  
51 nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and  
52 adolescents. *Blood* 2007;109(7):2736-43.  
53

54 48. Cairo MS, Sposto R, HooverRegan M, et al. Childhood and adolescent large-cell lymphoma (LCL): A  
55 review of the Children's Cancer Group experience. *American Journal of Hematology* 2003;72(1):53-63.  
56  
57  
58  
59  
60

- 1  
2  
3 49. Calandra T, Gaya H, Zinner SH, et al. Monotherapy with meropenem versus combination therapy  
4 with ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer.  
5 *Antimicrobial Agents and Chemotherapy* 1996;40(5):1108-15.  
6
- 7 50. Camitta BM, Pinkel D, Thatcher LG. Failure of early intensive chemotherapy to improve prognosis in  
8 childhood acute lymphocytic leukemia. *Medical and pediatric oncology* 1980;8(4):383-89.  
9
- 10 51. Cangir A, Ragab AH, Steuber P. Combination chemotherapy with vincristine (NSC-67574),  
11 procarbazine (NSC-77213), prednisone (NSC-10023) with or without nitrogen mustard (NSC-  
12 762)(MOPP vs OPP) in children with recurrent brain tumors. *Medical and pediatric oncology*  
13 1984;12(1):1-3.  
14
- 15 52. Carli M, Pastore G, Perilongo G, et al. Tumor response and toxicity after single high-dose versus  
16 standard five-day divided-dose dactinomycin in childhood rhabdomyosarcoma. *Journal of Clinical*  
17 *Oncology* 1988;6(4):654-58.  
18
- 19 53. Castleberry RP, Cantor AB, Green AA, et al. Phase II investigational window using carboplatin,  
20 iproplatin, ifosfamide, and epirubicin in children with untreated disseminated neuroblastoma: a Pediatric  
21 Oncology Group study. *Journal of Clinical Oncology* 1994;12(8):1616-20.  
22
- 23 54. Castleberry RP, Kun LE, Shuster JJ, et al. Radiotherapy improves the outlook for patients older than 1  
24 year with Pediatric Oncology Group stage C neuroblastoma. *Journal of Clinical Oncology* 1991;9(5):789-  
25 95.  
26
- 27 55. Chagaluka G, Stanley C, Banda K, et al. Kaposi's sarcoma in children: an open randomised trial of  
28 vincristine, oral etoposide and a combination of vincristine and bleomycin. *European journal of cancer*  
29 2014;50(8):1472-81. doi: <http://dx.doi.org/10.1016/j.ejca.2014.02.019>  
30
- 31 56. Chan HSL, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer  
32 chemotherapy-induced emesis in children: A double-blind, crossover trial. *Pediatrics* 1987;79(6):946-52.  
33
- 34 57. Chen RW, Li H, Bernstein SH, et al. RB but not R-HCVAD is a feasible induction regimen prior to  
35 auto-HCT in frontline MCL: results of SWOG Study S1106. *British Journal of Haematology*  
36 2017;176(5):759-69. doi: <https://dx.doi.org/10.1111/bjh.14480>  
37
- 38 58. Cherlow JM, Steinherz PG, Sather HN, et al. The role of radiation therapy in the treatment of acute  
39 lymphoblastic leukemia with lymphomatous presentation: a report from the Childrens Cancer Group.  
40 *International journal of radiation oncology, biology, physics* 1993;27(5):1001-09.  
41
- 42 59. Chessells JM, Bailey C, Richards SM. Intensification of treatment and survival in all children with  
43 lymphoblastic leukaemia: results of UK Medical Research Council trial UKALL X. Medical Research  
44 Council Working Party on Childhood Leukaemia. *Lancet* 1995;345(8943):143-48.  
45
- 46 60. Chessells JM, Durrant J, Hardy RM, et al. Medical Research Council leukaemia trial--UKALL V: an  
47 attempt to reduce the immunosuppressive effects of therapy in childhood acute lymphoblastic leukemia.  
48 Report to the Council by the Working Party on Leukaemia in Childhood. *Journal of Clinical Oncology*  
49 1986;4(12):1758-64.  
50
- 51 61. Chessells JM, Harrison G, Richards SM, et al. Failure of a new protocol to improve treatment results  
52 in paediatric lymphoblastic leukaemia: Lessons from the UK Medical Research Council trials UKALL X  
53 and UKALL XI. *British journal of haematology* 2002;118(2):445-55.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 62. Chou AJ, Kleinerman ES, Krailo MD, et al. Addition of muramyl tripeptide to chemotherapy for  
4 patients with newly diagnosed metastatic osteosarcoma: a report from the Children's Oncology Group.  
5 *Cancer* 2009;115(22):5339-48. doi: <http://dx.doi.org/10.1002/cncr.24566>  
6
- 7 63. Chow EJ, Asselin BL, Schwartz CL, et al. Late Mortality After Dexrazoxane Treatment: A Report  
8 From the Children's Oncology Group. *Journal of Clinical Oncology* 2015;33(24):2639-45. doi:  
9 <http://dx.doi.org/10.1200/JCO.2014.59.4473>  
10
- 11 64. Clarke M, Gaynon P, Hann I, et al. CNS-directed therapy for childhood acute lymphoblastic  
12 leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials. *Journal of clinical*  
13 *oncology : official journal of the American Society of Clinical Oncology* 2003;21(9):1798-809.  
14
- 15 65. Cohen BH, Zeltzer PM, Boyett JM, et al. Prognostic factors and treatment results for supratentorial  
16 primitive neuroectodermal tumors in children using radiation and chemotherapy: a Childrens Cancer  
17 Group randomized trial. *Journal of Clinical Oncology* 1995;13(7):1687-96.  
18
- 19 66. Conner K, Sandler E, Weyman C, et al. Intravenous midazolam versus fentanyl as premedication for  
20 painful procedures in pediatric oncology patients. *Journal of Pediatric Oncology Nursing* 1991;8(2):86-  
21 87.  
22
- 23 67. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab Vedotin with Chemotherapy for Stage III or  
24 IV Hodgkin's Lymphoma.[Erratum appears in N Engl J Med. 2018 Mar 1;378(9):878; PMID: 29490175].  
25 *New England Journal of Medicine* 2018;378(4):331-44. doi: <https://dx.doi.org/10.1056/NEJMoa1708984>  
26
- 27 68. Conter V, Schrappe M, Arico M, et al. Role of cranial radiotherapy for childhood T-cell acute  
28 lymphoblastic leukemia with high WBC count and good response to prednisone. *Journal of Clinical*  
29 *Oncology* 1997;15(8):2786-91.  
30
- 31 69. Cortelazzo S, Tarella C, Gianni AM, et al. Randomized Trial Comparing R-CHOP Versus High-Dose  
32 Sequential Chemotherapy in High-Risk Patients With Diffuse Large B-Cell Lymphomas. *Journal of*  
33 *Clinical Oncology* 2016;34(33):4015-22. doi: <https://dx.doi.org/10.1200/JCO.2016.67.2980>  
34
- 35 70. Couban S, Simpson DR, Barnett MJ, et al. A randomized multicenter comparison of bone marrow and  
36 peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. *Blood*  
37 2002;100(5):1525-31.  
38
- 39 71. CoustanSmith E, Sancho J, Hancock ML, et al. Clinical importance of minimal residual disease in  
40 childhood acute lymphoblastic leukemia. *Blood* 2000;96(8):2691-96.  
41
- 42 72. Coze C, Hartmann O, Michon J, et al. NB87 induction protocol for stage 4 neuroblastoma in children  
43 over 1 year of age: a report from the French Society of Pediatric Oncology. *Journal of Clinical Oncology*  
44 1997;15(12):3433-40.  
45
- 46 73. Creutzig U, Ritter J, Zimmermann M, et al. Idarubicin improves blast cell clearance during induction  
47 therapy in children with AML: Results of study AML-BFM 93. *Leukemia* 2001;15(3):348-54.  
48
- 49 74. Creutzig U, Ritter J, Zimmermann M, et al. Does cranial irradiation reduce the risk for bone marrow  
50 relapse in acute myelogenous leukemia? Unexpected results of the Childhood Acute Myelogenous  
51 Leukemia Study BFM-87. *Journal of Clinical Oncology* 1993;11(2):279-86.  
52
- 53 75. Creutzig U, Ritter J, Zimmermann M, et al. Superior results by cranial irradiation in children with  
54 acute myelogenous leukemia: An update of study AML-BFM-87. *Onkologie* 1994;17(1):66-68.  
55  
56  
57  
58  
59  
60

- 1  
2  
3 76. Creutzig U, Semmler J, Kaspers GL, et al. Re-induction with L-DNR/FLAG improves response after  
4 AML relapse, but not long-term survival. *Klinische Padiatrie* 2014;226(6-7):323-31. doi:  
5 <http://dx.doi.org/10.1055/s-0034-1385918>  
6
- 7 77. Crist W, Boyett J, Jackson J, et al. Prognostic importance of the pre-B-cell immunophenotype and  
8 other presenting features in B-lineage childhood acute lymphoblastic leukemia: a Pediatric Oncology  
9 Group study. *Blood* 1989;74(4):1252-59.  
10
- 11 78. Crist W, Gehan EA, Ragab AH, et al. The Third Intergroup Rhabdomyosarcoma Study. *Journal of*  
12 *Clinical Oncology* 1995;13(3):610-30.  
13
- 14 79. Crist W, Shuster J, Look T, et al. Current results of studies of immunophenotype-, age- and leukocyte-  
15 based therapy for children with acute lymphoblastic leukemia. *Leukemia* 1992;6(SUPPL. 2):162-66.  
16
- 17 80. Culbert SJ, Shuster JJ, Land VJ, et al. Remission induction and continuation therapy in children with  
18 their first relapse of acute lymphoid leukemia. A Pediatric Oncology Group study. *Cancer* 1991;67(1):37-  
19 42.  
20
- 21 81. Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with  
22 etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with  
23 high-risk malignant germ cell tumors: a pediatric intergroup study--Pediatric Oncology Group 9049 and  
24 Children's Cancer Group 8882. *Journal of Clinical Oncology* 2004;22(13):2691-700.  
25
- 26 82. Dahl GV, Lacayo NJ, Brophy N, et al. Mitoxantrone, etoposide, and cyclospine therapy in pediatric  
27 patients with recurrent or refractory acute myeloid leukemia. *Journal of Clinical Oncology*  
28 2000;18(9):1867-75.  
29
- 30 83. D'Angio GJ, Evans A, Breslow N. The treatment of Wilms' tumor: Results of the second National  
31 Wilms' Tumor Study. *Cancer* 1981;47(9):2302-11.  
32
- 33 84. D'Angio GJ, Littman P, Nesbit M. Evaluation of radiation therapy factors in prophylactic central  
34 nervous system irradiation for childhood leukemia: A report from the children's cancer study group.  
35 *International Journal of Radiation Oncology Biology Physics* 1981;7(8):1031-38.  
36
- 37 85. De Camargo B, Franco EL. Single-dose versus fractionated-dose dactinomycin in the treatment of  
38 Wilms' tumor: Preliminary results of a clinical trial. *Cancer* 1991;67(12):2990-96.  
39
- 40 86. De Camargo B, Franco EL. A randomized clinical trial of single-dose versus fractionated-dose  
41 dactinomycin in the treatment of Wilms' tumor: Results after extended follow- up. *Cancer*  
42 1994;73(12):3081-86.  
43
- 44 87. de Kraker J, Graf N, van Tinteren H, et al. Reduction of postoperative chemotherapy in children with  
45 stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial.  
46 *Lancet* 2004;364(9441):1229-35.  
47
- 48 88. De Moerloose B, Suciu S, Bertrand Y, et al. Improved outcome with pulses of vincristine and  
49 corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL)  
50 and lymphoblastic non-Hodgkin lymphoma (NHL): report of the EORTC randomized phase 3 trial 58951.  
51 *Blood* 2010;116(1):36-44. doi: <http://dx.doi.org/10.1182/blood-2009-10-247965>  
52
- 53 89. Deutsch M, Thomas PR, Krischer J, et al. Results of a prospective randomized trial comparing  
54 standard dose neuraxis irradiation (3,600 cGy/20) with reduced neuraxis irradiation (2,340 cGy/13) in  
55  
56  
57  
58  
59



- 1  
2  
3 patients with low-stage medulloblastoma. A Combined Children's Cancer Group-Pediatric Oncology  
4 Group Study. *Pediatric neurosurgery* 1996;24(4):167-76.  
5
- 6 90. Dharmarajan KV, Friedman DL, Schwartz CL, et al. Patterns of relapse from a phase 3 Study of  
7 response-based therapy for intermediate-risk Hodgkin lymphoma (AHOD0031): a report from the  
8 Children's Oncology Group. *International journal of radiation oncology, biology, physics* 2015;92(1):60-  
9 66. doi: <http://dx.doi.org/10.1016/j.ijrobp.2014.10.042>  
10
- 11 91. Dinndorf PA, Gootenberg J, Cohen MH, et al. FDA drug approval summary: Pegaspargase  
12 (Oncaspar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). *Oncologist*  
13 2007;12(8):991-98.  
14
- 15 92. Doering EJ, Nitschke R, Haggard ME. Phase II study demonstrating failure of both a five-drug  
16 continuous-therapy regimen and a two-drug pulse-therapy regimen in the treatment of metastatic  
17 neuroblastoma: Southwest Oncology Group Study 822. *Cancer treatment reports* 1979;63(8):1383-84.  
18
- 19 93. Donaldson SS, Asmar L, Breneman J, et al. Hyperfractionated radiation in children with  
20 rhabdomyosarcoma - Results of an intergroup rhabdomyosarcoma pilot study. *International Journal of*  
21 *Radiation Oncology Biology Physics* 1995;32(4):903-11.  
22
- 23 94. Donaldson SS, Meza J, Breneman JC, et al. Results from the IRS-IV randomized trial of  
24 hyperfractionated radiotherapy in children with rhabdomyosarcoma--a report from the IRSG.  
25 *International journal of radiation oncology, biology, physics* 2001;51(3):718-28.  
26
- 27 95. Donaldson SS, Torrey M, Link MP, et al. A multidisciplinary study investigating radiotherapy in  
28 Ewing's sarcoma: end results of POG #8346. Pediatric Oncology Group. *International journal of*  
29 *radiation oncology, biology, physics* 1998;42(1):125-35.  
30
- 31 96. Eden OB, Lilleyman JS, Richards S, et al. Results of Medical Research Council Childhood  
32 Leukaemia Trial UKALL VIII (report to the Medical Research Council on behalf of the Working Party on  
33 Leukaemia in Childhood). *British journal of haematology* 1991;78(2):187-96.  
34
- 35 97. Ehlers S, Herbst C, Zimmermann M, et al. Granulocyte colony-stimulating factor (G-CSF) treatment  
36 of childhood acute myeloid leukemias that overexpress the differentiation-defective G-CSF receptor  
37 isoform IV is associated with a higher incidence of relapse. *Journal of Clinical Oncology*  
38 2010;28(15):2591-97.  
39
- 40 98. Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with relapsed  
41 ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the  
42 Berlin-Frankfurt-Munster Group 87. *Journal of clinical oncology : official journal of the American*  
43 *Society of Clinical Oncology* 2005;23(31):7942-50.  
44
- 45 99. Ekert H, Waters KD, Matthews RN. A randomized study of intermittent chemotherapy with or  
46 without BCG inoculation in maintenance therapy of childhood ALL. *Medical and pediatric oncology*  
47 1980;8(4):353-60.  
48
- 49 100. Elder JS. Results of the Sixth International Society of Pediatric Oncology Wilms' tumor trial and  
50 study: a risk-adapted therapeutic approach in Wilms' tumor. *The Journal of urology* 1994;152(1):271-72.  
51
- 52 101. Escherich G, Zimmermann M, Janka-Schaub G. Doxorubicin or daunorubicin given upfront in a  
53 therapeutic window are equally effective in children with newly diagnosed acute lymphoblastic leukemia.  
54 A randomized comparison in trial CoALL 07-03. *Pediatric Blood and Cancer* 2013;60(2):254-57.  
55  
56  
57  
58  
59



- 1  
2  
3 102. Evans AE, Albo V, D'Angio GJ. Cyclophosphamide treatment of patients with localized and  
4 regional neuroblastoma. A randomized study. *Cancer* 1976;38(2):655-59.  
5  
6 103. Evans AE, Anderson JR, Lefkowitz-Boudreaux IB, et al. Adjuvant chemotherapy of childhood  
7 posterior fossa ependymoma: cranio-spinal irradiation with or without adjuvant CCNU, vincristine, and  
8 prednisone: a Childrens Cancer Group study. *Medical & Pediatric Oncology* 1996;27(1):8-14.  
9  
10 104. Evans WE, Crom WR, Stewart CF, et al. Methotrexate systemic clearance influences probability of  
11 relapse in children with standard-risk acute lymphocytic leukaemia. *Lancet* 1984;1(8373):359-62.  
12  
13 105. Falsini B, Chiaretti A, Rizzo D, et al. Nerve growth factor improves visual loss in childhood optic  
14 gliomas: A randomized, double-blind, phase II clinical trial. *Brain* 2016;139(2):404-14.  
15  
16 106. Feig SA, Ames MM, Sather HN, et al. Comparison of idarubicin to daunomycin in a randomized  
17 multidrug treatment of childhood acute lymphoblastic leukemia at first bone marrow relapse: a report  
18 from the Children's Cancer Group. *Medical & Pediatric Oncology* 1996;27(6):505-14.  
19  
20 107. Feig SA, Harris RE, Sather HN. Bone marrow transplantation versus chemotherapy for maintenance  
21 of second remission of childhood acute lymphoblastic leukemia: A study of the children's cancer group  
22 (CCG-1884). *Medical and pediatric oncology* 1997;29(6):534-40.  
23  
24 108. Fernbach DJ, George SL, Sutow WW, et al. Long-term results of reinforcement therapy in children  
25 with acute leukemia. *Cancer* 1975;36(5):1552-59.  
26  
27 109. Ferrant A, Hulhoven R, Bosly A, et al. Clinical trials with daunorubicin-DNA and adriamycin-DNA  
28 in acute lymphoblastic leukemia of childhood, acute nonlymphoblastic leukemia, and bronchogenic  
29 carcinoma. *Cancer Chemotherapy & Pharmacology* 1979;2(1):67-71.  
30  
31 110. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade  
32 astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen.  
33 Childrens Cancer Group. *Journal of Clinical Oncology* 1995;13(1):112-23.  
34  
35 111. Flaherty LE, Othus M, Atkins MB, et al. Southwest Oncology Group S0008: a phase III trial of high-  
36 dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in  
37 patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B, Children's  
38 Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Journal of*  
39 *Clinical Oncology* 2014;32(33):3771-78. doi: <http://dx.doi.org/10.1200/JCO.2013.53.1590>  
40  
41 112. Flamant F, Rodary C, Voute PA, et al. Primary chemotherapy in the treatment of rhabdomyosarcoma  
42 in children: Trial of the international society of pediatric oncology (SIOP) preliminary results.  
43 *Radiotherapy and Oncology* 1985;3(3):227-36.  
44  
45 113. Fouladi M, Stewart CF, Blaney SM, et al. A molecular biology and phase II trial of lapatinib in  
46 children with refractory CNS malignancies: a pediatric brain tumor consortium study. *Journal of neuro-*  
47 *oncology* 2013;114(2):173-79.  
48  
49 114. Freeman AI, Boyett JM, Glicksman AS, et al. Intermediate-dose methotrexate versus cranial  
50 irradiation in childhood acute lymphoblastic leukemia: a ten-year follow-up. *Medical & Pediatric*  
51 *Oncology* 1997;28(2):98-107.  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 115. Freeman AI, Weinberg V, Brecher ML, et al. Comparison of intermediate-dose methotrexate with  
4 cranial irradiation for the post-induction treatment of acute lymphocytic leukemia in children. *New*  
5 *England Journal of Medicine* 1983;308(9):477-84.  
6
- 7 116. Freeman CR, Kepner J, Kun LE, et al. A detrimental effect of a combined chemotherapy-  
8 radiotherapy approach in children with diffuse intrinsic brain stem gliomas? *International Journal of*  
9 *Radiation Oncology Biology Physics* 2000;47(3):561-64.  
10
- 11 117. Freyer DR, Devidas M, La M, et al. Postrelapse survival in childhood acute lymphoblastic leukemia  
12 is independent of initial treatment intensity: A report from the Children's Oncology Group. *Blood*  
13 2011;117(11):3010-15.  
14
- 15 118. Fujimoto T, Goya H, Nakagawa K. Comparison of high dose infusion of methotrexate (MTX) vs  
16 sequential complementary method for maintenance of remission in acute childhood leukemia. A  
17 cooperative study. *Proceedings of the American Association for Cancer Research* 1975;16(66):no.257.  
18
- 19 119. Gardner H, Grois N, Potschger U, et al. Improved outcome in multisystem Langerhans cell  
20 histiocytosis is associated with therapy intensification. *Blood* 2008;111(5):2556-62. doi: 10.1182/blood-  
21 2007-08-106211 [published Online First: 2007/12/20]  
22
- 23 120. Gamis AS, Alonzo TA, Meshinchi S, et al. Gemtuzumab ozogamicin in children and adolescents  
24 with de novo acute myeloid leukemia improves event-free survival by reducing relapse risk: results from  
25 the randomized phase III Children's Oncology Group trial AAML0531. *Journal of Clinical Oncology*  
26 2014;32(27):3021-32.  
27
- 28 121. Gangopadhyay AN, Rajeev R, Sharma SP, et al. Anterior intratumoural chemotherapy: a newer  
29 modality of treatment in advanced solid tumours in children. *Asian Journal of Surgery* 2008;31(4):225-  
30 29. doi: [http://dx.doi.org/10.1016/S1015-9584\(08\)60092-5](http://dx.doi.org/10.1016/S1015-9584(08)60092-5)  
31
- 32 122. Gautam A, Zhu Y, Ma E, et al. Brentuximab vedotin consolidation post-autologous stem cell  
33 transplant in Hodgkin lymphoma patients at risk of residual disease: number needed to treat. *Leukemia &*  
34 *Lymphoma* 2018;59(1):69-76. doi: <https://dx.doi.org/10.1080/10428194.2017.1324160>  
35
- 36 123. Gaynon PS, Steinherz PG, Bleyer WA, et al. Intensive therapy for children with acute lymphoblastic  
37 leukaemia and unfavourable presenting features. Early conclusions of study CCG-106 by the Childrens  
38 Cancer Study Group. *Lancet* 1988;2(8617):921-24.  
39
- 40 124. Gaynon PS, Steinherz PG, Bleyer WA, et al. Improved therapy for children with acute lymphoblastic  
41 leukemia and unfavorable presenting features: a follow-up report of the Childrens Cancer Group Study  
42 CCG-106. *Journal of Clinical Oncology* 1993;11(11):2234-42.  
43
- 44 125. George RE, London WB, Cohn SL, et al. Hyperdiploidy plus nonamplified MYCN confers a  
45 favorable prognosis in children 12 to 18 months old with disseminated neuroblastoma: a Pediatric  
46 Oncology Group study. *Journal of clinical oncology : official journal of the American Society of Clinical*  
47 *Oncology* 2005;23(27):6466-73.  
48
- 49 126. Geyer JR, Sposto R, Jennings M, et al. Multiagent chemotherapy and deferred radiotherapy in  
50 infants with malignant brain tumors: a report from the Children's Cancer Group. *Journal of Clinical*  
51 *Oncology* 2005;23(30):7621-31.  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 127. Gibson BES, Webb DKH, Howman AJ, et al. Results of a randomized trial in children with Acute  
4 Myeloid Leukaemia: Medical Research Council AML12 trial. *British journal of haematology*  
5 2011;155(3):366-76.  
6  
7 128. Gibson BES, Wheatley K, Hann IM, et al. Treatment strategy and long-term results in paediatric  
8 patients treated in consecutive UK AML trials. *Leukemia* 2005;19(12):2130-38.  
9  
10 129. Gilchrist GS, Tubergen DG, Sather HN, et al. Low numbers of CSF blasts at diagnosis do not predict  
11 for the development of CNS leukemia in children with intermediate-risk acute lymphoblastic leukemia: A  
12 Childrens Cancer Group report. *Journal of Clinical Oncology* 1994;12(12):2594-600.  
13  
14 130. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase  
15 and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*  
16 2001;97(10):2998-3003.  
17  
18 131. Goorin AM, Schwartzentruber DJ, Devidas M, et al. Presurgical chemotherapy compared with  
19 immediate surgery and adjuvant chemotherapy for nonmetastatic osteosarcoma: Pediatric Oncology  
20 Group Study POG-8651. *Journal of Clinical Oncology* 2003;21(8):1574-80.  
21  
22 132. Granowetter L, Womer R, Devidas M, et al. Dose-intensified compared with standard chemotherapy  
23 for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. *Journal of*  
24 *Clinical Oncology* 2009;27(15):2536-41. doi: <http://dx.doi.org/10.1200/JCO.2008.19.1478>  
25  
26 133. Green DM, Breslow NE, Beckwith JB, et al. Comparison between single-dose and divided-dose  
27 administration of dactinomycin and doxorubicin for patients with Wilms' tumor: a report from the  
28 National Wilms' Tumor Study Group. *Journal of Clinical Oncology* 1998;16(1):237-45.  
29  
30 134. Haas-Kogan DA, Swift PS, Selch M, et al. Impact of radiotherapy for high-risk neuroblastoma: a  
31 Children's Cancer Group study. *International journal of radiation oncology, biology, physics*  
32 2003;56(1):28-39.  
33  
34 135. Harris MB, Shuster JJ, Carroll A, et al. Trisomy of leukemic cell chromosomes 4 and 10 identifies  
35 children with B- progenitor cell acute lymphoblastic leukemia with a very low risk of treatment failure: A  
36 Pediatric Oncology Group Study. *Blood* 1992;79(12):3316-24.  
37  
38 136. Harris MB, Shuster JJ, Pullen J, et al. Treatment of children with early pre-B and pre-B acute  
39 lymphocytic leukemia with antimetabolite-based intensification regimens: A pediatric oncology group  
40 study. *Leukemia* 2000;14(9):1570-76.  
41  
42 137. Hasle H, Abrahamsson J, Forestier E, et al. Gemtuzumab ozogamicin as postconsolidation therapy  
43 does not prevent relapse in children with AML: Results from NOPHO-AML 2004. *Blood*  
44 2012;120(5):978-84.  
45  
46 138. Heath JA, Steinherz PG, Altman A, et al. Human granulocyte colony-stimulating factor in children  
47 with high-risk acute lymphoblastic leukemia: a Children's Cancer Group Study. *Journal of Clinical*  
48 *Oncology* 2003;21(8):1612-17.  
49  
50 139. Heerema NA, Carroll AJ, Devidas M, et al. Intrachromosomal amplification of chromosome 21 is  
51 associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary  
52 standard-risk children's oncology group studies: a report from the children's oncology group. *Journal of*  
53 *clinical oncology : official journal of the American Society of Clinical Oncology* 2013;31(27):3397-402.  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 140. Henze G, Fengler R, Hartmann R, et al. Six-year experience with a comprehensive approach to the  
4 treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85). A relapse study of  
5 the BFM group. *Blood* 1991;78(5):1166-72.  
6
- 7 141. Horstmann M, Escherich G. Treatment of acute lymphoblastic leucemia of childhood: Interim report  
8 CoALL 08-09. *78 Wissenschaftlichen Halbjahrestagung der Gesellschaft fur Padiatrische Onkologie und*  
9 *Hamatologie, GPOH Frankfurt Germany* 2011;159(10):1006-07. doi: [http://dx.doi.org/10.1007/s00112-](http://dx.doi.org/10.1007/s00112-011-2482-7)  
10 [011-2482-7](http://dx.doi.org/10.1007/s00112-011-2482-7)  
11
- 12 142. Hough R, Rowntree C, Goulden N, et al. Efficacy and toxicity of a paediatric protocol in teenagers  
13 and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from  
14 UKALL 2003. *British Journal of Haematology* 2016;172(3):439-51. doi:  
15 <https://dx.doi.org/10.1111/bjh.13847>  
16
- 17 143. Hutchinson RJ, Fryer CJ, Davis PC, et al. MOPP or radiation in addition to ABVD in the treatment  
18 of pathologically staged advanced Hodgkin's disease in children: results of the Children's Cancer Group  
19 Phase III Trial. *Journal of Clinical Oncology* 1998;16(3):897-906.  
20
- 21 144. Hutchinson RJ, Gaynon PS, Sather H, et al. Intensification of therapy for children with lower-risk  
22 acute lymphoblastic leukemia: long-term follow-up of patients treated on Children's Cancer Group Trial  
23 1881. *Journal of Clinical Oncology* 2003;21(9):1790-97.  
24
- 25 145. Igarashi S, Manabe A, Ohara A, et al. No advantage of dexamethasone over prednisolone for the  
26 outcome of standard- and intermediate-risk childhood acute lymphoblastic leukemia in the Tokyo  
27 Children's Cancer Study Group L95-14 protocol. *Journal of Clinical Oncology* 2005;23(27):6489-98.  
28
- 29 146. Jabbour E, Short NJ, Ravandi F, et al. A randomized phase 2 study of idarubicin and cytarabine with  
30 clofarabine or fludarabine in patients with newly diagnosed acute myeloid leukemia. *Cancer*  
31 2017;123(22):4430-39. doi: <https://dx.doi.org/10.1002/ncr.30883>  
32
- 33 147. Jacquillat C, Weil M, Auclerc MF. Application of the study of prognostic factors to the treatment of  
34 childhood (<20 years old) acute lymphoblastic leukemia. Protocol 08 LA 74. *Bulletin du cancer*  
35 1980;67(4):458-69.  
36
- 37 148. JankaSchaub GE, Winkler K, Gobel U, et al. Rapidly rotating combination chemotherapy in  
38 childhood acute lymphoblastic leukemia: Preliminary results of a randomized comparison with  
39 conventional treatment. *Leukemia* 1988;2(12 SUPPL):73s-78s.  
40
- 41 149. Jaramillo S, Benner A, Krauter J, et al. Condensed versus standard schedule of high-dose cytarabine  
42 consolidation therapy with pegfilgrastim growth factor support in acute myeloid leukemia. *Blood Cancer*  
43 *J* 2017;7(5):e564. doi: <https://dx.doi.org/10.1038/bcj.2017.45>  
44
- 45 150. Jenkin RD, Boesel C, Ertel I, et al. Brain-stem tumors in childhood: a prospective randomized trial  
46 of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Children's Cancer  
47 Study Group. *Journal of neurosurgery* 1987;66(2):227-33.  
48
- 49 151. Jennings MT, Sposto R, Boyett JM, et al. Preradiation chemotherapy in primary high-risk brainstem  
50 tumors: phase II study CCG-9941 of the Children's Cancer Group. *Journal of Clinical Oncology*  
51 2002;20(16):3431-37.  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 152. Johnson P, Federico M, Kirkwood A, et al. Adapted Treatment Guided by Interim PET-CT Scan in  
4 Advanced Hodgkin's Lymphoma. *New England Journal of Medicine* 2016;374(25):2419-29. doi:  
5 <https://dx.doi.org/10.1056/NEJMoa1510093>  
6
- 7 153. Johnson PWM, Sydes MR, Hancock BW, et al. Consolidation radiotherapy in patients with  
8 advanced Hodgkin's lymphoma: Survival data from the UKLG LY09 randomized controlled trial  
9 (ISRCTN97144519). *Journal of Clinical Oncology* 2010;28(20):3352-59.  
10
- 11 154. Jones PHM, Pearson D, Johnson AL. Management of nephroblastoma in childhood. Clinical study of  
12 two forms of maintenance chemotherapy. *Archives of Disease in Childhood* 1978;53(2):112-19.  
13
- 14 155. Junjun J, Xuelian Z, Dhruva K, et al. Efficacy of preoperative chemotherapy in treatment of children  
15 with wilms' tumor: A meta-analysis. *Iranian Journal of Pediatrics* 2015;25(2) (pagination):Arte Number:  
16 e366. ate of Pubaton: 2015. doi: <http://dx.doi.org/10.5812/ijp.366>  
17
- 18 156. Kamps WA, Bokkerink JP, Hahlen K, et al. Intensive treatment of children with acute lymphoblastic  
19 leukemia according to ALL-BFM-86 without cranial radiotherapy: results of Dutch Childhood Leukemia  
20 Study Group Protocol ALL-7 (1988-1991). *Blood* 1999;94(4):1226-36.  
21
- 22 157. Kamps WA, Bokkerink JPM, HakvoortCammel FG AJ, et al. BFM-oriented treatment for children  
23 with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk  
24 patients: Results of DCLSG protocol ALL-8 (1991-1996). *Leukemia* 2002;16(6):1099-111.  
25
- 26 158. Kantarjian HM, DeAngelo DJ, Stelljes M, et al. Inotuzumab Ozogamicin versus Standard Therapy  
27 for Acute Lymphoblastic Leukemia. *New England Journal of Medicine* 2016;375(8):740-53. doi:  
28 <https://dx.doi.org/10.1056/NEJMoa1509277>  
29
- 30 159. Karachunskiy A, Herold R, von Stackelberg A, et al. Results of the first randomized multicentre trial  
31 on childhood acute lymphoblastic leukaemia in Russia. *Leukemia* 2008;22(6):1144-53.  
32
- 33 160. Karol SE, CoustanSmith E, Cao X, et al. Prognostic factors in children with acute myeloid  
34 leukaemia and excellent response to remission induction therapy. *British journal of haematology*  
35 2015;168(1):94-101.  
36
- 37 161. Karon M, Freireich EJ, Frei E, et al. The role of vincristine in the treatment of childhood acute  
38 leukemia. *Clinical pharmacology and therapeutics* 1966;7(3):332-39.  
39
- 40 162. Kaspers GJL, Zimmermann M, Reinhardt D, et al. Improved outcome in pediatric relapsed acute  
41 myeloid leukemia: Results of a randomized trial on liposomal daunorubicin by the international BFM  
42 study group. *Journal of Clinical Oncology* 2013;31(5):599-607.  
43
- 44 163. Kato M, Koh K, Manabe A, et al. No impact of high-dose cytarabine and asparaginase as early  
45 intensification with intermediate-risk paediatric acute lymphoblastic leukaemia: results of randomized  
46 trial TCCSG study L99-15. *British journal of haematology* 2014;164(3):376-83. doi:  
47 <http://dx.doi.org/10.1111/bjh.12632>  
48
- 49 164. Katzenstein HM, Krailo MD, Malogolowkin MH, et al. Hepatocellular carcinoma in children and  
50 adolescents: results from the Pediatric Oncology Group and the Children's Cancer Group intergroup  
51 study. *Journal of Clinical Oncology* 2002;20(12):2789-97.  
52
- 53 165. Katzenstein HM, Krailo MD, Malogolowkin MH, et al. Fibrolamellar hepatocellular carcinoma in  
54 children and adolescents. *Cancer* 2003;97(8):2006-12.  
55  
56  
57  
58  
59



- 1  
2  
3 166. Kawano Y, Takaue Y, Mimaya J, et al. Marginal benefit/disadvantage of granulocyte colony-stimulating factor therapy after autologous blood stem cell transplantation in children: results of a  
4 prospective randomized trial. The Japanese Cooperative Study Group of PBSCT. *Blood*  
5 1998;92(11):4040-46.  
6  
7  
8 167. Ko RH, Jones TL, Radvinsky D, et al. Allergic reactions and anti-asparaginase antibodies in children  
9 with high-risk acute lymphoblastic leukemia: A children's oncology group report. *Cancer*  
10 2015;121(23):4205-11.  
11  
12 168. Kobrinsky NL, Packer RJ, Boyett JM, et al. Etoposide with or without mannitol for the treatment of  
13 recurrent or primarily unresponsive brain tumors: a Children's Cancer Group Study, CCG-9881. *Journal*  
14 *of neuro-oncology* 1999;45(1):47-54.  
15  
16 169. Kohler JA, Imeson J, Ellershaw C, et al. A randomized trial of 13-Cis retinoic acid in children with  
17 advanced neuroblastoma after high-dose therapy. *British journal of cancer* 2000;83(9):1124-27.  
18  
19 170. Koizumi S, Fujimoto T. Improvement in treatment of childhood acute lymphoblastic leukemia: a 10-  
20 year study by the Children's Cancer and Leukemia Study Group. *International journal of hematology*  
21 1994;59(2):99-112.  
22  
23 171. Koizumi S, Fujimoto T, Oka T, et al. Overview of clinical studies of childhood acute lymphoblastic  
24 leukemia for more than ten years by the Japanese Children's Cancer and Leukemia Study Group.  
25 *Pediatric hematology and oncology* 1997;14(1):17-28.  
26  
27 172. Koizumi S, Fujimoto T, Takeda T, et al. Comparison of intermittent or continuous methotrexate plus  
28 6-mercaptopurine in regimens for standard-risk acute lymphoblastic leukemia in childhood (JCCLSG-  
29 S811). The Japanese Children's Cancer and Leukemia Study Group. *Cancer* 1988;61(7):1292-300.  
30  
31 173. Kojima S, Hibi S, Kosaka Y, et al. Immunosuppressive therapy using antithymocyte globulin,  
32 cyclosporine, and danazol with or without human granulocyte colony-stimulating factor in children with  
33 acquired aplastic anemia. *Blood* 2000;96(6):2049-54.  
34  
35 174. Kortmann RD, Kuhl J, Timmermann B, et al. Postoperative neoadjuvant chemotherapy before  
36 radiotherapy as compared to immediate radiotherapy followed by maintenance chemotherapy in the  
37 treatment of medulloblastoma in childhood: results of the German prospective randomized trial HIT '91.  
38 *International journal of radiation oncology, biology, physics* 2000;46(2):269-79.  
39  
40 175. Krailo M, Ertel I, Makley J, et al. A randomized study comparing high-dose methotrexate with  
41 moderate-dose methotrexate as components of adjuvant chemotherapy in childhood nonmetastatic  
42 osteosarcoma: a report from the Children's Cancer Study Group. *Medical & Pediatric Oncology*  
43 1987;15(2):69-77.  
44  
45 176. Kramm C, Roth D, Wolff JEA. First results of the randomized clinical trial HIT-GBM-D for  
46 treatment of children and adolescents with high grade glioma. *78 Wissenschaftlichen Halbjahrestagung*  
47 *der Gesellschaft für Pädiatrische Onkologie und Hamatologie, GPOH Frankfurt Germany*  
48 2011;159(10):1005. doi: <http://dx.doi.org/10.1007/s00112-011-2482-7>  
49  
50 177. Krischer J, Land VJ, Civin CI, et al. Evaluation of AMSA in children with acute leukemia. A  
51 Pediatric Oncology Group study. *Cancer* 1984;54(2):207-10.  
52  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 178. Krischer JP, Ragab AH, Kun L, et al. Nitrogen mustard, vincristine, procarbazine, and prednisone as  
4 adjuvant chemotherapy in the treatment of medulloblastoma. A Pediatric Oncology Group study. *Journal*  
5 *of neurosurgery* 1991;74(6):905-09.  
6  
7 179. Kuhl J, Muller HL, Berthold F, et al. Preradiation chemotherapy of children and young adults with  
8 malignant brain tumors: results of the German pilot trial HIT'88/'89. *Klinische Padiatrie*  
9 1998;210(4):227-33.  
10  
11 180. Kurtzberg J, Asselin B, Bernstein M, et al. Polyethylene Glycol-conjugated L-asparaginase versus  
12 native L-asparaginase in combination with standard agents for children with acute lymphoblastic  
13 leukemia in second bone marrow relapse: a Children's Oncology Group Study (POG 8866). *Journal of*  
14 *Pediatric Hematology/Oncology* 2011;33(8):610-16. doi:  
15 <http://dx.doi.org/10.1097/MPH.0b013e31822d4d4e>  
16  
17 181. Lampkin BC, Woods WG, Buckley JD, et al. Preliminary results of intensive therapy of children and  
18 adolescents with acute nonlymphocytic leukemia--a Children's Cancer Study Group report. *Haematology*  
19 *and blood transfusion* 1990;33:210-14.  
20  
21 182. Land VJ, Shuster JJ, Crist WM, et al. Comparison of two schedules of intermediate-dose  
22 methotrexate and cytarabine consolidation therapy for childhood B-precursor cell acute lymphoblastic  
23 leukemia: a Pediatric Oncology Group study. *Journal of Clinical Oncology* 1994;12(9):1939-45.  
24  
25 183. Land VJ, Thomas PR, Boyett JM, et al. Comparison of maintenance treatment regimens for first  
26 central nervous system relapse in children with acute lymphocytic leukemia. A Pediatric Oncology Group  
27 study. *Cancer* 1985;56(1):81-87.  
28  
29 184. Landmann E, Burkhardt B, Zimmermann M, et al. Results and conclusions of the European  
30 Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma. *Haematologica*  
31 2017;102(12):2086-96. doi: <https://dx.doi.org/10.3324/haematol.2015.139162>  
32  
33 185. Lange BJ, Bostrom BC, Cherlow JM, et al. Double-delayed intensification improves event-free  
34 survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's  
35 Cancer Group. *Blood* 2002;99(3):825-33.  
36  
37 186. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG-2961, a children's oncology group phase 3  
38 trial for untreated pediatric acute myeloid leukemia: a report from the children's oncology group. *Blood*  
39 2008;111(3):1044-53.  
40  
41 187. Lannering B, Rutkowski S, Doz F, et al. Hyperfractionated versus conventional radiotherapy  
42 followed by chemotherapy in standard-risk medulloblastoma: Results from the randomized multicenter  
43 HIT-SIOP PNET 4 trial. *Journal of Clinical Oncology* 2012;30(26):3187-93.  
44  
45 188. Larsen EC, Devidas M, Chen S, et al. Dexamethasone and High-Dose Methotrexate Improve  
46 Outcome for Children and Young Adults With High-Risk B-Acute Lymphoblastic Leukemia: A Report  
47 From Children's Oncology Group Study AALL0232. *Journal of Clinical Oncology* 2016;34(20):2380-8.  
48 doi: <https://dx.doi.org/10.1200/JCO.2015.62.4544>  
49  
50 189. Laskar S, Gupta T, Vimal S, et al. Consolidation radiation after complete remission in Hodgkin's  
51 disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is  
52 there a need? *J Clin Oncol* 2004;22(1):62-8. doi: 10.1200/jco.2004.01.021 [published Online First:  
53 2003/12/06]  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 190. Laver JH, Barredo JC, Amylon M, et al. Effects of cranial radiation in children with high risk T cell  
4 acute lymphoblastic leukemia: A Pediatric Oncology Group report. *Leukemia* 2000;14(3):369-73.  
5
- 6 191. Laver JH, Mahmoud H, Pick TE, et al. Results of a randomized phase III trial in children and  
7 adolescents with advanced stage diffuse large cell non Hodgkin's lymphoma: a Pediatric Oncology Group  
8 study. *Leukemia & lymphoma* 2001;42(3):399-405.  
9
- 10 192. Le Deley MC, Guinebretiere JM, Gentet JC, et al. SFOP OS94: A randomised trial comparing  
11 preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and  
12 ifosfamide in osteosarcoma patients. *European journal of cancer* 2007;43(4):752-61.  
13
- 14 193. Lehrnbecher T, Varwig D, Kaiser J, et al. Infectious complications in pediatric acute myeloid  
15 leukemia: Analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukemia*  
16 2004;18(1):72-77.  
17
- 18 194. Lehrnbecher T, Zimmermann M, Reinhardt D, et al. Prophylactic human granulocyte colony-  
19 stimulating factor after induction therapy in pediatric acute myeloid leukemia. *Blood* 2007;109(3):936-43.  
20
- 21 195. Lemerle J, Voute PA, Tournade MF, et al. Preoperative versus postoperative radiotherapy, single  
22 versus multiple courses of actinomycin D, in the treatment of Wilms' tumor. Preliminary results of a  
23 controlled clinical trial conducted by the International Society of Paediatric Oncology (S.I.O.P.). *Cancer*  
24 1976;38(2):647-54.  
25
- 26 196. Lemerle J, Voute PA, Tournade MF, et al. Effectiveness of preoperative chemotherapy in Wilms'  
27 tumor: results of an International Society of Paediatric Oncology (SIOP) clinical trial. *Journal of Clinical*  
28 *Oncology* 1983;1(10):604-09.  
29
- 30 197. Lewis IJ, Nooij MA, Whelan J, et al. Improvement in histologic response but not survival in  
31 osteosarcoma patients treated with intensified chemotherapy: A randomized phase III trial of the european  
32 osteosarcoma intergroup. *Journal of the National Cancer Institute* 2007;99(2):112-28.  
33
- 34 198. Li X, Cui Y, Sun Z, et al. DDGP versus SMILE in Newly Diagnosed Advanced Natural Killer/T-  
35 Cell Lymphoma: A Randomized Controlled, Multicenter, Open-label Study in China. *Clinical Cancer*  
36 *Research* 2016;22(21):5223-28.  
37
- 38 199. Liang DC, Hung IJ, Yang CP, et al. Unexpected mortality from the use of E. coli L-asparaginase  
39 during remission induction therapy for childhood acute lymphoblastic leukemia: a report from the Taiwan  
40 Pediatric Oncology Group. *Leukemia* 1999;13(2):155-60.  
41
- 42 200. Liang DC, Yang CP, Lin DT, et al. Long-term results of Taiwan Pediatric Oncology Group studies  
43 1997 and 2002 for childhood acute lymphoblastic leukemia. *Leukemia* 2010;24(2):397-405. doi:  
44 <http://dx.doi.org/10.1038/leu.2009.248>  
45
- 46 201. Lilleyman JS, Campbell RHA. Vindesine in relapsed childhood ALL. A pilot study by the United  
47 Kingdom children's cancer study group. *European Paediatric Haematology and Oncology* 1984;1(1):37-  
48 38.  
49
- 50 202. Link MP, Goorin AM, Miser AW. The effect of adjuvant chemotherapy on relapse-free survival in  
51 patients with osteosarcoma of the extremity. *New England Journal of Medicine* 1986;314(25):1600-06.  
52
- 53 203. Link MP, Shuster JJ, Donaldson SS, et al. Treatment of children and young adults with early-stage  
54 non-hodgkin's lymphoma. *New England Journal of Medicine* 1997;337(18):1259-66.  
55  
56  
57  
58  
59

- 1  
2  
3 204. Lipshultz SE, Miller TL, Lipsitz SR, et al. Continuous Versus Bolus Infusion of Doxorubicin in  
4 Children With ALL: Long-term Cardiac Outcomes. *Pediatrics* 2012;130(6):1003-11. doi:  
5 <http://dx.doi.org/10.1542/peds.2012-0727>  
6
- 7 205. Lipton JH, Chuah C, Guerci-Bresler A, et al. Ponatinib versus imatinib for newly diagnosed chronic  
8 myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *Lancet Oncology*  
9 2016;17(5):612-21. doi: [https://dx.doi.org/10.1016/S1470-2045\(16\)00080-2](https://dx.doi.org/10.1016/S1470-2045(16)00080-2)  
10
- 11 206. Littman P, Coccia P, Bleyer WA, et al. Central nervous system (CNS) prophylaxis in children with  
12 low risk acute lymphoblastic leukemia (ALL). *International journal of radiation oncology, biology,*  
13 *physics* 1987;13(10):1443-49.  
14
- 15 207. Locatelli F, Zecca M, Rondelli R, et al. Graft versus host disease prophylaxis with low-dose  
16 cyclosporine-A reduces the risk of relapse in children with acute leukemia given HLA- identical sibling  
17 bone marrow transplantation: Results of a randomized trial. *Blood* 2000;95(5):1572-79.  
18
- 19 208. London WB, Frantz CN, Campbell LA, et al. Phase II randomized comparison of topotecan plus  
20 cyclophosphamide versus topotecan alone in children with recurrent or refractory neuroblastoma: a  
21 Children's Oncology Group study. *Journal of Clinical Oncology* 2010;28(24):3808-15. doi:  
22 <http://dx.doi.org/10.1200/JCO.2009.27.5016>  
23
- 24 209. Loning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-  
25 Munster therapy of acute lymphoblastic leukemia in childhood: Significantly lower risk without cranial  
26 radiotherapy. *Blood* 2000;95(9):2770-75.  
27
- 28 210. LopezHernandez MA, Alvarado M, De Diego J, et al. A randomized trial of dexamethasone before  
29 remission induction, in de novo childhood acute lymphoblastic leukemia. *Haematologica* 2004;89(3):365-  
30 66.  
31
- 32 211. Lucchese A, Matarese G, Manuelli M, et al. Reliability and efficacy of palifermin in prevention and  
33 management of oral mucositis in patients with acute lymphoblastic leukemia: A randomized, double-blind  
34 controlled clinical trial. *Minerva stomatologica* 2016;65(1):43-53.  
35
- 36 212. MacDonald TJ, Arenson EB, Ater J, et al. Phase II study of high-dose chemotherapy before radiation  
37 in children with newly diagnosed high-grade astrocytoma: Final Analysis of Children's Cancer Group  
38 Study 9933. *Cancer* 2005;104(12):2862-71.  
39
- 40 213. Mahoney Jr DH, Camitta BM, Devidas M. Does intravenous 6-mercaptopurine decrease salvage  
41 after relapse in childhood acute lymphoblastic leukemia? [3]. *Pediatric Blood and Cancer*  
42 2006;46(5):660-61.  
43
- 44 214. Malogolowkin MH, Katzenstein H, Krailo MD, et al. Intensified platinum therapy is an ineffective  
45 strategy for improving outcome in pediatric patients with advanced hepatoblastoma. *Journal of Clinical*  
46 *Oncology* 2006;24(18):2879-84.  
47
- 48 215. Manabe A, Tsuchida M, Hanada R, et al. Delay of the diagnostic lumbar puncture and intrathecal  
49 chemotherapy in children with acute lymphoblastic leukemia who undergo routine corticosteroid testing:  
50 Tokyo Children's Cancer Study Group Study L89-12. *Journal of Clinical Oncology* 2001;19(13):3182-87.  
51
- 52 216. Mandell LR, Kadota R, Freeman C, et al. There is no role for hyperfractionated radiotherapy in the  
53 management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric  
54  
55  
56  
57  
58  
59

Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. *International journal of radiation oncology, biology, physics* 1999;43(5):959-64.

217. Marina NM, Pappo AS, Parham DM, et al. Chemotherapy dose-intensification for pediatric patients with Ewing's family of tumors and desmoplastic small round-cell tumors: a feasibility study at St. Jude Children's Research Hospital. *Journal of Clinical Oncology* 1999;17(1):180-90.

218. Maris JM, Weiss MJ, Guo C, et al. Loss of heterozygosity at 1p36 independently predicts for disease progression but not decreased overall survival probability in neuroblastoma patients: A children's cancer group study. *Journal of Clinical Oncology* 2000;18(9):1888-99.

219. Mascarenhas L, Lyden ER, Breitfeld PP, et al. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. *Journal of Clinical Oncology* 2010;28(30):4658-63. doi: <http://dx.doi.org/10.1200/JCO.2010.29.7390>

220. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood* 2011;118(2):243-51. doi: <http://dx.doi.org/10.1182/blood-2010-12-322909>

221. Matloub Y, Lindemulder S, Gaynon PS, et al. Intrathecal triple therapy decreases central nervous system relapse but fails to improve event-free survival when compared with intrathecal methotrexate: results of the Children's Cancer Group (CCG) 1952 study for standard-risk acute lymphoblastic leukemia, reported by the Children's Oncology Group. *Blood* 2006;108(4):1165-73.

222. Matsuzaki A, Okamura J, Ishii E, et al. Treatment of standard-risk acute lymphoblastic leukemia in children: The results of protocol AL841 from the Kyushu-Yamaguchi Children's Cancer Study Group in Japan. *Pediatric hematology and oncology* 1999;16(3):187-99.

223. Matthay KK, Reynolds CP, Seeger RC, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *Journal of Clinical Oncology* 2009;27(7):1007-13. doi: <http://dx.doi.org/10.1200/JCO.2007.13.8925>

224. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. Children's Cancer Group. *New England Journal of Medicine* 1999;341(16):1165-73.

225. Maurer HM, Beltangady M, Gehan EA, et al. The Intergroup Rhabdomyosarcoma Study-I. A final report. *Cancer* 1988;61(2):209-20.

226. McWilliams NB, Hayes FA, Green AA, et al. Cyclophosphamide/doxorubicin vs. cisplatin/teniposide in the treatment of children older than 12 months of age with disseminated neuroblastoma: a Pediatric Oncology Group Randomized Phase II study. *Medical & Pediatric Oncology* 1995;24(3):176-80.

227. Meadows AT, Sposto R, Jenkin RD, et al. Similar efficacy of 6 and 18 months of therapy with four drugs (COMP) for localized non-Hodgkin's lymphoma of children: a report from the Children's Cancer Study Group. *Journal of Clinical Oncology* 1989;7(1):92-99.

- 1  
2  
3 228. Mehta P, Gardner R, Graham-Pole J, et al. Methylprednisolone is effective in chemotherapy-induced  
4 emesis: Results of a double blind randomized trial in children. *Proceedings of the American Association*  
5 *for Cancer Research* 1985;26:No. 602.  
6
- 7 229. Meyers PA, Schwartz CL, Krailo M, et al. Osteosarcoma: A randomized, prospective trial of the  
8 addition of ifosfamide and/or muramyl tripeptide to cisplatin, doxorubicin, and high-dose methotrexate.  
9 *Journal of Clinical Oncology* 2005;23(9):2004-11.  
10
- 11 230. Meyers PA, Schwartz CL, Krailo MD, et al. Osteosarcoma: the addition of muramyl tripeptide to  
12 chemotherapy improves overall survival--a report from the Children's Oncology Group. *Journal of*  
13 *Clinical Oncology* 2008;26(4):633-38. doi: <http://dx.doi.org/10.1200/JCO.2008.14.0095>  
14
- 15 231. Michel G, Landman-Parker J, Auclerc MF, et al. Use of recombinant human granulocyte colony-  
16 stimulating factor to increase chemotherapy dose-intensity: a randomized trial in very high-risk childhood  
17 acute lymphoblastic leukemia. *Journal of Clinical Oncology* 2000;18(7):1517-24.  
18
- 19 232. Michon JM, Hartmann O, Bouffet E, et al. An open-label, multicentre, randomised phase 2 study of  
20 recombinant human granulocyte colony-stimulating factor (filgrastim) as an adjunct to combination  
21 chemotherapy in paediatric patients with metastatic neuroblastoma. *European journal of cancer*  
22 1998;34(7):1063-69.  
23
- 24 233. Miller DR, Coccia PF, Bleyer WA, et al. Early response to induction therapy as a predictor of  
25 disease-free survival and late recurrence of childhood acute lymphoblastic leukemia: a report from the  
26 Children's Cancer Study Group. *Journal of Clinical Oncology* 1989;7(12):1807-15.  
27
- 28 234. Miller DR, Leikin SL, Albo VC, et al. Three versus five years of maintenance therapy are equivalent  
29 in childhood acute lymphoblastic leukemia: a report from the Children's Cancer Study Group. *Journal of*  
30 *Clinical Oncology* 1989;7(3):316-25.  
31
- 32 235. Milpied N, Deconinck E, Gaillard F, et al. Initial Treatment of Aggressive Lymphoma with High-  
33 Dose Chemotherapy and Autologous Stem-Cell Support. *New England Journal of Medicine*  
34 2004;350(13):1287-95.  
35
- 36 236. Miser JS, Krailo MD, Tarbell NJ, et al. Treatment of metastatic Ewing's sarcoma or primitive  
37 neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide--a Children's Cancer  
38 Group and Pediatric Oncology Group study. *Journal of Clinical Oncology* 2004;22(14):2873-76.  
39
- 40 237. Miser JS, Pritchard DJ, Rock MG, et al. Osteosarcoma in adolescents and young adults: new  
41 developments and controversies. The Mayo Clinic studies. *Cancer treatment and research* 1993;62:333-  
42 38.  
43
- 44 238. Miser JS, Roloff J, Blatt J, et al. Lack of significant activity of 2'-deoxycoformycin alone or in  
45 combination with adenine arabinoside in relapsed childhood acute lymphoblastic leukemia. A randomized  
46 phase II trial from the Children's Cancer Study Group. *American Journal of Clinical Oncology*  
47 1992;15(6):490-93.  
48
- 49 239. Mitchell C, Pritchard-Jones K, Shannon R, et al. Immediate nephrectomy versus preoperative  
50 chemotherapy in the management of non-metastatic Wilms' tumour: results of a randomised trial (UKW3)  
51 by the UK Children's Cancer Study Group. *European journal of cancer* 2006;42(15):2554-62.  
52
- 53 240. Mo XD, Zhang XH, Xu LP, et al. Comparison of outcomes after donor lymphocyte infusion with or  
54 without prior chemotherapy for minimal residual disease in acute leukemia/myelodysplastic syndrome  
55  
56  
57  
58  
59



- 1  
2  
3 after allogeneic hematopoietic stem cell transplantation. *Ann Hematol* 2017;96(5):829-38. doi:  
4 <https://dx.doi.org/10.1007/s00277-017-2960-7>  
5
- 6 241. Mo XD, Zhao XY, Liu DH, et al. Umbilical cord blood transplantation and unmanipulated  
7 haploidentical hematopoietic SCT for pediatric hematologic malignances. *Bone marrow transplantation*  
8 2014;49(8):1070-75.  
9
- 10 242. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL  
11 Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood* 2007;109(3):896-904.  
12
- 13 243. Moorman AV, Ensor HM, Richards SM, et al. Prognostic effect of chromosomal abnormalities in  
14 childhood B-cell precursor acute lymphoblastic leukaemia: Results from the UK Medical Research  
15 Council ALL97/99 randomised trial. *The Lancet Oncology* 2010;11(5):429-38.  
16
- 17 244. Mori T, Fukano R, Saito A, et al. Analysis of Japanese registration from the randomized  
18 international trial for childhood anaplastic large cell lymphoma (ALCL99-R1). [*Rinsho ketsueki*] *The*  
19 *Japanese journal of clinical hematology* 2014;55(5):526-33.  
20
- 21 245. Moricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia  
22 can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and  
23 adolescent patients enrolled in the trial ALL-BFM 95. *Blood* 2008;111(9):4477-89. doi:  
24 <http://dx.doi.org/10.1182/blood-2007-09-112920>  
25
- 26 246. Mott MG, Eden OB, Palmer MK. Adjuvant low dose radiation in childhood non-Hodgkin's  
27 lymphoma. (Report from the United Kingdom Childrens' Cancer Study Group - UKCCSG). *British*  
28 *journal of cancer* 1984;50(4):463-69.  
29
- 30 247. Movassaghi N, Higgins G, Pyesmany A. Evaluation of cycloctidine in reinduction and maintenance  
31 therapy of children with acute nonlymphocytic leukemia previously treated with cytosine arabinoside: A  
32 report from children's cancer study group. *Medical and pediatric oncology* 1984;12(5):352-56.  
33
- 34 248. Murphy SB, Hustu HO. A randomized trial of combined modality therapy of childhood non-  
35 Hodgkin's lymphoma. *Cancer* 1980;45(4):630-37.  
36
- 37 249. Nachman JB, La MK, Hunger SP, et al. Young adults with acute lymphoblastic leukemia have an  
38 excellent outcome with chemotherapy alone and benefit from intensive postinduction treatment: a report  
39 from the children's oncology group. *Journal of Clinical Oncology* 2009;27(31):5189-94. doi:  
40 <http://dx.doi.org/10.1200/JCO.2008.20.8959>  
41
- 42 250. Nesbit M, Sather H, Robison L. The duration of chemotherapy for childhood acute lymphoblastic  
43 leukemia (ALL): A randomized study of 316 patients. *Proceedings of the American Society of Clinical*  
44 *Oncology* Vol 1982;1:480.  
45
- 46 251. Nesbit ME, Jr., Buckley JD, Feig SA, et al. Chemotherapy for induction of remission of childhood  
47 acute myeloid leukemia followed by marrow transplantation or multiagent chemotherapy: a report from  
48 the Childrens Cancer Group. *Journal of Clinical Oncology* 1994;12(1):127-35.  
49
- 50 252. Nesbit ME, Sather H, Robison LL, et al. Sanctuary therapy: a randomized trial of 724 children with  
51 previously untreated acute lymphoblastic leukemia: A Report from Children's Cancer Study Group.  
52 *Cancer research* 1982;42(2):674-80.  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 253. Nesbit ME, Jr., Sather HN, Robison LL, et al. Presymptomatic central nervous system therapy in  
4 previously untreated childhood acute lymphoblastic leukaemia: comparison of 1800 rad and 2400 rad. A  
5 report for Children's Cancer Study Group. *Lancet* 1981;1(8218):461-66.  
6
- 7 254. Nesbit ME, Jr., Sather HN, Robison LL, et al. Randomized study of 3 years versus 5 years of  
8 chemotherapy in childhood acute lymphoblastic leukemia. *Journal of Clinical Oncology* 1983;1(5):308-  
9 16.  
10
- 11 255. Neudorf S, Sanders J, Kobrinsky N, et al. Autologous bone marrow transplantation for children with  
12 AML in first remission. *Bone marrow transplantation* 2007;40(4):313-18.  
13
- 14 256. Neudorf S, Sanders J, Kobrinsky N, et al. Allogeneic bone marrow transplantation for children with  
15 acute myelocytic leukemia in first remission demonstrates a role for graft versus leukemia in the  
16 maintenance of disease-free survival. *Blood* 2004;103(10):3655-61.  
17
- 18 257. Oberlin O, Rey A, Sanchez de Toledo J, et al. Randomized comparison of intensified six-drug versus  
19 standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other  
20 chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society  
21 of Pediatric Oncology MMT95 study. *Journal of Clinical Oncology* 2012;30(20):2457-65. doi:  
22 <http://dx.doi.org/10.1200/JCO.2011.40.3287>  
23
- 24 258. O'Connor D, Bartram J, Enshaei A, et al. Integration of minimal residual disease with other patient  
25 risk factors identifies a population with very poor overall survival in pediatric ALL: Results from the  
26 UKALL 2003 trial. *57th Annual Meeting of the American Society of Hematology, ASH 2015 San Diego,*  
27 *CA United States* 2015;126(23):1412.  
28
- 29 259. Ortega JA, Douglass EC, Feusner JH, et al. Randomized comparison of  
30 cisplatin/vincristine/fluorouracil and cisplatin/continuous infusion doxorubicin for treatment of pediatric  
31 hepatoblastoma: A report from the Children's Cancer Group and the Pediatric Oncology Group. *Journal*  
32 *of Clinical Oncology* 2000;18(14):2665-75.  
33
- 34 260. Ortega JJ, Javier G, Olive T. Treatment of standard- and high-risk childhood acute lymphoblastic  
35 leukaemia with two CNS prophylaxis regimens. *Haematology & Blood Transfusion* 1987;30:483-92.  
36
- 37 261. Ortega JJ, Ribera JM, Oriol A, et al. Early and delayed consolidation chemotherapy significantly  
38 improves the outcome of children with intermediate-risk acute lymphoblastic leukemia. Final results of  
39 the prospective randomized PETHEMA ALL-89 TRIAL. *Haematologica* 2001;86(6):586-95.  
40
- 41 262. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by  
42 adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *Journal of Clinical Oncology*  
43 2006;24(25):4202-08.  
44
- 45 263. Packer RJ, Zhou T, Holmes E, et al. Survival and secondary tumors in children with  
46 medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology  
47 Group trial A9961. *Neuro-oncology* 2013;15(1):97-103. doi: <http://dx.doi.org/10.1093/neuonc/nos267>  
48
- 49 264. Parker C, Waters R, Leighton C, et al. Effect of mitoxantrone on outcome of children with first  
50 relapse of acute lymphoblastic leukaemia (ALL R3): an open-label randomised trial. *Lancet*  
51 2010;376(9757):2009-17. doi: [http://dx.doi.org/10.1016/S0140-6736\(10\)62002-8](http://dx.doi.org/10.1016/S0140-6736(10)62002-8)  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 265. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for  
4 intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce  
5 treatment for the early responding patients. *Blood* 2007;109(7):2773-80.  
6
- 7 266. Patte C, Philip T, Rodary C, et al. High survival rate in advanced-stage B-cell lymphomas and  
8 leukemias without CNS involvement with a short intensive polychemotherapy: results from the French  
9 Pediatric Oncology Society of a randomized trial of 216 children. *Journal of Clinical Oncology*  
10 1991;9(1):123-32.  
11
- 12 267. Paulussen M, Craft AW, Lewis I, et al. Results of the EICESS-92 study: Two randomized trials of  
13 Ewing's sarcoma treatment - Cyclophosphamide compared with ifosfamide in standard-risk patients and  
14 assessment of benefit of etoposide added to standard treatment in high-risk patients. *Journal of Clinical*  
15 *Oncology* 2008;26(27):4385-93.  
16
- 17 268. Payandeh M, Najafi S, Shojaiyan FZ, et al. Phase III of Study of R-CHOP-21 vs R-CHOP-14 for  
18 Untreated Stage III and IV B-cell Non-Hodgkin's Lymphoma: a Report from Iran. *Asian Pac J Cancer*  
19 *Prev* 2016;17(3):1513-7.  
20
- 21 269. Pearson ADJ, Pinkerton CR, Lewis IJ, et al. High-dose rapid and standard induction chemotherapy  
22 for patients aged over 1 year with stage 4 neuroblastoma: a randomised trial. *Lancet Oncology*  
23 2008;9(3):247-56. doi: [http://dx.doi.org/10.1016/S1470-2045\(08\)70069-X](http://dx.doi.org/10.1016/S1470-2045(08)70069-X)  
24
- 25 270. Perel Y, Auvrignon A, Leblanc T, et al. Impact of addition of maintenance therapy to intensive  
26 induction and consolidation chemotherapy for childhood acute myeloblastic leukemia: Results of a  
27 prospective randomized trial, LAME 89/91. *Journal of Clinical Oncology* 2002;20(12):2774-82.  
28
- 29 271. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended use  
30 of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. *Journal of*  
31 *Clinical Oncology* 2005;23(28):7161-67.  
32
- 33 272. Place AE, Stevenson KE, Vrooman LM, et al. Intravenous pegylated asparaginase versus  
34 intramuscular native Escherichia coli L-asparaginase in newly diagnosed childhood acute lymphoblastic  
35 leukaemia (DFCI 05-001): a randomised, open-label phase 3 trial. *Lancet Oncology* 2015;16(16):1677-90.  
36 doi: [http://dx.doi.org/10.1016/S1470-2045\(15\)00363-0](http://dx.doi.org/10.1016/S1470-2045(15)00363-0)  
37
- 38 273. Pollack IF, Hamilton RL, Sobol RW, et al. O6-Methylguanine-DNA methyltransferase expression  
39 strongly correlates with outcome in childhood malignant gliomas: Results from the CCG-945 cohort.  
40 *Journal of Clinical Oncology* 2006;24(21):3431-37.  
41
- 42 274. Pollard JA, Loken M, Gerbing RB, et al. CD33 expression and its association with gemtuzumab  
43 ozogamicin response: Results from the randomized phase III children's oncology group trial AAML0531.  
44 *Journal of Clinical Oncology* 2016;34(7):747-55.  
45
- 46 275. Pratt CB, Maurer HM, Gieser P, et al. Treatment of unresectable or metastatic pediatric soft tissue  
47 sarcomas with surgery, irradiation, and chemotherapy: a Pediatric Oncology Group study. *Medical &*  
48 *Pediatric Oncology* 1998;30(4):201-09.  
49
- 50 276. Pratt CB, Pappo AS, Gieser P, et al. Role of adjuvant chemotherapy in the treatment of surgically  
51 resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: A Pediatric Oncology Group Study.  
52 *Journal of Clinical Oncology* 1999;17(4):1219-26.  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 277. Pritchard J, Cotterill SJ, Germond SM, et al. High dose melphalan in the treatment of advanced  
4 neuroblastoma: Results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group.  
5 *Pediatric Blood and Cancer* 2005;44(4):348-57.  
6
- 7 278. Pritchard-Jones K, Bergeron C, de Camargo B, et al. Omission of doxorubicin from the treatment of  
8 stage II-III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised  
9 controlled trial. *Lancet* 2015;386(9999):1156-64. doi: [http://dx.doi.org/10.1016/S0140-6736\(14\)62395-3](http://dx.doi.org/10.1016/S0140-6736(14)62395-3)  
10
- 11 279. Pui CH, Aur RJA, Bowman WP. Failure of late intensification therapy to improve a poor result in  
12 childhood lymphoblastic leukemia. *Cancer research* 1984;44(8):3593-98.  
13
- 14 280. Pui CH, Simone JV, Hancock ML, et al. Impact of three methods of treatment intensification on  
15 acute lymphoblastic leukemia in children: long-term results of St Jude total therapy study X. *Leukemia*  
16 1992;6(2):150-57.  
17
- 18 281. Pulsipher MA, Langholz B, Wall DA, et al. The addition of sirolimus to tacrolimus/methotrexate  
19 GVHD prophylaxis in children with ALL: a phase 3 Children's Oncology Group/Pediatric Blood and  
20 Marrow Transplant Consortium trial. *Blood* 2014;123(13):2017-25. doi: [http://dx.doi.org/10.1182/blood-](http://dx.doi.org/10.1182/blood-2013-10-534297)  
21 2013-10-534297  
22
- 23 282. Raemaekers JM, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission  
24 tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse:  
25 Clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial.  
26 *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*  
27 2014;32(12):1188-94.  
28
- 29 283. Ragab AH, Boyett JM, Frankel L, et al. Rubidazone in the treatment of recurrent acute leukemia in  
30 children. A Pediatric Oncology Group Study. *Cancer* 1986;57(8):1461-63.  
31
- 32 284. Rausen AR, Glidewell O, Cuttner J. Superiority of L-asparaginase combination chemotherapy in  
33 advanced acute lymphocytic leukemia of childhood. Randomized comparative trial of combination versus  
34 solo therapy. *Cancer clinical trials* 1979;2(2):137-44.  
35
- 36 285. Ravindranath Y, Yeager AM, Chang MN, et al. Autologous bone marrow transplantation versus  
37 intensive consolidation chemotherapy for acute myeloid leukemia in childhood. Pediatric Oncology  
38 Group. *New England Journal of Medicine* 1996;334(22):1428-34.  
39
- 40 286. Reinhard H, Semler O, Burger D, et al. Results of the SIOP 93-01/GPOH trial and study for the  
41 treatment of patients with unilateral nonmetastatic wilms tumor. *Klinische Padiatrie* 2004;216(3):132-40.  
42
- 43 287. Reiter A, Schrappe M, Ludwig WD, et al. Intensive ALL-type therapy without local radiotherapy  
44 provides a 90% event-free survival for children with T-cell lymphoblastic lymphoma: A BFM Group  
45 report. *Blood* 2000;95(2):416-21.  
46
- 47 288. Rescorla F, Billmire D, Stolar C, et al. The effect of cisplatin dose and surgical resection in children  
48 with malignant germ cell tumors at the sacrococcygeal region: A pediatric intergroup trial (POG  
49 9049/CCG 8882). *Journal of pediatric surgery* 2001;36(1):12-17.  
50
- 51 289. Richards S, Burrett J, Hann I, et al. Improved survival with early intensification: Combined results  
52 from The Medical Research Council childhood ALL randomised trials, UKALL X and UKALL XI.  
53 *Leukemia* 1998;12(7):1031-36.  
54  
55  
56  
57  
58  
59

- 1  
2  
3 290. Richards S, Gray R, Peto R, et al. Duration and intensity of maintenance chemotherapy in acute  
4 lymphoblastic leukaemia: Overview of 42 trials involving 12,000 randomised children. *Lancet*  
5 1996;347(9018):1783-88.  
6  
7 291. Rivera G, Avery T, Pratt C. 4' Demethylepipodophyllotoxin 9 (4,6 O 2 thenylidene beta D  
8 glucopyranoside) (NSC 122819; VM 26) and 4' demethylepipodophyllotoxin 9 (4,6 O ethylidene beta D  
9 glucopyranoside) (NSC 141540; VP 16 213) in childhood cancer: preliminary observations. *CANCER*  
10 *CHEMOTHERREP* 1975;59(4):743-49.  
11  
12 292. Rivera G, Murphy SB, Aur RJA. Recurrent childhood lymphocytic leukemia. Clinical and  
13 cytokinetic studies of cytosine arabinoside and methotrexate for maintenance of second hematologic  
14 remission. *Cancer* 1978;42(6):2521-28.  
15  
16 293. Rivera GK, Raimondi SC, Hancock ML, et al. Improved outcome in childhood acute lymphoblastic  
17 leukaemia with reinforced early treatment and rotational combination chemotherapy. *Lancet*  
18 1991;337(8733):61-66.  
19  
20 294. Rizzari C, Valsecchi MG, Arico M, et al. Effect of protracted high-dose L-asparaginase given as a  
21 second exposure in a Berlin-Frankfurt-Munster-based treatment: Results of the randomized 9102  
22 intermediate-risk childhood acute lymphoblastic leukemia study - A report from the Associazione Italiana  
23 Ematologia Oncologia Pediatrica. *Journal of Clinical Oncology* 2001;19(5):1297-303.  
24  
25 295. Rodeberg DA, Wharam MD, Lyden ER, et al. Delayed primary excision with subsequent  
26 modification of radiotherapy dose for intermediate-risk rhabdomyosarcoma: A report from the Children's  
27 Oncology Group Soft Tissue Sarcoma Committee. *International Journal of Cancer* 2015;137(1):204-11.  
28  
29 296. Roos DE, Smith JG. Randomized trial on radiotherapy for paediatric diffuse intrinsic pontine glioma  
30 (DIPG). *Radiotherapy & Oncology* 2014;113(3):425. doi: <http://dx.doi.org/10.1016/j.radonc.2014.08.041>  
31  
32 297. Rubnitz JE, Crews KR, Pounds S, et al. Combination of cladribine and cytarabine is effective for  
33 childhood acute myeloid leukemia: Results of the St Jude AML97 trial. *Leukemia* 2009;23(8):1410-16.  
34  
35 298. Rutkowski S, von Bueren A, von Hoff K, et al. Prognostic relevance of clinical and biological risk  
36 factors in childhood medulloblastoma: results of patients treated in the prospective multicenter trial  
37 HIT'91. *Clinical Cancer Research* 2007;13(9):2651-57.  
38  
39 299. Sackmann Muriel F, Svarch E, Pavlovsky S. Alternating pulses of vincristine-prednisone with  
40 cytarabine-cyclophosphamide versus vincristine-prednisone in the maintenance therapy of acute  
41 lymphoblastic leukemia. *Cancer treatment reports* 1984;68(4):581-86.  
42  
43 300. Sackmann Muriel F, Morgenfeld M, Kvicala R. Hodgkin's disease in childhood. Therapy results in  
44 Argentina. *American Journal of Pediatric Hematology/Oncology* 1981;3(3):247-54.  
45  
46 301. Sackmann-Muriel F, Zubizarreta P, Gallo G, et al. Hodgkin disease in children: results of a  
47 prospective randomized trial in a single institution in Argentina. *Medical & Pediatric Oncology*  
48 1997;29(6):544-52.  
49  
50 302. Sallan SE, Hitchcock Bryan S, Gelber R. Influence of intensive asparaginase in the treatment of  
51 childhood non-T-cell acute lymphoblastic leukemia. *Cancer research* 1983;43(11):5601-07.  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 303. Schmiegelow K, Bjork O, Glomstein A, et al. Intensification of mercaptopurine/methotrexate  
4 maintenance chemotherapy may increase the risk of relapse for some children with acute lymphoblastic  
5 leukemia. *Journal of Clinical Oncology* 2003;21(7):1332-39.  
6
- 7 304. Schrappe M, Reiter A, Henze G, et al. Prevention of CNS recurrence in childhood ALL: Results with  
8 reduced radiotherapy combined with CNS-directed chemotherapy in four consecutive ALL- BFM trials.  
9 *Klinische Padiatrie* 1998;210(4):192-99.  
10
- 11 305. Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic  
12 leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90.  
13 German-Austrian-Swiss ALL-BFM Study Group. *Blood* 2000;95(11):3310-22.  
14
- 15 306. Sebban C, Browman GP, Lepage E, et al. Prognostic value of early response to chemotherapy  
16 assessed by the day 15 bone marrow aspiration in adult acute lymphoblastic leukemia: A prospective  
17 analysis of 437 cases and its application for designing induction chemotherapy trials. *Leukemia research*  
18 1995;19(11):861-68.  
19
- 20 307. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves  
21 survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the  
22 Children's Oncology Group. *Blood* 2008;111(5):2548-55.  
23
- 24 308. Sellar RS, Rowntree C, Vora AJ, et al. Relapse in teenage and young adult (TYA) patients treated on  
25 a pediatric minimal residual disease (MRD) stratified protocol is associated with a poor outcome: Results  
26 from UKALL2003. *57th Annual Meeting of the American Society of Hematology, ASH 2015 San Diego,*  
27 *CA United States* 2015;126(23):2493.  
28
- 29 309. Sertoli MR, Santini G, Chisesi T, et al. MACOP-B versus ProMACE-MOPP in the treatment of  
30 advanced diffuse non- Hodgkin's lymphoma: Results of a prospective randomized trial by the Non-  
31 Hodgkin's Lymphoma Cooperative Study Group. *Journal of Clinical Oncology* 1994;12(7):1366-74.  
32  
33
- 34 310. Sexauer CL, Vietti T, Humphrey GB. Combination chemotherapy study for remission maintenance  
35 in ALL: An evaluation of vincristine, cyclophosphamide and vincristine, cyclophosphamide, and BCNU.  
36 A Southwest oncology group phase II study. *American Journal of Pediatric Hematology/Oncology*  
37 1981;3(3):255-57.  
38
- 39 311. Shamberger RC, Laquaglia MP, Krailo MD, et al. Ewing sarcoma of the rib: results of an intergroup  
40 study with analysis of outcome by timing of resection. *Journal of Thoracic & Cardiovascular Surgery*  
41 2000;119(6):1154-61.  
42
- 43 312. Shinagawa K, Yanada M, Sakura T, et al. Tamibarotene as maintenance therapy for acute  
44 promyelocytic leukemia: Results from a randomized controlled trial. *Journal of Clinical Oncology*  
45 2014;32(33):3729-35.  
46
- 47 313. Sievers EL, Lange BJ, Sondel PM, et al. Children's cancer group trials of interleukin-2 therapy to  
48 prevent relapse of acute myelogenous leukemia. *The cancer journal from Scientific American*  
49 2000;6(Suppl 1):S39-44.  
50
- 51 314. Skapek SX, Ferguson WS, Granowetter L, et al. Vinblastine and methotrexate for desmoid  
52 fibromatosis in children: Results of a Pediatric Oncology Group phase II trial. *Journal of Clinical*  
53 *Oncology* 2007;25(5):501-06.  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 315. Smith FO, Alonzo TA, Gerbing RB, et al. Long-term results of children with acute myeloid  
4 leukemia: a report of three consecutive Phase III trials by the Children's Cancer Group: CCG 251, CCG  
5 213 and CCG 2891. *Leukemia* 2005;19(12):2054-62.  
6  
7 316. Souhami RL, Craft AW, Van Der Eijken JW, et al. Randomised trial of two regimens of  
8 chemotherapy in operable osteosarcoma: A study of the European Osteosarcoma Intergroup. *Lancet*  
9 1997;350(9082):911-17.  
10  
11 317. Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high grade  
12 astrocytoma in children: results of a randomized trial. A report from the Children's Cancer Study Group.  
13 *Journal of neuro-oncology* 1989;7(2):165-77.  
14  
15 318. Sary J, Zimmermann M, Campbell M, et al. Intensive chemotherapy for childhood acute  
16 lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002. *Journal of*  
17 *Clinical Oncology* 2014;32(3):174-84. doi: <http://dx.doi.org/10.1200/JCO.2013.48.6522>  
18  
19 319. Steinherz PG, Gaynon PS, Breneman JC, et al. Treatment of patients with acute lymphoblastic  
20 leukemia with bulky extramedullary disease and T-cell phenotype or other poor prognostic features:  
21 randomized controlled trial from the Children's Cancer Group. *Cancer* 1998;82(3):600-12.  
22  
23 320. Steuber CP, Culbert SJ, Ravindranath Y, et al. Therapy of childhood acute nonlymphocytic  
24 leukemia: the Pediatric Oncology Group experience (1977-1988). *Haematology and blood transfusion*  
25 1990;33:198-209.  
26  
27 321. Steuber CP, Krischer J, Holbrook T, et al. Therapy of refractory or recurrent childhood acute  
28 myeloid leukemia using amsacrine and etoposide with or without azacitidine: a Pediatric Oncology Group  
29 randomized phase II study. *Journal of Clinical Oncology* 1996;14(5):1521-25.  
30  
31 322. Stevens MC, Rey A, Bouvet N, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood  
32 and adolescence: third study of the International Society of Paediatric Oncology--SIOP Malignant  
33 Mesenchymal Tumor 89. *Journal of clinical oncology : official journal of the American Society of*  
34 *Clinical Oncology* 2005;23(12):2618-28.  
35  
36 323. Stork LC, Matloub Y, Broxson E, et al. Oral 6-mercaptopurine versus oral 6-thioguanine and veno-  
37 occlusive disease in children with standard-risk acute lymphoblastic leukemia: report of the Children's  
38 Oncology Group CCG-1952 clinical trial. *Blood* 2010;115(14):2740-48. doi:  
39 <http://dx.doi.org/10.1182/blood-2009-07-230656>  
40  
41 324. Straus DJ, Portlock CS, Qin J, et al. Results of a prospective randomized clinical trial of  
42 doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus  
43 ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood* 2004;104(12):3483-89.  
44  
45 325. Strother DR, Lafay-Cousin L, Boyett JM, et al. Benefit from prolonged dose-intensive chemotherapy  
46 for infants with malignant brain tumors is restricted to patients with ependymoma: a report of the  
47 Pediatric Oncology Group randomized controlled trial 9233/34. *Neuro-oncology* 2014;16(3):457-65. doi:  
48 <http://dx.doi.org/10.1093/neuonc/not163>  
49  
50 326. Suh C, Kim HJ, Kim SH, et al. Low-dose lenograstim to enhance engraftment after autologous stem  
51 cell transplantation: A prospective randomized evaluation of two different fixed doses. *Transfusion*  
52 2004;44(4):533-38.  
53  
54  
55  
56  
57  
58  
59



- 1  
2  
3 327. Sullivan MP, Brecher M, Ramirez I, et al. High-dose cyclophosphamide-high-dose methotrexate  
4 with coordinated intrathecal therapy for advanced nonlymphoblastic lymphoma of childhood: results of a  
5 Pediatric Oncology Group study. *American Journal of Pediatric Hematology/Oncology* 1991;13(3):288-  
6 95.  
7  
8 328. Sullivan MP, Chen T, Dymont PG, et al. Equivalence of intrathecal chemotherapy and radiotherapy  
9 as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric oncology  
10 group study. *Blood* 1982;60(4):948-58.  
11  
12 329. Sullivan MP, Fuller LM, Chen T. Intergroup Hodgkin's disease in children study of stages I and II: A  
13 preliminary report. *Cancer treatment reports* 1982;66(4):937-47.  
14  
15 330. Suryanarayan K, Shuster JJ, Donaldson SS, et al. Treatment of localized primary non-Hodgkin's  
16 lymphoma of bone in children: A Pediatric Oncology Group Study. *Journal of Clinical Oncology*  
17 1999;17(2):456-59.  
18  
19 331. Tait DM, Thornton-Jones H, Bloom HJ, et al. Adjuvant chemotherapy for medulloblastoma: the first  
20 multi-centre control trial of the International Society of Paediatric Oncology (SIOP I). *European journal*  
21 *of cancer* 1990;26(4):464-69.  
22  
23 332. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic  
24 leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug  
25 chemotherapy: Results of trial ALL-REZ BFM 90. *Journal of Clinical Oncology* 2010;28(14):2339-47.  
26  
27 333. Tarbell NJ, Friedman H, Polkinghorn WR, et al. High-risk medulloblastoma: a pediatric oncology  
28 group randomized trial of chemotherapy before or after radiation therapy (POG 9031). *Journal of Clinical*  
29 *Oncology* 2013;31(23):2936-41. doi: <http://dx.doi.org/10.1200/JCO.2012.43.9984>  
30  
31 334. Taylor RE, Bailey CC, Robinson K, et al. Results of a randomized study of preradiation  
32 chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: The International Society of  
33 Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3 Study. *Journal of Clinical*  
34 *Oncology* 2003;21(8):1581-91.  
35  
36 335. Taylor RE, Bailey CC, Robinson KJ, et al. Impact of radiotherapy parameters on outcome in the  
37 International Society of Paediatric Oncology/United Kingdom Children's Cancer Study Group PNET-3  
38 study of preradiotherapy chemotherapy for M0-M1 medulloblastoma. *International journal of radiation*  
39 *oncology, biology, physics* 2004;58(4):1184-93.  
40  
41 336. Tebbi CK, London WB, Friedman D, et al. Dexrazoxane-associated risk for acute myeloid  
42 leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease.  
43 *Journal of Clinical Oncology* 2007;25(5):493-500.  
44  
45 337. Tebbi CK, Mendenhall NP, London WB, et al. Response-dependent and reduced treatment in lower  
46 risk Hodgkin lymphoma in children and adolescents, results of P9426: a report from the Children's  
47 Oncology Group. *Pediatric Blood & Cancer* 2012;59(7):1259-65. doi:  
48 <http://dx.doi.org/10.1002/pbc.24279>  
49  
50 338. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children  
51 and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. *British*  
52 *journal of haematology* 2013;162(6):792-801. doi: <http://dx.doi.org/10.1111/bjh.12460>  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 339. Testi AM, Biondi A, Lo Coco F, et al. GIMEMA-AIEOP AIDA protocol for the treatment of newly  
4 diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005;106(2):447-53.  
5  
6 340. Tolar J, Bostrom BC, La MK, et al. Intravenous 6-mercaptopurine decreases salvage after relapse in  
7 childhood acute lymphoblastic leukemia: a report from the Children's Cancer Group study CCG 1922.  
8 *Pediatric Blood & Cancer* 2005;45(1):5-9.  
9  
10 341. Tournade MF, ComNougue C, De Kraker J, et al. Optimal duration of preoperative therapy in  
11 unilateral and nonmetastatic Wilms' tumor in children older than 6 months: Results of the Ninth  
12 International Society of Pediatric Oncology Wilms' Tumor Trial and Study. *Journal of Clinical Oncology*  
13 2001;19(2):488-500.  
14  
15 342. Tournade MF, Com-Nougue C, Voute PA, et al. Results of the Sixth International Society of  
16 Pediatric Oncology Wilms' Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms' tumor.  
17 *Journal of Clinical Oncology* 1993;11(6):1014-23.  
18  
19 343. Tower RL, Jones TL, Camitta BM, et al. Dose intensification of methotrexate and cytarabine during  
20 intensified continuation chemotherapy for high-risk B-precursor acute lymphoblastic leukemia: POG  
21 9406: a report from the Children's Oncology Group. *Journal of Pediatric Hematology/Oncology*  
22 2014;36(5):353-61. doi: <http://dx.doi.org/10.1097/MPH.0000000000000131>  
23  
24 344. Tsuchida M, Akatsuka J, Bessho F, et al. Treatment of acute lymphoblastic leukemia in the Tokyo  
25 Children's Cancer Study Group--preliminary results of L84-11 protocol. *Acta Paediatrica Japonica*  
26 1991;33(4):522-32.  
27  
28 345. Tsuchida M, Ohara A, Manabe A, et al. Long-term results of Tokyo children's cancer study group  
29 trials for childhood acute lymphoblastic leukemia, 1984-1999. *Leukemia* 2010;24(2):383-96.  
30  
31 346. Tsukada M, Komiyama A, Nakazawa S, et al. Treatment of standard risk acute lymphoblastic  
32 leukemia in children with the Tokyo Children Cancer Study Group (TCCSG) L84-11 protocol in Japan.  
33 *International journal of hematology* 1993;57(1):1-7.  
34  
35 347. Tsurusawa M, Katano N, Yamamoto Y, et al. Improvement in CNS protective treatment in non-high-  
36 risk childhood acute lymphoblastic leukemia: report from the Japanese Children's Cancer and Leukemia  
37 Study Group. *Medical & Pediatric Oncology* 1999;32(4):259-56.  
38  
39 348. Tsurusawa M, Watanabe T, Gosho M, et al. Randomized study of granulocyte colony stimulating  
40 factor for childhood B-cell non-Hodgkin lymphoma: a report from the Japanese pediatric  
41 leukemia/lymphoma study group B-NHL03 study. *Leukemia & Lymphoma* 2016;57(7):1657-64. doi:  
42 <https://dx.doi.org/10.3109/10428194.2015.1106534>  
43  
44 349. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Prevention of CNS disease in intermediate-risk acute  
45 lymphoblastic leukemia: comparison of cranial radiation and intrathecal methotrexate and the importance  
46 of systemic therapy: a Children's Cancer Group report. *Journal of Clinical Oncology* 1993;11(3):520-26.  
47  
48 350. Tubergen DG, Krailo MD, Meadows AT, et al. Comparison of treatment regimens for pediatric  
49 lymphoblastic non-Hodgkin's lymphoma: a Children's Cancer Group study. *Journal of Clinical Oncology*  
50 1995;13(6):1368-76.  
51  
52 351. Tulstrup M, Frandsen TL, Abrahamsson J, et al. Individualized 6-mercaptopurine increments in  
53 consolidation treatment of childhood acute lymphoblastic leukemia: A NOPHO randomized controlled  
54 trial. *Eur J Haematol* 2018;100(1):53-60. doi: <https://dx.doi.org/10.1111/ejh.12979>  
55  
56  
57  
58  
59

- 1  
2  
3 352. Van Eys J, Berry D, Crist W, et al. Treatment intensity and outcome for children with acute  
4 lymphocytic leukemia of standard risk. A Pediatric Oncology Group Study. *Cancer* 1989;63(8):1466-71.  
5
- 6 353. Van Eys J, Chen T, Moore T. Adjuvant chemotherapy for medulloblastoma and ependymoma using  
7 Iv vincristine, intrathecal methotrexate, and intrathecal hydrocortisone: A southwest oncology group  
8 study. *Cancer treatment reports* 1981;65(7-8):681-84.  
9
- 10 354. Vilmer E, Suci S, Ferster A, et al. Long-term results of three randomized trials (58831, 58832,  
11 58881) in childhood acute lymphoblastic leukemia: A CLCG-EORTC report. *Leukemia*  
12 2000;14(12):2257-66.  
13
- 14 355. Vitolo U, Trneny M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide,  
15 Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma.  
16 *Journal of Clinical Oncology* 2017;35(31):3529-37. doi: <https://dx.doi.org/10.1200/JCO.2017.73.3402>  
17
- 18 356. Von Bueren AO, Von Hoff K, Pietsch T, et al. Treatment of young children with localized  
19 medulloblastoma by chemotherapy alone: Results of the prospective, multicenter trial HIT 2000  
20 confirming the prognostic impact of histology. *Neuro-oncology* 2011;13(6):669-79.  
21
- 22 357. von Hoff K, Hinkes B, Gerber NU, et al. Long-term outcome and clinical prognostic factors in  
23 children with medulloblastoma treated in the prospective randomised multicentre trial HIT'91. *European*  
24 *journal of cancer* 2009;45(7):1209-17. doi: <http://dx.doi.org/10.1016/j.ejca.2009.01.015>  
25
- 26 358. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk  
27 acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised  
28 controlled trial. *Lancet Oncology* 2013;14(3):199-209. doi: [http://dx.doi.org/10.1016/S1470-  
29 2045\(12\)70600-9](http://dx.doi.org/10.1016/S1470-2045(12)70600-9)  
30
- 31 359. Vora AJ, Mitchell C, Goulden N, et al. UKALL 2003, a randomised trial investigating treatment  
32 reduction for children and young adults with minimal residual disease defined low risk acute  
33 lymphoblastic leukaemia. *52nd Annual Meeting of the American Society of Hematology, ASH 2010*  
34 *Orlando, FL United States* 2010;116 (21) (no pagination)  
35
- 36 360. Vose JM, Carter S, Burns LJ, et al. Phase III randomized study of rituximab/carmustine, etoposide,  
37 cytarabine, and melphalan (BEAM) compared with iodine-131 tositumomab/BEAM with autologous  
38 hematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: results from the BMT CTN  
39 0401 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*  
40 2013;31(13):1662-68.  
41
- 42 361. Vrooman LM, Neuberg DS, Stevenson KE, et al. The low incidence of secondary acute  
43 myelogenous leukaemia in children and adolescents treated with dexrazoxane for acute lymphoblastic  
44 leukaemia: a report from the Dana-Farber Cancer Institute ALL Consortium. *European journal of cancer*  
45 2011;47(9):1373-79. doi: <http://dx.doi.org/10.1016/j.ejca.2011.03.022>  
46
- 47 362. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction dexamethasone and individualized  
48 dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly  
49 diagnosed acute lymphoblastic leukemia: results from a randomized study--Dana-Farber Cancer Institute  
50 ALL Consortium Protocol 00-01. *Journal of Clinical Oncology* 2013;31(9):1202-10. doi:  
51 <http://dx.doi.org/10.1200/JCO.2012.43.2070>  
52  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 363. Vu K, Busaidy N, Cabanillas ME, et al. A randomized controlled trial of an intensive insulin  
4 regimen in patients with hyperglycemic acute lymphoblastic leukemia. *Clinical Lymphoma, Myeloma and*  
5 *Leukemia* 2012;12(5):355-62.  
6  
7 364. Waber DP, Silverman LB, Catania L, et al. Outcomes of a randomized trial of hyperfractionated  
8 cranial radiation therapy for treatment of high-risk acute lymphoblastic leukemia: Therapeutic efficacy  
9 and neurotoxicity. *Journal of Clinical Oncology* 2004;22(13):2701-07.  
10  
11 365. Weiner MA, Leventhal B, Brecher ML, et al. Randomized study of intensive MOPP-ABVD with or  
12 without low-dose total-nodal radiation therapy in the treatment of stages IIB, IIIA2, IIIB, and IV  
13 Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. *Journal of Clinical Oncology*  
14 1997;15(8):2769-79.  
15  
16 366. Weiner MA, Leventhal BG, Marcus R, et al. Intensive chemotherapy and low-dose radiotherapy for  
17 the treatment of advanced-stage Hodgkin's disease in pediatric patients: A Pediatric Oncology Group  
18 study. *Journal of Clinical Oncology* 1991;9(9):1591-98.  
19  
20 367. Wells RJ, Woods WG, Buckley JD, et al. Therapy for acute myeloid leukemia: intensive timing of  
21 induction chemotherapy. *Current oncology reports* 2000;2(6):524-28.  
22  
23 368. Wells RJ, Woods WG, Buckley JD, et al. Treatment of newly diagnosed children and adolescents  
24 with acute myeloid leukemia: A Childrens Cancer Group study. *Journal of Clinical Oncology*  
25 1994;12(11):2367-77.  
26  
27 369. Winick NJ, Smith SD, Shuster J, et al. Treatment of CNS relapse in children with acute  
28 lymphoblastic leukemia: A Pediatric Oncology Group study. *Journal of Clinical Oncology*  
29 1993;11(2):271-78.  
30  
31 370. Winkler K, Beron G, Delling G, et al. Neoadjuvant chemotherapy of osteosarcoma: Results of a  
32 randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor  
33 response. *Journal of Clinical Oncology* 1988;6(2):329-37.  
34  
35 371. Winter SS, Dunsmore KP, Devidas M, et al. Safe integration of nelarabine into intensive  
36 chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group  
37 Study AALL0434. *Pediatric Blood & Cancer* 2015;62(7):1176-83. doi:  
38 <http://dx.doi.org/10.1002/psc.25470>  
39  
40 372. Woessmann W, Seidemann K, Mann G, et al. The impact of the methotrexate administration  
41 schedule and dose in the treatment of children and adolescents with B-cell neoplasms: a report of the  
42 BFM Group Study NHL-BFM95. *Blood* 2005;105(3):948-58.  
43  
44 373. Wolden SL, Chen L, Kelly KM, et al. Long-term results of CCG 5942: a randomized comparison of  
45 chemotherapy with and without radiotherapy for children with Hodgkin's lymphoma--a report from the  
46 Children's Oncology Group. *Journal of Clinical Oncology* 2012;30(26):3174-80. doi:  
47 <http://dx.doi.org/10.1200/JCO.2011.41.1819>  
48  
49 374. Wolden SL, Lyden ER, Arndt CA, et al. Local Control for Intermediate-Risk Rhabdomyosarcoma:  
50 Results From D9803 According to Histology, Group, Site, and Size: A Report From the Children's  
51 Oncology Group. *International journal of radiation oncology, biology, physics* 2015;93(5):1071-76. doi:  
52 <http://dx.doi.org/10.1016/j.ijrobp.2015.08.040>  
53  
54  
55  
56  
57  
58  
59

- 1  
2  
3 375. Wolff JA, D'Angio G, Hartmann J, et al. Long-term evaluation of single versus multiple courses of  
4 actinomycin D therapy of Wilm's tumor. *The New England journal of medicine* 1974;290(2):84-86.  
5
- 6 376. Wolff JA, Newton WA, Jr., Krivit W, et al. Single versus multiple dose dactinomycin therapy of  
7 Wilms's tumor. A controlled co-operative study conducted by the Children's Cancer Study Group A  
8 (formerly Acute Leukemia Co-operative Chemotherapy Group A). *New England Journal of Medicine*  
9 1968;279(6):290-94.  
10
- 11 377. Womer RB, West DC, Krailo MD, et al. Randomized controlled trial of interval-compressed  
12 chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology  
13 Group. *Journal of Clinical Oncology* 2012;30(33):4148-54. doi:  
14 <http://dx.doi.org/10.1200/JCO.2011.41.5703>  
15
- 16 378. Woods WG, Barnard DR, Alonzo TA, et al. Prospective study of 90 children requiring treatment for  
17 juvenile myelomonocytic leukemia or myelodysplastic syndrome: A report from the Children's Cancer  
18 Group. *Journal of Clinical Oncology* 2002;20(2):434-40.  
19
- 20 379. Woods WG, Neudorf S, Gold S, et al. A comparison of allogeneic bone marrow transplantation,  
21 autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid  
22 leukemia in remission: A report from the Children's Cancer Group. *Blood* 2001;97(1):56-62.  
23
- 24 380. Wu J, Song Y, Su L, et al. Rituximab plus chemotherapy as first-line treatment in Chinese patients  
25 with diffuse large B-cell lymphoma in routine practice: a prospective, multicentre, non-interventional  
26 study. *BMC Cancer* 2016;16:537. doi: <https://dx.doi.org/10.1186/s12885-016-2523-7>  
27
- 28 381. Yang CP, Lin ST, Liang DC, et al. Treatment of childhood acute lymphoblastic leukemia with  
29 protocol TCL-842 in Taiwan: the Taiwan Children's Cancer Study Group. *Journal of the Formosan*  
30 *Medical Association* 1993;92(5):431-39.  
31
- 32 382. Yetgin S, Tuncer MA, Cetin M, et al. Benefit of high-dose methylprednisolone in comparison with  
33 conventional-dose prednisolone during remission induction therapy in childhood acute lymphoblastic  
34 leukemia for long-term follow-up. *Leukemia* 2003;17(2):328-33.  
35
- 36 383. Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and  
37 isotretinoin for neuroblastoma. *N Engl J Med* 2010;363(14):1324-34. doi: 10.1056/NEJMoa0911123  
38 [published Online First: 2010/10/01]  
39
- 40 384. Zaghoul MS, Eldebawy E, Ahmed S, et al. Hypofractionated conformal radiotherapy for pediatric  
41 diffuse intrinsic pontine glioma (DIPG): a randomized controlled trial. *Radiotherapy & Oncology*  
42 2014;111(1):35-40. doi: <http://dx.doi.org/10.1016/j.radonc.2014.01.013>  
43
- 44 385. Zeltzer PM, Boyett JM, Finlay JL, et al. Metastasis stage, adjuvant treatment, and residual tumor are  
45 prognostic factors for medulloblastoma in children: conclusions from the Children's Cancer Group 921  
46 randomized phase III study. *Journal of Clinical Oncology* 1999;17(3):832-45.  
47
- 48 386. Zhang L, Jia S, Ma Y, et al. Efficacy and safety of cisplatin, dexamethasone, gemcitabine and  
49 pegaspargase (DDGP) regimen in newly diagnosed, advanced-stage extranodal natural killer/T-cell  
50 lymphoma: Interim analysis of a phase 4 study NCT01501149. *Oncotarget* 2016;7(34):55721-31. doi:  
51 <http://dx.doi.org/10.18632/oncotarget.10124>  
52  
53  
54  
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56  
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59



1  
2  
3 387. Zintl F, Plenert W, Malke H. Results of acute lymphoblastic leukemia therapy in childhood with a  
4 modified BFM protocol in a multicenter study in the German Democratic Republic. *Haematology &*  
5 *Blood Transfusion* 1987;30:471-79.  
6  
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### Appendix C: Recommendation on how to calculate and assess the number needed to treat to inform decision-making

#### Step 1:

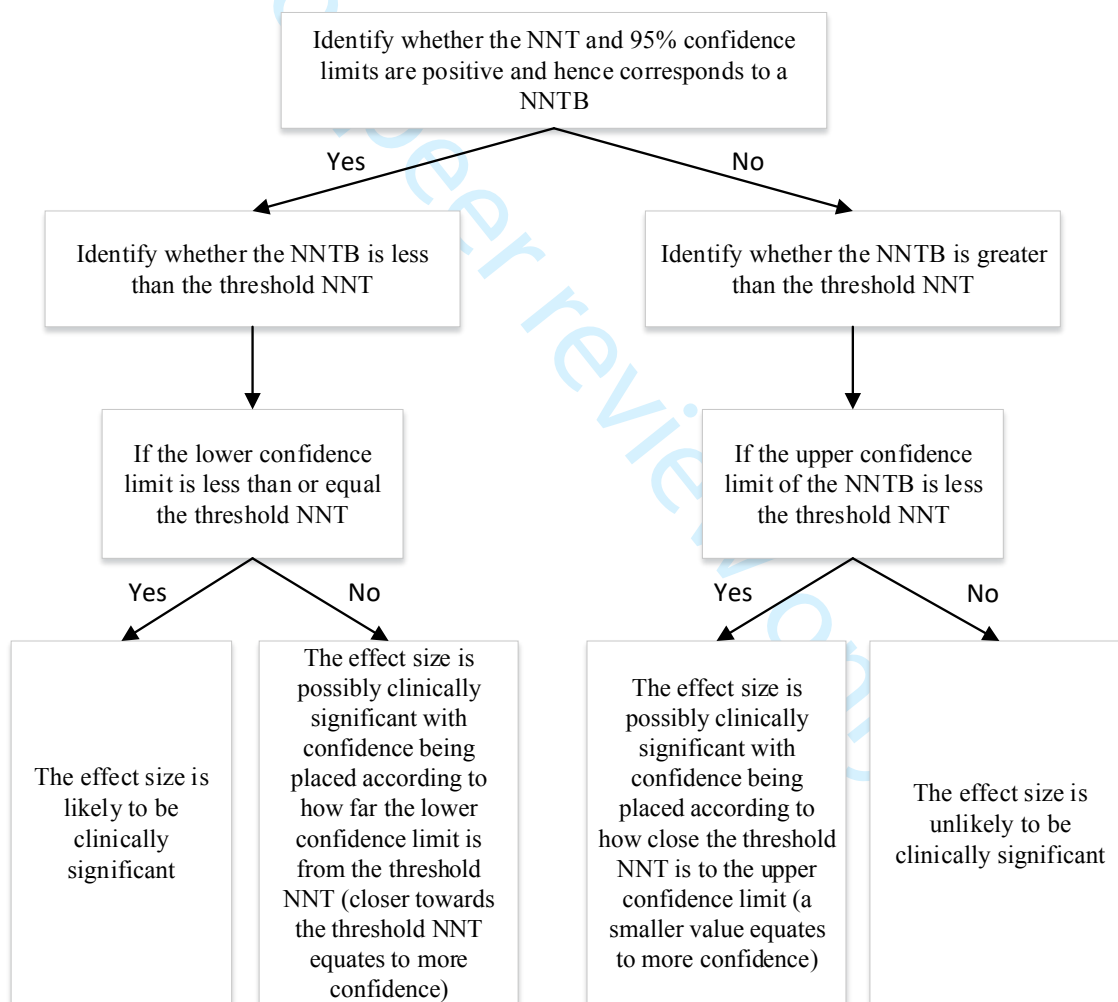
Identify the delta value reported in the sample size calculation and whether the authors reported on the way in which the delta value was chosen. A delta value informed by a previous trial or systematic review should be given more confidence in comparison to one from pilot data or clinical expertise. 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<sup>19</sup>. 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