Systematic review of costs and cost-effectiveness of treatment for relapsed/refractory acute leukaemia in children

Protocol prepared by

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Introduction

Leukemia is the most common cancer in children accounting for approximately 35% of all childhood cancers [1]. Around 75% of leukemias among children are acute lymphoblastic leukemia (ALL), and most of the remaining cases include acute myeloid leukemia (AML), whereas, chronic leukemias are rare in children [1] Although the overall survival in children with newly diagnosed ALL has improved dramatically over the years reaching almost 90% today [2], relapse is the most common cause of treatment failure occurring in approximately 15%-20% of patients, and around 2% patients are refractory to induction chemotherapy [2,3,4]. Thus, relapsed ALL is considered as the fourth most common childhood malignancy [4]. The treatment of relapsed ALL requires very intensive chemotherapy and stem cell transplantation (SCT) [4,5,6and expensive newer agents/drugs [7], where only 30–50% of patients can be cured [4].

During the past decade, numerous promising immunotherapeutic drugs have been developed, and current research focuses on how to best incorporate these drugs into salvage regimens, changing the treatment landscape for children with relapsed ALL [8]. Relapsed ALL patients incur almost three times greater costs, with four times longer hospital stays, and four times more admissions than patients who did not relapse [9]. Children with AML experience high relapse rates of about 30% [10]. Outcomes of pediatric relapsed AML remain poor despite intensive therapy, based on a recent systematic review, with overall survival reaching up to 40% [11]. Similarly, the costs of relapsed AML in children are very high, with inpatient resource utilization being the largest cost driver [12].

As such, the treatment of relapsed acute leukemia in children (ALL and AML) impose great financial and economic burden on health systems. Yet, the outcomes of treatment are not very rewarding, and there is a need to generate the evidence to determine which treatment interventions have the greatest value for money, in terms of costs relative to improved health outcomes/effects through cost-effectiveness analysis [13]. Optimal decisions would require best evidence of cost-effectiveness outcomes [13]. Although a previous systematic review by Russell et al (2013) summarized the evidence about economic evaluation of pediatric cancer treatment, nevertheless it did not address cost-effectiveness of treatments for relapsed ALL or AML [14]. Therefore, there is a gap in evidence about the cost-effectiveness of treatment for children with relapsed and/or refractory acute leukaemia. This systematic review will establish the health-economic evidence base for costs and cost-effectiveness of the treatment interventions for relapsed/refractory acute leukemia in children.

Review question/aim

What is the health-economic evidence on the cost-effectiveness of treatment interventions for relapsed/refractory acute leukaemia in children?

The primary objective is to summarize the health-economic evidence on the cost-effectiveness of treatment for relapsed/refractory acute leukemia in children.

Secondary objective is to determine the cost-effectiveness of treatment for relapsed/refractory acute leukemia in children in LMICs or developing countries.

Methods

We followed the guidelines by the Centre for Reviews and Dissemination (CRD) for conducting systematic reviews of economic evaluation [15]. and the Campbell and Cochrane Economic Methods Group (CCEMG) guidance for incorporating economics evidence [13]. The review was developed and will be reported according to PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) checklist [16]. The systematic review protocol will be registered on PROSPERO database.

Types of studies to be included

Full economic evaluation studies will be included in this review. These are defined and classified in accordance with the definitions provided by the Campbell and Cochrane Economic Methods Group (CCEMG) [13]. Full economic evaluation studies include a comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes, effects), where costs and outcomes data of the alternatives are examined and a comparison of two or more interventions is undertaken [13]. These include primary economic evaluation studies with either cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), or cost-utility analysis (CUA) of treatment interventions, using any of the following approaches:

- Trial-based model (in RCTs)
- Non-trial based
- Simulation-based
- Decision model

Other inclusion criteria:

- Cost-effectiveness studies assessing primary (first line) and second-line treatment (treatment of relapse/refractory) of paediatric acute leukemia in children.
- There will be no restrictions based on perspective, follow-up duration, sample size or setting.

- Studies from both developed and developing countries will be included.
- Studies will be included if published in the English language from inception till date of the searches.

The following types of studies will be excluded:

- Partial economic evaluation studies that do not make clear comparisons between alternative interventions in terms of both costs (resource use) and consequences (effects), including cost comparison/cost analysis, cost descriptions and/or cost-of-illness (CoI) studies, and cost-outcome descriptions [13].
- Studies reporting only survival outcomes, quality of life (QOL), patient-reported outcomes and utilities without the costs;
- Qualitative studies, conference abstracts, reviews, editorials, commentaries or methodological articles. Bibliographies of systematic reviews will be utilized to examine relevant studies for inclusion. However, the reviews will not be eligible for inclusion.

Condition or domain being studied

Cost-effectiveness of treatment for relapsed/refractory acute leukemia in children; including acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). This may include first-line and subsequent lines of treatment for relapsed disease.

Participants/population

Children (aged 0–18 years) with relapsed/refractory acute leukaemia (ALL and AML) who received any treatment intervention will be included. There will be no restrictions on patient or disease characteristics such as gender, ethnicity, disease risk at diagnosis, or country. Patients will be included if they received treatment after first or subsequent relapses.

Intervention(s), exposure(s)

The cost-effectiveness of any treatment intervention used to manage relapsed/refractory acute leukemia in children will be evaluated, including (but not limited to): chemotherapy, immunotherapy, bone marrow transplant (BMT). This may include first-line and subsequent lines of treatment for relapsed disease. The treatment interventions for ALL and AML will be evaluated and reported separately.

Comparator(s)/control

There will be no restrictions on the types of comparator(s). For example, the comparator can be either no intervention or another intervention. However, the study should have a clear definition of the comparison.

Context

There will be no restrictions on settings.

Outcomes

Main outcomes

a) **Measures of Cost-effectiveness:** cost-effectiveness outcomes [13] will be reported in terms of: -
   - "Incremental Cost-Effectiveness Ratio" (ICER),
   - "Incremental cost per Quality-Adjusted Life Year (QALY)"
   - "Incremental cost per Disability-Adjusted Life Year (DALY)",
   - "Incremental cost-benefit ratio", and
   - other measures of economic evaluations without restrictions.

Additional outcomes

All outcomes as mentioned above.

Search strategy

The following electronic bibliographic databases of published studies will be searched:

- MEDLINE
- EMBASE (Ovid)
- Web of Science
- EconLit
- Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR)
- Centre for Reviews and Dissemination (CRD) Databases (Database of Abstracts of Reviews of Effects (DARE), the National Health Service, Economic Evaluation Databases (NHS EED), Health Technology Assessment Database (HTA))
- Cost-Effectiveness Analysis (CEA) Registry

Search will be done from inception to date (30th July 2021) and will be restricted only to the English language. We will scan the reference lists of eligible full-text articles to search for potential articles not identified in the original database search. The searches will be re-run just before the final analyses and further studies retrieved for inclusion, as appropriate. The search strategy will include use of a combination

of free text, indexing terms, database-specific limits and databases-specific subject headings/vocabulary (e.g. MeSH).

The first step will involve developing multiple search terms for each of the four domains. The domains will then be combined using "AND". Finally, database-specific filters will be used to limit the search to "Humans", and "English".

Combining the four domains below:

1. Acute leukaemia; acute lymphoblastic leukaemia; acute myeloid leukaemia
2. Children; paediatric; infants
3. Relapse; recurrence, refractory disease
4. Cost-effectiveness; costs, economic evaluation, economic analysis

Potential search terms

1. Acute leukaemia; acute lymphoblastic leukaemia; acute myeloid leukaemia

((Acute leukemia) OR (Acute leukaemia) OR (leukaemia) OR (leukemia) OR (acute lymphoblastic leukemia) OR (acute lymphoblastic leukaemia) OR (acute myeloid leukemia) OR (acute myeloid leukaemia)) OR (Acute lymphocytic leukemia) OR (Acute lymphocytic leukaemia) OR (acute lymphoid leukemia) OR (acute lymphoid leukaemia) OR (Acute myelogenous leukemia) OR (Acute myelogenous leukaemia))

2. Children; paediatric; infants

(infan* or newborn* or new-born* or perinat* or neonat* or baby* or babies or toddler* or minors or minors* or kid or kids or child* or schoolchild* or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).

3. Relapse; recurrence, refractory disease

((Relapse) OR (relapsed) OR (relapsing) OR (recurrent) OR (recurrence) OR (refractory) OR (refractory disease) OR (Treatment failure) OR (Induction failure))

4. Cost-effectiveness; costs, economic evaluation, economic analysis

"costs and cost analysis"/ or "cost allocation"/ or cost-benefit analysis/ or cost-utility analysis/ or "cost savings"/ or "cost of illness"/ or health care costs/ or direct service costs/ or drug costs/ or hospital costs/ or health expenditures/
Clinical outcomes/ survival/ survival rate/ life years saved/ complete remission/
Health Expenditures/
ECONOMICS/
quality-adjusted life years/ QALYs/ QUALYs/ Cost per QALY gained/ Incremental cost-effectiveness ratio
disability-adjusted life years/ DALYs/ Cost per DALY averted/ Cost per life saved
(costs or "cost analysis" or economics or "cost savings" or "cost of illness" or "health care costs" or "healthcare costs" or "health costs" or "direct service costs" or "drug costs" or "treatment costs" or "hospital costs" or "health expenditures" or "cost effectiveness" or "cost-effectiveness" or "cost of treatment" or "cost of disease" or "cost of care" or "health care cost" or "healthcare cost" or "economic evaluation" or "cost analyses" or "economic analysis" or "cost benefit analysis" or “cost-utility analysis” or "cost allocation" or "cost of services" or "medicine costs" or "hospital cost" or "health expenditure" or "out-of-pocket" or expenses or expenditure or "household expense" or "household expenditure" or QALY or "quality-adjusted life year" or DALY or "disability-adjusted life year")

Study selection procedure

The studies will be reviewed by **one author (RS)** and paper selection will be based on the predefined inclusion and exclusion criteria on two stages:

a) First, screening of titles and abstracts against the selection criteria, and when in doubt the full-text article will be reviewed.
b) Second, all full-text papers will be reviewed and a final decision made based on the inclusion/exclusion criteria.

Any disagreement or conflicting views over the eligibility of specific studies will be resolved by discussion or the final judgement of another reviewer. Both stages of the selection process will be piloted and if necessary modified. A PRISMA flow diagram will be used to illustrate the study selection processes [17]. Details of articles excluded at the second stage will be recorded along with the reason for exclusion [17].

Data extraction (selection and coding)

Data extraction will be performed on a pilot-tested standardized form on Microsoft Excel by **one author (RS**) and reviewed by other two author (IS and SM). The form will be structured based on the format and guidelines used to summarize findings of economic evaluations studies, such as the NHS Economic Evaluation Database (NHS EED) [18] the CCEMG [13], the "Consolidated Health Economics Evaluation Reporting Standards (CHEERS)" statement [19], and data items included in published studies [14,20] Disagreements between the authors will be resolved by discussion and consensus in the presence of senior reviewers (AE and CH).

Extracted information in the data extraction sheet may include (as appropriate):

- Authors
- Publication year
- Country
- Currency unit
- Study design
- Setting
- Target population
- Sample size
- intervention
- Comparator
- Measures of effectiveness
- Model specification
- Study perspective
- Length of follow-up
- Time horizon
- Methods for collecting resource use
- Price year
- Costs categories
- Largest cost drivers
- Opportunity cost
- Excluded costs
- Discount rate
- Total/average intervention costs
- ICER
- Uncertainty analysis
- Sensitivity analysis
- Funding source

Quality assessment of included studies

Risk of bias and quality assessment will be done as per *Murthy et al* (2017) depending on the type of economic evaluation in the study [21], as appropriate:

- Trial-based economic evaluation studies: CHEERS statement [19], Consensus Health Economic Criteria (CHEC) Criteria list [22], and Drummond Checklist [23]
- Model-based economic evaluation studies: CHEERS statement [19], and the Phillips checklist [24] [35]
- Cost-Benefit Analysis studies: Benefit-Cost Validity scale [25]

Additionally, a few questions that are relevant to the pediatric setting will be used from the Pediatric Quality Appraisal Questionnaire (PQAQ) to appraise the quality of the pediatric health economics literature [28].

One reviewer (RS) will appraise the methodological quality of the studies. To validate the quality assessment process, the process will be independently checked for completeness and accuracy by two other reviewers (IS and SM). Discordance in quality assessment was resolved by discussion.

Strategy for data synthesis

We will summarize the characteristics and results of the included studies using "Characteristics of included studies" tables for ALL and AML separately. This will be supported by a narrative summary that will compare and evaluate the methods used and the main results among the included studies. We will also report the findings of the critique of methods used for economic evaluation in the included studies, including the CHEERS checklist score for each study.

The currency and price year will be reported. Available costs, incremental costs and cost-effectiveness outcomes will be converted to 2020 International Dollars value using implicit price deflators for GDP and GDP Purchasing Power Parities as recommended by CCEMG [13].

Analysis of subgroups or subsets

Subgroups analysis will be conducted and reporting of findings will separated individually for children with ALL and AML.

References

[1] (ACS). American Cancer Society (ACS). Key Statistics for Childhood Leukemia. ACS. Accessed on 28 July 2021 at https://www.cancer.org/cancer/leukemia-in-children/about/key-statistics.html

[2] (Sun, 2018). Sun, W., Malvar, J., Sposto, R. et al. Outcome of children with multiply relapsed B-cell acute lymphoblastic leukemia: therapeutic advances in childhood leukemia & lymphoma study. *Leukemia* 32, 2316–2325 (2018).

[3] (Martin, 2012). Martin A, Morgan E, Hijiya N. Relapsed or refractory pediatric acute lymphoblastic leukemia: current and emerging treatments. *Paediatr Drugs*. 2012 Dec 1;14(6):377-87.

[4] (Locatelli, 2012). Locatelli F, Schrappe M, Bernardo M, and Rutella S. How I treat relapsed childhood acute lymphoblastic leukemia. *Blood*. 2012:4(12).

[5] (Scalo, 2014). Scalo, J. F. , and Rascati K. L.. 2014. Trends and issues in oncology costs. *Expert Rev. Pharmacoecon. Outcomes Res*. 14:35–44.

[6] (Chhatwal, 2015). Chhatwal, J. , Mathisen M., and Kantarjian H.. 2015. Are high drug prices for hematologic malignancies justified? A critical analysis. *Cancer* 121:3372–3379.10.1002/cncr.29512

[7] (Pui, 2013). Pui, C. H. , and Evans W. E.. 2013. A 50-year journey to cure childhood acute lymphoblastic leukemia. *Semin. Hematol*. 50:185–196.

[8] (Hunger, 2020). Stephen P. Hunger,Elizabeth A. Raetz, How I treat relapsed acute lymphoblastic leukemia in the pediatric population, *Blood*, 2020:136(15).

[9] (Kaul, 2016). Kaul S, Korgenski EK, Ying J, et al. A retrospective analysis of treatment-related hospitalization costs of pediatric, adolescent, and young adult acute lymphoblastic leukemia. *Cancer Med*. 2016;5(2):221-229.

[10] (Rasche, 2021). Rasche M, Steidel E, Zimmermann M, et al. Second Relapse of Pediatric Patients with Acute Myeloid Leukemia: A Report on Current Treatment Strategies and Outcome of the AML-BFM Study Group. Cancers (Basel). 2021;13(4):789. Published 2021 Feb 14.

[11] (Hoffman, 2020). Anne E Hoffman, Linda J Schoonmade & Gertjan JL Kaspers (2021) Pediatric relapsed acute myeloid leukemia: a systematic review, Expert Review of Anticancer Therapy, 21:1, 45-52.

[12] (Forsythe, 2021). Forsythe A, Sandman KE. What Does the Economic Burden of Acute Myeloid Leukemia Treatment Look Like for the Next Decade? An Analysis of Key Findings, Challenges and Recommendations. *J Blood Med*. 2021;12:245-255.

[13] (CCEMG, 2011). Shemilt I, Mugford M, Byford S, Drummond M, Eisenstein E, Knapp M, Mallender J, McDaid D, Vale L, Walker D. **Chapter 15**: Incorporating economics evidence. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org. p. 449-80. Accessed: 28 Jul 2021.

[14] (Russell, 2013). Russell HV, Panchal J, Vonville H, Franzini L, Swint JM. Economic evaluation of pediatric cancer treatment: a systematic literature review. *Pediatrics*. 2013 Jan;131(1):e273-87.

[15] (CRD) Centre for Reviews and Dissemination (CRD). Systematic Reviews: CRD's guidance for undertaking reviews in healthcare. CRD, University of York. 2009. ISBN 978-1-900640-47-3.

[16] (30) Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst.* 2015;4(1):1.

[17] (PRISMA) Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;51:264-269.

[18] (NHS-EED). Craig D, Rice S. NHS economic evaluation database handbook: Centre for Reviews and Dissemination, University of York. 2007.

[19] (CHEERS). Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. *Cost Eff Resour Alloc*. 2013;11(1):6.

[20] (Fung, 2019). Fung A, Horton S, Zabih V, et al Cost and cost-effectiveness of childhood cancer treatment in low-income and middle-income countries: a systematic review BMJ Global Health 2019;4:e001825.

[21] (Murthy et al). Murthy S, John D, Godinho IP, Godinho MA, Guddattu V, Nair NS. A protocol for a systematic review of economic evaluation studies conducted on neonatal systemic infections in South Asia. *Syst Rev*. 2017 Dec 12;6(1):252.

[22] (CHEC). Evers S, Goossens M, De Vet H, Van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care. 2005;21(02):240–5.

[23] (Drummond). Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ: the BMJ economic evaluation working party. BMJ. 1996;313(7052):275–83. doi:10.1136/bmj.313.7052.275.

[25] (McDougall). McDougall C, Cohen M, Swaray R, Perry A. Benefit-cost analyses of sentencing. Campbell. *Syst Rev*. 2008;10 https://doi.org/10.4073/csr.2008.10.

[26] (Larg & Moss). Larg A, Moss JR. Cost-of-illness studies: a guide to critical evaluation. PharmacoEconomics. 2011;9(8):653–71. doi:10.2165/11588380-000000000-00000.

[27] (PHO Wales). Public Health Observatory Wales. Cost of Illness Studies-Critical Appraisal Checklist (29/12/2014). http://www.publichealthwalesobservatory.wales.nhs. uk/. Accessed 20 Jan 2017.

[28] Ungar WJ, Santos MT. The Pediatric Quality Appraisal Questionnaire (PQAQ).: an instrument for evaluation of the pediatric health economics literature. Value Health. 2003;6(5):584–94

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