Application to add azacitidine to WHO Model List of Essential Medicines

As a Medicine for Treatment of acute myeloid leukaemia

Submitted by:

Ignacio Neumann, MD, PhD. Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

Pamela Burdiles, MSc. Faculty of Medicine, Universidad Andrés Bello, Santiago, Chile.

Paula Nahuelhual MSc. Faculty of Clinical Medicine, Clínica Alemana de Santiago-Universidad del Desarrollo, Santiago, Chile.

Eduardo Quiñelen, MSc. Department of Kinesiology, Universidad Metropolitana de Ciencias de la Educación, Santiago, Chile.

Katherine Cerda, RN, MSc. Department of Health Technology Assessment and Evidence Based Health, Ministerio de Salud de Chile, Santiago, Chile.

Felipe Vera, MSc. Unidad de Evaluación de Tecnologías en Salud, Centro de Investigación Clínica, Pontificia Universidad Católica de Chile

Potential conflicts of interest

All the authors declare no conflict of interest

Date: January 2021 (a new version of the original application was republished on 27th April – see Correction note).

Correction note

In the original application the absolute survival benefit associated with the use of azacitidine was estimated using an approach that was lately recognized as suboptimal by the GRADE Working Group and Cochrane Cancer. In agreement with the Secretariat of the Expert Committee of the Selection and Use of the Essential Medicines the application authors have corrected the estimates of the absolute effect of azacytidine using the following method:

- First identify the median of the median survival time among control groups.

- Then use the following formula to estimate the absolute difference:

MST1 = MST0 / HR; being MST1 the median survival time with intervention

MST0 the median of the median survival time in control

HR the hazard ratio obtained from the meta-analysis

Based on Skoetz et al. GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles. *J Clin Epidemiol*. 2020 Feb;118:124-131

- Repeat the process with the limits of the confidence interval of the HR to obtain the confidence interval for the absolute effect estimate.

Therefore, in the Review of benefits section - Summary of Potential Benefits table, the anticipated absolute effect with azacitidine was corrected from 3.9 to 0.2 months. The correction has been reported consistently throughout the text.

General items

1. Summary statement of the proposal for inclusion, change or deletion.

This application proposes to add azacitidine to the list of WHO Essential Medicine as treatment for individuals with acute myeloid leukaemia.

Acute myeloid leukaemia is a common type of leukaemia and has a poor prognosis. Worldwide, Western Europe and South Asia have the highest incidence (Western Europe: 20 per 100.000; South Asia: 21 per 100.000 in 2017). However, Andean Latin America and East Asia have experienced a substantial increase over the past 30 years. Further, the number of acute myeloid leukaemia related deaths worldwide has almost doubled: from 52 per 100.000 in 1990 to 100 per 100.000 in 2017.

The use of azacitidine has been studied in the induction as well the maintenance of individuals with acute myeloid leukaemia. Also, in individuals with high and low bone marrow blasts counts. The data available shows that azacitidine may increase the overall survival in approximately 0.2 months (HR 0.96, 95% CI 0.69 - 1.35; low certainty evidence) without a substantial increase in adverse events (RR 0.99, 95% CI 0.80 - 1.23; low certainty evidence). One of the barriers for the use of azacitidine it is cost. Economic evidence shows that at the current price, azacitidine is at the limit of the willingness to pay in rich countries and probably is not a cost-effective alternative in low- and middle-income settings without a price discount. Nevertheless, different agencies, including one from Peru, have recommended its coverage given the poor prognosis of acute myeloid leukaemia and the absence of other treatments in individuals not suitable for intensive chemotherapy.

2. Relevant WHO technical department and focal point.

Department of Health Products Policy and Standards, World Health Organization, Geneva, Switzerland

3. Name of organization(s) consulted and/or supporting the application.

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

WHO Collaborating Center for Evidence Informed Policy, McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

International Nonproprietary Name (INN)	Anatomical Therapeutic Chemical (ATC) code
Azacitidine	L01BC07

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

The recommended starting dose for the first treatment cycle is 75 mg/m2 of body surface area, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle).

No specific dose adjustments are recommended for the elderly.

Azacitidine can be administered to patients with renal impairment without initial dose adjustment.

The safety and efficacy of Azacitidine in children aged 0-17 years have not yet been established.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

As individual medicine.

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details

Azacitidine has been studied in the induction as well the maintenance of individuals with acute myeloid leukaemia. Also, in individuals with high and low bone marrow blasts counts. Different schemes are available.

8. Information supporting the public health relevance.

Acute myeloid leukaemia is a common type of leukaemia and has a poor prognosis. According to the SEER database, there were approximately 20.000 new cases in the USA in 2020 and around 11.000 estimated deaths. In this country, the 5-years survival rate between 2010 and 2016 was 28%.[1]

Worldwide, Western Europe and South Asia have the highest incidence (Western Europe: 20 per 100.000; South Asia: 21 per 100.000 in 2017). However, Andean Latin America and East Asia have experienced a substantial increase over the past 30 years.[2] Further, the number of acute myeloid leukaemia related deaths worldwide has almost doubled: from 52 per 100.000 in 1990 to 100 per 100.000 in 2017.[2]

More than half of incident cases occur in adults older than 65 years and this group has a particularly poor prognosis.[3] Patients with acute myeloid leukaemia have a lower baseline

quality of life than individuals with other cancers and the quality of life may be affected significantly as a consequence of treatment.[4]

9. Review of benefits: summary of evidence of comparative effectiveness.

Methods

We searched for randomized trials up to December 2020 on MEDLINE and EMBASE, from date of inception and without language limits. Additionally, we searched for up-to-date systematic reviews in MEDLINE, EMBASE and The Cochrane Library (see appendix). We used the systematic reviews as a way to identify relevant studies but conducted our own meta-analysis.

We used the following inclusion criteria:

1. Study design: Randomized trial
2. Population: Individuals with acute myeloid leukaemia
3. Intervention: azacitidine
4. Comparison: any therapy without azacitidine

We assessed the risk of bias using the Cochrane Collaboration Risk of Bias Tool. We also made judgments about precision, consistency, directness, and likelihood of publication bias following the GRADE approach.

We meta-analysed the data using the Mantel–Haenszel method, random effect model. We assessed heterogeneity with the Chi-square test and with the I2 statistic. Meta-analyses were conducted using RevMan (Version 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) or STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

Results

We identified 4 systematic reviews[5-8] and 9 randomized trials.[9-17] In general, trials included patients older than 65 years and randomized participants to receive azacitidine or a conventional care regimen, which included standard chemotherapy, cytarabine in low dose, lenalidomide or observation only. In the majority of the trials identified, azacitidine was used

from the induction phase. However, in four trials, azacitidine was used only in the consolidation phase after an induction with standard chemotherapy.[10,14,15,17]

Despite this variability in the designs, results were relatively homogeneous, with the exception of the trial by Feneaux et al.[16] There was no clear difference between the study by Feneaux et al and the rest of the trials. We explored the potential effect of patients' characteristics such and age, percentage of bone marrow blasts and proportion with high risk cytogenetic, but none of these hypotesis accounted for the heterogeneity (data not shown).

The metanalysis of the studies identified, showed that the use of azacitidine in patients with acute myeloid leukemia may increase the overall survival in approximately 0.2 months (HR 0.96, 95% CI 0.69-1.35). The certainty of the evidence was judged low due imprecision, since the confidence interval do not exclude potential harm with azacitidine; and due to inconsistency, given the unexplained heterogeneity introduced by the trial by Feneaux et al.[16]

It is important to note, that the effect of azacitidine was observed in patients with low and high bone marrow blast count.

Summary of Potential Benefits

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Azacitidine	WITHOUT Azacitidine	Difference (CI 95%)	
Overall survival 6 RCTs (n=1,125)	**HR 0.96** (0.69 - 1.35)	**6.7** months	**6.5** months	**0.2** months more[a] (from 1.6 less to 2.9 more)	⨁⨁◯◯[b,c] **LOW**

Abbreviations: HR: Hazard ratio; CI: Confidence interval

a. The anticipated absolute effect was estimated from the median survival observed in controls groups and the hazard ratio.
b. We rated down the certainty of the evidence due to imprecision, since the confidence interval do not exclude potential harm with azacitidine.
c. We rated down the certainty of the evidence due to inconsistency. A significant heterogeneity was observed on the meta-analysis. The heterogeneity decreased substantially when the trial by Feneaux et al. was removed from the meta-analysis. There was no clear difference between this trial and the rest of the body of evidence.

10. Review of harms and toxicity: summary of evidence of safety.

Compared to standard chemotherapy, azacitidine may not increase the risk of adverse events. In the trials included, a similar incidence of adverse events was observed with or without azacitidine (RR 0.99, 95% CI 0.80-1-13; low certainty evidence). The most common adverse events were febrile neutropenia, thrombocytopenia, infection and gastrointestinal symptoms.

Summary of Potential Harms

Outcomes	Relative Effect (CI 95%)	Anticipated absolute effect			Certainty of the Evidence (GRADE)
		WITH Azacitidine	WITHOUT Azacitidine	Difference (CI 95%)	
Adverse Events grade 3 or more [a] 9 RCT (n=1409)	**RR 0.99** (0.80 - 1.23)	**635** per 1000	**641** per 1000	**6 fewer** (128 fewer to 147 more)	⨁⨁◯◯[b,c] **LOW**

Abbreviations: RR: Risk ratio; CI: Confidence interval

a. Common grade ≥3 adverse events included: febrile neutropenia, thrombocytopenia, infection, gastrointestinal symptoms.
b. We rated down the certainty of the evidence due to imprecision, since the confidence interval probably crosses decisions thresholds
c. We rated down the certainty of the evidence due to inconsistency. A significant heterogeneity was observed on the meta-analysis.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

Methods

We searched for economic evaluations up to December 2020 on MEDLINE, EMBASE and the Cochrane library (see appendix). Additionally, we hand-searched the websites of the following agencies and organizations: The National Institute of Health Research, The Center of Review and Dissemination, The Canadian Agency for Drugs and Technologies in Health (CADTH), The National Institute for Health and Care Excellence (NICE), Pharmaceutical Benefits Advisory

Committee (PBAC) and The International Network of Agencies for Health Technology Assessment (INHATA).

Inclusion/exclusion

Inclusion

We included full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population.

Exclusion

We excluded studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects. Also, we excluded abstracts, posters, reviews, letters/editorials, and unpublished studies

Results

We identified a total of 8 studies/reports.[18-21] Four of them were cost-utility analysis[18-21] and 4 were agencies reports. We excluded one study from the evidence synthesis due to very serious limitations that made the results unreliable.[21]

The first study included, was a cost-utility analysis from the Canadian health system in a third payer perspective.[18] Investigators used a Markov model comparing azacitidine vs conventional care regimens. At a 25 months' time horizon, the ICER was CA $160,438 per QALY and for the lifetime perspective CA $160,373 per QALY. Both, over the Canadian thresholds of CA $20.000-$100.000 per QALY.

Another cost-utility analysis was done from the Spanish health care system perspective.[19] Investigators used a lifetime Markov model that compared azacitidine (AZA) against conventional care regimen (CCR), best supportive care (BSC), low-dose chemotherapy (LDC) or standard-dose chemotherapy (SDC). The different ICERs were: AZA vs. BSC € 39,610/QALY gained, AZA vs. LDC €30,531/QALY gained, AZA vs. SDC €23,804/QALY gained, AZA vs. CCR €34,673/QALY gained. Spain does not have an official threshold of willingness to pay. However, considering a threshold of €20,000 – 30,000,[22] these results suggests that the use of azacitidine may be cost effective with a price discount.

The last study included was cost-utility analysis from the Canadian public payer perspective.[20] Using a probabilistic Markov model, investigators compared azacitidine against best supportive care alone (BSC), low-dose chemotherapy (LDC) and with standard-dose chemotherapy (SDC). The ICERs per QALY gained were $86,973, $84,829, and $2,152 for azacitidine compared with BSC, LDC and SDC respectively. Considering the Canadian thresholds of CA $20.000-$100.000 per QALY, the use of azacitidine was a cost-effective alternative to standard-dose chemotherapy, and it may be cost-effective with a price discount in the other scenarios.

Three agencies, The National Institute for Health and Care Excellence (NICE, https://www.nice.org.uk; UK), The Pharmaceutical Benefits Advisory Committee (PBAC, https://www.pbs.gov.au/pbs/home; Australia) and the Instituto de Evaluación de Tecnologías en Salud e Investigación (IETSI, http://www.essalud.gob.pe/ietsi; Perú) published a report evaluating azacitidine. In all three agencies, the ICER was considered over the regular thresholds, but recommended coverage nevertheless given the effectiveness of the treatment and the lack of other treatments in individuals not suitable for intensive chemotherapy. In the Canadian Agency for Drugs and Technologies in Health (CADTH, https://www.cadth.ca; Canada) the drug is still under review, but it already has coverage in some Canadian provinces.

Summary of Economic Evaluations

Study	Limitations	Other comments		Cost-effectiveness (ICER)	Uncertainty
Coyle, D. 2020	Minor limitations	Model	Markov model comparing Azacitidine vs Conventional care regimens	Azacitidine vs Conventional care regimens. For the 25 months' time horizon $160,438 per QALY. For the lifetime perspective $160,373 per QALY	Investigators run a Deterministic sensitivity analysis (DSA) and a probabilistic sensitivity analysis (PSA), in the case of the DSA a tornado plot was used, where mortality rates had a higher impact. In the case of the PSA At a willingness-to-pay threshold of $Can 100,000, the probability that azacitidine was cost-effective was only 11%; at a willingness-to-pay threshold of $Can 50,000, the probability was < 1%.
		Population	Patients entered the model in the AML state (> 30% blasts in the bone marrow) at age 69 years		
		Time horizon	25 months (converge of the OS curves) and lifetime		
		costs	Costs included medication, human health resource, routine physician follow-up, hospitalization and laboratory investigations, this was calculated using a mix of papers and clinicians.		
		Utilities	Baseline utility values were obtained from the results presented in the AZA-AML-001 study. The subsequent changes in utility scores were obtained after converting the EORTC QLQ-C30 scores		

			collected alongside the AZA-AML-001 clinical trial		
		Perspective	Third payer		
		Others	The model was for the Canadian health system, there is no explicit threshold, but the decisions are med from 20.000 to 100.000 per QALY. Conventional care regimens include best supportive care, low-dose cytarabine and induction chemotherapy.		
Study	**Limitations**	**Other comments**		**cost-effectiveness (ICER)**	**Uncertainty**
Crespo C. 2013	potentially serious limitations [a]	Model	Life-time Markov model. Patients were assumed to start in the MDS state and receive first-line treatment (azacitidine, BSC, LDC or SDC) and then either die or progress to AML with consequent progression to death.	The different comparators vs AZA in a life-time horizon AZA vs. BSC € 39,610/QALY gained AZA vs. LDC €30,531/QALY gained AZA vs. SDC €23,804/QALY gained AZA vs. CCR €34,673/QALY gained	Probabilistic sensitivity analysis was performed to examine the combined effect of the uncertainty in all the variable parameters (survival, treatment cessation, unit cost, use of resources, etc.). Where there were no estimates of parameter uncertainty, ±30% intervals were assumed. The sensitivity analysis showed that azacitidine was a cost-effective option in 96.49% of the simulated cases €50,000/ QALY willingness-to-pay. In the subgroup analysis, the comparison shows that the probability of azacitidine being cost-effective below the €50,000/QALY threshold was 83.21% vs. BSC and 91.21% vs. LDC. In most PSA scenarios de AZA alternative was cost-effective in the €50,000/QALY threshold
		Population	Patients with MDS		
		Time horizon	life-time horizon,		
		costs	The cost included drugs, hospital cost, test, transfusions, adverse events and cost per cycle		
		Utilities	MDS and BSC utility scores were mapped to translate the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) scores from the CALGB study to EQ- 5D scores using regression analysis. SF-12 utility scores for LDC and SDC] were mapped to EQ-5D values using regression analysis and Monte Carlo simulation		
		Perspective	The Spanish health care		
		Others	Azacitidine was compared with CCR treatment options		
Study	**Limitations**	**Other comments**		**cost-effectiveness (ICER)**	**Uncertainty**
Levy A. 2014	Minor limitations	Model	Probabilistic Markov model with a 35-day cycle length consisting of 3 health states	The incremental cost-effectiveness ratios (ICERS) per QALY gained was $86,973, $84,829, and $2,152 for azacitidine compared with BSC, with low-dose chemotherapy plus BSc, and with standard-dose chemotherapy plus BSc respectively.	Uncertainty in model parameters was characterized through probability distributions. Monte Carlo simulation with 1000 iterations was used to include parameter uncertainty in the results. At a willingness-to-pay threshold of $80,000, the likelihood that azacitidine is cost-effective relative to the conventional care regimens BSC combined with low- dose chemotherapy, BSC, low-dose chemotherapy, and standard-dose chemotherapy—was 33.1%, 30.6%, 38.2%, and 100.0% respectively There was a deterministic scenario analysis In all the scenarios analyzed, the ICER of azacitidine compared with conventional care (BSC combined with low-dose chemotherapy) was between $82,000 and $120,000 per QALY gained.
		Population	Hypothetical patients 70 years of age (69 years was the median age at enrolment into aza-001) entered the model in the MDS state and could then remain in that state or progress to aml>30 or death.		
		Time horizon	Lifetime		
		costs	Health resources covered in the questionnaire included medications and administration, routine physician follow-up, and laboratory and monitoring tests. Only direct medical costs were considered; nonmedical direct costs and lost productivity were excluded. Canadian dollars		
		Utilities	For MDS patients treated with azacitidine or BSc, used individual patient-level data from the Cancer and Leukemia Group B (calgb) 9221 trial. The associated EORTC QLQ-C30		

			scores were collected and converted to EQ-5D scores using a mapping algorithm		
		Perspective	Canadian public payer perspective.		
		Others	The model was for the Canadian health system, there is no explicit threshold, but the decisions are med from 20.000 to 100.000 per QALY.		

Abbreviations: Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), conventional care regimen (CCR), best supportive care (BSC), low-dose chemotherapy (LDC) or standard-dose chemotherapy (SDC), Azacitidine (AZA), Quality-adjusted life year (QALY).

a. All of the utilities were mapped, this could generate a loss of values or data, especially in health states of low utility gain. Some of the populations compared in each alternative had a small number of participants, this could overestimate, or sub estimate the real survival. Pharmaceutical costs were taken from a specific local database, this could be different for the national average.

Regulatory information

12. Summary of regulatory status and market availability of the medicine.

US Food and Drug Administration: Approved

European Medicines Agency: Approved

Australian Government: Approved

Japanese Pharmaceuticals and Medical Devices Agency: Approved

Health Canada: Approved

13. Availability of pharmacopoeial standards

Azacitidine

International Pharmacopoeia: No

British Pharmacopoeia: No

European Pharmacopoeia: No

United States Pharmacopoeia: No

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Appendix

Appendix 1: Search strategies

Search strategy for randomized trials in MEDLINE and EMBASE (via OVID)

DATE: December 2020

1. exp Azacitidine/
2. azacytidine.mp.
3. exp Leukemia, Myeloid, Acute/
4. acute myeloid leukaemia.mp.
5. randomized controlled trial.pt.
6. random allocation/
7. double-blind method/
8. single-blind method/
9. randomi?ed controlled trial$.mp.
10. Randomi?ed clinical trial$.mp.
11. controlled clinical trial.pt.
12. ((singl$ or double$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
13. random$.mp.
14. placebo$.mp.
15. cross-over studies.sh.
16. latin square.tw.
17. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. animals/ not humans/
19. 17 not 18
20. 1 or 2

21. 3 or 4
22. 19 and 20 and 21

Search strategy for systematic reviews in MEDLINE and EMBASE (via OVID)

DATE: December 2020

1. exp Azacitidine/
2. azacytidine.mp.
3. exp Leukemia, Myeloid, Acute/
4. acute myeloid leukaemia.mp.
5. systematic review/
6. meta-analysis/
7. (meta analy* or metanaly* or metaanaly*).ti,ab.
8. ((systematic or evidence) adj2 (review* or overview*)).ti,ab.
9. (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
10. (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
11. cochrane.jw.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. 1 or 2
14. 3 or 4
15. 12 and 13 and 14

Search strategy for economic evaluations in MEDLINE (via OVID)

DATE: December 2020

Azacitidine OR (azacitidine[MeSH Terms]) OR (pharmion brand of azacitidine[MeSH Terms])) AND (Economics[Mesh:NoExp] OR "Cost-Benefit Analysis"[Mesh] OR "Costs and Cost Analysis"[mh] OR Economics, Nursing[mh] OR Economics, Medical[mh] OR Economics, Pharmaceutical[mh] OR Economics, Hospital[mh] OR Economics, Dental[mh] OR "Fees and Charges"[mh] OR Budgets[mh] OR budget*[tiab] OR economic*[tiab] OR cost[tiab] OR costs[tiab] OR costly[tiab] OR costing[tiab] OR price[tiab] OR prices[tiab] OR pricing[tiab] OR pharmacoeconomic*[tiab] OR pharmaco-economic*[tiab] OR expenditure[tiab] OR expenditures[tiab] OR expense[tiab] OR expenses[tiab] OR financial[tiab] OR finance[tiab] OR finances[tiab] OR financed[tiab] OR value for money[tiab] OR monetary value*[tiab] OR models, economic[mh] OR economic model*[tiab] OR markov chains[mh] OR markov[tiab] OR monte carlo method[mh] OR monte carlo[tiab] OR Decision Theory[mh] OR decision tree*[tiab] OR decision analy*[tiab] OR decision model*[tiab])

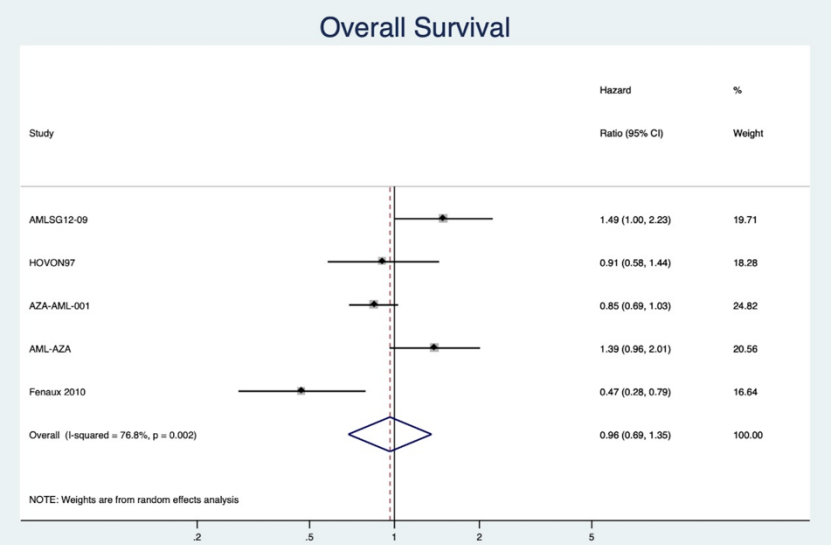
Search strategy for economic evaluations in EMBASE (via OVID)

DATE: December 2020

azacitidine/ OR Azacitidine.mp. [mp=hw, ab, ti, ct, sh, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] AND acute myeloid leukaemia.mp. [mp=hw, ab, ti, ct, sh, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, an, ui, sy] OR acute myeloid leukemia/
AND (Cost-effectiveness.mp. or "cost utility analysis"/ or "cost benefit analysis"/ or "cost minimization analysis"/ or "cost"/ or "cost effectiveness analysis"/ or QALY.mp. or quality adjusted life year/ or health technology assessment.mp. or biomedical technology assessment/ or economics/ or willingness to pay.mp. or "health care cost"/ or life years gained.mp. or disability-adjusted life years.mp. or disability-adjusted life year/ or Statistical Model/ or economic model*.ab,ti. or Probability/ or markov.ti,ab,kw. or monte carlo method/ or monte carlo.ti,ab. or Decision Theory/ or Decision Tree/)

Appendix 2: Forest plots

Azacitidine in individuals with acute myeloid leukaemia - Overall survival.



Azacitidine in individuals with acute myeloid leukaemia – Adverse events