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The utility of the number needed to treat in pediatric hematological cancer randomized controlled 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.

Strengths and Limitations of this Study

Strengths	• 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. • 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. • 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.
Limitations	• We excluded a number of trials due to reporting that precluded calculating the numbers needed to treat. • 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.

Introduction

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

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

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

threshold NNT, which is the point where the therapeutic benefit equals the therapeutic risk[17]. The threshold NNT should correspond to the inverse of the ARR that a RCT is designed to detect and a clinically significant effect size that would lead to a clinical practice change. Therefore, a decision to administer a therapeutic intervention over the standard of care should occur when the NNT is less than the threshold NNT[17]. The primary study objective was to assess the utility of the NNT in pediatric hematologic cancer, by calculating the NNT in all superiority RCTs assessing treatment related survival, relapse or remission, and comparing the NNT to the threshold NNT. A secondary study objective was to assess the proportion of published studies (specifically randomized questions) that reported the NNT.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary File)[18].

This review consisted of a subset of studies from a previous systematic review conducted by our research team. Methods describing the search strategy, eligibility criteria, study identification and data extraction for our previous systematic review have been detailed in the protocol (Supplementary File). The subset consisted of superiority, parallel group, RCTs in pediatric patients diagnosed with a hematological cancer that assessed an outcome related to survival, relapse or remission and those that reported either confidence intervals (CIs) or standard errors associated with both the experimental and control estimates, or numbers of patients at risk on a Kaplan Meier curve.

The number needed to treat to benefit (NNTB), which corresponds to a positive NNT, or number needed to treat to harm (NNTH), which corresponds to a negative NNT, and associated 95% confidence intervals were calculated for each randomized question as per the validated methodology described by Altman & Andersen[19]. The NNT was based on the primary outcome and time point as specified in the sample size calculation. In the event that the time point specified in the sample size calculation was not reported, the information was inferred if a Kaplan Meier curve with the number of patients at risk was reported[19]. If the aforementioned was not provided, the time point reported in the results was used, and thus, these trials were prone to selective reporting bias.

The ARR, NNT and delta value (i.e., threshold ARR and NNT), as reported in the sample size calculation, were visualized on a forest plot, grouped by disease (Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Lymphoma and Mixed, which corresponds to the inclusion of multiple diseases), to

allow for identification of NNTB (defined as the NNT and 95% CI that only included positive numbers), NNTH (defined as the NNT and 95% CI that only included negative numbers) and inconclusive NNT (defined as the NNT where the 95% CI included both a positive and a negative number). Descriptive statistics were used to summarize the frequency and percentage of randomized questions reporting the NNT, as well as the NNTB, NNTH, and inconclusive NNT by disease site.

In order to ascertain whether the NNTB was clinically significant, we calculated the frequency and percentage of randomized questions where the NNT < threshold NNT, NNT > threshold NNT or NNT = threshold NNT. The threshold NNT was considered to be the inverse of the ARR (i.e., delta value) as specified in the sample size calculation and was assumed to correspond to a clinically significant effect size that would lead to a change in clinical practice. The threshold NNT was compared to the treatment NNT and classified as definitely clinically significant, possibly clinical significant, inconclusive clinical significance and definitely not clinically significant as specified in Figure 1. These categories were informed by methods described by Man-Son-Hing et al.[20]. RCTs where an ARR of zero occurred were excluded from the analysis because the inverse corresponds to an undefined NNT. SAS (Statistical Analysis Software) version 9.4 (SAS Institute, Cary, NC) was used to perform all analyses.

Results

Included studies

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

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

Number needed to treat

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

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

Comparison of NNT and Threshold NNT

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

Discussion

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

Strengths and weaknesses

Our review provides a comprehensive analysis of the utility of the NNT through an evaluation of all pediatric hematological RCTs assessing relapse, remission and survival from inception to 2016. Furthermore, we provide the NNT and ARR with 95% CI along with the threshold NNT and ARR for these RCTs using a validated methodological approach, which will serve as a valuable tool for decision-makers, clinicians and researchers to assess treatment effects. A weakness of this study is the exclusion of a number of trials due to reporting that precluded calculating the NNT. However, as the exclusion is due to reporting deficits, this limitation is beyond our control and serves as an important finding that reporting quality is limited in the pediatric oncology RCT literature. An additional weakness is that 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 ARR and NNT. 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.

Comparison with existing literature

Considerable published literature has evaluated the utility of the NNT. The overarching conclusion is that the NNT is a metric of value in clinical, health policy and formulary decision-making when interpreted correctly [4-8]. However, the NNT and ARR are rarely reported or poorly reported in the literature despite being recommended in the CONSORT statement and are often calculated using inappropriate methods [6 12-16 21-26]. Our findings corroborate the existing literature because no studies reported the NNT in our review. Previous studies have not highlighted the utility of the NNT specifically in the pediatric oncology literature or evaluated the clinical significance of the NNT using the approach described in our study and thus, our study is a novel and important addition to the literature.

Study explanations and implications

Our study quantified the NNT as a means to better understand the utility of this tool to facilitate decision making in pediatric oncology. The NNT allows for an intuitive understanding of the absolute effect size in terms of patients and can help considerably when comparing one treatment to another, after ensuring baseline characteristics, the outcome and time point for the patient population of interest are comparable[12]. For instance, a RCT conducted by Creutizig et al.[27] in pediatric AML patients assessing 5-year event free survival, found a 6% (95% CI, 1%-10%) absolute increase associated with the experimental treatment compared to the control treatment. The associated NNT corresponded to 15 (33-10), meaning that it is estimated that by administering the experimental treatment, 1 extra patient would survive at 5 years for every 15 patients treated (95% CI, 33-10). Of note, this RCT was powered to detect an absolute increase in 5-year EFS of 13% (i.e., delta value), which would correspond to a NNTB of 8 (i.e., threshold NNT). Although the NNTB is 15, the lower confidence limit is 33 and the upper confidence limit is 10 (a range that does not include 8), which, given the range, would lead one to believe that the effect size does not provide strong enough evidence to change clinical practice. In situations where the lower confidence limit of the NNTB is less than the threshold NNT, one can be more confident that the treatment confers a clinically improved outcome as compared to the control. On the other hand, if the NNTB is less than the threshold NNT and the lower confidence limit is greater than the threshold NNT, one should exercise greater caution in concluding that the effect size is clinically significant. As demonstrated in our study, a forest plot is a convenient method to visualize the relationship between the

NNT (and the associated 95% CI) evident in study results compared to the NNT that the study was designed to detect as a proxy for the threshold NNT and that would be considered clinically significant.

The aforementioned approach is recommended in light of smaller sample sizes that are often attained in pediatric oncology RCTs and rare disease trials in general. This was demonstrated in our study where the majority of randomized questions found to have a NNTB had a NNT less than the specified threshold NNT, with the majority of those in ALL having an upper confidence limit exceeding the threshold NNT.

The utility of the NNT, however, is inherently reliant on three major areas, baseline risk, the outcome and the time point[12]. In order for the NNT from an RCT demonstrating a NNTB to have utility, the patient population of interest should share a similar baseline risk because the desired treatment effect may be overestimated and thus the NNTB may by underestimated. Outcomes related to event-free survival often differ in what is considered an event and thus it is critical to ensure that the NNTB being applied to the population of interest is identical in terms of the outcome in question. Numerous studies have demonstrated how the NNT varies with time and thus, comparability in time points is critical to ensure accurate interpretation of the NNT to a population of interest[4 12 22 23].

Recommendations

We recommend that clinicians and decision-makers in pediatric oncology consider using the NNT as a supportive tool to evaluate evidence from RCTs, while placing careful attention to the inherent limitation of this measure. Figure 4 provides a summary of how the NNT can be calculated and assessed to inform decision-making[19 20].

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

NNT[1]	**Hematological Cancer Randomized Questions (N = 65)**			
	ALL (N = 40)	**Lymphoma (N = 15)**	**AML (N = 8)**	**Mixed Diagnoses**[2] **(N = 2)**
NNTB (n, %)	13 (32.5%)	0 (0.0%)	5 (62.5%)	1 (50.0%)
NNT < Threshold NNT	4 (30.8%)	0 (0.0%)	1 (20.0%)	1 (100.0%)
NNT Lower Confidence Limit ≥ Threshold NNT	3 (75.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
NNT > Threshold	8 (61.5%)	0 (0.0%)	4 (80.0%)	0 (0.0%)
NNT Upper Confidence Limit ≤ Threshold NNT	5 (62.5%)	0 (0.0%)	1 (25.0%)	0 (0.0%)
NNT = Threshold NNT	1 (7.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Inconclusive NNT (n, %)	21 (52.5%)	13 (86.7%)	3 (37.5%)	1 (50.0%)
NNTH (n, %)	6 (15.0%)[3]	2 (13.3%)	0 (0.0%)	0 (0.0%)

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

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

[1] Denominator for indented corresponds to above row

[2] Mixed diagnoses refer to RCTs where more than one hematological cancer was included

[3] One randomized question (Bostrom et al. 2003) was included where the outcome was related to a decrease in CNS relapse rate and thus NNTH is actually beneficial

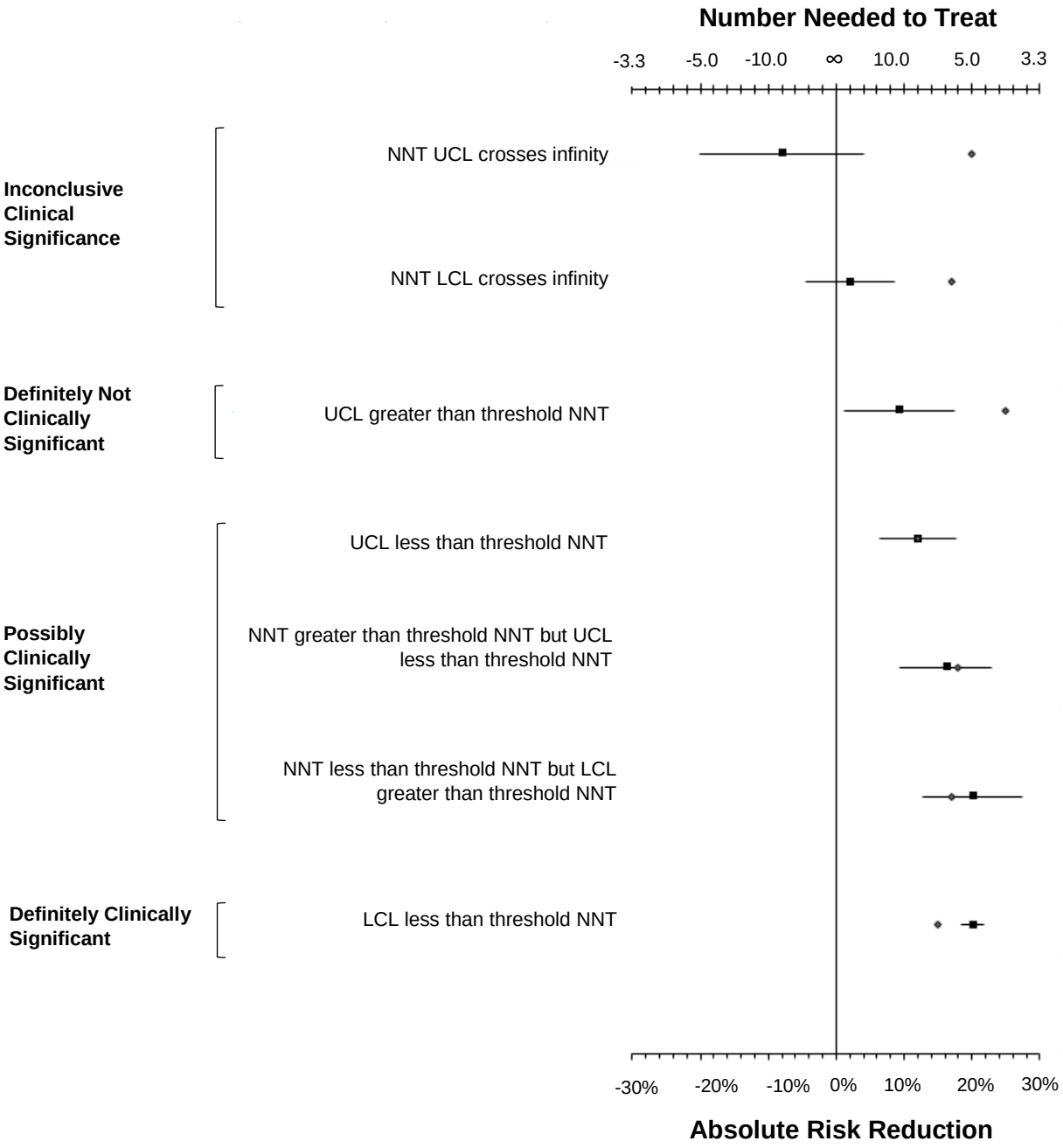


Figure 1: Guideline to assess level of clinical significance using numbers needed to treat

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

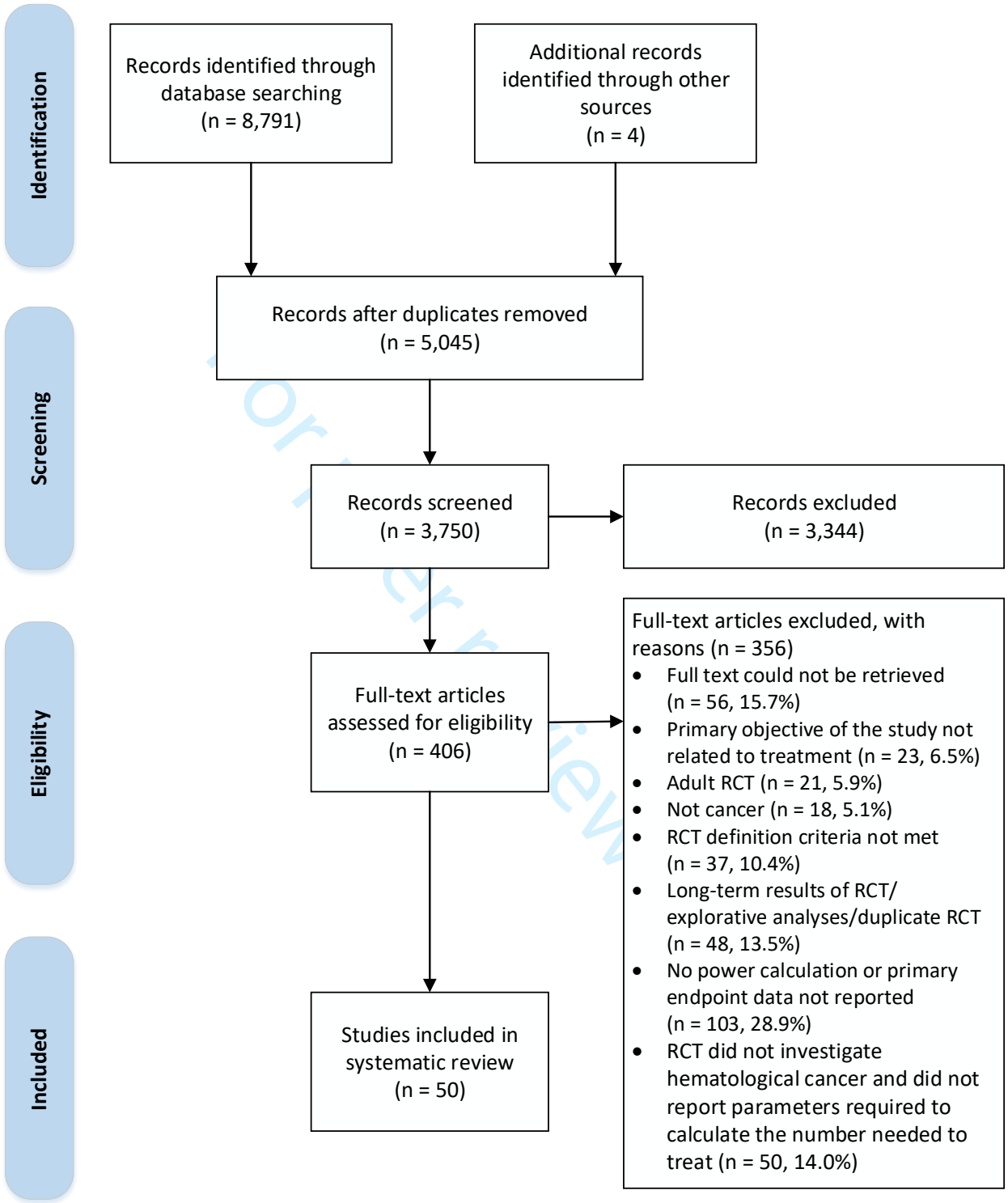
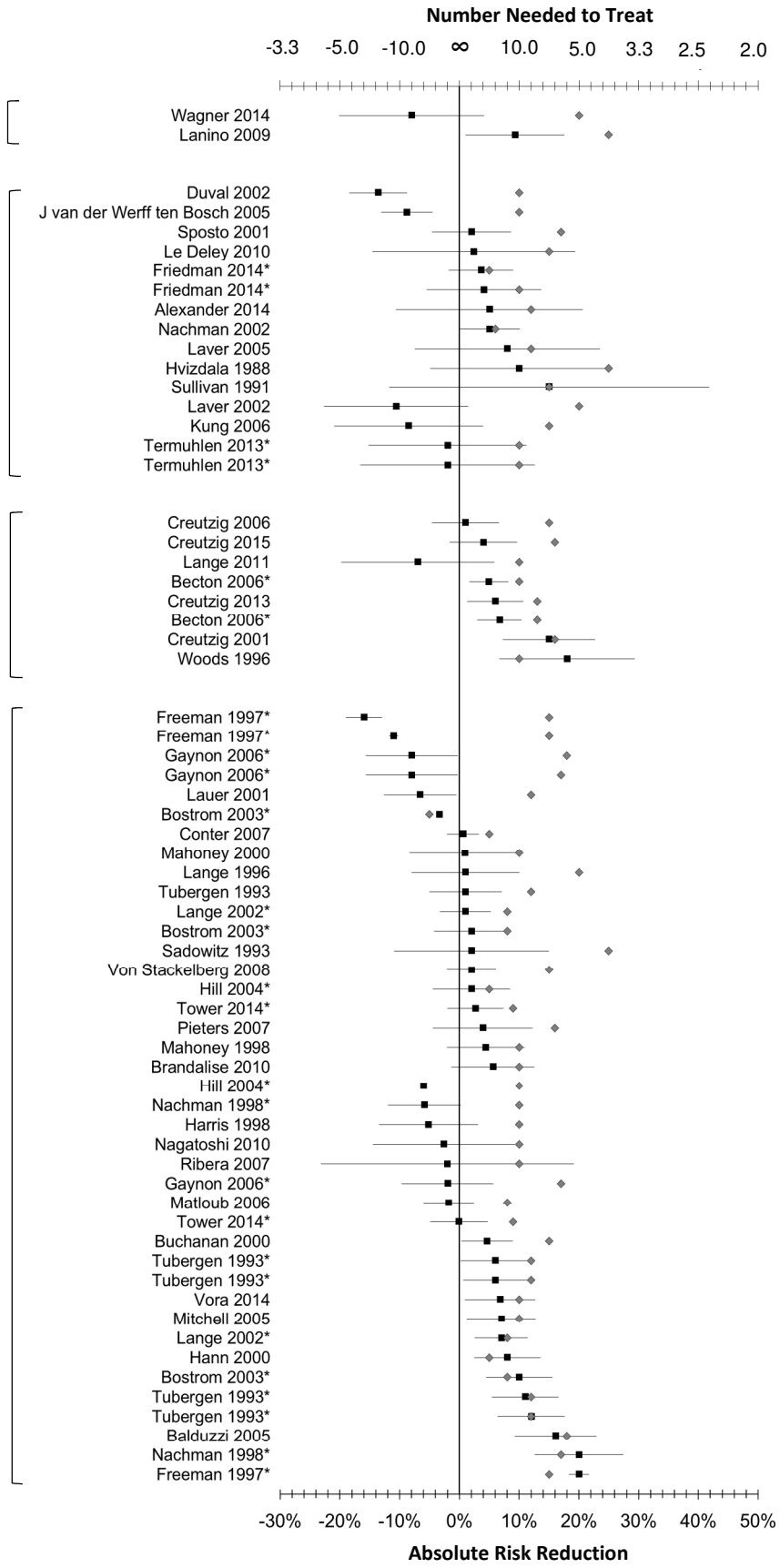


Figure 2: Selection of randomized controlled trials in the systematic review



	NNT (95% CI)	ARR (95% CI)	THRESHOLD NNT	THRESHOLD ARR	OUTCOME
Wagner 2014	-12.5 (-5 - 24.2)	-8% (-20.1% - 4.1%)	5.0	20%	OS 1YR
Lanino 2009	10.8 (95.4 - 5.7)	9.3% (1% - 17.6%)	4.0	25%	EFS 8YR
Duval 2002	-7.4 (-5.4 - -11.4)	-13.6% (-18.4% - -8.8%)	10.0	10%	EFS 6YR
J van der Werff ten Bosch 2005	-11.4 (-7.7 - -22.1)	-8.8% (-13.1% - -4.5%)	10.0	10%	DFS 5YR
Sposto 2001	50.0 (-21.8 – 11.6)	2% (-4.6% - 8.6%)	5.9	17%	EFS 10YR
Le Deley 2010	41.7 (-6.9 – 5.2)	2.4% (-14.5% - 19.3%)	6.7	15%	EFS 2YR
Friedman 2014*	27.8 (-56.3 – 11.1)	3.6% (-1.8% - 9%)	20.0	5%	EFS 4YR
Friedman 2014*	24.4 (-18.3 – 7.3)	4.1% (-5.5% - 13.7%)	10.0	10%	EFS 4YR
Alexander 2014	20.0 (-9.4 – 4.9)	5% (-10.6% - 20.6%)	8.3	12%	EFS 3YR
Nachman 2002	20.0 (-1250 – 9.9)	5% (-0.1% - 10.1%)	16.7	6%	EFS 3YR
Laver 2005	12.5 (-13.4 – 4.3)	8% (-7.5% - 23.5%)	8.3	12%	EFS 4YR
Hvizdala 1988	10.0 (-20.4 – 4.0)	10% (-5% - 25%)	4.0	25%	OS 3YR
Sullivan 1991	6.7 (-8.5- 2.4)	15% (-11.8% - 41.8%)	6.7	15%	CCR 5YR
Laver 2002	-9.4 (-4.4 – 68.9)	-10.6% (-22.7% - 1.5%)	5.0	20%	EFS 5YR
Kung 2006	-11.8 (-4.8 – 25.1)	-8.5% (-21% - 4%)	6.7	15%	EFS 3YR
Termuhlen 2013*	-50.0 (-6.6 – 9.0)	-2% (-15.2% - 11.2%)	10.0	10%	EFS 5YR
Termuhlen 2013*	-50.0 (-6.0 – 8.0)	-2% (-16.6% - 12.6%)	10.0	10%	EFS 5YR
Creutzig 2006	100.0 (-21.7 – 15.2)	1% (-4.6% - 6.6%)	6.7	15%	EFS 5YR
Creutzig 2015	25.0 (-60.3 – 10.4)	4% (-1.7% - 9.7%)	6.3	16%	EFS 5YR
Lange 2011	-14.3 (-5.1 – 17.3)	-7% (-19.8% - 5.8%)	10.0	10%	DFS 5YR
Becton 2006*	20.4 (60.9 – 12.3)	4.9% (1.6% - 8.2%)	10.0	10%	EFS 2YR
Creutzig 2013	16.7 (74.8 – 9.4)	6% (1.3% - 10.7%)	7.7	13%	EFS 5YR
Becton 2006*	14.9 (33.2 – 9.6)	6.7% (3% - 10.4%)	7.7	13%	DFS 2YR
Creutzig 2001	6.7 (13.7 – 4.4)	15% (7.3% - 22.7%)	6.3	16%	EFS 5YR
Woods 1996	5.6 (14.9 – 3.4)	18% (6.7% - 29.3%)	10.0	10%	DFS 2YR
Freeman 1997*	-6.3 (-5.3 - -7.7)	-16% (-19% - -13%)	6.7	15%	RR 12YR
Freeman 1997*	-9.1 (-8.5 - -9.8)	-11% (-11.8% - -10.2%)	6.7	15%	RR 12YR
Gaynon 2006*	-12.5 (-6.4- -303)	-8% (-15.7% - -0.3%)	5.6	18%	DFS 2YR
Gaynon 2006*	-12.5 (-6.4- -303)	-8% (-15.7% - -0.3%)	5.9	17%	DFS 2YR
Lauer 2001	-15.2 (-7.9 - -181.5)	-6.6% (-12.6% - -0.6%)	8.3	12%	CCR 4YR
Bostrom 2003*	-29.4 (-28.1 - -30.9)	-3.4% (-3.6% - -3.2%)	-20	-5%	RR 6YR
Conter 2007	166.7 (-48.9 – 30.8)	0.6% (-2% - 3.2%)	20.0	5%	DFS 5YR
Mahoney 2000	111.1 (-12 – 9.8)	0.9% (-8.4% - 10.2%)	10.0	10%	CCR 4YR
Lange 1996	100.0 (-12.5 - 10)	1% (-8% - 10%)	5.0	20%	EFS 6YR
Tubergen 1993	100.0 (-19.9 – 14.2)	1% (-5% - 7%)	8.3	12%	EFS 5YR
Lange 2002*	100.0 (-30.9 – 19.1)	1% (-3.2% - 5.2%)	12.5	8%	EFS 6YR
Bostrom 2003*	50.0 (-23.5 – 12.1)	2% (-4.3% - 8.3%)	12.5	8%	EFS 5YR
Sadowitz 1993	50.0 (-9.2 – 6.7)	2% (-10.9% - 14.9%)	4.0	25%	DFS 2YR
Von Stackelberg 2008	50.0 (-47.5 – 16.4)	2% (-2.1% - 6.1%)	6.7	15%	EFS 10YR
Hill 2004*	50.0 (-22.5 – 11.8)	2% (-4.4% - 8.4%)	20.0	5%	EFS 4YR
Tower 2014*	37.0 (-50.7 – 13.6)	2.7% (-2% - 7.4%)	11.1	9%	DFS 5YR
Pieters 2007	25.6 (-22.5 – 8.2)	3.9% (-4.5% - 12.3%)	6.3	16%	DFS 4YR
Mahoney 1998	22.7 (-47.9 – 9.2)	4.4% (-2.1% - 10.9%)	10.0	10%	CCR 4YR
Brandalise 2010	17.9 (-74.2 – 8.0)	5.6% (-1.3% - 12.5%)	10.0	10%	EFS 5YR
Hill 2004*	-16.7 (-4.0 – 7.6)	-6% (-25.2% - 13.2%)	10.0	10%	EFS 4YR
Nachman 1998*	-16.9 (-8.3 – 558.7)	-5.9% (-12% - 0.2%)	10.0	10%	EFS 5YR
Harris 1998	-19.2 (-7.4 – 32.6)	-5.2% (-13.5% - 3.1%)	10.0	10%	EFS 5YR
Nagatoshi 2010	-38.5 (-6.9 – 10.8)	-2.6% (-14.5% - 9.3%)	10.0	10%	EFS 5YR
Ribera 2007	-50.0 (-4.3 – 5.2)	-2% (-23.1% - 19.1%)	10.0	10%	EFS 5YR
Gaynon 2006*	-50.0 (-10.3 – 17.6)	-2% (-9.7% - 5.7%)	5.9	17%	DFS 3YR
Matloub 2006	-55.6 (-16.7 – 41.9)	-1.8% (-6% - 2.4%)	12.5	8%	EFS 6YR
Tower 2014*	-1000.0 (-20.5 – 21.4)	-0.1% (-4.9% - 4.7%)	11.1	9%	DFS 5YR
Buchanan 2000	21.7 (311.5 – 11.3)	4.6% (0.3% - 8.9%)	6.7	15%	CCR 1YR
Tubergen 1993*	16.7 (574.7 – 8.5)	6% (0.2% - 11.8%)	8.3	12%	EFS 5YR
Tubergen 1993*	16.7 (148.8 – 8.8)	6% (0.7% - 11.3%)	8.3	12%	EFS 5YR
Vora 2014	14.7 (106.6 – 7.9)	6.8% (0.9% - 12.7%)	10.0	10%	EFS 5YR
Mitchell 2005	14.3 (79.2 – 7.9)	7% (1.3% - 12.7%)	10.0	10%	EFS 4YR
Lange 2002*	14.3 (38.6 – 8.8)	7% (2.6% - 11.4%)	12.5	8%	EFS 6YR
Hann 2000	12.5 (40.7 – 7.4)	8% (2.5% - 13.5%)	20.0	5%	EFS 5YR
Bostrom 2003*	10.0 (22.3 – 6.4)	10% (4.5% - 15.5%)	12.5	8%	EFS 5YR
Tubergen 1993*	9.1 (18.3 – 6.0)	11% (5.5% - 16.5%)	8.3	12%	EFS 5YR
Tubergen 1993*	8.3 (15.6 – 5.7)	12% (6.4% - 17.6%)	8.3	12%	EFS 5YR
Balduzzi 2005	6.2 (10.8 – 4.4)	16.1% (9.3% - 22.9%)	5.6	18%	DFS 4YR
Nachman 1998*	5.0 (7.9 – 3.6)	20% (12.6% - 27.4%)	5.9	17%	EFS 5YR
Freeman 1997*	5.0 (5.5 – 4.6)	20% (18.3% - 21.7%)	6.7	15%	RR 12YR

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 RCTs 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, number needed to treat; 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

Step 1:

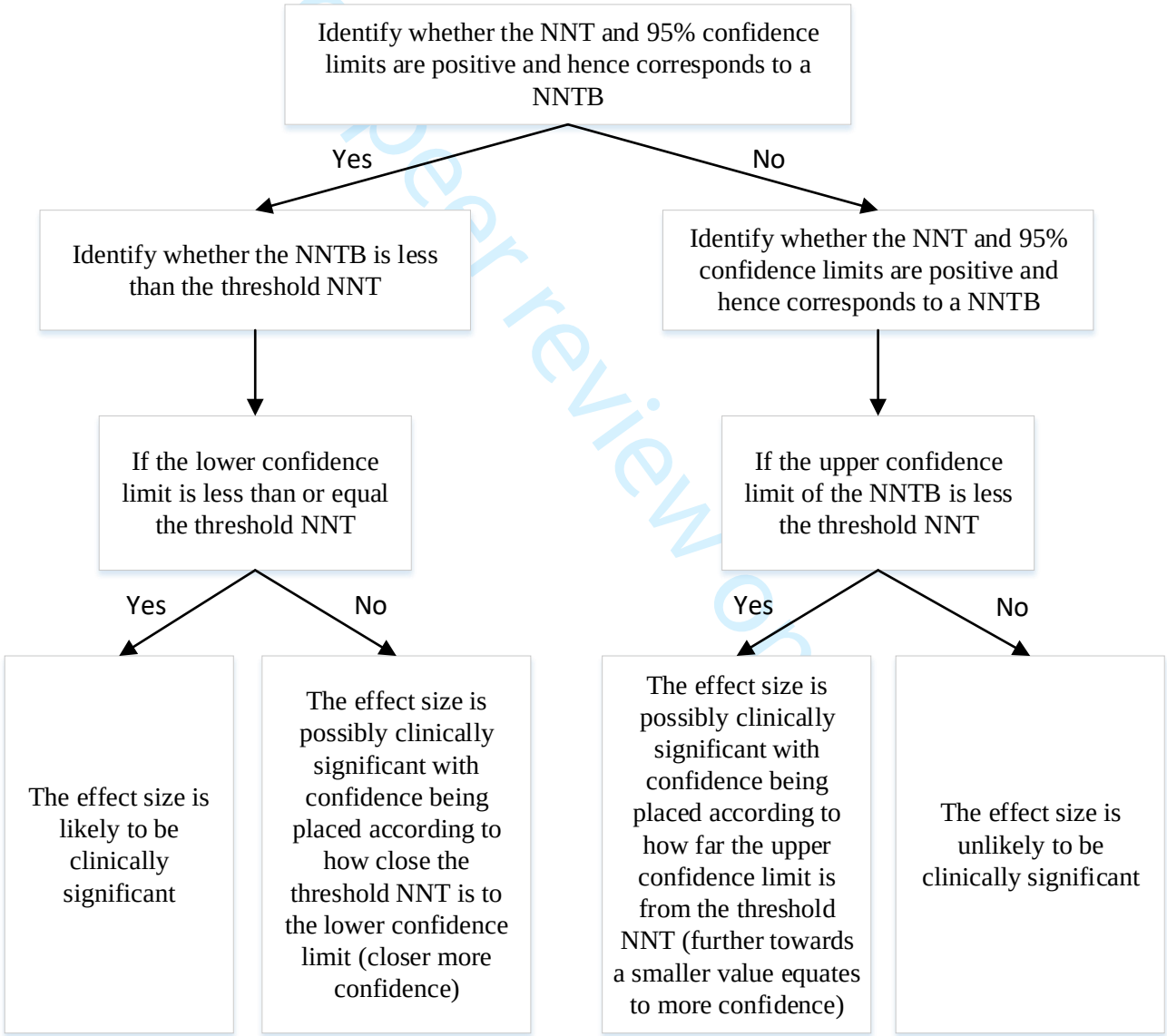
Identify the delta value reported in the sample size calculation and whether the authors reported on the way in which the delta value was chosen. A delta value informed by a previous trial or systematic review should be given more confidence in comparison to one from pilot data or clinical expertise.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

Step 2:

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

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 searched from their conception until the present day (July 2016) and limited to the English language.

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

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

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

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

Search Strategies

EMBASE

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

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

MEDLINE

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

CENTRAL (Wiley)

1. SR-CHILDCA

Appendix B

List of Included 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, Suciu S, Ferster A, et al. Comparison of Escherichia coli-asparaginase with Erwinia-asparaginase in the treatment of childhood lymphoid malignancies: results of a randomized European Organisation for Research and Treatment of Cancer-Children's Leukemia Group phase 3 trial. Blood 2002;99(8):2734-2739.

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.

25. 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.

26. 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):635-642.

27. Laver JH, Kraveka JM, Hutchison RE, et al. Advanced-stage large-cell lymphoma in children and adolescents: results of a randomized trial incorporating intermediate-dose methotrexate and high-dose cytarabine in the maintenance phase of the APO regimen: a Pediatric Oncology Group phase III trial. Journal of Clinical Oncology 2005;23(3):541-547.

28. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council ALL97 randomized trial. British journal of haematology 2005;129(6):734-745.

29. van der Werff ten Bosch J, Suciu S, Thyss A, et al. Value of intravenous 6-mercaptopurine during continuation treatment in childhood acute lymphoblastic leukemia and non-Hodgkin's lymphoma: Final results of a randomized phase III trial (58881) of the EORTC CLG. Leukemia 2005;19(5):721-726.

30. Becton D, Dahl GV, Ravindranath Y, et al. Randomized use of cyclosporin A (CsA) to modulate P-glycoprotein in children with AML in remission: Pediatric Oncology Group Study 9421. Blood 2006;107(4):1315-1324.

31. 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):4499-4506.

32. 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):3150-3156.

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34. 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):1165-1173.

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36. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. Lancet 2007;370(9583):240-50.

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

38. Von Stackelberg A, Hartmann R, Buhrer C, et al. High-dose compared with intermediate-dose methotrexate in children with a first relapse of acute lymphoblastic leukemia. Blood 2008;111(5):2573-2580.

39. 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. Biol Blood Marrow Transplant 2009;15(6):741-8.

40. 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):1911-1918.

41. Nagatoshi Y, Matsuzaki A, Suminoe A, et al. Randomized trial to compare LSA2L2-type maintenance therapy to daily 6-mercaptopurine and weekly methotrexate with vincristine and dexamethasone pulse for children with acute lymphoblastic leukemia. Pediatric Blood & Cancer 2010;55(2):239-247.

42. 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.

43. 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.

44. Termuhlen AM, Smith LM, Perkins SL, et al. Disseminated lymphoblastic lymphoma in children and adolescents: results of the COG A5971 trial: a report from the Children's Oncology Group. British journal of haematology 2013;162(6):792-801.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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
RESULTS			
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

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
DISCUSSION			
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
FUNDING			
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

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

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Page 2 of 2

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

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The utility of the number needed to treat in pediatric hematological cancer randomized controlled 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 parallel 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 August 2018.

Eligibility criteria for selecting studies: Superiority parallel 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 interval.

Results: A total of 43 RCTs were included, representing 45 randomized questions, of which none reported the NNT. Among acute lymphoblastic leukemia RCTs, 29.2% (7/24) of randomized questions were found to have a NNT corresponding to benefit, in comparison to acute myeloid leukemia RCTs with 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 less than the threshold NNT for acute lymphoblastic leukemia and acute myeloid leukemia, respectively. Of these, 100% (2/2 acute lymphoblastic leukemia and 1/1 acute myeloid leukemia) were determined to be possibly clinically significant.

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

Strengths and Limitations of this Study

Strengths	• 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. • Comparing the threshold NNT to the NNT and its confidence interval is an effective method to assess the level of clinical significance. • 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.
Limitations	• 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. • 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.

Introduction

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

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

At this time, the utility of the NNT to support evidence-based practice in pediatric oncology treatment trials remains unexamined, as does the degree to which the NNT has been reported in the pediatric oncology literature. We specifically aimed to assess the utility of the NNT with consideration of a threshold NNT, which is the point where the therapeutic benefit equals the therapeutic risk[17]. The threshold NNT should correspond to the inverse of the ARR that a RCT is designed to detect and a

clinically significant effect size that would lead to a clinical practice change. Therefore, a decision to administer a therapeutic intervention over the standard of care should occur when the NNT is less than the threshold NNT[17]. The primary study objective was to assess the utility of the NNT in pediatric hematologic cancer, by calculating the NNT in all superiority parallel RCTs assessing treatment related survival, relapse or remission, and comparing the NNT to the threshold NNT. A secondary study objective was to assess the proportion of published studies (specifically randomized questions) that reported the NNT.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary File)[18]. This review consisted of a subset of studies from a previous systematic review conducted by our research team, which was conducted from inception of the databases searched to July 2016. The search strategy used in that systematic review was re-run to capture studies published from July 2016 to August 2018. Methods describing the search strategy, eligibility criteria, study identification and data extraction for our previous systematic review have been detailed in the protocol (Supplementary File – Appendix A).

Search Strategy and Study Inclusion

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

Study Identification and Data Extraction

Two investigators (HH and KN) screened the titles and abstracts non-independently to identify studies that fulfilled the study inclusion criteria. Discrepancies were settled by discussion and consensus, with the principal investigator (AFH) available as an adjudicator. Studies that fulfilled the inclusion criterion at the title and abstract screening stage were selected for full-text review by one investigator (HH) to confirm study eligibility. A data extraction template was developed and piloted with 15 included studies to ensure

all pertinent data was captured. One investigator (HH) then extracted all of the data, of which a random sample was selected and verified by the principal investigator (AFH) as a quality assurance measure.

Analysis

The number needed to treat to benefit (NNTB), which corresponds to a positive NNT, or number needed to treat to harm (NNTH), which corresponds to a negative NNT, and associated 95% CI were calculated for each randomized question as per the validated methodology described by Altman & Andersen[19]. A randomized question is defined as an intervention comparison assessing a primary outcome for which a sample size calculation is reported. The NNT was based on the primary outcome and time point as specified in the sample size calculation. In the event that the time point specified in the sample size calculation was not reported, the information was inferred if a Kaplan Meier curve with the number of patients at risk was reported[19]. If the aforementioned was not provided, the time point reported in the results was used, and thus, these trials were prone to selective reporting bias. All analyses were conducted based on randomized questions to account for the possibility that a RCT could have more than one parallel group.

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

In order to ascertain whether the NNTB was clinically significant, we calculated the frequency and percentage of randomized questions where the NNT < threshold NNT, NNT > threshold NNT or NNT = threshold NNT. The threshold NNT was considered to be the inverse of the ARR (i.e., delta value) as specified in the sample size calculation and was assumed to correspond to a clinically significant effect size that would lead to a change in clinical practice. The threshold NNT was compared to the treatment NNT and classified as definitely clinically significant, possibly clinical significant, inconclusive clinical significance and definitely not clinically significant as specified in Figure 1. These categories, as well as the overall method, were informed by methods described by Man-Son-Hing et al.[20] and Guyatt et al.[21] Randomized controlled trials where an ARR of zero occurred were excluded from the analysis because

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

Patient and Public Involvement

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

Results

Included studies

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

Number needed to treat

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

Comparison of NNT and Threshold NNT

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

Reporting of NNT

There were no randomized questions that reported the NNT to support the reporting of the primary outcome of the study.

Discussion

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

Strengths and weaknesses

Our review provides a comprehensive analysis of the utility of the NNT through an evaluation of all superiority parallel group pediatric hematological RCTs assessing relapse, remission and survival from inception to August 2018. We provide the NNT and ARR with its 95% CI along with the threshold NNT and ARR for these RCTs using a validated methodological approach, which will serve as a valuable tool for decision-makers, clinicians and researchers to assess treatment effects. A weakness of this study is the exclusion of a number of RCTs due to reporting that precluded calculating the NNT. However, as the exclusion is due to reporting deficits, this limitation is beyond our control and serves as an important finding that reporting quality is limited in the pediatric hematological cancer RCT literature. An additional weakness is that 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 (i.e., minimal clinically important difference), if not explicitly indicated, and a proxy for the threshold ARR and NNT. This assumption, thus, would lead to the possibility of effect sizes being chosen that might be more reflective of study feasibility as opposed to clinical benefit. This approach may be limited in terms of generalisability given that this is not a universally recognized approach. Additionally, this assumption implies that the threshold NNT is equivalent to the threshold ARR even though the NNT results in a transformation of scale and is expressed using a unit measured in patients. Therefore, a threshold ARR may not correspond to a minimal clinically important difference in terms of NNT. However, as there were

no studies that reported a threshold NNT, our approach represents a feasible method to apply in the absence of a reported threshold NNT. This method is nonetheless not validated and further studies will need to be undertaken to compare whether researchers would equate the minimal clinical important difference in terms of ARR to the NNT.

Comparison with existing literature

Considerable published literature has evaluated the utility of the NNT. The overarching conclusion is that the NNT is a metric of value in clinical, health policy and formulary decision-making when interpreted correctly [4-8]. However, the NNT and ARR are rarely reported or poorly reported in the literature despite being recommended as a helpful tool in the CONSORT statement and are often calculated using inappropriate methods [6 12-16 22-27]. Our findings corroborate the existing literature because no studies reported the NNT in our review. Previous studies have not highlighted the utility of the NNT specifically in the pediatric oncology literature or evaluated the clinical significance of the NNT using the approach described in our study and thus, our study is a novel and important addition to the literature.

Study explanations and implications

Our study quantified the NNT as a means to better understand the utility of this tool to facilitate decision-making in pediatric oncology. The NNT allows for an intuitive understanding of the absolute effect size in terms of patients and can help considerably when comparing one treatment to another, after ensuring baseline characteristics, the outcome and time point for the patient population of interest are comparable[12]. For instance, a RCT conducted by Creutzig et al.[28] in pediatric AML patients assessing 5-year event free survival found a 6.0% (95% CI, 1.3%-10.7%) absolute increase associated with the experimental treatment (liposomal daunorubic induction) compared to the control treatment (idarubicin induction). The associated NNT corresponded to 17 (95% CI; 75-9), or NNTB 17 (95% CI, NNTB 75 to NNTB 9), meaning that it is estimated that by administering the experimental treatment, 1 extra patient would survive at 5 years for every 17 patients treated (95% CI, NNTB 75 to NNTB 9). Of note, this RCT was powered to detect an absolute increase in 5-year event free survival of 13% (i.e., delta value), which would correspond to a NNTB of 8 (i.e., threshold NNT). Although the NNTB is 17, the lower confidence limit is 75 and the upper confidence limit is 9 (a range that does not include 8), which, given the range, would lead one to believe that the effect size does not provide strong enough evidence to change clinical practice. In situations where the lower confidence limit of the NNTB is less than the threshold NNT, one

can be more confident that the treatment confers a clinically improved outcome as compared to the control. On the other hand, if the NNTB is less than the threshold NNT and the lower confidence limit is greater than the threshold NNT, one should exercise greater caution in concluding that the effect size is clinically significant (refer to Figure 1 for visual). As demonstrated in our study, a forest plot is a convenient method to visualize the relationship between the NNT (and the associated 95% CI) evident in study results compared to the NNT that the study was designed to detect as a proxy for the threshold NNT and that would be considered clinically significant.

The aforementioned approach is recommended in light of smaller sample sizes that are often attained in pediatric oncology RCTs and rare disease trials in general, as it allows for assessment of the precision of the treatment effect as well as clinical and statistical significance. This was demonstrated in our study where the majority of randomized questions found to have a NNTB had a NNT greater than the threshold NNT, of which the upper confidence limit was less than or equal to the threshold NNT. If these RCTs were designed with higher power it is possible that definite clinical significance may have been obtained. On the other hand, based on statistical significance these findings would be considered not significant. Since statistical significance does not provide an indication on the size of the treatment effect, one would not be able to discern whether the findings could have possible clinical significance. An assessment of clinical significant, therefore requires a summary measure be presented with a CI. By presenting a CI, an assessment can be made of both statistical and clinical significance, which can inform clinical decision-making. Interpreting results from RCTs based solely on statistical significance, without taking into consideration clinical significance, can result in misappraisal of evidence. Using the results of our study as an example, we demonstrated that all randomized questions, for which the NNTB was less than threshold NNT, had a lower confidence limit that was equal to, or greater than, the threshold NNT. Although these results were statistically significant, none had definite clinical significance and were only possibly clinically significant. These findings have clinical implications because clinicians often have to make decisions about administering treatments that are not standard of care, and rely on an accurate appraisal of evidence to inform these decisions. Inconclusive evidence, however, does not necessarily infer an ineffective intervention. Rather, inconclusive evidence (when the CI of the NNT crosses infinity as a result of the CI of the ARR crossing 0) infers that the level of clinical significance cannot be determined from the study results. The use of the NNT and the method we describe can be one more tool to support clinical decision-making within this context.

Scenarios where the NNT results in inconclusive evidence is a limitation in the utility of NNT, as discussed by Altman[29]. To illustrate, Lange et al.[30] 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%)

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

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

Recommendations

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

decision making and not a replacement. Supplementary file Appendix C provides a summary of how the NNT can be calculated and assessed to inform decision-making[19 20].

Figure Legends

Figure 1: Guideline to assess level of clinical significance using number 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

*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

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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Data Sharing Statement: Unpublished data will be made available upon request to the corresponding author.

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

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

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

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

[1] Denominator for indented corresponds to above row

[2] Mixed diagnoses refer to RCTs where more than one hematological cancer was included

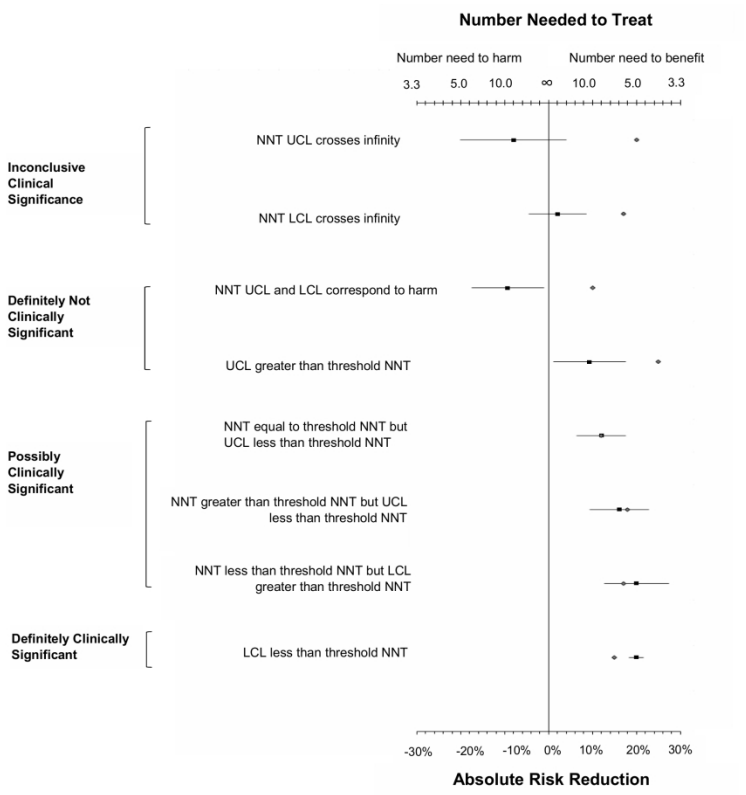

Figure 1: Guideline to assess level of clinical significance using numbers needed to treat
Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study ARR or NNT.
ARR corresponds to the absolute difference between the experimental and control estimates. The 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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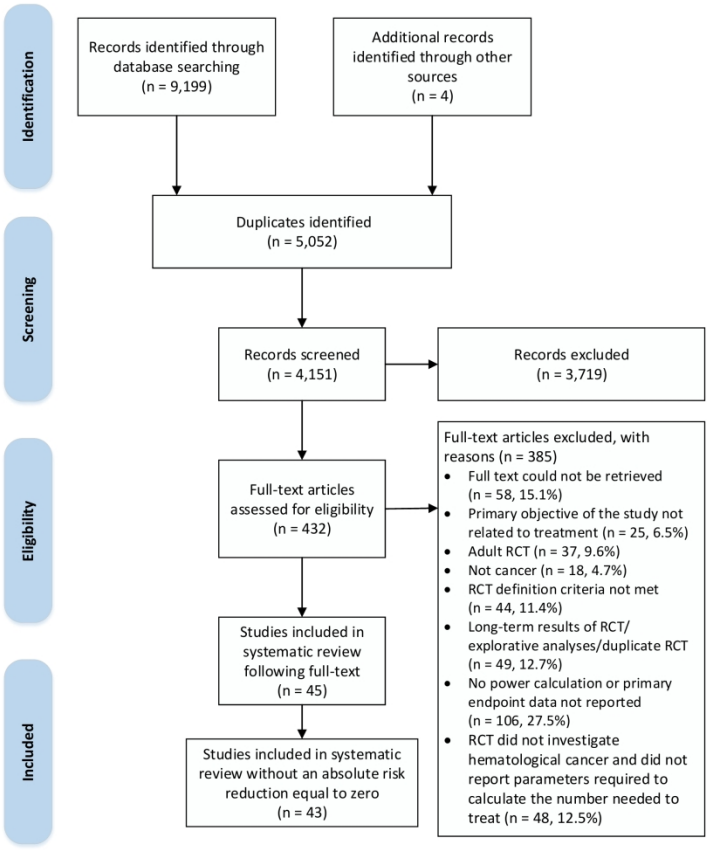

Figure 2: Selection of randomized controlled trials in the systematic review

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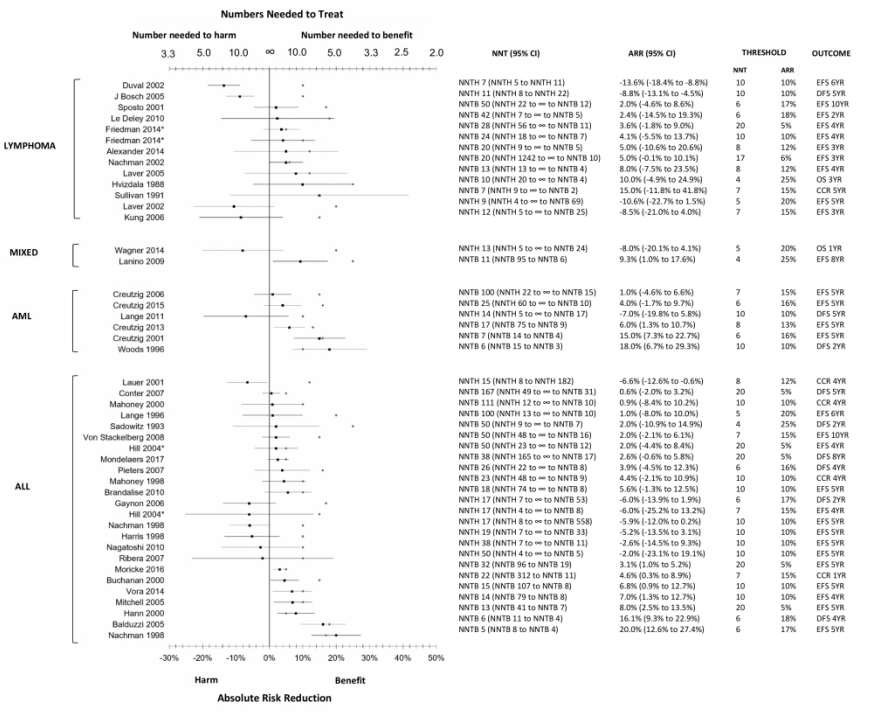

Figure 3: Forest plot summarizing randomized questions by the number needed to treat relative to the threshold number needed to treat according to hematological cancer type

*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

279x215mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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^2) for each meta-analysis.	6

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
RESULTS			
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
DISCUSSION			
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
FUNDING			
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**.

Page 2 of 2

Appendix A

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

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

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

Methods:

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

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

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

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

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

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

Study type:
Randomized controlled trials

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

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

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

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

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

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

Search Strategies

EMBASE

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

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

MEDLINE

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

CENTRAL (Wiley)

1. SR-CHILDCA

Appendix B – List of included and excluded studies

List of Included Studies:

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

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

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

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

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

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

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

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

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

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

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

Step 1:

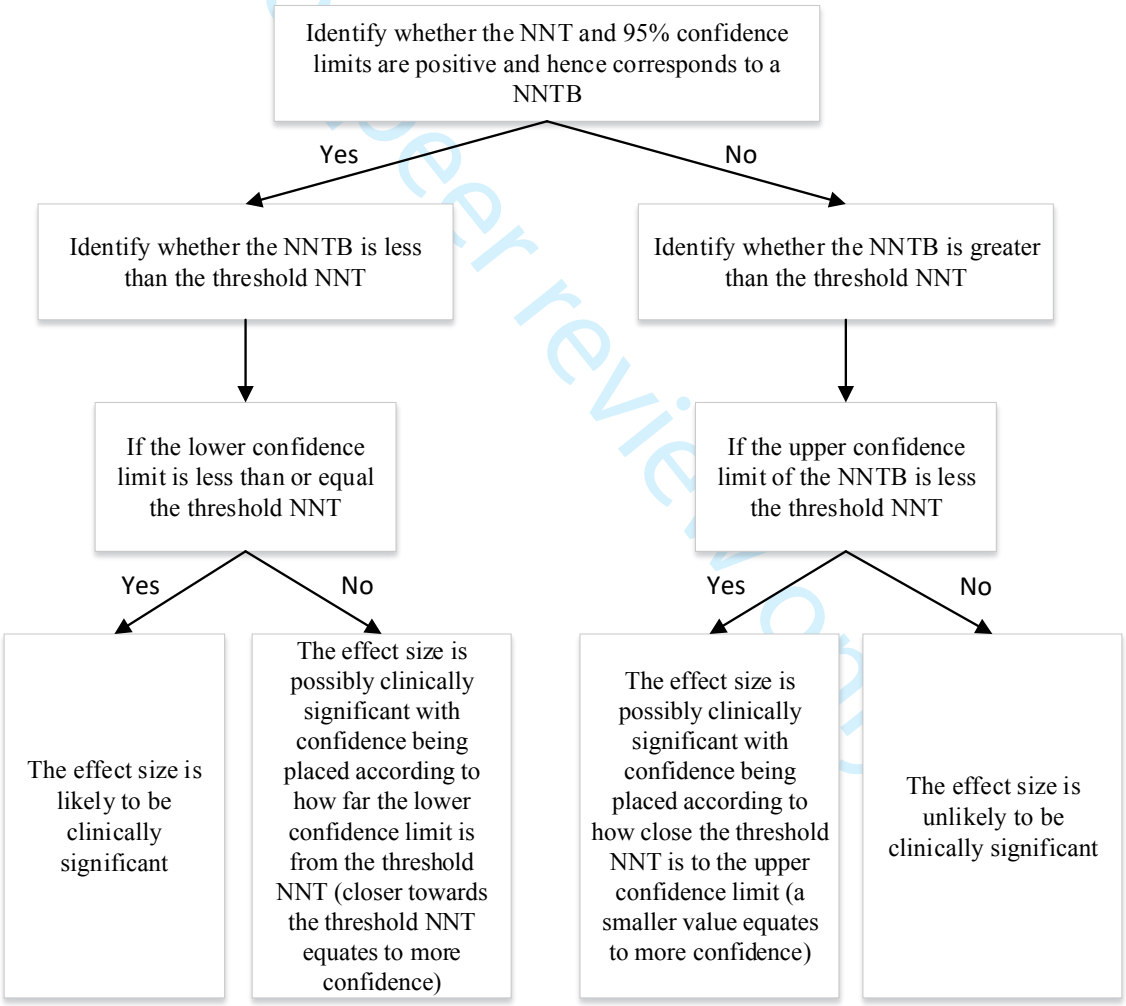
Identify the delta value reported in the sample size calculation and whether the authors reported on the way in which the delta value was chosen. A delta value informed by a previous trial or systematic review should be given more confidence in comparison to one from pilot data or clinical expertise.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

Step 2:

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

Step 3:

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



Step 4:

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

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

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The utility of the number needed to treat in pediatric hematological cancer randomized controlled 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, parallel, 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 August 2018.

Eligibility criteria for selecting studies: Superiority, parallel 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 interval.

Results: A total of 43 RCTs were included, representing 45 randomized questions, of which none reported the NNT. Among acute lymphoblastic leukemia RCTs, 29.2% (7/24) of randomized questions were found to have a NNT corresponding to benefit, in comparison to acute myeloid leukemia RCTs with 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 less than the threshold NNT for acute lymphoblastic leukemia and acute myeloid leukemia, respectively. Of these, 100% (2/2 acute lymphoblastic leukemia and 1/1 acute myeloid leukemia) were determined to be possibly clinically significant.

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

Strengths and Limitations of this Study

Strengths	• 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. • 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.
Limitations	• A number of RCTs were excluded from this review due to reporting that precluded calculating the NNT. • 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. • 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.

Introduction

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

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

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

threshold NNT should correspond to the inverse of the ARR that a RCT is designed to detect and a clinically significant effect size that would lead to a clinical practice change. Therefore, a decision to administer a therapeutic intervention over the standard of care should occur when the NNT is less than the threshold NNT[17]. The primary study objective was to assess the utility of the NNT in pediatric hematologic cancer, by calculating the NNT in all superiority parallel RCTs assessing treatment related survival, relapse or remission, and comparing the NNT to the threshold NNT. A secondary study objective was to assess the proportion of published studies (specifically randomized questions) that reported the NNT.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary File)[18]. This review consisted of a subset of studies from a previous systematic review conducted by our research team, which was conducted from inception of the databases searched to July 2016. The search strategy used in that systematic review was re-run to capture studies published from July 2016 to August 2018. Methods describing the search strategy, eligibility criteria, study identification and data extraction for our previous systematic review have been detailed in the protocol (Supplementary File – Appendix A).

Search Strategy and Study Inclusion

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

Study Identification and Data Extraction

Two investigators (HH and KN) screened the titles and abstracts non-independently to identify studies that fulfilled the study inclusion criteria. Discrepancies were settled by discussion and consensus, with the principal investigator (AFH) available as an adjudicator. Studies that fulfilled the inclusion criterion at the title and abstract screening stage were selected for full-text review by one investigator (HH) to confirm study eligibility. A data extraction template was developed and piloted with 15 included studies to ensure

all pertinent data was captured. One investigator (HH) then extracted all of the data, of which a random sample was selected and verified by the principal investigator (AFH) as a quality assurance measure.

Analysis

The number needed to treat to benefit (NNTB), which corresponds to a positive NNT, or number needed to treat to harm (NNTH), which corresponds to a negative NNT, and associated 95% CI were calculated for each randomized question as per the validated methodology described by Altman & Andersen[19]. A randomized question is defined as an intervention comparison assessing a primary outcome for which a sample size calculation is reported. The NNT was based on the primary outcome and time point as specified in the sample size calculation. In the event that the time point specified in the sample size calculation was not reported, the information was inferred if a Kaplan Meier curve with the number of patients at risk was reported[19]. If the aforementioned was not provided, the time point reported in the results was used, and thus, these trials were prone to selective reporting bias. All analyses were conducted based on randomized questions to account for the possibility that a RCT could have more than one parallel group.

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

In order to ascertain whether the NNTB was clinically significant, we calculated the frequency and percentage of randomized questions where the NNT < threshold NNT, NNT > threshold NNT, or NNT = threshold NNT. The threshold NNT was considered to be the inverse of the ARR (i.e., delta value), as specified in the sample size calculation, and was assumed to correspond to a clinically significant effect size that would lead to a change in clinical practice. The threshold NNT was compared to the treatment NNT and classified as definitely clinically significant, possibly clinical significant, inconclusive clinical significance, and definitely not clinically significant as specified in Figure 1. These categories, as well as the overall method, were informed by methods described by Man-Son-Hing et al.[20] and Guyatt et al.[21] Randomized controlled trials where an ARR of zero occurred were excluded from the analysis because

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

Patient and Public Involvement

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

Results

Included studies

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

Number needed to treat

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

Comparison of NNT and Threshold NNT

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

Reporting of NNT

There were no randomized questions that reported the NNT to support the reporting of the primary outcome of the study.

Discussion

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

Strengths and weaknesses

Our review provides a comprehensive analysis of the utility of the NNT through an evaluation of all superiority parallel group pediatric hematological RCTs assessing relapse, remission and survival from inception to August 2018. We provide the NNT and ARR with its 95% CI along with the threshold NNT and ARR for these RCTs using a validated methodological approach, which will serve as a valuable tool for decision-makers, clinicians and researchers to assess treatment effects. A weakness of this study is the exclusion of a number of RCTs due to reporting that precluded calculating the NNT. However, as the exclusion is due to reporting deficits, this limitation is beyond our control and serves as an important finding that reporting quality is limited in the pediatric hematological cancer RCT literature. An additional weakness is that 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 (i.e., minimal clinically important difference), if not explicitly indicated, and a proxy for the threshold ARR and NNT. This assumption, thus, would lead to the possibility of effect sizes being chosen that might be more reflective of study feasibility as opposed to clinical benefit. This approach may be limited in terms of generalisability given that this is not a universally recognized approach. Additionally, this assumption implies that the threshold NNT is equivalent to the threshold ARR even though the NNT results in a transformation of scale and is expressed using a unit measured in patients. Therefore, a threshold ARR may not correspond to a minimal clinically important difference in terms of NNT. However, as there were

no studies that reported a threshold NNT, our approach represents a feasible method to apply in the absence of a reported threshold NNT. This method is nonetheless not validated and further studies will need to be undertaken to compare whether researchers would equate the minimal clinical important difference in terms of ARR to the NNT.

Comparison with existing literature

Considerable published literature has evaluated the utility of the NNT. The overarching conclusion is that the NNT is a metric of value in clinical, health policy and formulary decision-making when interpreted correctly [4-8]. However, the NNT and ARR are rarely reported or poorly reported in the literature despite being recommended as a helpful tool in the CONSORT statement and are often calculated using inappropriate methods [6 12-16 22-27]. Our findings corroborate the existing literature because no studies reported the NNT in our review. Previous studies have not highlighted the utility of the NNT specifically in the pediatric oncology literature or evaluated the clinical significance of the NNT using the approach described in our study and thus, our study is a novel and important addition to the literature.

Study explanations and implications

Our study quantified the NNT as a means to better understand the utility of this tool to facilitate decision-making in pediatric oncology. The NNT allows for an intuitive understanding of the absolute effect size in terms of patients and can help considerably when comparing one treatment to another, after ensuring baseline characteristics, the outcome and time point for the patient population of interest are comparable[12]. For instance, a RCT conducted by Creutzig et al.[28] in pediatric AML patients assessing 5-year event free survival found a 6.0% (95% CI, 1.3%-10.7%) absolute increase associated with the experimental treatment (liposomal daunorubic induction) compared to the control treatment (idarubicin induction). The associated NNT corresponded to 17 (95% CI; 75-9), or NNTB 17 (95% CI, NNTB 75 to NNTB 9), meaning that it is estimated that by administering the experimental treatment, 1 extra patient would survive at 5 years for every 17 patients treated (95% CI, NNTB 75 to NNTB 9). Of note, this RCT was powered to detect an absolute increase in 5-year event free survival of 13% (i.e., delta value), which would correspond to a NNTB of 8 (i.e., threshold NNT). Although the NNTB is 17, the lower confidence limit is 75 and the upper confidence limit is 9 (a range that does not include 8), which, given the range, would lead one to believe that the effect size does not provide strong enough evidence to change clinical practice. In situations where the lower confidence limit of the NNTB is less than the threshold NNT, one

can be more confident that the treatment confers a clinically improved outcome as compared to the control. On the other hand, if the NNTB is less than the threshold NNT and the lower confidence limit is greater than the threshold NNT, one should exercise greater caution in concluding that the effect size is clinically significant (refer to Figure 1 for visual). As demonstrated in our study, a forest plot is a convenient method to visualize the relationship between the NNT (and the associated 95% CI) evident in study results compared to the NNT that the study was designed to detect as a proxy for the threshold NNT and that would be considered clinically significant.

The aforementioned approach is recommended in light of smaller sample sizes that are often attained in pediatric oncology RCTs and rare disease trials in general, as it allows for assessment of the precision of the treatment effect as well as clinical and statistical significance. This was demonstrated in our study where the majority of randomized questions found to have a NNTB had a NNT greater than the threshold NNT, of which the upper confidence limit was less than or equal to the threshold NNT. If these RCTs were designed with higher power, it is possible that definite clinical significance may have been obtained. On the other hand, these findings would not be considered significant based on statistical significance. Since statistical significance does not provide an indication of the size of the treatment effect, one would not be able to discern whether the findings could have possible clinical significance. An assessment of clinical significance, therefore, requires a summary measure be presented with a CI. By presenting a CI, an assessment can be made of both statistical and clinical significance, which can inform clinical decision-making. Interpreting results from RCTs based solely on statistical significance, without taking into consideration clinical significance, can result in misappraisal of evidence. Using the results of our study as an example, we demonstrated that all randomized questions, for which the NNTB was less than threshold NNT, had a lower confidence limit that was equal to, or greater than, the threshold NNT. Although these results were statistically significant, none had definite clinical significance and were only possibly clinically significant. These findings have clinical implications because clinicians often have to make decisions about administering treatments that are not standard of care, and rely on an accurate appraisal of evidence to inform these decisions. Inconclusive evidence, however, does not necessarily infer an ineffective intervention. Rather, inconclusive evidence (when the CI of the NNT crosses infinity as a result of the CI of the ARR crossing 0) infers that the level of clinical significance cannot be determined from the study results. The use of the NNT and the method we describe can be one more tool to support clinical decision-making within this context.

Scenarios where the NNT results in inconclusive evidence is a limitation in the utility of NNT, as discussed by Altman[29]. To illustrate, Lange et al.[30] 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%)

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

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

Recommendations

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

decision making and not a replacement. Supplementary file Appendix C provides a summary of how the NNT can be calculated and assessed to inform decision-making[19 20].

Figure Legends

Figure 1: Guideline to assess level of clinical significance using number 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

*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

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.

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34. Katz N, Paillard FC, Van Inwegen R. A review of the use of the number needed to treat to evaluate the efficacy of analgesics. *The journal of pain : official journal of the American Pain Society* 2015;16(2):116-23. doi: 10.1016/j.jpain.2014.08.005 [published Online First: 2014/11/25]

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

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

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

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

[1] Denominator for indented corresponds to above row

[2] Mixed diagnoses refer to RCTs where more than one hematological cancer was included

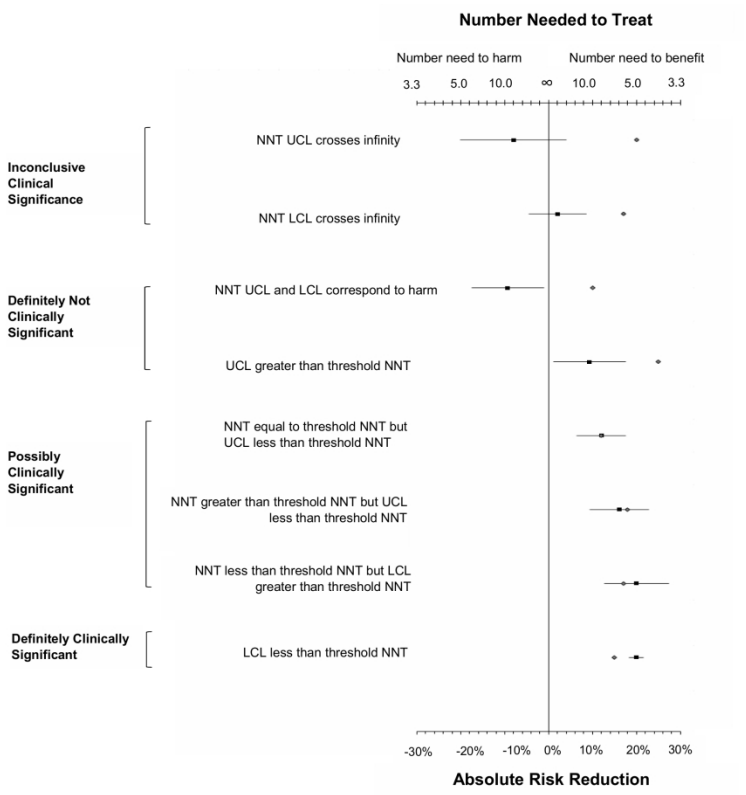

Figure 1: Guideline to assess level of clinical significance using numbers needed to treat
Grey diamond refers to the delta value for the threshold ARR or NNT while the black square to the study ARR or NNT.
ARR corresponds to the absolute difference between the experimental and control estimates. The 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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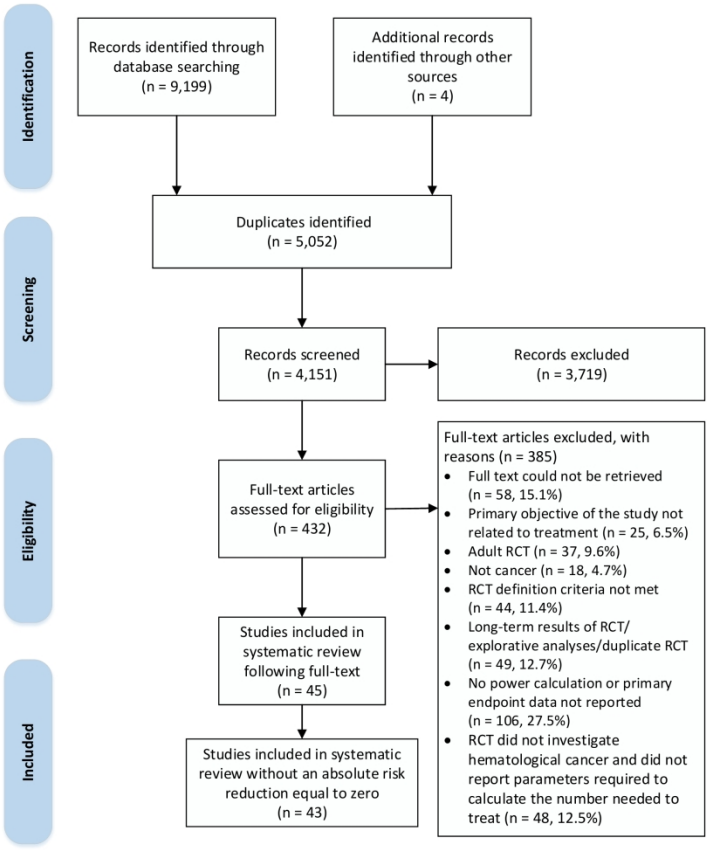

Figure 2: Selection of randomized controlled trials in the systematic review

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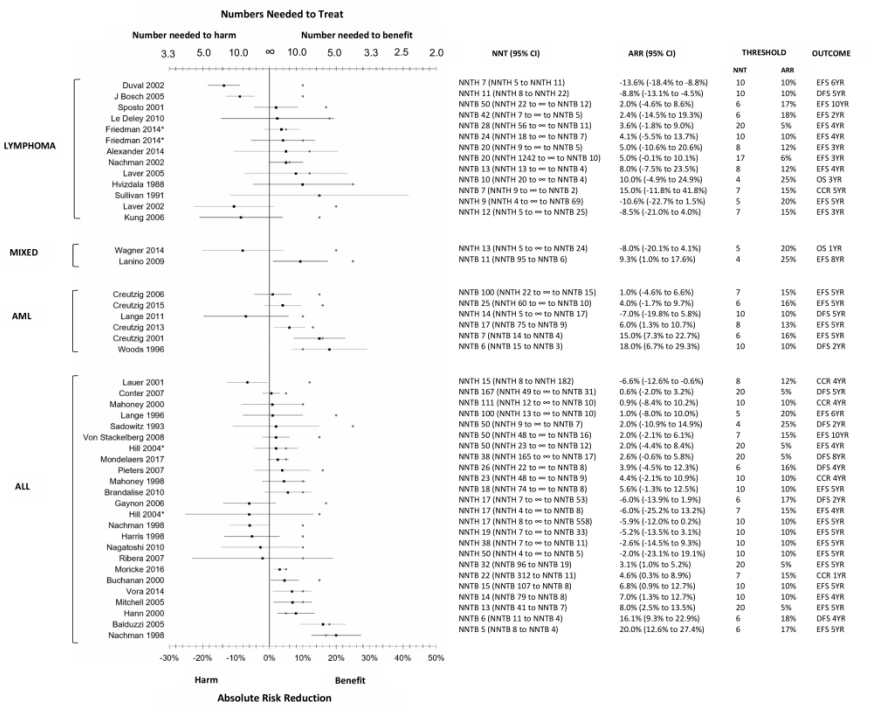

Figure 3: Forest plot summarizing randomized questions by the number needed to treat relative to the threshold number needed to treat according to hematological cancer type

*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

279x215mm (300 x 300 DPI)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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^2) for each meta-analysis.	6

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
RESULTS			
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
DISCUSSION			
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
FUNDING			
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**.

Page 2 of 2

Appendix A

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

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

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

Methods:

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

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

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

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

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

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

Study type:
Randomized controlled trials

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

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

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

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

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

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

Search Strategies

EMBASE

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

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

MEDLINE

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

CENTRAL (Wiley)

1. SR-CHILDCA

Appendix B – List of included and excluded studies

List of Included Studies:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Step 1:

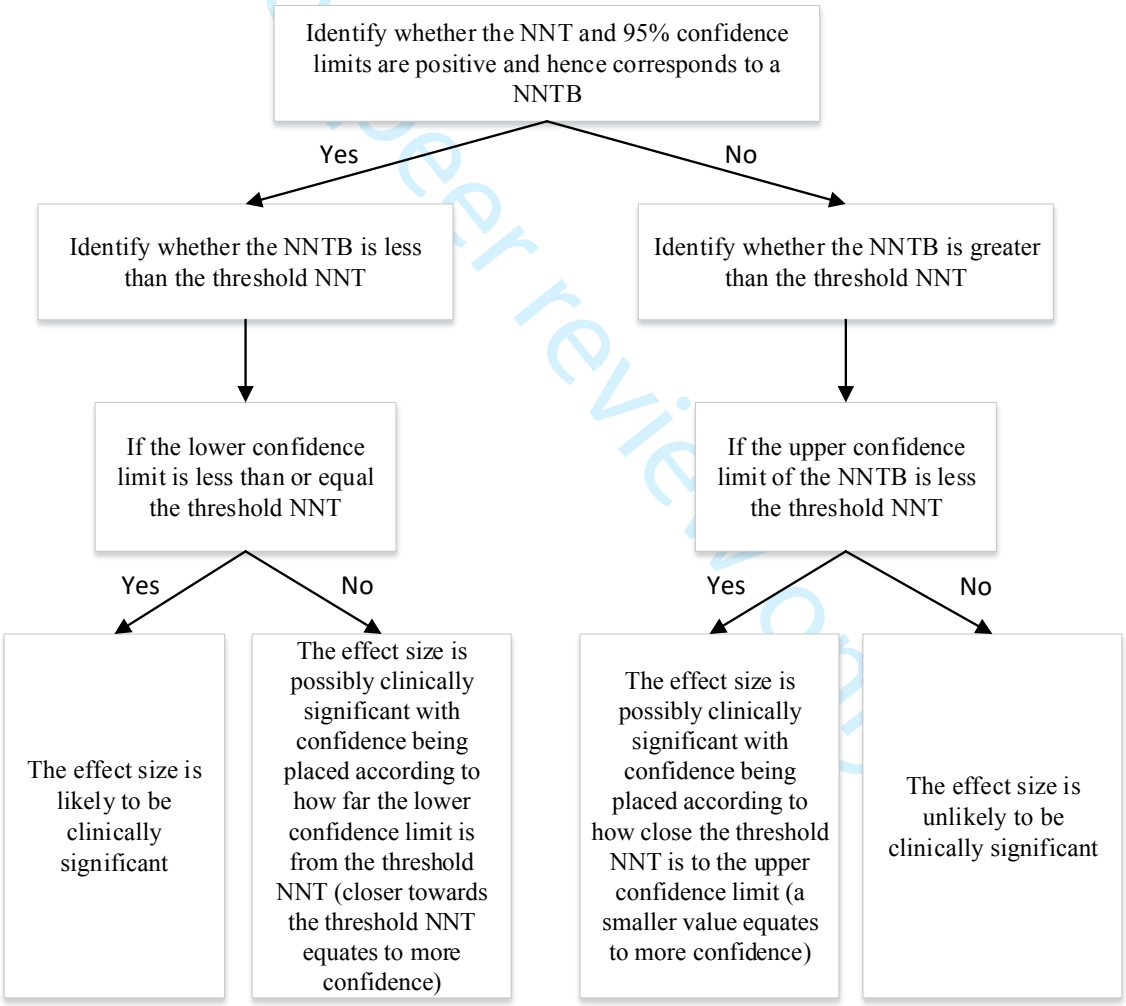
Identify the delta value reported in the sample size calculation and whether the authors reported on the way in which the delta value was chosen. A delta value informed by a previous trial or systematic review should be given more confidence in comparison to one from pilot data or clinical expertise.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

Step 2:

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

Step 3:

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



Step 4:

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

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