Medicinrådet

Bilag til Medicinrådets vurdering af natriumthiosulfat til forebyggelse af ototoksicitet forårsaget af cisplatin kemoterapi

Hos patienter i alderen 1 måned til 17 år med lokaliserede solide tumorer

Vers. 1.1

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. natriumthiosulfat
2. Forhandlingsnotat fra Amgros vedr. natriumthiosulfat
3. Ansøgers endelige ansøgning vedr. natriumthiosulfat

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3. Oktober 2025

Til Medicinrådet,

Vedrørende Medicinrådets vurdering af natriumthiosulfat til forebyggelse af ototoksicitet forårsaget af cisplatin-kemoterapi hos børn og unge (1 måned til 17 år) med lokaliserede solide tumorer.

Norgine anerkender det omfattende arbejde, som sekretariatet og fagudvalget har lagt i vurderingsrapporten, og sige tak for et god forløb med en konstruktiv dialog undervejs. Vi finder det dog beklageligt, at der i vurderingen af indvirkning og konsekvenserne af cisplatin-induceret høretab (HT) hos børn og unge er valgt en tilgang, der afviger fra international praksis og eksisterende studier. En sådan tilgang risikerer at undervurdere de daglige udfordringer, som børn og unge med HT i varierende sværhedsgrad oplever.

Når det er sagt, vil vi gerne sig tak for anerkendelsen af den dokumenterede beskyttende effekt PEDMARQSI har mod cisplatin-induceret HT på tværs af forskellige cancertyper.

Nytteværdier for høretabsstadier:

I vurderingsrapport præsenteres to scenarier baseret på ±5% af en opdateret basecase for nytteværdierne. Norgine vurdere, at både basecasen (den opdateret) og de to scenarier undervurdere den reelle sygdomsbyrde. Vi mener desuden, at den fremlagte argumentation mangler tilstrækkeligt belæg og derfor fremstår som udokumenterede postulater. På den baggrund ønsker vi at præsentere en række faglige argumenter, der bl.a. imødegår sidestillingen af mild HT med minimal/intet HT. Det skal i den forbindelse også nævnes, at vores tilgang har opnået accept hos NICE, SMC og DMP, hvilket understøtter dens faglige validitet.

Ved modtagelsen af vurderingsrapport indhentede vi en faglig vurdering fra Dr. [redacted] i UK. [redacted] udtalte bl.a.; "*To state that mild hearing loss is the same as no hearing loss is totally incorrect*" og "*As mild hearing loss has an impact on listening and causes difficulties educationally as well as can ultimately have an impact on quality of life based on many published studies*." Disse udtalelser understreger, at det er misvisende og undervurderende at sidestille mild HT med intet HT, da det ikke afspejler den faktiske sygdomsbyrde.

EMA skriver I EPAR'en[2]; "*Threshold levels greater than 40dB indicate hearing loss that will cause disability. Hearing loss at Grades 1, 2, 3, and 4 are considered clinically significant and have potential impact on communicative and educational development.*" En sidestilling af grad 0 og 1 kan derfor tolkes som fejlagtig.

Clemens et al. (2019)[3] påpeget, at børn har betydelige vanskeligheder med at forstå tale i omgivelser med baggrundsstøj, når høretærskelen overstiger 20 dB ved 6.000 Hz. Brock-skalaen definerer mild HT som ≥40 dB ved 8.000 Hz, mens SIOP Boston-skalaen definerer det som ≥20 dB ved >4.000 Hz - begge værre end det interval, Clemens et al. angiver. Dette understøtter, at mild HT har en væsentlig indvirkning på livskvaliteten. Gumbie et al. (2022)[4] skelner ligeledes skelner mellem mildt og intet HT.

Ved moderat HT anbefaler vi også en justering. EPAR'en[2] beskriver, at børn med moderat HT har vanskeligheder med at opfatte konsonantlyde, forstå tale i støj eller på afstand, og ofte har behov for høretekniske hjælpemidler. Et kompromis, som vi vurderer mere retvisende end Medicinrådets basecase, er at opjustere den oprindelige nytteværdi på 0,68 og med 5 % til 0,71.

Generelt vurderer vi, på baggrund af den præsenterede evidens, at nytteværdierne for alle grader af HT er undervurderet. Vi anerkender, at der er usikkerhed forbundet med disse estimater, og accepterer derfor kompromiser for markant og svær HT - samt delvist for moderat HT. De justeringer vi foreslår for mildt og moderat HT, afspejler efter vores vurdering et mere retvisende og balanceret billede af den reelle påvirkning.

Dialog med Amgros:

Selvom vi mener, at der er et stærkt grundlag for at støtte vores basisscenarie, som netop forklaret, har vi, for at imødekomme de eksisterende usikkerheder og finde en balance mellem vores basisscenarie og jeres

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scenarier, baseret vores prissætning på scenarie 2. Under forhandlingen tilkendegav Amgros støtte til bruget af scenarie 2 i vores vurdering, baseret på vores redegørelse for nytteværdierne. Vi håber derfor, at dette inddrages i jeres endelige vurdering.

Som et udtryk for vores samarbejdsvilje har vi accepteret størstedelen af jeres antagelser, med det formål at fremskynde adgangen til PEDMARQSI for alle børn og unge, der har behov for det. På baggrund af dialogen med Amgros har vi fastsat en pris, der ligger væsentligt under den nævnte tærskel for cost-effectiveness i scenarie 2. For at nå denne pris har vi valgt at gå på kompromis med både vores oprindelige vurdering og tilbud, og har som nævnt imødekommet de fleste af jeres antagelser og justeringer. Den tilbudte rabat medfører en lav årlig omkostning per patient og dermed en begrænset samlet budgetpåvirkning.

Alvorlighedsprincippet:

I vurderingen af PEDMARQSI appellerer vi til anvendelsen af alvorlighedsprincippet. Vi vurderer, at PEDMARQSI opfylder tre af de foreslåede kriterier for, hvornår princippet bør anvendes[5]:

- **Målrettet børn og unge (0-25 år):** Den indikerede population omfatter børn fra 1 måned til under 18 år, hvilket falder direkte inden for den definerede aldersgruppe.
- **Kurerer, forebygger eller modificerer kronisk invaliditet med livsbegrænsende konsekvenser:** Cisplatin-induceret ototoksicitet medfører HT, som udgør en kronisk invaliditet med betydelig negativ indvirkning på livskvalitet og udvikling - særligt hos børn.
- **Eneste sygdomsmodificerende eller kurative behandling:** Der findes aktuelt ingen anden behandling, der kan forebygge cisplatin-induceret HT, hvilket gør PEDMARQSI til den eneste reelle mulighed for intervention

Inklusionen af alvorlighedsprincippet vil anerkende den nuværende mangel på behandlingsmuligheder og imødekomme det væsentlige behov for beskyttelsen af børns og unges hørelse.

Høretabsskalaer:

De fleste målemetoder inkludere usikkerheder. For eksempel har audiogrammer begrænset evne til at lokaliser HT og har en kontekstuel begrænsning, da det ikke tester med baggrundsstøj - kan være vigtig for den funktionelle påvirkning[6]. ASHA-skalaen, anvendt i COG ACCL0431-studiet[7], kunne identificere ototoksicitet, men ikke graden af den. Til dette formål, tilbyder SIOP- og Brock-skalaerne en mere nuanceret vurderinger af HT, og reevalueringen af COG-studiet i Orgel et al. (2023)[8] bekræftede, at PEDMARQSI effektivt forebygger ototoksicitet ifølge SIOP-skalaen. Clemens et al. (2019)[3] viste god overensstemmelse mellem flere ototoksicitetsskalaer, herunder SIOP- og Brock-skalaerne, men fremhævede forskelle i, hvordan funktionsevne defineres.

Studedesign og datagrundlag:

I vurderingsrapporten nævnes en række usikkerheder i datagrundlaget for klinisk effekt og sikkerhed. Centralt for disse ligger studiepopulationerne for SIOPEL-6 og COG-studierne[7,9]. De to fase-3-studiers størrelser er berettiget af tilstandens sjældenhed og det begrænset antal børn, der kan rekrutteres til kliniske forsøg. På trods af den begrænsede populationsstørrelse var studierne relativt store og havde tilstrækkelig statistisk styrke til at påvise signifikante forskelle. De ensartede resultater i begge studier bekræfter deres styrke[7,9].

Studierne var ikke blindet, da behandling med PEDMARQSI kan medføre genkendelige bivirkninger såsom kvalme og opkast. I SIOPEL-6 blev det primære effektmål vurderet blindet, og i COG-studiet var randomiseringen blindet for de centrale reviewers af audiometridata[7,9].

Vi ser frem til rådsmødet d. 29 oktober, hvor sagen vil blive taget op. Vi håber, at vores kommentarer vil blive taget godt imod, og vi står naturligvis til rådighed, hvis der skulle være opfølgende spørgsmål.

3. Oktober 2025

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17.03.2026

MBA/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	TBD
Leverandør	Norgine
Lægemiddel	Pedmarqsi (natriumthiosulfate)
Ansøgt indikation	Forebyggelse af ototoksicitet induceret af cisplatin kemoterapi hos patienter fra 1 måned til < 18 år gamle med lokaliserede, ikke-metastatiske, solide tumorer.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel, revurdering

Prisinformation

Amgros har forhandlet følgende pris på Pedmarqsi (natriumthiosulfat):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Pedmarqsi	8 mg, 1 hætteglas	72.637,85	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Pedmarqsi, indkøbes Pedmarqsi til AIP.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2 viser lægemiddeludgiften til Pedmarqsi for et gennemsnitlig behandlingsforløb, jf. Medicinrådets vurdering af natriumthiosulfat til forebyggelse af ototoksicitet forårsaget af cisplatin kemoterapi.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Pedmarqsi	8 mg, 1 hætteglas	6,79 administrationer med 1,87 hætteglas per administration*	[redacted]	[redacted]

*Baseret på Medicinrådets vurderingsrapport er et gennemsnitligt behandlingsforløb på 6,79 administrationer med et forbrug på 1,87 hætteglas per administration.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Ikke ansøgt	

Opsummering

[redacted]

Application for the assessment of PEDMARQSI for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours

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	Confidential information

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Abbreviations

Abbreviation	Definition	Abbreviation	Definition
AdEERS	Adverse Event Expedited Reporting System	kg	Kilogram
AE	Adverse event	L	Litre
AHL	Average hearing level	LS	Least squares
AFP	Alpha-fetoprotein	max	Maximum
ASCO	American Society of Clinical Oncology	MESH	Medical Subject Heading
ASHA	American Speech Language and Hearing Association	mg	Milligram
CEA	Cost-effectiveness analysis	min	Minimum/Minute
CENTRAL	Cochrane Central Register of Controlled Trials	mL	Millilitre
CI	Confidence interval	ng	Nanogram
CMH	Cochrane-Mantel-Haenszel	NHS	National Health Service
COG	Children's Oncology Group	NHSCII	National Health Service cost inflation index
CRD	Centre for Reviews and Dissemination	NR	Not reported
CTCAE	Common terminology criteria for Adverse events	OECD	Office for Economic Co-operation and Development
CTYA	Children, teenagers and young adults	OR	Odds ratio
dB	Decibel	PFS	Progression-free survival
DKK	Danish krone	PICOS	Population, Intervention, Comparator, Outcome, Study design
DMC	Danish Medicines Council	PNET	Primitive neuroectodermal tumour
DRG	Diagnosis Related Group	PP	Per Protocol
EED	Economic Evaluation Database	PRETEXT	Pre-treatment Tumour Extension
EFS	Event-free survival	PSA	Probabilistic sensitivity analysis
EMA	European Medicines Agency	PTA	Pure-tone audiometry
EQ-5D	EuroQol 5-dimensions	QALY	Quality-adjusted life year
ESMO	European Society for Medical Oncology	QoL	Quality of life
g	Gram	RCT	Randomised controlled trial
GFR	Glomerular filtration rate	RePEc	Research papers in Economics
HL	Hearing loss	RHR	Relative hazard ratio

HR	Hazard ratio	RR	Relative risk
HRQoL	Health-related quality of life	SAE	Serious adverse event
HUI	Health Utilities Index	SIOP	International Society of Paediatric Oncology
Hz	Hertz	SmPC	Summary of Product Characteristics
ICER	Incremental cost-effectiveness ratio	SMR	Standardised mortality ratio
ICEP	Incremental cost-effectiveness plane	STS	Sodium thiosulfate
ICTRP	International Clinical Trials Registry Platform	TA	Technology appraisal
INAHTA	Internation health technology assessment	TTO	Time trade-off
ISPOR	International Society for Pharmacoeconomics and Outcomes Research	UK	United Kingdom
ITT	Intent-to-treat	US	United States (of America)
IV	Intravenous	WHO	World Health Organisation

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	PEDMARQSI
Generic name	Sodium thiosulfate
Therapeutic indication as defined by EMA	PEDMARQSI is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.
Marketing authorization holder in Denmark	Norgine B.V.
ATC code	V03AB06
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	26/05/2023
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? [yes/no] Yes Is the product suitable for a joint Nordic assessment? [yes/no] No If no, why not? [redacted]
Dispensing group	BEGR

Overview of the medicine	
Packaging – types, sizes/number of units and concentrations	8 g per vial with a pack size of 1 vial per package

2. Summary table

Summary	
Indication relevant for the assessment	PEDMARQSI is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.
Dosage regiment and administration	The recommended dose of intravenous PEDMARQSI for the prevention of cisplatin-induced ototoxicity is weight based and normalised to body surface area according to the table below: **Body Weight** / **Anhydrous dose** / **Volume** > 10 kg / 12.8 g/m^2 / 160 mL/m^2 5 to 10 kg / 9.6 g/m^2 / 120 mL/m^2 < 5 kg / 6.4 g/m^2 / 80 mL/m^2 PEDMARQSI must be administered 6 hours after each cisplatin dose. A subsequent cisplatin dose can be administered no earlier than 6 hours after the last dose of PEDMARQSI.
Choice of comparator	Cisplatin without PEDMARQSI
Prognosis with current treatment (comparator)	No treatment for the prevention of cisplatin-induced ototoxicity exists. Affected patients will experience permanent HL and management involves the use of non-pharmacological interventions which are not preventative or curative e.g. hearing aids or cochlear implants.
Type of evidence for the clinical evaluation	No-treatment controlled study
Most important efficacy endpoints (Difference/gain compared to comparator)	**Incidence of hearing loss:** In COG ACCL0431 (efficacy population*): Share of patients experiencing HL with PEDMARQSI: 28.6%. Share of patients with HL without PEDMARQSI: 56.4%. The RR was 0.516 (95% CI 0.318, 0.839). In SIOPEL-6 (mITT): Share of patients experiencing HL with PEDMARQSI: 32.7%. Share of patients with HL without PEDMARQSI: 63%. The RR was 0.52 (95% CI 0.349, 0.778) (Freyer et al. 2017, Brock et al. 2018, European Medicines Agency 2023a). **Severity of hearing loss:** Relative difference of experiencing mild, moderate, marked, or severe HL between patients with PEDMARQSI and patients without PEDMARQSI in COG ACCL0431 (Orgel et al. (2023) re-evaluation + Knight et al. (2005)): mild = 77.78% vs. 40.78%, moderate: 18.06% vs. 48.12%, marked: 1.39% vs. 3.70%, severe: 2.78% vs. 7.4%. In SIOPEL-6: mild = 56% vs. 41%, moderate: 33% vs. 38%, marked: 6% vs. 17%, severe: 6% vs. 3%. (Brock et al. 2018, Orgel et al. 2023, Knight et al. 2005, [redacted]). **Event-free survival:** In COG ACCL0431:

Summary	
	Number of patients with event in the cisplatin without PEDMARQSI arm: 39%, versus in the cisplatin with PEDMARQSI arm: 44.3%. The hazard ratio (with PEDMARQSI vs. without PEDMARQSI) was 1.27 (95% CI 0.73, 2.18). In SIOPEL-6: Number of patients with event in the cisplatin without PEDMARQSI arm: 21.2%, versus in the cisplatin with PEDMARQSI arm: 19.3%. The hazard ratio (with PEDMARQSI vs. without PEDMARQSI) was 0.89 (95% CI 0.39, 2.05). **Overall survival:** In COG ACCL0431: cisplatin without PEDMARQSI: 81.3%, versus cisplatin with PEDMARQSI: 70.5%. The hazard ratio (with PEDMARQSI vs. without PEDMARQSI) was 1.79 (95% CI 0.89, 3.72). In SIOPEL-6: cisplatin without PEDMARQSI: 92.3%, versus cisplatin with PEDMARQSI: 96.5%. The hazard ratio (with PEDMARQSI vs. without PEDMARQSI) was 0.44 (95% CI 0.08, 2.41).
Most important serious adverse events for the intervention and comparator (≥grade 3)	**COG ACCL0431**: number of events in cisplatin with PEDMARQSI vs. cisplatin without PEDMARQSI arms - neutrophil count decrease (n=49 vs. n=53), white blood cell count decrease (n=38 vs. n=42), platelet count decrease (n=38 vs. n=39), anaemia (n=30 vs. n=36), febrile neutropenia (n=14 vs. n=19), gastrointestinal disorders (n=12 vs. n=8) **SIOPEL-6**: number of events in cisplatin with PEDMARQSI vs. cisplatin without PEDMARQSI arms - neutrophil count decrease (n=12 vs. n=9), infection (n=14 vs. n=15), haemoglobin decrease (n=10 vs. n=9), febrile neutropenia (n=8 vs. n=9)
Impact on health-related quality of life	**Clinical documentation**: No HRQoL data was collected in the pivotal trials. **Health economic model**: HRQoL was informed from Barton et al. (2006), using the Health Utilities Index mark 3 (HUI3) utility measurement. The model produces an incremental gain of 1.449 QALYs with PEDMARQSI compared to without PEDMARQSI
Type of economic analysis that is submitted	**Type of analysis**: Cost-utility; **Type of model**: Decision tree and Markov model
Data sources used to model the clinical effects	COG ACCL0431 clinical trial
Data sources used to model the health-related quality of life	Barton et al. (2006)
Life years gained	0 years
QALYs gained	1.449 QALY
Incremental costs	849,931 DKK
ICER (DKK/QALY)	586,536 DKK/QALY

Summary	
Uncertainty associated with the ICER estimate	Proportions with HL alongside with distribution in severity of HL
Number of eligible patients in Denmark	**Incidence**: 22 patients (2025) ; **Prevalence**: Not quantifiable.
Budget impact (in year 5)	The budget impact in year 5 is 13.8 million DKK.

* The efficacy population included all children in the ITT population who had both baseline and 4-week follow-up hearing assessments.
Abbreviations: CI: confidence interval, DKK: Danish krone, g: gram, HL: hearing loss, HRQoL: health-related quality of life, HUI3: Health Utilities Index Mark 3, ICER: incremental cost-effectiveness ratio, (m)ITT: (modified) intent-to-treat, kg: kilogram, m^2: square meter, mL: millilitre, QALY: quality-adjusted life year, RR: relative risk
Sources: [redacted], Brock et al. 2018, Freyer et al. 2017, [redacted], Orgel et al. 2023, European Medicines Agency 2023a)

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

On March 30, 2023, a positive opinion was issued by the Committee for Medicinal Products for Human Use to grant marketing authorisation for PEDMARQSI for the prevention of cisplatin-induced ototoxicity in children between the ages of 1 month and <18 years with localised, non-metastatic solid tumours (European Medicines Agency 2023b). Final market authorisation was granted by the European Commission on May 26, 2023 (European Medicines Agency 2023c). Reimbursement is sought for the registered indication.

Given the nature of the disease and the patient population, it is recommended to consider the severity principle when evaluating PEDMARQSI. The Danish Medicines Council (DMC) plays an important role in ensuring that Danish patients with severe health conditions can receive the necessary treatment. This can be facilitated using the severity principle, an approach that allows the DMC to justify a higher willingness to pay for patient groups with worse health, based on the belief that these cases hold greater moral value. According to the guidelines, the DMC has identified five scenarios where considering disease severity in decision-making could be appropriate (Medicinrådet 2021). Of these five scenarios, four are applicable to PEDMARQSI and are outlined in Table 1, along with explanations of how they apply to PEDMARQSI for preventing cisplatin-induced hearing loss (HL) in Denmark.

Table 1 Situations relevant for the severity principle (alvorlighedsprincippet)

Situation	Relevance for PEDMARQSI for the prevention of cisplatin-induced HL in Denmark
The intervention is aimed at children and young people (0-25 years)	PEDMARQSI was developed to prevent HL in children between the age 1 month to <18 years receiving cisplatin chemotherapy and received market authorisation for this age group.
The intervention cures, prevents or modifies chronic disability or other symptoms that are life limiting	PEDMARQSI successfully reduces the incidence and severity of HL in patients receiving cisplatin treatment and therefore prevents or weakens an otherwise chronic disability. This was shown in two separate clinical trials (see Section 0 and Appendix B).
The intervention targets a severe disease	Cisplatin-induced HL has a profound and debilitating impact on QoL, particularly in younger patients under the age of 5. The consequences of HL are far-reaching, severely compromising the patient's ability to lead an independent life. It results in significant academic and social challenges, with lasting effects on mental health and overall development (see Section 3.1.2.1).
The intervention is the only disease modifying or potentially curative treatment	To date, PEDMARQSI is the first and only treatment licensed in Europe and the United States for the prevention of cisplatin-induced HL.

Abbreviations: HL: hearing loss, QoL: Quality of life

Source: (Medicinrådet 2021)

3.1 The medical condition

3.1.1 Disease description

Ototoxicity refers to inner ear damage caused by substances like medications or chemicals, leading to hearing and balance problems. Symptoms include HL, tinnitus (ringing in the ears), and dizziness or balance issues.

Cisplatin is a widely used chemotherapy drug for treating various cancers in children, including solid tumors such as neuroblastoma, osteosarcoma, and retinoblastoma (Freyer et al. 2017, Brock et al. 2021). Although cisplatin remains one of the most effective treatments for childhood cancer, a major concern is its potential to cause irreversible HL due to ototoxicity (Rajput et al. 2020, Neuwelt and Brock 2010). This typically begins as bilateral, high-frequency sensorineural HL, which can occur after the first cycle of treatment (Stavroulaki et al. 2001). As the cumulative dose of cisplatin increases, the HL tends to worsen and extend to lower frequencies related to speech (Rajput et al. 2020, Brock et al. 2021, Gurney and Bass 2012). This permanent HL affects up to 60% of children treated with cisplatin, with the risk rising to around 70% when the cumulative dose exceeds 400 mg/m2 (Knight et al. 2005, Brock et al. 2012, Punnett et al.

2004, Bass et al. 2016). Children under the age of 5 are particularly at higher risk (Li et al. 2004). About half of the affected patients experience moderate-to-severe HL, often requiring hearing aids or other interventions (Knight et al. 2005, Bass et al. 2016, Landier et al. 2014).

3.1.2 Pathophysiology

HL is a common and permanent side effect of cisplatin treatment, caused by the drug's toxic effects on the inner ear. Unlike other organs, cisplatin remains in the cochlea for months to years (Breglio et al. 2017). Cisplatin causes HL by affecting the organ of Corti, spiral ganglion cells, and the lateral wall (stria vascularis and spiral ligament) (Gurney and Bass 2012, Landier 2016, Rybak et al. 2019). Cisplatin enters the cochlea via the vasculature of the stria vascularis, where it accumulates at high concentrations (Breglio et al. 2017). Toxic reactive oxygen species (ROS) cause inflammation and damage to sensory outer hair cells, worsening with prolonged retention due to the blood-labyrinth barrier (Gurney and Bass 2012, Landier 2016, Rybak et al. 2019, Wang et al. 2023).

Cisplatin induces HL by crosslinking DNA, triggering apoptosis, increasing ROS production, and reducing antioxidants (Banfi et al. 2004, Mohri et al. 2021, Mukherjea et al. 2006, Rybak et al. 2000, Campbell et al. 2003, Tanida et al. 2012). This results in mitochondrial dysfunction, amplifying ROS production in a feedback loop and promoting mitochondrial-mediated apoptosis (Yu et al. 2020, Steyger 2021b, Steyger 2021a, Tan and Song 2023).

3.1.2.1 Patient prognosis and impact on QoL

Cisplatin-induced ototoxicity often causes permanent HL, with 36% of adults and up to 70% of pediatric cancer patients affected, significantly impacting health-related quality of life (HRQoL) (Chattaraj et al. 2023, Bass et al. 2016). The risk of ototoxicity is dose-dependent, with higher cumulative doses increasing the likelihood and severity of HL (Zand et al. 2024). This typically presents as bilateral, symmetrical, irreversible sensorineural HL, primarily affecting high frequencies and often accompanied by tinnitus (Voruz et al. 2023). Even minimal HL above 2,000 hertz (Hz) can increase the risk of academic, social, emotional issues, and fatigue in children (Knight et al. 2005).

HL impacts quality of life (QoL) across all ages:

- Pre-lingual: impact on development of verbal and communication skills, comprehension ability, and social development (Fligor 2019, Bess et al. 1998, Bass et al. 2016, Gurney et al. 2007)
- In-school age: impact on educational achievement, social-emotional development, and self-esteem/ behaviour issues (Bess et al. 1998)
- Adolescents and young adults: social isolation, career limitations, and the inability to live independently (Brinkman et al. 2015)

HL reduces QoL in children, affecting schooling, social interaction, and physical activity (Roland et al. 2016). It can also cause anxiety, depression, and mental health concerns in survivors (Bass et al. 2016, Khan et al. 2020). In adulthood, survivors often feel socially

excluded and fatigued, which can lead to anxiety and depression (Bass et al. 2016, Brinkman et al. 2015, Khan et al. 2020). A study of adult childhood cancer survivors with treatment-induced HL found that 45% had never married (vs. 37.9% of the general population) and 34% were unemployed (vs. 5.3% of non-disabled adults) or had not graduated high school (Brinkman et al. 2015). HL is also associated with accelerated aging (van Atteveld et al. 2023), and an increased risk of dementia (Chern et al. 2022, Hendriks et al. 2024). Caregivers of children with HL, including parents and teachers, face a QoL burden, managing the communicative, behavioural, and social consequences of childhood hearing impairment (Mundayoor et al. 2022). Around 60% of children with moderate HL require specialized tutoring ([redacted].

3.2 Patient population

The indicated population for the use of PEDMARQSI are children between 1 month to <18 years of age with localised, non-metastatic, solid tumours of which children at a younger age (under 5 years) are most vulnerable (Norgine 2023, Li et al. 2004). Based on the tumour-specific usage of cisplatin in patients with solid tumours, it is difficult to determine the exact population of patients that qualify for PEDMARQSI treatment. Accordingly, information about each solid tumour present in children needs to be extracted to receive an estimate about the extent of cisplatin usage (more details in Section 13).

The age at diagnosis differs between patients due to the large range of tumour types included in the indication. Based on the Children's Oncology Group (COG) ACCL0431 clinical trial, patient age ranged from 1 year to 18 years, with a mean age of 8.6 years of which a third were below the age of 5 (Freyer et al. 2017). No local study exists informing about the mean age of patients with solid tumours in Denmark. A Danish clinical expert validated the mean age from COG ACCL0431 as applicable for clinical practice (Norgine 2025b).The eligible population for the prevention of HL in patients treated with cisplatin chemotherapy is not a single specific disease population (i.e. a single type of cancer), and includes all children diagnosed with tumours that are treated with cisplatin. Therefore, disease prevalence is not simply defined.

Given the above, an incidence statistic (i.e. the identification of new cases where patients would undergo cisplatin treatment), as opposed to a prevalence statistic, is considered the most representative method to identify the population of interest, which was confirmed by a Danish clinical expert (Norgine 2025b), see Table 2 and Table 3.

Table 2 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	20.9	21.1	21.3	21.6	21.8
Prevalence in Denmark	N/A	N/A	N/A	N/A	N/A
Global prevalence	N/A				

Abbreviations: N/A: Not available

Table 3 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	22	22	22	23	23

3.3 Current treatment options

In Denmark, no official pharmacological interventions or nationwide treatment guide exists for treating or preventing HL caused by cisplatin-induced ototoxicity. Despite this, the Danish Paediatric Haematology and Oncology (DAPHO) working symposium recently published a treatment guideline recommending PEDMARQSI for preventing ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours (DAPHO 2024). This indicates an early, albeit unofficial, recognition of the need for interventions, such as PEDMARQSI. Regardless, current cisplatin-based treatment pathway and international guidelines suggest close monitoring for ototoxicity (American Academy of Audiology 2009, ASHA 1994). Based on the input of a Danish clinical expert, auditory function is assessed prior to, during, and after each cisplatin dose (Norgine 2025b).

Once HL has occurred, the current management strategies involve the use of non-pharmacological interventions which cannot reverse HL and are of a quality incomparable to that of natural hearing. The most common management strategy for those with lesser severities of HL is the use of hearing aids throughout the patient's life (Landier 2016). For those children with severe to profound sensorineural HL, bilateral cochlear implants may be used (Gurney and Bass 2012, Clemens et al. 2019). These provide a modified sense of sound but require commitment to an audiology and speech therapy rehabilitation program (Landier 2016). However, as with hearing aids, they present limitations inclusive of the need for external processors requiring replacement every five years, and the internal electrode also being at risk of replacement due to device failure (Dionne et al. 2012, [redacted], Bond et al. 2009).

Finally, a third mainstream approach to HL management is the use of frequency modulation systems in classrooms to support all children with HL in the educational environment (Knight et al. 2005, Bess et al. 1998). These devices allow the transmission of sounds (e.g. lessons in a classroom) directly to a child's hearing device, however these systems typically need replacement every five years [redacted]).

3.4 The intervention

PEDMARQSI, a novel formulation of anhydrous sodium thiosulfate (STS) specifically developed for use in paediatric patients, is the first and only treatment licensed in Europe and the United States (US) for the prevention of cisplatin-induced ototoxicity (US

Food and Drug Administration 2024, European Medicines Agency 2023c). Below, in Table 4, follows a summary of the intervention.

Table 4 Overview of intervention | PEDMARQSI (sodium thiosulfate)

Overview of intervention	PEDMARQSI
Indication relevant for the assessment	PEDMARQSI is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.
ATMP	No
Method of administration	Intravenously as a 15-minute infusion
Dosing	The recommended dose is weight based and normalised to body surface area according to the table below: **Body Weight** / **Anhydrous dose** / **Volume** > 10 kg / 12.8 g/m^2 / 160 mL/m^2 5 to 10 kg / 9.6 g/m^2 / 120 mL/m^2 < 5 kg / 6.4 g/m^2 / 80 mL/m^2 PEDMARQSI must be administered 6 hours after each cisplatin dose.
Dosing in the health economic model (including relative dose intensity)	1 dose of [redacted]) PEDMARQSI after each cisplatin treatment (total average of [redacted] doses throughout the entire treatment), based on patients in the COG ACCL0431 trial (relative dose intensity not available).
Should the medicine be administered with other medicines?	Anti-emetic premedication 30 minutes before the PEDMARQSI dose
Treatment duration / criteria for end of treatment	One dose after each cisplatin treatment, as long as cisplatin treatment is continued.
Necessary monitoring, both during administration and during the treatment period	Monitoring of electrolyte balance and blood pressure as well as serum magnesium, potassium, and phosphate levels is recommended. Further, renal function should be monitored.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No.
Package size(s)	8 g per vial with a pack size of 1 vial per package

Abbreviations: g: gram, kg: kilogram, m^2: square meter, mL: millilitre

Sources: (Freyer et al. 2017, [redacted], Norgine 2023)

PEDMARQSI (anhydrous STS) is a water-soluble inorganic salt with reducing agent properties and is a normal metabolite in humans and other mammals ([redacted]. Following intravenous (IV) injection, PEDMARQSI is distributed throughout the extracellular fluid; up to 95% is excreted unchanged in the urine and the biological half-life is 0.65 hours ([redacted]). Although not entirely understood, PEDMARQSI is thought to act in several ways, including inactivating cisplatin through platinum-thiosulfate complex formation complex formation (MHRA 2024, Sooriyaarachchi et al. 2012), quenching ROS, and protecting the activity of endogenous antioxidant enzymes (Bijarnia et al. 2015). The former produces an inactive platinum species which is not cytotoxic and is readily excretable (Ivankovich et al. 1983, MHRA 2024).

Concurrent incubation of PEDMARQSI with cisplatin decreased *in vitro* cytotoxicity to tumour cells; delaying the addition of PEDMARQSI to these cultures prevented the protective effect (MHRA 2024). Studies have emphasised the importance of separating platinum chemotherapy from thiosulfate chemoprotection by either the route or timing of administration (Neuwelt et al. 1996, Doolittle et al. 2001).

3.4.1 The intervention in relation to Danish clinical practice

PEDMARQSI is expected to be used as per label, for the prevention of cisplatin-induced ototoxicity development in children between the age 1 month and <18 years with localised, non-metastatic solid tumours. No direct treatment algorithm for cisplatin-induced ototoxicity exists as PEDMARQSI is the first pharmacological intervention indicated for the prevention of cisplatin-induced ototoxicity. PEDMARQSI has no direct impact on the cisplatin treatment algorithm of non-metastatic solid tumours, however, an interruption of cisplatin hydration is required for PEDMARQSI administration.

As described in Section 3.3, the DAPHO working symposium issued guidelines and recommendations for the routine use of PEDMARQSI in the treatment of non-metastatic hepatoblastoma (DAPHO 2024).

3.5 Choice of comparator(s)

No approved active treatment is currently available for the prevention of cisplatin-induced ototoxicity in Denmark (see Section 3.3). Accordingly, no treatment guidelines exist. Therefore, the suggested comparator is “cisplatin without PEDMARQSI” according to the submission guidelines (Danish Medicines Council 2021). This comparator was also used in the clinical trials COG ACCL0431 and SIOPEL-6, assessing the efficacy of PEDMARQSI in cisplatin-treated children with solid tumours. Based on this, Table 5 is not applicable.

Table 5 Overview of comparator

Overview of comparator	
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Method of administration	N/A
Dosing	N/A
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	N/A
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	N/A

3.6 Cost-effectiveness of the comparator(s)

Not applicable for this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The COG ACCL0431 and SIOPEL-6 trials are crucial in determining the efficacy of PEDMARQSI for the prevention of cisplatin-induced ototoxicity in children, without compromising patient survival. In the absence of comparable treatments, the relevance of efficacy outcomes was assessed based on their influence on treatment results and their inclusion in the health economic model. Consequently, outcomes related to the incidence and severity of HL, as well as overall survival (OS) and event-free survival (EFS), were deemed relevant. To inform the health economic evaluation, only results from COG ACCL0431 were used based on the broader patient population. However, results from SIOPEL-6 support these findings and were included in scenario analyses.

Other study outcomes were not included in the health economic evaluation and are thus excluded from Table 6.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Incidence of hearing loss COG ACCL0431 (NCT00716976)	4 weeks after last dose of cisplatin	HL defined by comparing hearing sensitivity at follow up evaluation relative to baseline measurements using ASHA criteria.	Hearing assessments were performed at baseline, within 8 days prior to each cisplatin course, 4 weeks following completion of the final cisplatin course, and 1 year later.
Rate of Brock grade ≥ 1 hearing loss SIOPEL-6 (NCT00652132)	End of trial treatment or at an age of 3.5 years, whichever is later	Rate of HL with a Brock grade ≥ 1, which corresponds to slight or mild HL or worse.	Audiologic assessments by means of PTA were performed before and throughout treatment when possible and were performed in all the children who were alive at 3.5 years of age or older.
Severity of hearing loss (Mean change in hearing threshold) COG ACCL0431 (NCT00716976)	4 weeks after last dose of cisplatin	Mean change in hearing threshold (post-pre) at 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz.	Audiometry was included to measure bilateral pure tone air conduction thresholds at 500–8000 Hz with earphones or in the sound field using paediatric hearing assessment methods; otoscopy; immittance evaluation of middle ear function; and evoked otoacoustic emissions, if available.
Severity of hearing loss SIOPEL-6 (NCT00652132)	End of trial treatment or at an age of 3.5 years, whichever is later	Evaluation of HL distribution according to the Brock scale (Grade 0 to 4) included in the primary efficacy endpoint (Rate of Brock grade ≥ 1 HL)	Audiograms were uploaded, centrally reviewed, and graded on the Brock scale (grades 0 to 4)
Overall survival (OS) COG ACCL0431 (NCT00716976)	4 Years after enrolment	OS was defined as the time from enrolment to death or last date confirmed alive.	Data for OS was collected in combination with EFS data collection. Required information was recorded on standardized report forms.
Overall survival (OS) SIOPEL-6 (NCT00652132)	Until event or up to 5 years	Proportion of patients alive at 5 years following randomisation.	Data were collected by means of a Web-based electronic clinical research form that was designed and monitored by the authors in collaboration with Consorzio

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			Interuniversitario (CINECA) under the responsibility of the national principal investigators.
Event-free survival (EFS) COG ACCL0431 (NCT00716976)	4 years after enrolment	EFS was defined as the time from study enrolment until disease relapse or progression, diagnosis of a second malignant neoplasm, or death, whichever came first.	Disease progression was evaluated at baseline, at completion of the cancer treatment regimen, every 6 months for 3 years following completion of the cancer treatment regimen, and at disease progression or recurrence, should such occur. Institutions will report disease status at those time points, as well as every 12 months for 10 years post completion of cancer therapy.
Event-free survival (EFS) SIOPEL-6 (NCT00652132)	Until first event or up to 5 years	Proportion of patients being event free at 5 years following randomisation.	Data were collected by means of a Web-based electronic clinical research form that was designed and monitored by the authors in collaboration with Consorzio Interuniversitario (CINECA) under the responsibility of the national principal investigators.

* Time point for data collection used in analysis (follow up time for time-to-event measures)Abbreviations: EFS: event-free survival, HL: hearing loss, Hz: hertz, OS: overall survival
Abbreviations: ASHA: American Speech Language and Hearing Association, PTA: pure-tone audiometry
Sources: (Brock et al. 2018, Freyer et al. 2017, [redacted], ClinicalTrials.gov 2021, ClinicalTrials.gov 2018)

3.7.1.1 Validity of outcomes

The validity of outcomes was evaluated to ensure the credibility and generalizability of the studies, ensuring the potential of evidence-based decision-making and avoiding misinterpretations. For the studies COG ACCL0431 and SIOPEL-6, the incidence of HL, severity of hearing, EFS, and OS were validated. The validity of outcomes was reviewed and accepted in the previous NICE application (NICE 2024).

Incidence of hearing loss

The incidence of cisplatin treatment-related ototoxic changes in children ranges from 26% to 100% depending on the criteria used to define ototoxicity, dosing and patient-related factors (Berg et al. 1999, Punnett et al. 2004, Li et al. 2004). As described in

Section 3.1.2.1, this results in reduced QoL which emphasizes the importance of preventing HL. Therefore, evaluating the incidence of HL upon PEDMARQSI treatment is essential to determine the drug's benefit. A treatment effect of PEDMARQSI with a 50% reduction in HL for the cisplatin with PEDMARQSI arm was hypothesized; in other words, a 22.5% HL in the cisplatin with PEDMARQSI arm was assumed.

Severity of hearing loss

The patient's QoL strongly depends on the severity of HL caused by cisplatin ototoxicity, determining the extent to which induced HL will impact the patient's life. This in turn informs treatment plans and interventions. To investigate the severity, the International Society of Paediatric Oncology (SIOP) ototoxicity grading scale and the Brock ototoxicity grading scale were used for COG ACCL0431 re-evaluation and SIOPEL-6, respectively. Both scales distribute HL severities into five grades ranging from no HL to severe HL, depending on the ability to hear noise at a specific frequency and volume (Clemens et al. 2019). The Brock grading system was specifically developed for paediatric patients treated with cisplatin (Brock et al. 1991). This system is designed to assess the progression of HL across different frequencies, from high to low, while considering the typical high-frequency loss associated with cisplatin use. It is important to note that HLs up to 40 decibel (dB) at any frequency are not accounted for in the Brock criteria, meaning that a Brock grade 0 does not indicate normal hearing status (Clemens et al. 2019). The SIOP grading system was introduced as an improved version of the Brock scale and other HL grading systems and validated for detecting ototoxicity severity in paediatric patients and intended to be used at the end of treatment (Clemens et al. 2019, Brock et al. 2012). A short summary of each grade for the SIOP and Brock grading systems is shown in Table 7. Although no minimal clinically important difference has been established for this efficacy endpoint, any degree of hearing loss is considered clinically significant.

Table 7 Summary of the Brock and SIOP grading scales

Grade	Brock grading scale	SIOP grading scale
0	<40 dB at all frequencies	≤20 dB at all frequencies
1	≥40 dB at 8,000 Hz	>20 dB at >4,000 Hz
2	≥40 dB at ≥4,000 Hz	>20 dB at ≥4,000 Hz
3	≥40 dB at ≥2,000 Hz	>20 dB at 2,000 Hz or 3,000 Hz
4	≥40 dB at ≥1,000 Hz	>40 dB at ≥2,000 Hz

Abbreviations: dB: decibel, Hz: hertz, SIOP: International Society of Paediatric Oncology

Source: (Clemens et al. 2019)

Event-free survival and overall survival

It was considered essential to monitor any potential impact of PEDMARQSI on the response to cisplatin chemotherapy for tumour treatment. Therefore, EFS and OS were

monitored to identify any impact on patient survival. EFS informed the length of time after treatment during which a patient remains free from specific events or complications related to their cancer, which include cancer recurrence, progression, or the development of metastasis, but may also involve treatment-related complications, such as severe side effects or secondary cancers. OS informed the model on all-cause mortality, a patient-relevant and directly measurable endpoint in paediatric tumour patients. EFS and OS were previously validated as important endpoints (Assouline et al. 2022, Tanaka et al. 2020, Delgado and Guddati 2021).

4. Health economic analysis

The developed cost-utility model aims to evaluate the cost-effectiveness of PEDMARQSI (cisplatin with PEDMARQSI) compared to established clinical management (cisplatin without PEDMARQSI) for the prevention of HL in cisplatin-treated patients aged 1 month to <18 years of age with localized, non-metastatic, solid tumours. Outcomes of the cost-utility model is total costs and quality-adjusted life years (QALYs). Cost-utility results are expressed in terms of incremental cost (in Danish krone [DKK]) per gained QALY.

The economic analysis conducted as part of this appraisal has undergone external testing by the NICE EAG as part of the technology appraisal process for NICE TA1034. The model structure and base case are broadly aligned to the final recommended NICE base case.

4.1 Model structure

Due to the lack of existing economic analyses in the specified license population, a de novo cost-effectiveness model was developed in Microsoft Excel® using both deterministic and probabilistic (Monte Carlo simulation) frameworks.

The submitted cost-utility model is a two-part model, first of a decision tree model that in part two transfers to a health state Markov model with a life-time perspective to analyse the long-term effects of suffering from HL.

The efficacy of PEDMARQSI is captured in the one year decision tree by two elements: firstly, the percentage of patients assigned to the Minimal/no HL health state (hereafter referred to as the “yes/no” aspect of the decision tree); secondly, the severity of HL for those who experience it, as depicted by the distribution of patients between the Mild HL, Moderate HL, Marked HL and Severe HL health states, see Figure 1.

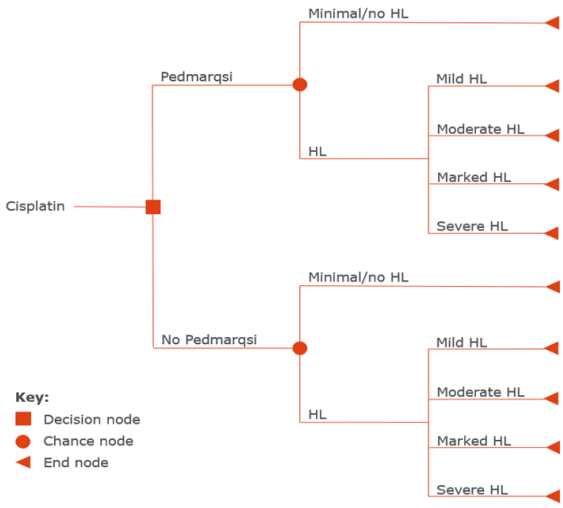


Figure 1 Model schematic – decision tree (year 1)

Abbreviations: HL: hearing loss

From year 2 onwards, a post-decision tree health state model is used in which patients are only at risk of moving to an absorbing state for death, see Figure 2. The five HL health states used in the model are based on the Brock grading scale used in SIOPEL-6; Minimal/no HL, Mild HL, Moderate HL, Marked HL and Severe HL, with an absorbing state for Dead. From year two onwards, patients cannot transition between HL health states and are only at risk of moving to the Dead health state (Figure 2).

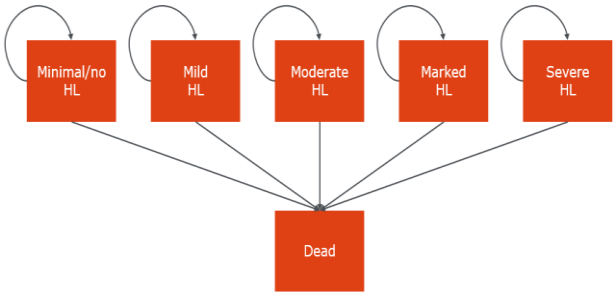


Figure 2 Model schematic - post-decision-tree health state model (years 2+)

Abbreviations: HL: hearing loss

The model structure was selected based on the following reasons:

- It appropriately captures the efficacy data that is available for PEDMARQSI; the primary outcome of COG ACCL0431 and SIOPEL-6 was the proportion of patients with HL after the end of study treatment, as defined by American Speech Language and Hearing Association (ASHA) criteria (COG ACCL0431) or the Brock grading scale (SIOPEL-6).
- The inability of patients in the model to revert to less severe HL health states is representative of the fact that cisplatin-induced ototoxicity is permanent and

irreversible as defined by cisplatin's mechanism of action (see Section 3.1.2) (Rajput et al. 2020, Neuwelt and Brock 2010).

- To avoid uncertainty associated with the lack of data on the timing and rate of deterioration, patients are unable to move to more severe HL health states over the time horizon. As reported by Weissenstein et al. (2012), only patients with some degree of HL at the end of treatment are at risk of further deterioration. Therefore, excluding this deterioration from the economic model base case is a conservative assumption given that more patients in the cisplatin without PEDMARQSI arm of the model would be assigned to one of the four HL health states, and thus be susceptible to HL deterioration.

Similarly, to avoid uncertainty associated with the lack of data surrounding the rate of natural hearing decline for the general population, age-related HL is not included in the model.

4.2 Model features

Features of the economic model are summarised in Table 8.

Table 8 Features of the economic model

Model features	Description	Justification
Patient population	Cisplatin-treated patients aged 1 month to <18 years of age with localised, non-metastatic, solid tumours	In line with patient population described in section 3.2
Perspective	Limited societal perspective	According to DMC guidance
Time horizon	91.4 years (calculated as 100 minus the baseline age)	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	1 year	Cisplatin treatment (and therefore PEDMARQSI treatment) is completed within one year on average. After one year, patients reside in their respective health states and are not a risk of transition between HL health states.
Half-cycle correction	Yes	According to DMC guidance
Discount rate	3.5 %	According to DMC guidance
Intervention	PEDMARQSI (labelled as cisplatin with PEDMARQSI)	
Comparator(s)	Established clinical management without PEDMARQSI (labelled as cisplatin without PEDMARQSI)	There is no approved active treatment currently available for the prevention of cisplatin-induced ototoxicity in Denmark.

Model features	Description	Justification
Outcomes	Proportion of patients experiencing HL Distribution of HL severity	PEMARQSI has an effect on the incidence and severity of HL. PEDMARQSI does not impact the underlying cancer and has no impact on mortality.

Abbreviations: DMC: Danish Medicines Council, HL: hearing loss

Cycle length

A cycle length of one year is selected because, on average, cisplatin treatment (and therefore PEDMARQSI treatment) is completed within one year. This was validated by Danish clinical expert feedback (Norgine 2025b) and is also demonstrated by the total duration of treatment in COG ACCL0431 (in the safety population, the mean duration of cisplatin treatment in patients with localised disease was 22.2 weeks (standard deviation [SD]: 9.7; Range: 9-45) and 16.8 weeks (SD: 8.9; Range: 3-47) for the cisplatin without PEDMARQSI and cisplatin with PEDMARQSI arms, respectively). Furthermore, in the Markov part of the model patients only had a risk to transition to the health state 'Death'. Hence, a one-year cycle length is considered short enough to adequately capture and reflect changes in costs and QoL over the lifetime horizon. Finally, the majority of costs and outcomes occur in the first year of the model.

The model applies a half-cycle correction. However, PEDMARQSI acquisition, administration and antiemetic premedication costs, as well as adverse event (AE) costs in both treatment arms were applied in the first cycle only to all patients entering the model and therefore a half-cycle correction was not applied for these. This is a conservative approach, which assumes that patients will incur these costs even if they move to the Dead state throughout the first cycle.

5. Overview of literature

5.1 Literature used for the clinical assessment

The present application has clinical evidence (efficacy and safety) based on the pivotal Phase III clinical trials for the efficacy and safety of PEDMARQSI, COG ACCL0431 and SIOPEL-6, which directly compared the addition of PEDMARQSI 6 hours after each cisplatin dose to cisplatin treatment alone (ClinicalTrials.gov, ClinicalTrials.gov). A systematic literature review (SLR), summarised below, was conducted to ensure an exhaustive review of relevant literature and to increase understanding of the prevention and treatment of cisplatin-induced ototoxicity. No other trials than COG ACCL0431 and SIOPEL-6 with the relevant comparator was identified pertaining to this drug (PEDMARQSI), comparison (cisplatin without PEDMARQSI), and patient group (children between the age 1 month and <18 years with localised, non-metastatic solid tumours receiving cisplatin treatment). The relevant publications used for the clinical assessment of this application include the three records identified in the efficacy SLR for the COG ACCL0431 and SIOPEL-6 trials (Brock et al. 2018, Freyer et al. 2017, Orgel et al. 2023). The SLR is summarized in Appendix H.

Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Freyer DR, Chen L, Krailo MD, Knight K, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017 Jan;18(1):63-74. (Freyer et al. 2017)	COG ACCL0431	NCT00716976	Start: 23/06/08 Completion: 30/06/21	Cisplatin with PEDMARQSI vs. cisplatin without PEDMARQSI for patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.

Orgel E, Knight KR, Villaluna D, et al. Reevaluation of sodium thiosulfate otoprotection using the consensus International Society of Paediatric Oncology Ototoxicity Scale: A report from the Children's Oncology Group study ACCL0431. Pediatr Blood Cancer. 2023 Jul 7:e30550. (Orgel et al. 2023)				
Brock PR, Maibach R, Childs M, et al. Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. N Engl J Med. 2018 Jun 21;378(25):2376-2385. (Brock et al. 2018)	SIOPEL-6	NCT00652132	Start: 15/12/07 Completion: 28/02/18	Cisplatin with PEDMARQSI vs. cisplatin without PEDMARQSI for patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.

* If there are several publications connected to a trial, include all publications used.

Sources: (Brock et al. 2018, Freyer et al. 2017, ClinicalTrials.gov 2018, ClinicalTrials.gov 2021)

5.2 Literature used for the assessment of health-related quality of life

An SLR to identify relevant HRQoL studies for patients with acquired HL was conducted on 25th October 2023, with an update conducted the 14th of October 2024 to identify studies published since 31st October 2023. The population of this SLR was expanded from the population criteria in the clinical search (which aligned with the licensed indication of PEDMARQSI), identifying three for the indication relevant studies. To overcome the small number of publications found in the SLR that consider paediatric patients and report utilities according to HL severity, a targeted literature search (TLR) for HRQoL in paediatric patients with HL was conducted. Barton et al. (2006) was identified through the TLR and was the main source of utility inputs for two of the SLR papers identified above. The SLR as well as the TLR are described in detail in Appendix I.

Table 10 Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Barton GR, Stacey PC, Fortnum HM, Summerfield AQ. Hearing-impaired children in the United Kingdom, IV: cost-effectiveness of pediatric cochlear implantation. Ear Hear. 2006 Oct;27(5):575-88. (Barton et al. 2006)	Utility values for HL	Section 10.3
Pogany L, Barr RD, Shaw A, Speechley KN, Barrera M, Maunsell E. Health status in survivors of cancer in childhood and adolescence. Qual Life Res. 2006 Feb;15(1):143-57. doi: 10.1007/s11136-005-0198-7. PMID: 16411038. (Pogany et al. 2006)	HUI3 population norms	Section 10.3.3
Chen, P., Hudson, M.M., Li, M. et al. Health utilities in pediatric cancer patients and survivors: a systematic review and meta-analysis for clinical implementation. Qual Life Res 31, 343–374 (2022). https://doi.org/10.1007/s11136-021-02931-0 (Chen et al. 2022)	Cancer-related disutilities	Section 10.3.3
McCrone, P, Dhanasiri, S, Patel, A, Knapp, M & Lawton-Smith, S 2008, Paying the price: the cost of mental health care in England to 2026. The King's Fund, London. (McCrone et al. 2008)	Hearing aid utilities	Section 10.3.3
Gumbie M, Parkinson B, Dillon H, Bowman R, Song R, Cutler H. Cost-Effectiveness of Screening Preschool Children for Hearing Loss in Australia. Ear Hear. 2022	Hearing aid utilities	Section 10.3.3

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
May/Jun;43(3):1067-1078. doi: 10.1097/AUD.0000000000001134. (Gumbie et al. 2022)		

Abbreviations: HL: hearing loss, HRQoL: Health-related quality of life, HUI3: Health Utility Index 3

5.3 Literature used for inputs for the health economic model

An SLR to identify relevant studies informing inputs for the health economic model for patients with acquired HL was conducted on 25th October 2023. An updated SLR was performed in October 2024. Furthermore, input values were sourced from publications identified through thorough desk research, which identified several publications that were not included in the SLR. The SLR is described in detail in Appendix J. Table 11 is supplemented with HRQoL and clinical literature, used for the health economic model (see Table 9 and Table 10).

Table 11 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Freyer DR, Chen L, Krailo MD, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017 Jan;18(1):63-74. (Freyer et al. 2017)	Age, gender, intervention posology, treatment duration, co-medication schedule	Primary clinical trial study for the intervention	Section 6.1.4 and Appendix B
Brock PR, Maibach R, Childs M, et al. Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. N Engl J Med. 2018 Jun 21;378(25):2376-2385. (Brock et al. 2018)	Input to scenario analyses	Primary clinical trial study for the intervention	Section 6.1.5 and Appendix B

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Barton GR, Stacey PC, Fortnum HM, Summerfield AQ. Hearing-impaired children in the United Kingdom, IV: cost-effectiveness of pediatric cochlear implantation. Ear Hear. 2006 Oct;27(5):575-88. (Barton et al. 2006)	HRQoL utilities	Targeted literature review	Section 10.3
Orgel E, Knight KR, Villaluna D, et al. Reevaluation of sodium thiosulfate otoprotection using the consensus International Society of Paediatric Oncology Ototoxicity Scale: A report from the Children's Oncology Group study ACCL0431. Pediatr Blood Cancer. 2023 Jul 7:e30550. (Orgel et al. 2023)	HL severity	Secondary clinical trial study based on COG ACCL0431 data	Section 8.2 and Section B.1.6
Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 2005 Dec 1;23(34):8588-96. (Knight et al. 2005)	HL severity	Desk research	Section 8.2
Dionne F, Mitton C, Rassekh R, et al. Economic impact of a genetic test for cisplatin-induced ototoxicity. Pharmacogenomics J. 2012 Jun;12(3):205-13. doi: 10.1038/tpj.2011.15. Epub 2011 Apr 19. Erratum in: Pharmacogenomics J. 2012 Aug;12(4):359. (Dionne et al. 2012)	Resource use of speech and language therapy in patients aged <18 years	Systematic literature review	Appendix L

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Chorozoglou M, Mahon M, Pimperton H, et al. Societal costs of permanent childhood hearing loss at teen age: a cross-sectional cohort follow-up study of universal newborn hearing screening. BMJ Paediatr Open. 2018 Feb 24;2(1):e000228. (Chorozoglou et al. 2018)	Proportion of patients receiving cochlear implants	Desk research	Appendix L
Bond M, Mealing S, Anderson R, et al. The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. Health Technol Assess. 2009 Sep;13(44):1-330. (Bond et al. 2009)	Cochlear implant replacement frequency	Desk research	Sections 0, 10.3.3 and Appendix L.2.
Smulders YE, van Zon A, Stegeman I, et al. Cost-Utility of Bilateral Versus Unilateral Cochlear Implantation in Adults: A Randomized Controlled Trial. Otol Neurotol. 2016 Jan;37(1):38-45. (Smulders et al. 2016)	Resource use of speech and language therapy in patients aged >18 years	Systematic literature review	Appendix L.3
Fidler MM, Reulen RC, Winter DL, et al. Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. BMJ. 2016 Sep 1;354:i4351. doi: 10.1136/bmj.i4351. PMID: 27586237; PMCID: PMC5008696. (Fidler et al. 2016)	Age-dependent standardised mortality ratios	Desk research	Section 8.4
Cutler H, Gumbie M, Olin E, et al. The cost-effectiveness of unilateral cochlear implants in UK adults. Eur J Health Econ.	Resource use connected to	Systematic literature review	Appendix J.1.8

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
2022 Jul;23(5):763-779. doi: 10.1007/s10198-021-01393-y. Epub 2021 Nov 2. PMID: 34727294; PMCID: PMC9170662. (Cutler et al. 2022)	cochlear implants		
Pogany L, Barr RD, Shaw A, et al. Health status in survivors of cancer in childhood and adolescence. Qual Life Res. 2006 Feb;15(1):143-57. doi: 10.1007/s11136-005-0198-7. PMID: 16411038. (Pogany et al. 2006)	HUI3 population norms	Desk research	Section 10.3.3
Chen, P., Hudson, M.M., Li, M. et al. Health utilities in pediatric cancer patients and survivors: a systematic review and meta-analysis for clinical implementation. Qual Life Res 31, 343–374 (2022). https://doi.org/10.1007/s11136-021-02931-0 (Chen et al. 2022)	Cancer-related disutilities	Desk research	Section 10.3.3
McCrone, P, Dhanasiri, S, Patel, A, Knapp, M & Lawton-Smith, S 2008, Paying the price: the cost of mental health care in England to 2026. The King's Fund, London. (McCrone et al. 2008)	Hearing aid utilities	Systematic literature review	Section 10.3.3
Gumbie M, Parkinson B, Dillon H, et al. Cost-Effectiveness of Screening Preschool Children for Hearing Loss in Australia. Ear Hear. 2022 May/Jun;43(3):1067-1078. doi: 10.1097/AUD.0000000000001134. (Gumbie et al. 2022)	Hearing aid utilities	Systematic literature review	Section 10.3.3

Abbreviations: HL: hearing loss, HRQoL: health-related quality of life, HUI3: Health Utilities Index Mark 3

6. Efficacy

6.1 Efficacy of cisplatin with PEDMARQSI compared to cisplatin without PEDMARQSDI for patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours

6.1.1 Relevant studies

6.1.1.1 COG ACCL0431 (NCT00716976)

The COG ACCL0431 study was a multicentre, open-label, Phase 3 randomised trial investigating the efficacy of PEDMARQSI infusion for preventing HL in children with different types of solid tumours, including localised or disseminated disease (European Medicines Agency 2023b, [redacted]. The study design (Figure 3), study duration and PICO criteria are summarised in Table 12.

Further information is available in Appendix A.

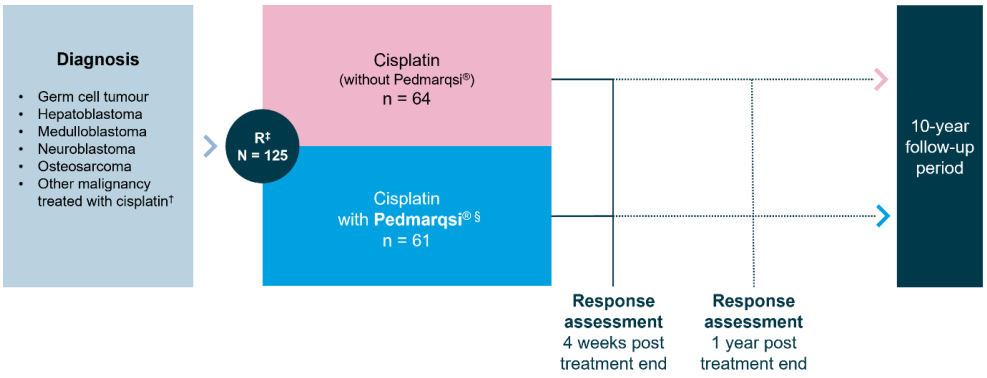


Figure 3 COG ACCL0431 trial design

† Treatment to include ≥ 200 mg/m2 cisplatin administered according to disease specific regimen

‡ 1:1 randomisation was stratified by prior cranial irradiation (yes vs no), age (< 5 years old vs ≥ 5 years old) and duration of cisplatin infusion (< 2 hours vs ≥ 2 hours), resulting in 5 strata as follows: 1. no prior cranial irradiation, < 5 years of age, < 2 hours cisplatin infusion; 2. no prior cranial irradiation, < 5 years of age, ≥ 2 hours cisplatin infusion; 3. no prior cranial irradiation, ≥ 5 years of age, < 2 hours cisplatin infusion; 4. no prior cranial irradiation, ≥ 5 years of age, ≥ 2 hours cisplatin infusion; 5. prior cranial irradiation, regardless of age or duration of cisplatin infusion

§ PEDMARQSI dosage was 10.2 g/m2, administered 6 hours after cisplatin chemotherapy

Abbreviations: R: randomisation

Sources: adapted from COG ACCL0431 study schema (European Medicines Agency 2023b, [redacted])

6.1.1.2 SIOPEL-6 (NCT00652132)

SIOPEL-6 was an open-label, Phase 3, randomised trial to assess the efficacy of PEDMARQSI for reducing hearing impairment caused by cisplatin chemotherapy in children with standard-risk hepatoblastoma (non-metastasised) (Brock et al. 2018, European Medicines Agency 2023b). The study design (Figure 4), study duration and PICO criteria are summarised in Table 12.

Further information is available in Appendix A.

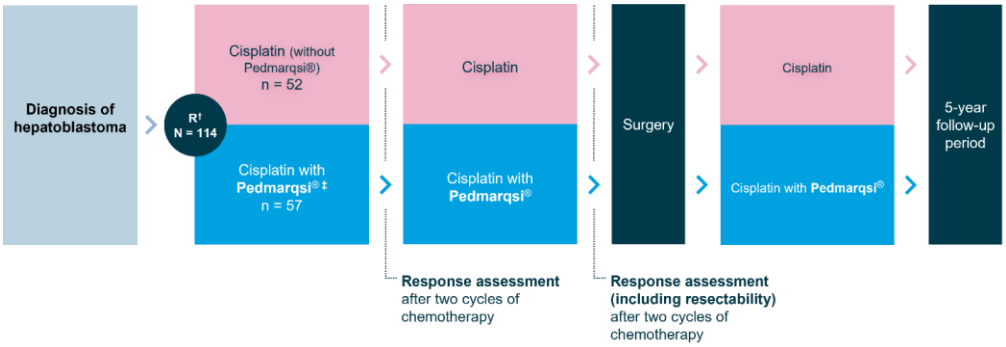


Figure 4 SIOPEL-6 trial design

† Randomisation was stratified by country, median age (above vs below 15 months), and PRETEXT classification (I and II vs III). Of the 114 children randomised, 5 were not treated (2 children were withdrawn due to parental consent, 2 children were reclassified as high-risk, and 1 child was ineligible for treatment). If surgery was delayed for any reason, two further courses of preoperative chemotherapy could have been given on Day 57 and Day 71.

‡ PEDMARQSI was dosed according to body weight: > 10 kg, 5 kg to 10 kg, and < 5 kg received PEDMARQSI 12.8 g/m2, 9.6 g/m2, and 6.4 g/m2, respectively (anhydrous dosing), administered 6 hours after cisplatin chemotherapy

Abbreviations: kg: kilogram, PRETEXT: Pre-treatment Tumour Extension, R: randomisation

Source: adapted from SIOPEL-6 Study Schema. (European Medicines Agency 2023b, [redacted])

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy (**COG ACCL0431**) NCT00716976 (Freyer et al. 2017)	The trial was a multicentre, randomised, open-label, phase 3 trial. Patients were randomly assigned 1:1. Allocation sequences were generated using a permuted block algorithm with balanced 2:2 randomizations per block.	Study start: 23/06/2008 Primary completion: 09/04/2015 Study completion: 30/06/2021	125 children with solid tumours between the age 1 and <18 years receiving cisplatin treatment (PEDMARQSI n=61, control n=65).	Cisplatin with PEDMARQSI Cisplatin treatment according to the patient's treatment protocol and IV PEDMARQSI (6.4 g/m^2 to 12.8 g/m^2) after each cisplatin dose.	Cisplatin without PEDMARQSI Cisplatin treatment according to the patient's treatment protocol without additional PEDMARQSI treatment.	**Incidence of Hearing Loss**: HL defined by comparing hearing sensitivity at follow up evaluation relative to baseline measurements using ASHA criteria. Measurements were performed 4 weeks after the last dose of cisplatin. **Change in Hearing Threshold For Key Frequencies at 500 Hz, 1000 Hz, 2000 Hz, 400 Hz, and 800 Hz**: Evaluation of the mean change in hearing threshold (after treatment – before treatment) at 500 Hz, 1000 Hz, 2000 Hz, 400 Hz, and 800 Hz. Measurements were performed 4 weeks after the last dose of cisplatin. **Event-Free Survival**: Proportion of patients event-free (no disease relapse, progression, second malignant neoplasm, or death) at 4 years following enrolment. **Overall Survival**: OS was defined as the time from enrolment to death or last date confirmed alive (4 years following enrolment). Participants who died were considered to have experienced an OS-event or otherwise were considered censored at time of last contact. **Haematological and Renal Toxicity**: Each participant-cycle was evaluated for the presence of haematological and/or renal toxicity based on pre-determined components. Measurements were performed after each cisplatin cycle.
Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III	The trial was a multicentre, randomised, controlled, open-label study. Children were	12 weeks double blinded period follow by 40 weeks open label	109 children with solid tumours who are to receive cisplatin treatment (PEDMARQSI	Cisplatin with PEDMARQSI Four preoperative and two postoperative	Cisplatin without PEDMARQSI Four preoperative and two postoperative	**Proportional Incidence of Hearing Loss**: Defined as Brock Grade ≥ 1 HL, determined of the better ear by PTA after the end of treatment or at age ≥ 3.5 years (whichever timepoint was later). **Overall Survival**: Defined as the time from enrolment to death (relating to underlying cancer) until the event or up to 5 years after the last dose. **Event-free Survival**: calculated from the time of randomisation to the first of the following events:

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Childhood Liver Cancer (**SIOPEL-6**) NCT00652132 (Brock et al. 2018)	randomised 1:1 to receive PEDMARQSI after each cisplatin dose (cisplatin + PEDMARQSI arm) or cisplatin without subsequent PEDMARQSI (cisplatin alone arm).	Study start: 15/12/2007 Primary completion: 04/09/2017 Study completion: 28/02/2018	n=57, no PEDMARQSI n=52) were stratified according to country, median age (<15 months vs ≥15 months), and PRETEXT tumour classification (I vs II vs III).	cisplatin cycles and IV PEDMARQSI (6.4 g/m^2 to 12.8 g/m^2) after each cisplatin dose. If surgery was delayed for any reason, two further courses may also have been given (on Days 57 and 71).	cisplatin treatments without additional PEDMARQSI treatment. If surgery was delayed for any reason, two further courses may also have been given (on Days 57 and 71)	progression, relapse, second primary malignancy, or death (all relating to the underlying cancer). The follow-up time was until the first event or up to 5 years after the last cisplatin dose. **Percentage of Children per Disease Status**: Includes evaluation of complete remission, partial remission, stable disease, and progressive disease (all relating to the underlying cancer). Response assessments were performed following two cycles of chemotherapy and the completion of preoperative chemotherapy. Complete resection was evaluated within two weeks after the surgery. Complete remission was determined at the end of trial treatment. **Toxicity as Graded by CTCAE v 3.0**: Adverse drug reactions are defined as adverse events, which are possibly, probably or definitely related to trial treatment. Toxicity was graded 30 days post treatment. **Long-term Renal Clearance**: defined as a calculated creatinine clearance of ≥ 60 mL/min/1.73m^2 until an event or up to 5 years after the last treatment. Feasibility of Central Audiology Review: The feasibility of central review was determined at the end of trial treatment or at an age of 3.5 years, whichever was later.

Abbreviations: ASHA: American Speech Language and Hearing Association, CTCAE: common terminology criteria for adverse event, g: gram, HL: hearing loss, Hz: hertz, m^2: square meter, OS: overall survival, PRETEXT: Pre-treatment Tumour Extension, PTA: pure-tone audiometry

6.1.2 Comparability of studies

Not applicable, the comparison is based on the head-to-head studies COG ACCL0431 and SIOPEL-6 (cisplatin with PEDMARQSI versus cisplatin without PEDMARQSI). However, only COG ACCL0431 was used to inform the health economic analysis based on its broader patient population covering multiple solid tumours and paediatric patients of all ages (see Table 13). The results of COG ACCL0431 and SIOPEL-6 are highly consistent, showing an approximate 50% reduction in the relative risk (RR) of HL. In both trials, no statistically significant differences were observed in OS and EFS (see Section 6.1.5).

6.1.2.1 Comparability of patients across studies

Baseline characteristics of the patients included in COG ACCL0431 are presented in Table 13. Furthermore, PEDMARQSI was investigated in the SIOPEL-6 trial, focusing on patients with hepatoblastoma. This trial is used to inform sensitivity analyses and supports the results observed in COG ACCL0431. Baseline characteristics of the patients included in SIOPEL-6 are presented in Table 13. The patient characteristics in both trials were well balanced across both treatment arms.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	COG ACCL0431		SIOPEL-6	
	Cisplatin with PEDMARQSI (N=61)	**Cisplatin without PEDMARQSI (N=64)**	**Cisplatin with PEDMARQSI (N=57)**	**Cisplatin without PEDMARQSI (N=52)**
Age, median (range), months	NR	NR	12.8 (1.2–98.6)	13.4 (3.0–70.2)
<5, n (%)	22 (36%)	22 (34%)	NR	NR
5-9, n (%)	7 (11%)	13 (20%)	NR	NR
10–14, n (%)	16 (26%)	14 (22%)	NR	NR
15–18, n (%)	16 (26%)	15 (23%)	NR	NR
Sex				
Male, n (%)	35 (57%)	41 (64%)	30 (53%)	29 (56%)
Female, n (%)	26 (43%)	23 (36%)	27 (47%)	23 (44%)
Ethnicity				
Non-Hispanic, n (%)	41 (67%)	46 (72%)	NR	NR

Hispanic, n (%)	18 (30%)	15 (23%)	NR	NR
Unknown, n (%)	2 (3%)	3 (5%)	NR	NR
Race				
White, n (%)	42 (69%)	39 (61%)	32 (56.1%)	32 (61.5%)
Non-white, n (%)	19 (32%)	21 (34%)	14 (24.5%)	14 (26.9%)
Unknown, n (%)	0	4 (6%)	11 (19.3%)	6 (11.5%)
Diagnosis				
Germ cell tumour, n (%)	16 (26%)	16 (25%)	0	0
Hepatoblastoma, n (%)	2 (3%)	5 (8%)	57 (100%)	52 (100%)
Medulloblastoma or CNS PNET, n (%)	12 (20%)	14 (22%)	0	0
Neuroblastoma, n (%)	14 (23%)	12 (19%)	0	0
Osteosarcoma, n (%)	14 (23%)	15 (23%)	0	0
Other, n (%)	3 (5%)	2 (3%)	0	0
Extend of disease*				
Localised, n (%)	39 (64%)	38 (59%)	55 (96.5%)	52 (100%)
Disseminated, n (%)	21 (34%)	26 (41%)	NR	NR
Unknown, n (%)	1 (2%)	0	2 (3.5)	0
Alpha-fetoprotein level, median (range), ng/mL	NR	NR	181,500 (273–5,489,165)	79,251.50 (187–2,632,584.9)
PRETEXT score†				
I or II, n (%)	NR	NR	41 (72%)	31 (60%)
III, (%)	NR	NR	16 (28%)	21 (40%)

*Determined post hoc (i.e., retrospectively during the preliminary data analysis after completion of accrual).

† Tumour extent was assessed with the use of the Pretreatment Extent of Disease (PRETEXT) system. Scores range from I to IV, with higher scores indicating increased extent of the disease in the liver. Children with a score of IV were not included in this trial.

Abbreviations: mL: millilitre, ng: nanogram, NR: not reported, PNET: primitive neuroectodermal tumour, PRETEXT: Pre-treatment Tumour Extension

Sources: ([redacted], Freyer et al. 2017, Brock et al. 2018)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The economic analysis utilises baseline patient characteristics from the intent-to-treat (ITT) population of the COG ACCL0431 trial, including data from patients with localised disease only from both treatment arms, as described previously in Section 6.1.2. As a scenario, efficacy and baseline characteristics data from SIOPEL-6 are used. Baseline patient characteristics used in the model are presented in Table 14.

Table 14 Baseline patient characteristics informing the economic model

Characteristics	Trial	Value (SE)	Use in model
Proportion male, %	COG ACCL0431* ITT	60.94% (N/A)	Used to inform the estimation of background mortality and for adjusting utilities according to age.
Mean age, years	COG ACCL0431* ITT	8.6 (0.69)	Age at baseline impacts the time horizon and the mean age of the cohort in each cycle of the model, subsequently impacting the period in which costs for those aged <18 years are applied.
Age distribution, %	COG ACCL0431*	≥1mo - <1yr: 0.00%	Age distribution is used to inform the weighted average unit costs for patients <18 years old. These costs are applied for every model cycle where the mean age of the cohort <18 years old.
		≥1yr - <2yrs: 18.18%	
		≥2yrs - <3yrs: 14.29%	
		≥3yrs - <4yrs: 3.90%	
		≥4yrs - <5yrs: 3.90%	
		≥5yrs - <6yrs: 3.90%	
		≥6yrs - <7yrs: 3.90%	
		≥7yrs - <8yrs: 1.30%	
		≥8yrs - <9yrs: 2.60%	
		≥9yrs - <10yrs: 2.60%	

≥10yrs - <11yrs: 2.60%
≥11yrs - <12yrs: 3.90%
≥12yrs - <13yrs: 6.49%
≥13yrs - <14yrs: 3.90%
≥14yrs - <15yrs: 7.79%
≥15yrs - <16yrs: 5.19%
≥16yrs - <17yrs: 6.49%
≥17yrs - <18yrs: 9.09%

*Only data from localised patients is considered to align with the PEDMARQSI license.

Note: Information provided by Norgine.

Abbreviations: ITT: intention-to-treat, N/A: not applicable, SE: standard error

Overall, the patient population from the clinical trial used in the health economic model is consistent with the patient characteristics expected in the patient population observed in Danish clinical practice, as confirmed by a Danish clinical expert (Norgine 2025b). A summary and comparison of the patient population (age and sex) is displayed in Table 15. The average age of 9.2 years in the COG ACCL0431 study is based on the entire study population whereas for the health economic model, only patients from the COG ACCL0431 study with localised disease were included. A detailed age distribution is depicted in Table 14.

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (Norgine 2025b)*	Value used in health economic model (Freyer et al. 2017)
Age	8.6 years	8.6 years**
Gender	61.04% male	61.04% male
Patient weight	35.14 kg	35.14 kg

*Values used to inform the health economic model were confirmed to represent the Danish population.

** Includes only patients from the COG ACCL0431 study with localised disease.

Abbreviations: kg: kilogram

6.1.4 Efficacy – results COG ACCL0431

A summary of outcomes from the COG ACCL0431 trial is shown in Table 16. More details about the respective outcomes are described in Appendix B.

Table 16 Summary of outcomes from the COG ACCL0431 trial

Outcome	Chosen population	Cisplatin with PEDMARQSI	Cisplatin without PEDMARQSI	Relative Risk/ Hazard Ratio (95% CI)	p-value
Incidence of hearing loss, Yes, n	Efficacy population* (N=49/N=55)	14 (28.57%)	31 (56.36%)	RR: 0.516 (0.318, 0.839)	0.004
Change in hearing threshold, SD	Efficacy population* (N=49/N=55)	Values are displayed in Table 64	Values are displayed in Table 64	NR	Values are displayed in Table 64
Overall survival, censored, n	ITT population	43 (70.5%)	52 (81.3%)	HR: 1.79 (0.86, 3.72)	0.1132
Event-free survival, censored, n	ITT population	34 (55.7%)	39 (60.9%)	HR: 1.27 (0.73, 2.18)	0.3964
Duration of follow-up (minimum, median, maximum), years	ITT population	0.23, 4.95, 8.28	0.57, 5.60, 8.27	NR	NR

* The efficacy population included all children in the ITT population who had both baseline and 4-week follow-up hearing assessments.

Abbreviations: CI: confidence interval, Hz: hertz, HR: hazard ratio, ITT: intention-to-treat, NR: not reported, RR: Relative risk, SD: standard deviation

Sources: (Freyer et al. 2017, [redacted], Norgine 2023)

For outcomes evaluating HL, the efficacy population is considered appropriate and robust to use as input to the economic model as it included all children in the ITT population who had both baseline and four-week follow-up hearing assessments, and in whom an assessment of the change in HL can be conducted. As the efficacy population was pre-specified in the trial protocol ([redacted], any bias associated with the exclusion of patients without a hearing assessment is considered to be minimal (as discussed by Rehman et al. (2020)). Furthermore, by excluding patients without their HL assessed, the analysis focuses on patients who contribute relevant data to the assessment of HL, thereby enhancing the reliability of the results.

6.1.5 Efficacy – results per SIOPEL-6

A summary of outcomes from the SIOPEL-6 trial is shown in Table 17. More details about the respective outcomes are described in Appendix B.

Table 17 Summary of outcomes from the SIOPEL-6 trial

Outcome	Chosen population	Cisplatin with PEDMARQSI	Cisplatin without PEDMARQSI	Relative risk/Hazard ratio (95% CI)	p-value
Proportional incidence of hearing loss, Yes, n	ITT population (N=57/N=52)	20 (35.1%)	35 (67.3%)	RR: 0.521 (0.349, 0.778)	< 0.001
Overall survival, censored, n		55 (96.5%)	48 (92.3%)	HR: 0.44 (0.08, 2.41)	0.332
Event-free survival, censored, n		46 (80.7%)	41 (78.8%)	HR: 0.89 (0.39, 2.05)	0.785
Percentage of children per disease status (reported by central reviewer), n		Complete remission: 52 (91.2%) Not complete remission: 5 (8.8%)	Complete remission: 44 (84.6%) Not complete remission: 8 (15.4%)	NR	0.378
Long-term renal clearance, mean (SD)		-1.33 (76.247)	0.77 (71.017)	NR	0.887
Log10 change in AFP from baseline (end of treatment change), mean (SD)	ITT population (N=56/N=49)	-3.780 (1.088)	-3.714 (1.149)	NR	< 0.001

Abbreviations: AFP: alpha-fetoprotein, CI: confidence interval, HR: hazard ratio, ITT: intention to treat, NR: not reported, RR: relative risk, SD: standard deviation

Sources: (Brock et al. 2018, [redacted], European Medicines Agency 2023b)

7. Comparative analyses of efficacy

Not applicable as COG ACCL0431 was a randomised controlled study comparing the intervention (cisplatin with PEDMARQSI) with the comparator (cisplatin without PEDMARQSI) directly.

7.1.1 Differences in definitions of outcomes between studies

Not applicable for this application.

7.1.2 Method of synthesis

Not applicable for this application.

7.1.3 Results from the comparative analysis

The COG ACCL0431 and SIOPEL-6 trials are head-to-head comparisons of the intervention ''cisplatin with PEDMARQSI'' and the comparator ''cisplatin without PEDMARQSI''.

Table 18 Results from the comparative analysis of cisplatin with PEDMARQSI vs. cisplatin without PEDMARQSI for the prevention of ototoxicity induced by cisplatin chemotherapy (COG ACCL0431 ITT and efficacy population)

Outcome measure	Cisplatin with PEDMARQSI (N=61)	Cisplatin without PEDMARQSI (N=64)	Result
Proportional incidence of hearing loss (efficacy population, N=49 vs N=55), experiencing hearing loss, n (%) (4 weeks after last dose of cisplatin)	14 (28.6%)	31 (56.4%)	RR: 0.516 (CI 95% 0.318, 0.839), p-value: 0.004
Change in hearing threshold (from baseline to 4 weeks after cisplatin treatment)	Values are displayed in Table 64	Values are displayed in Table 64	Results are displayed in Table 64
Overall survival, number of patients who died, n (%) (4 years after enrolment)	18 (29.5%)	12 (18.8%)	HR: 1.79 (95% CI 0.86, 3.72), p-value: 0.1132
Event-free survival, number of patients with event, n (%) (4 years after enrolment)	27 (44.3%)	25 (39.1%)	HR: 1.27 (95% CI 0.73, 2.18), p-value: 0.3964

Abbreviations: CI: confidence interval, HR: hazard ratio, Hz: hertz, N/A: not available, RR: Relative risk

Source: [redacted])

As explained in Section 6.1.4, outcomes regarding HL were evaluated in the efficacy population.

7.1.4 Efficacy – results per [outcome measure]

Not applicable for this application.

8. Modelling of efficacy in the health economic analysis

The health economic model consists of two parts: a decision-tree model for year one and a Markov-model for year two and onwards, as illustrated in Figure 1 and Figure 2. The efficacy of PEDMARQSI (incidence and severity of HL) is captured in the decision-tree part of the model and in the subsequent Markov model patients are only at risk of mortality. The efficacy of PEDMARQSI is captured in:

- Proportion of patients experiencing HL (Section 8.1)
- Distribution of HL severity (Section 8.2)

Mortality is modelled independent of treatment and described in Section 8.4.

8.1 Presentation of efficacy data from the clinical documentation used in the model

There are two clinical trials that have evaluated the safety and efficacy of PEDMARQSI for the prevention of cisplatin-induced ototoxicity. The principal source of clinical data used to inform the economic analysis is the COG ACCL0431 clinical trial, as it included patients with a range of tumour types which were considered generalisable to the patient population in Denmark. As SIOPEL-6 was limited to patients with standard-risk hepatoblastoma (defined by Pre-treatment Tumour Extension [PRETEXT] criteria, no extrahepatic features, and no distant metastasis (Hiyama 2014)) with an average age of 1.54 years, data are used in scenario analyses only, see Appendix K.1.1.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of incidence of hearing loss

The efficacy of PEDMARQSI on the incidence of HL is captured in the one-year decision tree model based on results in the COG ACCL0431 efficacy population. After the first year and onwards patients are not subjected to deteriorating hearing, see Section 4. Hence, the incidence of HL was not extrapolated in the model.

Table 19 Summary of assumptions associated with extrapolation of incidence of hearing loss

Method/approach	Description/assumption
Data input	COG ACCL0431 efficacy population
Model	Not applicable
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Not applicable
Function with best BIC fit	Not applicable
Function with best visual fit	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Not applicable
Adjustment of background mortality with data from Statistics Denmark	Yes, background mortality is adjusted by mortality data observed in the COG ACCL0431 trial year 1-5 and cancer related SMR from year 6 and onwards. However, the incidence of HL is not affected by probability of mortality.
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviation: SMR: standardised mortality ratio, HL: hearing loss

8.1.2 Calculation of transition probabilities

Data from the clinical trial COG ACCL0431 was used to inform the base case and SIOPEL-6 and Orgel et al. (2023) for scenario analyses. The efficacy of PEDMARQSI on the incidence of HL is modelled in the decision-tree part of the health economic model, see Table 20.

Table 20 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Incidence of HL	Yes	Description in text (Section 8.1.2)	COG ACCL0431 efficacy population ([redacted], Freyer et al. 2017).
	No		

Abbreviation: HL: hearing loss

Sources: ([redacted], Freyer et al. 2017)

The primary efficacy endpoint was the proportional incidence of HL between the cisplatin with PEDMARQSI arm and the cisplatin without PEDMARQSI arm, measured in the efficacy population. The efficacy population includes both patients with localised and metastatic disease. It was also considered appropriate to base the efficacy inputs of the model on both metastatic and localised patients from COG ACCL0431. In this trial, assessment of HL was not powered for an analysis in the sub-population of localised patients (n=33/55 children treated with PEDMARQSI). Such categorisation was not considered in the stratification variables at randomisation and therefore a subgroup analysis in localised only patients breaks randomisation. Furthermore, restricting the overall trial population to localised only patients would restrict an analysis of treatment effect from an already limited population size, as both the intention-to-treat (ITT) population (47/125 patients) and efficacy population (40/104 patients) included 38% of patients with metastatic disease. Therefore, restricting the trial population to localised patients considerably reduces the sample size and increases the uncertainty in the analysis.

It should also be noted that PEDMARQSI is a treatment for the prevention of HL and not a treatment for the underlying cancer, see Appendix B.1.3 and B.1.4. The efficacy of PEDMARQSI in terms of hearing outcomes is independent of whether the patient has localised or metastatic disease ([redacted]). This is supported by PEDMARQSI's mechanism of action being confined to the ear, and hence there is no reason that PEDMARQSI's efficacy differs based on cancer stage. Taken together, this suggest that the most robust approach to modelling the efficacy of PEDMARQSI in the model is to use the overall population efficacy dataset from the COG ACCL0431 trial, which includes both localised and metastatic patients.

Based on analyses in the efficacy population, following the last dose of cisplatin, the proportion of children in the cisplatin with PEDMARQSI arm with HL (14 children, 28.57%) was approximately one-half of the proportion in the cisplatin without PEDMARQSI arm (31 children, 56.36%). The RR of having HL as defined by ASHA criteria were statistically significantly lower in the cisplatin with PEDMARQSI arm compared with the cisplatin without PEDMARQSI arm, when adjusted for the stratification variables of prior cranial irradiation (yes vs no), age subgroup (< 5 years or ≥ 5 years), and duration of cisplatin infusion (< 2 vs ≥ 2 hours) (Table 21) ([redacted], Freyer et al. 2017).

Table 21 Summary of HL (COG ACCL0431 efficacy population)

Results	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)
n	55	49
Yes, n (%)	31 (56.36)	14 (28.57)
No, n (%)	24 (43.64)	35 (71.43)
RR (95% CI)[†]	0.516 (0.318, 0.839)	
P-value[†]	0.004	

[†]Based on logistic regression including treatment and stratification variables as covariates in the model.
Abbreviation: CI: confidence interval, RR: relative risk
Source: ([redacted]) (percentages as reported in Freyer et al. (Freyer et al. 2017)).

To explore uncertainty, a scenario analysis was conducted involving the SIOPEL-6 modified intent-to-treat (mITT) population and the results from Orgel et al. (Orgel et al. 2023), see Appendix K.1.1.

8.2 Presentation of efficacy data from Orgel et al. 2023 and Knight et al. 2005

HL severity was not measured in COG ACCL0431. However, in a post-hoc analysis conducted by Orgel et al. (2023), the trial data was re-analysed. Using the SIOP scale, the study reported patients with Grade 1+ and Grade 2+ HL at the end of cisplatin therapy (see Appendix B.1.6). Hence, data from Orgel et al. (2023) in combination with Knight et al. (2005) Knight et al. was used as the base case.

8.2.1 Extrapolation of severity of hearing loss

The efficacy of PEDMARQSI on the severity of HL is captured in the one-year decision tree. After the first year and onwards, patients are not subjected to deteriorating hearing, see Section 4. Hence, the severity of HL was not extrapolated in the model.

Table 22 Summary of assumptions associated with extrapolation of severity of hearing loss

Method/approach	Description/assumption
Data input	Not applicable
Model	Not applicable
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Not applicable
Function with best BIC fit	Not applicable

Method/approach	Description/assumption
Function with best visual fit	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Not applicable
Adjustment of background mortality with data from Statistics Denmark	Background mortality is adjusted by mortality data observed in the COG ACCL0431 trial year 1-5 and cancer related SMR from year 6 and onwards. However, the incidence of HL is not affected by probability of mortality.
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviation: SMR: standardised mortality ratio, HL: hearing loss

8.2.2 Calculation of transition probabilities

Data from Orgel et al. (2023) and Knight et al. (2005) was used for the distribution of severity of HL modelled in the decision-tree part of the health economic model, see Table 23.

Table 23 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Severity of HL (if yes)	Mild HL	Post-hoc analysis of COG ACCL0431, hearing thresholds of SIOP Grade ≥ 2 and Grade ≥ 1 were evaluated.	Orgel et al. (2023)
	Moderate-Severe HL		
Severity of HL (if Moderate- Severe HL)	Moderate HL	Re-weighted distribution for Brock Grades 2-4.	Knight et al. (2005)
	Marked HL		

Severe HL	

Abbreviations: HL: hearing loss, SIOP: International Society of Paediatric Oncology

Sources: (Orgel et al. 2023, Knight et al. 2005)

Orgel et al. (2023) conducted a re-analysis of COG ACCL0431 data using the International SIOP scale and reported the number of patients with Grade 1+ and Grade 2+ HL at the end of cisplatin therapy. These data are used to inform the percentage of HL patients with Grade 1 (Mild HL health state), and the percentage of patients with Grade 2+ (Moderate HL, Marked HL and Severe HL health states) (Orgel et al. 2023). Orgel et al. (2023) is an appropriate source to use in the model since the study population is taken from the COG ACCL0431 trial, used for the ”yes/no” aspect of the decision tree, see Section 4.1. Patients with Grade 2+ HL are further differentiated into Grades 2, 3 and 4 (i.e. the Moderate HL, Marked HL and Severe HL health states, respectively) using the percentage distribution of these grades reported in Knight et al. (2005), see Table 24.

Table 24 Hearing loss severity reported by Knight et al. (2005)

Hearing loss severity	Distribution of patients	Re-weighted distribution for Brock Grades 2-4
Brock grade 1	12 (42.9%)	N/A
Brock grade 2	13 (46.4%)	81.25%
Brock grade 3	1 (3.6%)	6.25%
Brock grade 4	2 (7.1%)	12.50%

Abbreviation: N/A: not applicable

Source: (Knight et al. 2005)

Knight et al. (2005) was considered appropriate as the population characteristics of patients within this study (such as mean age and the distribution of tumour types) closely align with that of the main source of data in the model (COG ACCL0431), as shown in Table 25. It is also worth noting that the Knight et al. (2005) paper was recommended as a valid source of HL outcomes data following consultation with a United Kingdom (UK) clinician as part of the model development process (Norgine 2024b).

Table 25 Baseline characteristics, tumour types and chemotherapy treatment in COG ACCL0431 and Knight et al. (2005)

	Knight et al. (2005)	COG ACCL0431
Baseline characteristics		
Mean age (years)	9.65	8.60

Percentage male	67.2%	60.8%
Most common tumour types		
Medulloblastoma	17/67 (25.4%)	26/125 (20.8%)
Neuroblastoma	12/67 (17.9%)	26/125 (20.8%)
Osteosarcoma	12/67 (17.9%)	29/125 (23.2%)
Germ cell tumour	9/67 (13.4%)	32/125 (25.6%)

*Patients within COG ACCL0431 were on cisplatin combination protocols, none of which were cisplatin with carboplatin alone.
Abbreviation: NR: not reported
Sources: (Knight et al. 2005, Freyer et al. 2017)

The sources and data used to inform the distribution of HL severity in the base case are summarised in Figure 5.

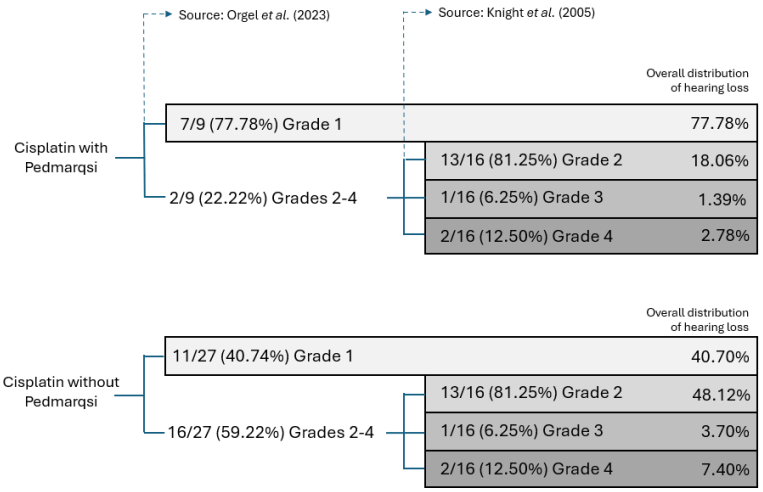


Figure 5 Sources and data used to inform the severity of hearing loss (as a proportion of those with hearing loss)

Although SIOPEL-6 reported the percentage of patients experiencing HL, this trial focused on paediatric patients with one tumour type, hepatoblastoma. It is therefore less representative of the distribution of patients observed in Denmark. As a result, SIOPEL-6 is not used in the base case. However, scenarios are considered to inform the HL severity in the model using either SIOPEL-6 data alone to distribute patients into the Mild HL, Moderate HL, Marked HL and Severe HL health states ([redacted]) or a scenario using Orgel et al. (2023) in combination with SIOPEL-6 ([redacted]). Similar to the base case, Orgel et al. (2023) data is used to inform the percentage of patients within the Mild HL health state. However, instead of Knight et al. (2005), SIOPEL-6 data is used to further differentiate the remaining patients into the Moderate HL, Marked HL and Severe HL health states, see Appendix K.1.2.

8.3 Modelling effects of subsequent treatments

Not applicable for this application.

8.4 Other assumptions regarding efficacy in the model

The pivotal trials SIOPEL-6 and COG ACCL0431 showed no statistically significant difference in the proportion of children who died between the cisplatin with PEDMARQSI and cisplatin without PEDMARQSI treatment arms (see B.1.3 and B.2.2). As such, the mortality inputs of the cost-effectiveness model are not treatment dependent. For the first five years of the model, mortality probabilities are based on the percentage of patients with localised disease alive at years one, two, three, four and five after treatment initiation, as observed in COG ACCL0431. Five-year trial mortality probabilities from COG ACCL0431 are presented in Table 26. Where mortality risk is less than that of the general population mortality, the Danish general population mortality risk is used.

Table 26 Percentage of patients alive and mortality probability in years 1-5*

Year	COG ACCL0431	
	Percentage of patients alive*	Mortality probability
1	[redacted]	
2	[redacted]	
3	[redacted]	
4	[redacted]	
5	[redacted]	

*Only data from localised patients is considered to align with the PEDMARQSI license. **Where mortality percentages are less than that of the general population mortality, the general population values are used.

Sources: ([redacted]

As the OS data from both trials are immature, it is not appropriate to use these data to extrapolate OS over the time horizon of the model. However, it is acknowledged that, beyond five years, patients are likely to still have an increased risk of mortality compared to that of the general population. Therefore, from year 6 of the model onwards, a post-cancer standardised mortality ratio (SMR) is applied to general population mortality rate, adjusted for the patients age, to reflect this increased risk of mortality (see Table 27). The age-dependent SMR values were sourced from a large population-based cohort study (Fidler et al. 2016). This increased risk of mortality can equally be assumed for the Nordics due to the large population and treatment similarities, as confirmed by a Danish clinical expert (Norgine 2025b).

Table 27 Age-dependent SMRs

Follow-up (years)	SMR

5-19	19.90
20-29	5.40
29-39	4.20
40-49	3.30
50-59	2.40
60+	2.30

Abbreviations: SMR: standardised mortality ratio

Source: (Fidler et al. 2016)

8.5 Overview of modelled average treatment length and time in model health state

With PEDMARQSI being an add-on treatment to cisplatin, the comparator in the health economic analysis is "cisplatin without PEDMARQSI". There was no statistically significant difference (p>0.05) in mean cumulative dose of cisplatin by treatment arm in COG ACCL0431 (localised only patients) and there is no reason to expect doses to differ from a clinical perspective ([redacted], Callejo et al. 2015). Hence, cisplatin is not explicitly modelled in the health economic model and average treatment length and time between health states do not differ between cisplatin without PEDMARQSI and cisplatin with PEDMARQSI.

Table 28 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
PEDMARQSI	N/A	N/A	N/A
Without PEDMARQSI	N/A	N/A	N/A

In Table 29 the modelled average treatment length and time in model health state are presented. It is assumed that patients HL does not deteriorate over time. Therefore, once the patient enters the health state in year one, the patient will stay in that health state and generate costs and QALYs until death.

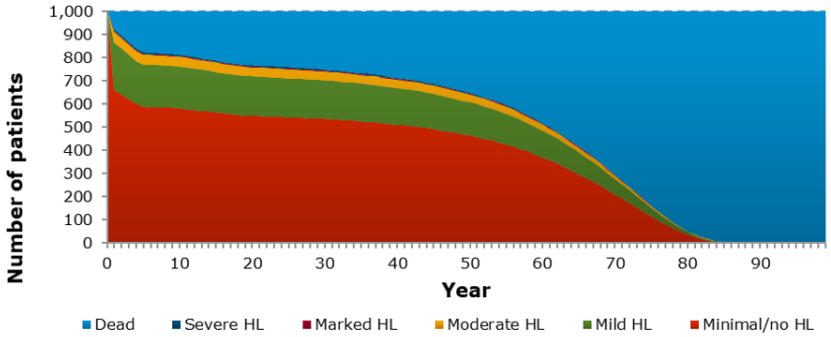
Table 29 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Minimal/No HL	Mild HL	Moderate HL	Marked HL	Severe HL	Dead
PEDMARQSI	35.8	11.0	2.6	0.2	0.4	50.0

Without PEDMARQSI	22.1	11.4	13.4	1.0	2.1	50.0

Abbreviation: HL: hearing loss

Figure 6 and Figure 7 show the flow of patients through health states overtime, based on a modelled cohort of 1000 patients, and the basis for data provided in Table 29.



Abbreviations: HL: hearing loss

Figure 6 Cisplatin with PEDMARQSI results: number of patients in each state over time, as seen in model

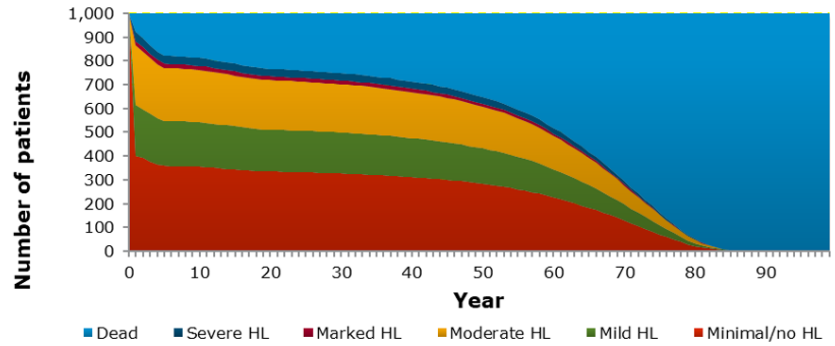


Figure 7 Cisplatin without PEDMARQSI results: number of patients in each state over time as seen in model

Abbreviations: HL: hearing loss

Patients with PEDMARQSI are more likely to remain in health states with lower disease severity compared to patients without PEDMARQSI. As previously mentioned, there is no difference in mortality, meaning both treatment arms spend the same amount of time in the absorbing "death" health state.

9. Safety

9.1 Safety data from the clinical documentation

The documentation of the safety of PEDMARQSI is based on the trials COG ACCL0431 and SIOPEL-6. Table 32 provides an overview of safety events. AEs used in the HE model are summarized in Table 34.

9.1.1 COG ACCL0431

Adverse reactions in the COG ACCL0431 trial were analysed in the safety population, which included 59 children in the cisplatin with PEDMARQSI arm and 64 children in the cisplatin without PEDMARQSI arm. AEs were summarised by AEs Grade > 3, serious adverse events (SAEs), and drug-related AEs (only applicable to the cisplatin with PEDMARQSI arm). The overall incidence of Grade ≥ 3 AEs was similar in both treatment arms of the COG ACCL0431 trial. In the cisplatin with PEDMARQSI arm and cisplatin without PEDMARQSI arm, 55 children (93.2%) and 57 children (89.1%), respectively, experienced an AE graded Common Terminology Criteria for Adverse Events (CTCAE) Category 3 or higher. Table 30 presents a summary of Grade ≥ 3 AEs occurring in ≥ 10% of children in either treatment arm ([redacted]).

Table 30 Summary of most common Grade 3 severity or higher AEs (frequency of ≥ 10% in either arm) (COG ACCL0431 safety population)

Adverse event (Based on CTCAE Version 4)	Cisplatin without PEDMARQSI (N = 64) n (%)	Cisplatin with PEDMARQSI (N = 59) n (%)	Total (N = 123) n (%)
Any Grade 3 Severity or Higher AE	57 (89.1)	55 (93.2)	112 (91.1)
Investigations	57 (89.1)	54 (91.5)	111 (90.2)
Neutrophil count decreased	53 (82.8)	49 (83.1)	102 (82.9)
White blood cell count decreased	42 (65.6)	38 (64.4)	80 (65.0)
Platelet count decreased	39 (60.9)	38 (64.4)	77 (62.6)
Alanine aminotransferase increased	9 (14.1)	10 (16.9)	19 (15.4)
Lymphocyte count decreased	9 (14.1)	6 (10.2)	15 (12.2)
Blood and lymphatic system disorders	38 (59.4)	32 (54.2)	70 (56.9)
Anaemia	36 (56.3)	30 (50.8)	66 (53.7)

Adverse event (Based on CTCAE Version 4)	Cisplatin without PEDMARQSI (N = 64) n (%)	Cisplatin with PEDMARQSI (N = 59) n (%)	Total (N = 123) n (%)
Febrile neutropenia	19 (29.7)	14 (23.7)	33 (26.8)
Metabolism and nutrition disorders	22 (34.4)	29 (49.2)	51 (41.5)
Hypokalaemia	13 (20.3)	16 (27.1)	29 (23.6)
Hypophosphatemia	7 (10.9)	12 (20.3)	19 (15.4)
Hyponatremia	4 (6.3)	7 (11.9)	11 (8.9)
Gastrointestinal disorders	8 (12.5)	12 (20.3)	20 (16.3)
Stomatitis	4 (6.3)	8 (13.6)	12 (9.8)

Abbreviations: AE: adverse event

Source: ([redacted]) (as reported in EPAR 2023 (European Medicines Agency 2023b)).

Serious AEs were only reported for patients in the cisplatin with PEDMARQSI arm and were defined as AEs that fulfilled the Adverse Event Expedited Reporting System requirement. In total, 21 children (35.6%) in the cisplatin with PEDMARQSI arm experienced at least one SAE (see Table 32). A summary of SAEs with a frequency of ≥ 5% is provided in Table 33. All SAEs are listed in Appendix E. Although the COG ACCL0431 trial did not specifically report discontinuations due to AEs, it has been noted that one patient in the cisplatin with PEDMARQSI arm discontinued due to reasons related to a Grade 2 hypersensitivity reaction, and an additional four children discontinued PEDMARQSI in close proximity to an AE, but not specifically due to an AE. No additional fatal AEs were observed during the trial, demonstrating that PEDMARQSI was well tolerated by patients in this study and had a safety profile similar to that of cisplatin without PEDMARQSI ([redacted], European Medicines Agency 2023b).Findings related to haematological toxicity may be particularly relevant as these concern an effect of cisplatin on proliferating cells. AEs pertaining to renal and haematological toxicities from COG ACCL0431 and SIOPEL-6 suggest there is no protection offered by PEDMARQSI against cisplatin-induced renal or haematological toxicity when it was given 6 hours after a cisplatin infusion. The rates of haematological toxicity were similar between the cisplatin with PEDMARQSI and cisplatin without PEDMARQSI arms, suggesting that PEDMARQSI does not interfere with the toxicity of cisplatin in rapidly multiplying cells, and therefore, does not affect its antitumoral efficacy ([redacted], European Medicines Agency 2023b).

9.1.2 SIOPEL-6

Adverse reactions in the SIOPEL-6 trial were analysed in the safety population, which included 53 children in the cisplatin with PEDMARQSI arm and 56 children in the cisplatin

without PEDMARQSI arm (four children that were randomised to the cisplatin with PEDMARQSI arm did not receive PEDMARQSI and were included in the cisplatin without PEDMARQSI arm) ([redacted]). AEs were summarised by AE Grade, SAE, and AE Grade 3 or higher. A summary of AEs that occurred at CTCAE Grade ≥3 at a frequency of ≥10% in either arm is presented below in Table 31.

Table 31 Summary of most common (frequency of ≥ 10% in either arm) AEs with maximum severity of CTCAE Grade 3 or higher during the treatment phase (SIOPEL-6 Safety Population)

Adverse event (Based on CTCAE Version 4)	Cisplatin without PEDMARQSI (N=56) n (%)	Cisplatin with PEDMARQSI (N=53) n (%)	Total (N=109) n (%)
Any Grade 3 Severity or Higher AE	34 (60.7)	35 (66.0)	69 (63.3)
Investigations	19 (33.9)	20 (37.7)	39 (35.8)
Neutrophil count decreased*	9 (16.1)	12 (22.6)	21 (19.3)
Haemoglobin decreased	9 (16.1)	10 (18.9)	19 (17.4)
Infections and infestations	15 (26.8)	14 (26.4)	29 (26.6)
Infection**	15 (26.8)	14 (26.4)	29 (26.6)
Blood and lymphatic system disorders	10 (17.9)	8 (15.1)	18 (16.5)
Febrile neutropenia	9 (16.1)	8 (15.1)	17 (15.6)

** One instance of neutrophil count decreased was attributed as probably related to PEDMARQSI in the cisplatin with PEDMARQSI arm. *** One instance of infection was attributed as probably related to PEDMARQSI in the cisplatin with PEDMARQSI arm. No additional fatal AEs were observed during the trial.
Abbreviations: AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events
Source: ([redacted])

SAEs were assessed as to whether they were related to PEDMARQSI. During the treatment and follow-up phases, a total of four children (7.5%) in the cisplatin with PEDMARQSI arm experienced an SAE that was determined to be related to PEDMARQSI. Of these four children, two (3.8%) experienced an SAE of neutrophil count decreased, one (1.9%) experienced an SAE of infection, and one (1.9%) experienced an SAE of hypersensitivity, which led to discontinuation of PEDMARQSI and was also considered as a suspected unexpected serious adverse reaction. No additional AEs led to discontinuation of PEDMARQSI. There was one fatal SAE in the cisplatin without PEDMARQSI arm (1.8%) after a tumour relapse in which the patient died due to cardiac arrest, which was determined to be related to paclitaxel chemotherapy [redacted]). A summary of SAEs with a frequency of ≥ 5% is provided in Table 33. All SAEs are listed in Appendix E.

Table 32 Overview of safety events during the respective treatment period

	COG ACCL0431		SIOPEL-6		
	Cisplatin with PEDMARQSI (N=59)	Cisplatin without PEDMARQSI (N=64)	Cisplatin with PEDMARQSI (N=53)	Cisplatin without PEDMARQSI (N=56)	Difference, % (95 % CI)
Number of adverse events, n	ND	ND	ND	ND	ND
Number and proportion of patients with ≥1 adverse events, n (%)	55 (93.2%)	57 (89.1%)	51 (96.2%)	49 (87.5%)	ND
Number of serious adverse events*, n	ND	ND	ND	ND	ND
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	21 (35.6%)	ND	21 (39.6 %)	19 (33.9%)	ND
Number of CTCAE grade ≥ 3 events, n	ND	ND	ND	ND	ND
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	55 (93.2%)	57 (89.1%)	35 (66%)	34 (60.7%)	ND
Number of adverse reactions, n	ND	N/A	ND	N/A	ND
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	23 (39%)	N/A	ND	N/A	ND
Number and proportion of patients who had a dose reduction, n (%)	ND	N/A	0 (%)	N/A	ND

Number and proportion of patients who discontinue treatment regardless of reason, n (%)	5 (8.5%)	4 (6.3%)	ND	ND	ND
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	3 (5.1%)	0 (0%)	1 (1.9%)	1 (1.8%)	ND

Abbreviations: CTCAE: Common terminology criteria for adverse event, N/A: not applicable, ND: Not determined

Sources: [redacted]

§ CTCAE v. 5.0 must be used if available.

Table 33 Serious adverse events during the respective treatment periods (ACCL0431 and SIOPEL-6 Safety population, ≥5% in COG ACCL0431).

Adverse events	COG ACCL0431				SIOPEL-6			
	Cisplatin with PEDMARQSI (N=59)		Cisplatin without PEDMARQSI (ND)		Cisplatin with PEDMARQSI (N=53)		Cisplatin without PEDMARQSI (N=56)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Patients with at least 1 SAE	21 (35.6%)	ND	ND	ND	21 (39.6%)	ND	18 (32.1%)	ND
Infections and infestations	5 (8.5%)	ND	ND	ND	7 (13.2%)	ND	5 (8.9%)	ND
Investigations	13 (22.0%)	ND	ND	ND	6 (11.3%)	ND	3 (5.4%)	ND
Neutrophil count decreased	10 (16.9%)	ND	ND	ND	6 (11.3%)	ND	1 (1.8%)	ND

Adverse events	COG ACCL0431				SIOPEL-6			
	Cisplatin with PEDMARQSI (N=59)		Cisplatin without PEDMARQSI (ND)		Cisplatin with PEDMARQSI (N=53)		Cisplatin without PEDMARQSI (N=56)	
Platelet count decreased	8 (13.6%)	ND	ND	ND	0	ND	0	ND
White blood cell count decreased	8 (13.6%)	ND	ND	ND	0	ND	0	ND
Lymphocyte count decreased	4 (6.8%)	ND	ND	ND	0	ND	0	ND
Alanine aminotransferase increased	3 (5.1%)	ND	ND	ND	0	ND	0	ND
General disorders and administration site conditions	0	ND	ND	ND	5 (9.4%)	ND	3 (5.4%)	ND
Pyrexia	0	ND	ND	ND	5 (9.4%)	ND	3 (5.4%)	ND
Gastrointestinal disorders	7 (11.9%)	ND	ND	ND	2 (3.8%)	ND	2 (3.6%)	ND
Stomatitis	5 (8.5%)	ND	ND	ND	0	ND	0	ND
Metabolism and nutrition disorders	5 (8.5%)	ND	ND	ND	2 (3.8%)	ND	2 (3.6%)	ND

Adverse events	COG ACCL0431				SIOPEL-6			
	Cisplatin with PEDMARQSI (N=59)		Cisplatin without PEDMARQSI (ND)		Cisplatin with PEDMARQSI (N=53)		Cisplatin without PEDMARQSI (N=56)	
Blood and lymphatic system disorders	14 (23.7%)	ND	ND	ND	1 (1.9%)	ND	2 (3.6%)	ND
Anemia	7 (11.9%)	ND	ND	ND	0	ND	0	ND
Febrile neutropenia	12 (20.3%)	ND	ND	ND	0	ND	1 (1.8%)	ND
Nervous system disorder	4 (6.8%)	ND	ND	ND	0	ND	0	ND

Note: A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Serious AEs were recorded in the clinical database only for patients in the cisplatin with PEDMARQSI arm and were defined as AEs that fulfilled the Adverse Event Expedited Reporting System (AdEERS) requirements.
Abbreviations: ND: Not determined

Sources: [redacted])

Table 34 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Neutrophil count decreased	83.05%	82.81%	[redacted]	Included based on a threshold of 10%
Febrile neutropenia	23.73%	29.69%		
WBC count decreased	64.41%	65.63%		
Platelet count decreased	64.41%	60.94%		
ALT increased	16.95%	14.06%		
Lymphocyte count decreased	10.17%	14.06%		
Anaemia	50.85%	56.25%		
Hypokalaemia	27.12%	20.31%		
Hypophosphatemia	20.34%	10.94%		
Hyponatremia	11.86%	6.25%		
Stomatitis	13.56%	6.25%		

9.2 Safety data from external literature applied in the health economic model

Not applicable for this application.

Table 35 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A: not applicable

10. Documentation of health-related quality of life (HRQoL)

As no HRQoL data was collected in the pivotal trials, HRQoL data used in the health economic model was identified through an SLR followed by a targeted literature review (TLR). The SLR and TLR is described in detail in Appendix I. The EuroQol 5-dimensions (EQ-5D), though one of the most commonly used generic utility measures, is known to lack construct validity in patients with hearing impairment (Grutters et al. 2007, Yang et al. 2013). In contrast, the Health Utilities Index Mark 3 (HUI3), a validated generic utility measure (Horsman et al. 2003) includes 'hearing' as an attribute, making it the preferred HRQoL measurement in a population with hearing impairment (Grutters et al. 2007, Yang et al. 2013), and is used by the UK cochlear implant study group in research (U.K. Cochlear Implant Study Group 2004a, U.K. Cochlear Implant Study Group 2004b).

While we recognise that EQ-5D is DMC's preferred instrument and if the EQ-5D is not available, it is common practice to map the available instrument to the EQ-5D. However, to the best of our knowledge, no mapping algorithm exists between HUI3 and EQ-5D, and there are no social preference weights for the Danish population, only for Canada and the US. Therefore, HUI3 is considered the appropriate utility measure for this submission.

Table 36 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
HUI3	Barton et al. 2006	Barton et al. (2006) is used to inform the HRQoL associated with HL

Abbreviations: HL: hearing loss, HRQoL: health-related quality of life, HUI3: Health Utilities Index 3
Sources: (Barton et al. 2006)

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

Section 10.1 is not applicable for this application as HRQoL was not collected in the pivotal trials.

10.1.1 Study design and measuring instrument

Not applicable for this application.

10.1.2 Data collection

Not applicable for this application.

Table 37 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	N/A	N/A	N/A	N/A

Abbreviations: N/A: not applicable

10.1.3 HRQoL results

Not applicable for this application.

Table 38 HRQoL [instrument 1] summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	N/A		N/A	N/A	N/A

Abbreviations: N/A: not applicable

10.2 Health state utility values (HSUVs) used in the health economic model

Section10.2 is not applicable for this application as HRQoL was not collected in the pivotal trials.

10.2.1 HSUV calculation

Not applicable for this application.

10.2.1.1 Mapping

Not applicable for this application.

10.2.2 Disutility calculation

Not applicable for this application.

10.2.3 HSUV results

Not applicable for this application.

Table 39 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs	N/A	N/A	N/A	N/A

Abbreviations: N/A: not applicable

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

As no HRQoL data was collected in the pivotal trials, other sources are used to inform the health economic model. Due to a low number of studies identified in the SLR, a TLR was performed (Appendix I). Through the TLR, Barton et al. (2006) was identified. The main HRQoL associated with HL was derived from Barton et al. (2006). Utility values from

Barton et al. (2006) were used in Bond et al. (2009), which was the basis of the economic evaluation within the UK HTA submission for cochlear implants for severe to profound deafness in both children and adults (NICE). Barton et al. (2006) informs the main HRQoL in the model and is described below.

10.3.1 Study design

In a cross-sectional study from UK, hearing-impaired children had their HRQoL assessed by proxy from parents using a modified HUI3 questionnaire (Barton et al. 2006). The questionnaire was modified due to being conceptually and linguistically complex. The researchers applied linear regression analysis to estimate health utility gains from cochlear implantation while controlling for factors such as hearing level, age, gender, disabilities, and socioeconomic status. For the study reported health utility values per average hearing level (AHL) level, see Table 41. A reduction in health utility is expected to correlate with the increasing severity of HL, leading to a decrease in overall QoL.

10.3.2 Data collection

The parents of 8,876 children with hearing impairment were invited to participate in the study. The sample included children with cochlear implants (N=993), profoundly impaired (AHL >95 dB, N=3,288), severely impaired (AHL 71-95 dB, N=3,580) and a stratified random sample of around one in nine of the moderately impaired (AHL 41-70 dB, N=1,015) (Barton et al. 2006). Please see Barton et al. (2006) for full description.

37% of those invited to take part in the study gave consent (their parent) to participate. Of these did 88% (2,858) return the questionnaire. 69% of those consented to participate (2,266) and 403 of whom had an implant completed the revised HUI3 questionnaire (Barton et al. 2006).

10.3.3 HSUV and disutility results

The utility values in Barton et al. (2006) (see Table 41) were considered to be equal to the Moderate HL, Marked HL and Severe HL health states respectively (a weighted average of the profound utility values was used for the Severe HL health state, based on patient numbers in the publication). For the Mild HL health state, utilities were calculated as an average of the Minimal/no HL health state and the Moderate HL health state value mentioned above.

Barton et al. (2006) also reported the utility gain associated with cochlear implant use for subsets of paediatric patients according to their age at implantation (<5 years and ≥5 years old) and duration of use. To align with the baseline age of the model and the assumption that once used, cochlear implant would be used by patients for their entire lifetime, the model utilises the cochlear implant utility gain reported for paediatric patients implanted over five years old and with a duration of cochlear implant use more than four years (utility gain of 0.183). This was applied to each health state according to the percentage of patients using cochlear implants (as shown in Table 41). Barton et al. (2006) included patients with moderate to profound HL, therefore it was assumed that all patients not using cochlear implants would have received hearing aids, and therefore

a hearing aid utility gain was not applied to patients with moderate to profound HL. Gumbie et al. (2022) reported a utility gain for hearing aids of 0.120 therefore this was also applied to health state utilities according to the percentage of patients using hearing aids.

For the Minimal/no HL health state the utility values were taken from Pogany et al. (2006), which is the source of the HUI3 population norms for the Canadian general population. The utility reported for children aged 5-12 years old was used (0.920), as this is in line with the baseline starting age in the model. There are likely to be small differences between the health preferences of the Canadian and Danish general populations but using a HUI3 value for the Minimal/no HL health state is appropriate given that HUI3 values are used for other health states in the model. Given the assumptions required to derive utility values for the four HL health states mentioned above, expert validation was sought from an audiovestibular physician who confirmed that the health state utilities in the model (using values from Barton et al. (2006) with the methods described above), would generalise across the Brock scales 1-4 and similarly, across the SIOP scales 1-4 (Norgine 2024a). A scenario analysis considering utility values from Gumbie et al. (2022) was conducted. Gumbie et al. (2022) was identified in the SLR described more in detail in Appendix I. It was decided to only include utilities from Gumbie et al. as a scenario (rather than in the base case) due to limitations described in Appendix K.3.1. For full description of the scenario analysis see Appendix K.3.1.

Since the utility values from Barton et al. (2006) are not specific to cancer patients, it is likely that they represent an overestimation for the patient cohort considered within the cost-effectiveness analysis in the initial years following completion of their cisplatin treatment. Therefore, a cancer-related disutility was applied to all health states in the model for the first 10 years of the model. The cancer-related disutility was sourced from Chen et al. (2022), a recent systematic review and meta-analysis of health utilities in paediatric cancer patients. The HUI3 proxy-reported disutility value for patients on treatment was applied in the first year of the model, and between years 2 and 10 of the model, the HUI3 proxy-reported disutility for patients off treatment for 2-5 years was applied. Chen et al. (2022) did not report a disutility for patients off treatment for 0-2 years or 5+ years, so it was assumed that the same disutility value could be applied between years two and 10 of the model. The off treatment cancer-related disutility was applied up to year 10 of the model to align with the cure points reported in UK NICE TA538 and TA817 (NICE 2018, NICE 2022a). Table 40 is not applicable in this submission as health state utility values are sources from the literature, see Table 41.

Table 40 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A: not applicable

Table 41 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Base case				
Minimal/no HL	0.92 [0,915, 0,925]	HUI3	Canadian value set	Calculated based on SD and total N 2,152 Derived from (Pogany et al. 2006), as there is no Danish value set to HUI3
Mild HL	0.80 [0.7892, .8088]	HUI3	Canadian value set	Average of the Minimal/no HL and Moderate HL health states due to lack of data Calculated based on standard error
Moderate HL	0.68 [0.652, 0.702]	HUI3	Canadian value set	Derived from Barton et al. (2006) and previously used within (Bond et al. 2009)
Marked HL	0.62 [0.598, 0.633]	HUI3	Canadian value set	Sever HL is calculated as a weighted average between Profound (AHL 96 –105 dB; N=259) 0.497 [0,469, 0,525] and Profound (AHL 105 dB;N=290) 0.353 [0,327, 0,379]
Severe HL	0.41 [0.401, 0.441]	HUI3	Canadian value set	
Disutility and utility gain				
Gain of cochlear implant	0.183	HUI3	Canadian value set	Derived from Barton et al. (2006). Applied to each health state according to the percentage of patients using cochlear implants: • Marked: 6% • Severe: 52%
Gain of hearing aid	0.120 [0.08, 0.17]	HUI3	Canadian value set	Derived from Gumbie et al. (2022) and McCrone et al. (2008)
Cancer-related disutility, on treatment	-0.15 [-0.24, -0.05]	HUI3	Canadian value set	Applied to all health states in year 1. Derived from (Chen et al. 2022). Applied to account for the additional disutility that cancer patients experience

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Cancer-related disutility, off treatment	-0.07 [-0.20, 0.06]	HUI3	Canadian value set	Applied to all health states in years 2+. Derived from (Chen et al. 2022). Applied to account for the additional disutility that cancer patients experience

Abbreviations: HL: hearing loss, HUI3: Health Utilities Index Mark 3, NR: Not reported; AHL: Average hearing level, CI: confidence interval, dB: Decibel
Sources: (Pogany et al. 2006, Barton et al. 2006, Bond et al. 2009, Chen et al. 2022, Gumbie et al. 2022, McCrone et al. 2008)

Age adjustment for health state utility values (HSUV) was implemented in the base case analysis according to the DMC guidelines Utility values were age-adjusted over the model time horizon using the EQ-5D Danish general population values reported by DMC, see Table 42. A multiplicative approach was used, meaning in each cycle, the EQ-5D derived utility norm for the average age of the cohort was compared to the EQ-5D derived utility norm of the baseline starting age of the cohort entering the model, and an adjustment factor (multiplier) was applied to the baseline HUI3 derived health state utilities mentioned above in Table 41. As stated in DMCs Appendix: Age Adjustment for Health-Related Quality of Life, no quality-of-life data has been collected for children and young people under the age of 18. So, no age adjustment should be made for this age group. This means that utility values should not be adjusted until the patients reach the age of 30 at the earliest (Medicinrådet 2017).

Table 42 Danish general population utility values stratified by age groups

Age group	Utility values	Multiplicator index
0-17	1	1
18-29	0.871	1
30-39	0.848	0.973
40-49	0.834	0.958
50-69	0.818	0.939
70-79	0.813	0.933
80+	0.721	0.828

Source: (Medicinrådet 2017)

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Table 43 summarizes medicines used in the model. The pharmaceuticals included in the model are PEDMARQSI and two different antiemetics pharmaceuticals that is administrated alongside PEDMARQSI.

Table 43 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
PEDMARQSI	Body weight-dependent: 6.4 g/m^2 to 12.8 g/m^2	N/A	After each cisplatin dose	No
No PEDMARQSI	Not applicable	N/A	N/A	N/A
Ondansetron	0.15 (mg/kg)	N/A	Before each cisplatin dose	N/A
Palonosetron	0.02 (mg/kg)	N/A	Before each cisplatin dose	N/A

Abbreviations: g: gram, kg: kilogram, m2: square meter, mg: milligram, N/A: not available

The price for PEDMARQSI is based on the only available vial size of 8 g. The average acquisition cost of PEDMARQSI in the model is based on the average number of doses per patient, and the average number of 8 g PEDMARQSI vials required per dose as stated in Table 45. The cost of cisplatin was not considered in the economic analysis as it is assumed to be equal between each treatment arm. This is supported by the mean cumulative dose of cisplatin by treatment arm in COG ACCL0431 (localised only patients)[redacted].

Despite the numerical differences in the cumulative dose of cisplatin between treatment arms, there is no statistically significant difference (p>0.05) and there is no reason to expect doses to differ from a clinical perspective ([redacted], Callejo et al. 2015). Therefore, cisplatin is not considered in the health economic model.

Table 44 PEDMARQSI acquisition costs

	Strength	Pack size	AIP excluding VAT, pr. Pack*

PEDMARQSI	8 g per vial	1 vial	72,638 DKK

*Price provided by Norgine.

Abbreviations: AIP: Pharmacy purchase price, DKK: Danish krone, VAT: value added tax

Source: (European Medicines Agency 2023a)

In the base case, it was conservatively assumed that no vial sharing is allowed and therefore full drug wastage is accounted for. Note that the number of vials required per dose, including wastage, is calculated on a per patient basis before being combined into an average for all patients in the trial, and therefore the number of vials is not a whole number even when wastage is included. Taking this approach to calculate wastage at the patient-level is considered more accurate than calculating wastage at the cohort level, where the distribution of doses is not fully reflected.

In clinical practice, if only a small amount of a new vial is required, it is plausible that clinicians may not open the new vial after considering the associated cost and wastage, which is called dose-banding. Based on the input of a Danish clinical expert, this practice is not common in Denmark (Norgine 2025b). Regardless, the impact of assuming a dose-banding approach was tested via scenario analyses.

The mean number of doses and mean number of vials per dose (with and without wastage scenarios) are reported in Table 45.

Table 45 PEDMARQSI dose inputs used in the model

Trial	Average number of doses	Average number of 8 g PEDMARQSI vials per dose			
		Wastage (base case)	Wastage (new vial not opened if less than 10% required) (scenario)	Wastage (new vial not opened if less than 5% required) (scenario)	No wastage (scenario)
COG ACCL0431 (base case)	[redacted]				
SIOPEL-6 (scenario)	[redacted]				

Abbreviation: g: Grams

Sources: ([redacted])

11.2 Medicines– co-administration

Antiemetic medication should be given to all patients receiving cisplatin to prevent chemotherapy-induced nausea and vomiting. Similarly, the PEDMARQSI Summary of Product Characteristics (SmPC) recommends that antiemetics are given around 30 minutes prior to PEDMARQSI administration to reduce the chance of nausea and vomiting (Norgine 2023). Although the use of antiemetics was not recorded in COG ACCL0431 or SIOPEL-6, the costs of antiemetics are considered in the economic model base case given the recommendation for their use in the PEDMARQSI SmPC.

It is assumed that one dose of ondansetron and palonosetron each is required prior to each PEDMARQSI administration (in addition to the antiemetics administered for cisplatin). The choice of antiemetics is based on a Danish clinical expert opinion for the management of nausea and vomiting (Norgine 2025b). The average weight used for the purpose of dose calculations aligns with the trial data used to inform the efficacy of the model (COG ACCL0431 in the base case and SIOPEL-6 as a scenario) [redacted], European Medicines Agency 2023c).

Only data from localised patients was used to align with PEDMARQSI's licence.

Table 46 Antiemetic medication costs

	Strength	Pack size	Dose (mg/kg) *	Dose per administration (mg)	AIP excluding VAT, pr. Pack, DKK
Ondansetron	2mg/ml	5 x 4 ml	0.15	5.27	45
Palonosetron	50 microgram/ml	5 ml	0.02	0.70	40

* Dose mg/kg used in the model, based on patients weighing 35 kg on average.

Abbreviations: DKK: Danish krone, kg: kilogram, mg: milligrams, ml: milliliters.

Sources: Apotekets indkøbspris (Laegemiddelstyrelsen 2025b, Laegemiddelstyrelsen 2025a)

11.3 Administration costs

PEDMARQSI is administered intravenously as a 15-minute infusion, ideally through a central vein, six hours after the completion of every cisplatin infusion (Norgine 2023). Patients receiving PEDMARQSI are therefore already in hospital or a specialised oncology clinic for their cisplatin treatment, so no additional infrastructure is needed to administer PEDMARQSI.

In addition to the nurse time required for cisplatin treatment, it is assumed that an additional 30 minutes of hospital nurse time may be required to administer PEDMARQSI (15 minutes for infusion and 15 minutes for set up). Nurse time is estimated to cost 468 DKK per hour sourced from DMCs unit cost guideline and inflated to year 2024 (Medicinrådet 2024).

No additional resource costs are required for the administration as patients are already receiving IV cisplatin treatment for their cancer.

11.4 Disease management costs

Disease management costs in the model include the cost of hearing assessments, HL management (hearing aids, cochlear implants), speech and language therapy costs, and the costs associated with depression and anxiety. Inputs for health state costs are largely based on an SLR sourcing for inputs to the health economic model, detailed in Appendix J.

Table 47 summarizes all disease management costs included in the model. See Appendix L where the different disease management inputs are described in detail.

Table 47 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Hearing assessment	Age and health state dependent	289	N/A	Takstkort 11A, Øre-, næse- og halsspecialet, Legeaudiometri (høreprøve for børn)
Speech and language therapy costs	1 month to <18 years, Marked and Severe HL once a week. >18 years Severe HL annually	1,286	03MA09	Interaktiv DRG: Diagnose: DH906: Dobbeltsidigt blandet konduktivt og perceptivt høreta b. Procedure: ZZ0190E: Tværfaglig logopædisk konference med patienten til stede
Hearing aid	Every fifth year	17,980 (8,990*2)	N/A	(AudioNova 2025)
Fitting of hearing aid	Every fourth year	1,286	03MA09	Interaktiv DRG: Diagnose: DH919: Høretab UNS. Procedure: BDDD6: Tilpasning af høreapparat
Follow-up of hearing aid	Annual	1,286	03MA09	Interaktiv DRG: Diagnose: DH919: Høretab UNS. Procedure: BDDD6: Tilpasning af høreapparat
Initial cost of bilateral cochlear implant (including external processor)	Once	114,373	03MP02	Interaktiv DRG: Diagnose: DH919. Procedure: KDFE00: Indsættelse af implantat i cochlea In the model the cost is doubled to account for implant in both ears.
Initial cost of fitting bilateral cochlear implant	Once	134,393	03PR07	DRG: 03PR07, Takst 134393 Udskiftning af processor i cochlear implantat, dobbeltsidigt
Annual cost of maintenance and programming	Annual	1,159	03PR09	Interaktiv DRG: DH919: Høretab UNS. Procedure: BDDD62: Indstilling og justering af cochlea-implantat

Replacement external processor cost	Every fifth year	134,393	03PR08	DRG: 03PR07, Takst 134393 Udskiftning af processor i cochlear implantat, dobbeltsidigt
Depression	Included first year	26,633	19MA08	DRG Takster 2025: 19MA08: Sindslidelser hos børn

Abbreviation: DKK: Danish krone, DRG: Diagnosis Related Group, N/A: not applicable

Sources: (Sundhedsdatastyrelsen 2025, Laeger.dk 2024)

11.5 Costs associated with management of adverse events

As described in the Section 9, the base case includes PEDMARQSI treatment-related SAEs occurring in ≥2% of patients sourced from COG ACCL0431, but no AEs met this criterion. Hence, a scenario analysis of PEDMARQSI treatment-related SAEs occurring in ≥2% sourced from SIOPEL-6, and AEs graded CTCAE Grade ≥3 and occurring in ≥10% in either arm sourced from COG ACCL0431, see Appendix K.3.2 for full description.

11.6 Subsequent treatment costs

No subsequent treatment is relevant to include in the health economic model.

11.7 Patient costs

Patient costs were estimated by the time spent due to administration and visits and transportation costs (round trip) (Medicinrådet 2024).

Patients and caregivers time were valued based on the average hourly wage for an employee in Denmark after tax. Based on LONS20 in Denmark Statistics' Statistical Bank, inflated to 2024 the cost is estimated to be 205 DKK per hour. In addition to the time spent, expenses for transport to and from the treatment was included in the analysis. The valuation of transport costs was based on the Danish state's tax-free mileage allowance of 3.79 DKK per km in 2024. The Medicines Council assumes that the distance to a hospital was 20 km by driving distance, corresponding to a transport cost to and from hospital treatment of approximately 152 DKK.

Patient costs and transportation costs were sourced from the DMC's guidance (Medicinrådet 2024). The costs and resource use applied in the analysis are presented in Table 48 below.

Table 48 Patient costs used in the model

Activity	Time spent	Unit cost (DKK)
Visit	1 hours (per patient)	191 per hour
Round trip	N/A	152 per round trip

Abbreviations: DKK: Danish krone, N/A: Not applicable

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable for this application.

12. Results

12.1 Base case overview

Base case settings for the cost-effectiveness model are presented in Table 49 below.

Table 49 Base case overview

Feature	Description
Comparator	Cisplatin treatment without PEDMARQSI
Type of model	One-year initial decision tree, from year 2 onwards a Markov model
Time horizon	91.40 years (lifetime)
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	HRQoL measured with HUI3 in study Barton et al (Barton et al. 2006). Danish population weights were used to estimate age-adjusted health-state utility values
Costs included	Treatment costs; Management costs; Depression and anxiety costs; Adverse event costs; Transportation costs; Patient costs
Dosage of medicine	Based on weight
Average time on treatment	Intervention: within 1 year; Comparator: 0
Parametric function for PFS	Intervention: N/A; Comparator: N/A
Parametric function for OS	Intervention: N/A; Comparator: N/A
Inclusion of waste	Yes
Average time in model health state with PEDMARQSI	
Minimal/No HL	35.8 years
Mild HL	11.0 years
Moderate HL	2.6 years
Marked HL	0.2 years
Severe HL	0.4 years

Dead	50 years
Average time in model health state without PEDMARQSI	
Minimal/No HL	22.1 years
Mild HL	11.4 years
Moderate HL	13.4 years
Marked HL	1.0 years
Severe HL	2.1 years
Dead	50.0 years

Abbreviations: HRQoL: Health-related quality of life, OS: overall survival, PFS: progression-free survival

12.1.1 HRQoL Results

When not adjusting for the effects of other variables, average health utility decreased with less favourable AHL (see Section 10) (Barton et al. 2006).

Table 50 Estimated levels of utility Barton et al (2006)

	Moderate (AHL 40-70 dB)	Severe (AHL 71-95 dB)	Profound (AHL 96-105 dB)	Profound (AHL >105 dB)	Implanted
HUI3 score (95% CI) N	0.677 (0.652-0.702) 260	0.616 (0.598-0.634) 464	0.497 (0.469-0.525) 259	0.353 (0.327-0.379) 290	0.575 (0.553-0.598) 403

Abbreviations: AHL: Average hearing level, CI: confidence interval, dB: Decibel, HUI3: Health Utilities Index Mark 3.

Source: (Barton et al. 2006)

12.1.2 Base case results

Base case results are presented in Table 51 below. The results demonstrate that, compared with cisplatin without PEDMARQSI, cisplatin with PEDMARQSI is associated with a QALY gain of 1.449. This suggests a substantial improvement in QoL in children receiving cisplatin chemotherapy. This benefit is associated with incremental costs of 849,931 DKK per patient over a lifetime, translating into an incremental cost-effectiveness ratio (ICER) of 586,536 DKK.

Table 51 Base case results, discounted estimates, DKK

	PEDMARQSI	Without PEDMARQSI	Difference
Treatment costs	923,890	0	923,890
Management costs	28,566	94,493	-65,927

	PEDMARQSI	Without PEDMARQSI	Difference
Depression and anxiety costs	4,186	4,550	-365
Adverse event costs	0	0	0
Transportation/ Patient costs	2,800	10,467	-7667
Total costs	**959,442**	**109,511**	**849,931**
Total life years	**20.724**	**20.724**	**0**
Minimal/no HL	13.122	8.167	4.955
Mild HL	3.425	3.543	-0.118
Moderate HL	0.670	3.525	-2.854
Marked HL	0.048	0.250	-0.203
Severe HL	0.078	0.409	-0.331
Total QALYs	**17.343**	**15.894**	**1.449**
Incremental costs per life year gained		**N/A no LY gain**	
Incremental cost per QALY gained (ICER)		**586,536**	

Abbreviations: DKK: Danish krone, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year

12.2 Sensitivity analyses

To explore uncertainty around the base case deterministic sensitivity analysis (DSA), probabilistic sensitivity analyses (PSA), scenario analyses was performed according to DMC guidelines.

12.2.1 Deterministic sensitivity analyses

Percentages of patient with or without Minimal/no HL have the largest impact in the one-way sensitivity analysis. Deterministic one-way analysis was conducted to test the impact of individual parameters when their values are set to the lower and upper limits of the CIs (Table 52) whilst all other parameters are maintained at the base case setting. If the variance in any inputs was not available, a simplified assumption was made assuming that the standard error (SE) was 20% of the mean value.

Table 52 presents the 10 parameters which had the largest impact on the ICER, and these results are also represented in a tornado plot in Figure 8.

The percentage of patients with Minimal/no HL in the cisplatin with PEDMARQSI treatment arm had the largest impact on the ICER followed by the percentage of patients with Minimal/no HL in the cisplatin without PEDMARQSI arm. Other parameters had a marginal impact on the ICER when varied between their upper and lower bounds.

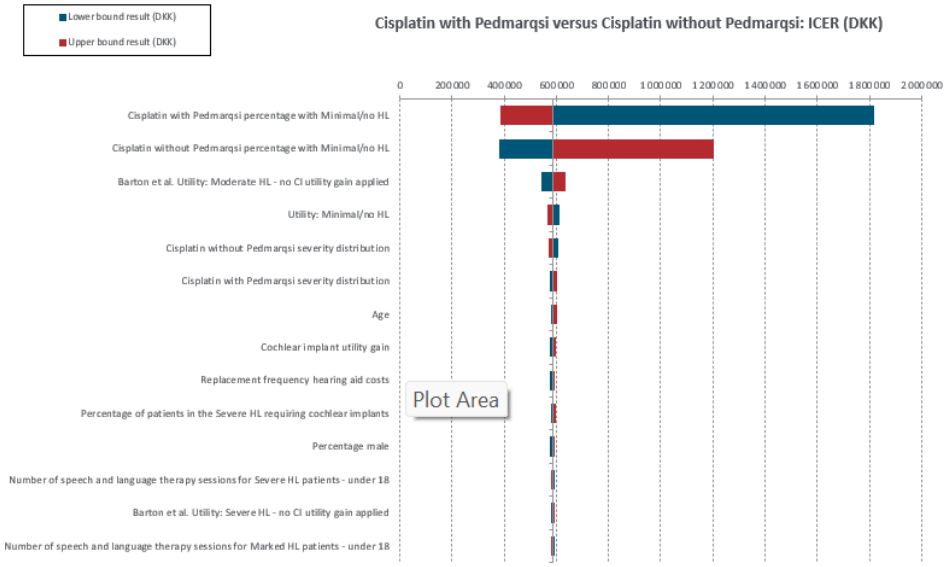
Table 52 One-way sensitivity analyses results (DKK)

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					586,536
Cisplatin with PEDMARQSI percentage with Minimal/no HL: 0.714	HL: 0.40/0.94	Lower bound/Upper bound of CI	884,846/824,839	0.49/2.14	1,809,712/385,606
Cisplatin without PEDMARQSI percentage with Minimal/no HL 0.436	0.27/0.61	Lower bound/Upper boundof CI	818,813/882,495	2.13/0.73	383,943/1202,754
Mortality probability - year 1: 0.078	0.011/0.203	Lower bound/Upper bound of CI	844,521/859,901	1.56/1.25	543,080/685,875
Barton et al. Utility: Moderate HL - no CI utility gain applied: 0.677	0.652/0.702	Lower bound/Upper bound of CI	849,931/849,931	1.56/1.34	545,078/633,788
Utility: Minimal/no HL 0.92	0.91/0.93	Lower bound/Upper bound of CI	849,931/849931	1.40/1.50	608,666/566,974
Cisplatin without PEDMARQSI severity distribution	Health state severity distribution	Lower bound/Upper bound of CI	841,673/827,174	1.42/1.48	592,439/560,340
Cisplatin with PEDMARQSI severity distribution	Health state severity distribution	Lower bound/Upper bound of CI	831,019/837,646	1.47/1.43	564,297/587,680
Age: 8.60	7.30/10.00	Lower bound/Upp	847,053/856,084	1.46/1.42	579,799/602,230

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
		er bound of CI			
Mortality probability - year 3: 0.032	0.019/0.048	Lower bound/Upper bound of CI	849,150/850,902	1.47/1.43	578,923/596,263
Cochlear implant utility gain: 0,183	0,13/0,243	Lower bound/Upper bound of CI	849,931/849,931	1.47/1.43	578716/595648

Abbreviations: CI: confidence interval, HL: hearing loss, ICER: incremental cost-effectiveness ratio, DKK: Danish krone, QALY: quality-adjusted life year

Figure 8 Tornado plot cisplatin with PEDMARQSI versus cisplatin without PEDMARQSI



Abbreviations: CI: confidence interval, HL: hearing loss, ICER: incremental cost-effectiveness ratio, DKK: Danish krone

12.2.2 Probabilistic sensitivity analyses

Joint parameter uncertainty was explored through a PSA where all parameters are assigned probability distributions and varied jointly. A summary of the base case variables applied in the economic model and their associated distribution that was applied in the PSA analysis can be viewed in detail in Appendix G. If variance in any inputs was not available, a simplified assumption was made assuming that the SE was 20% of the mean value. PSA was run for 10,000 iterations, by which point, results had stabilised and therefore considered reliable to explore the uncertainty.

The mean results from the probabilistic analysis are presented in Table 52 and the incremental cost-effectiveness plane (ICEP) in Figure 9. The probabilistic results show consistency with the deterministic analysis, providing a mean incremental QALY of 1.443 at an incremental cost of 849,007 DKK resulting in an ICER of 588,412 DKK. As shown in Figure 9, the majority of iterations lie in the North-East quadrant demonstrating a positive QALY gain and confirming the clinical benefit of cisplatin with PEDMARQSI versus cisplatin without PEDMARQSI.

Table 53 Mean PSA results

Technologies	Total		Incremental		ICER (DKK/QALY)
	Costs (DKK)	QALYs	Costs (DKK)	QALYs	
Cisplatin without PEDMARQSI	111,406	15.881	849,007	1.443	588,412
Cisplatin with PEDMARQSI	960,413	17.324			

Abbreviations: ICER: Incremental cost-effectiveness ratio, DKK: Danish krone, PSA: probabilistic sensitivity analysis, QALY: Quality-adjusted life year

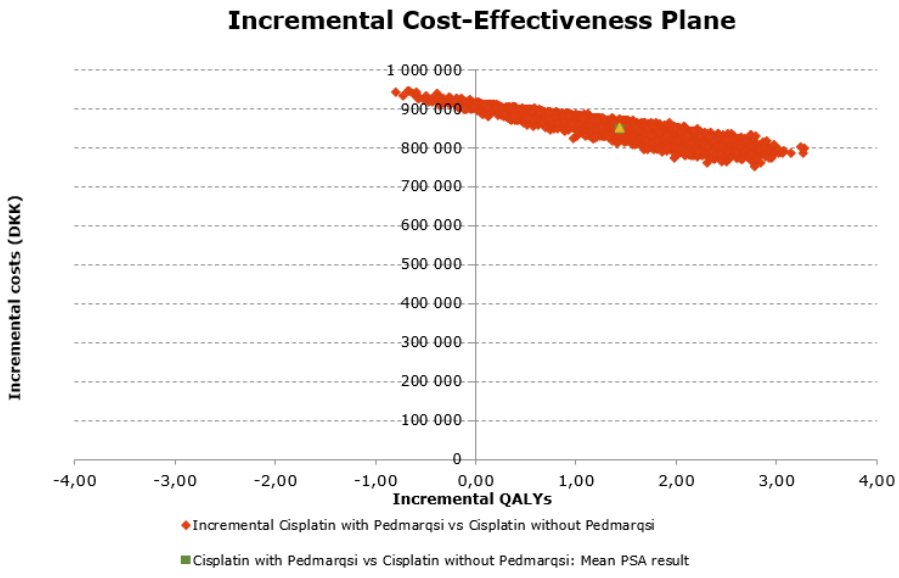


Figure 9 Incremental cost-effectiveness plane

Abbreviations: DKK: Danish krone, PSA: probabilistic sensitivity analysis, QALY: quality-adjusted life year

Figure 10 presents the cost-effectiveness acceptability curve for cisplatin with PEDMARQSI versus cisplatin without PEDMARQSI that shows a 50% probability of with PEDMARQSI to be considered cost effective at a willingness to pay threshold at 600,000 DKK per QALY. The results from some iterations of the PSA lie in the North-West quadrant of the ICEP, suggesting cisplatin with PEDMARQSI is associated with fewer

QALYs and increased costs compared with cisplatin without PEDMARQSI. This is caused through varying two parameters in the PSA: the percentage of patients assigned to the Minimal/no HL health state in the cisplatin with PEDMARQSI arm, and the percentage of patients assigned to the Minimal/no HL health state in the cisplatin without PEDMARQSI arm of the model.

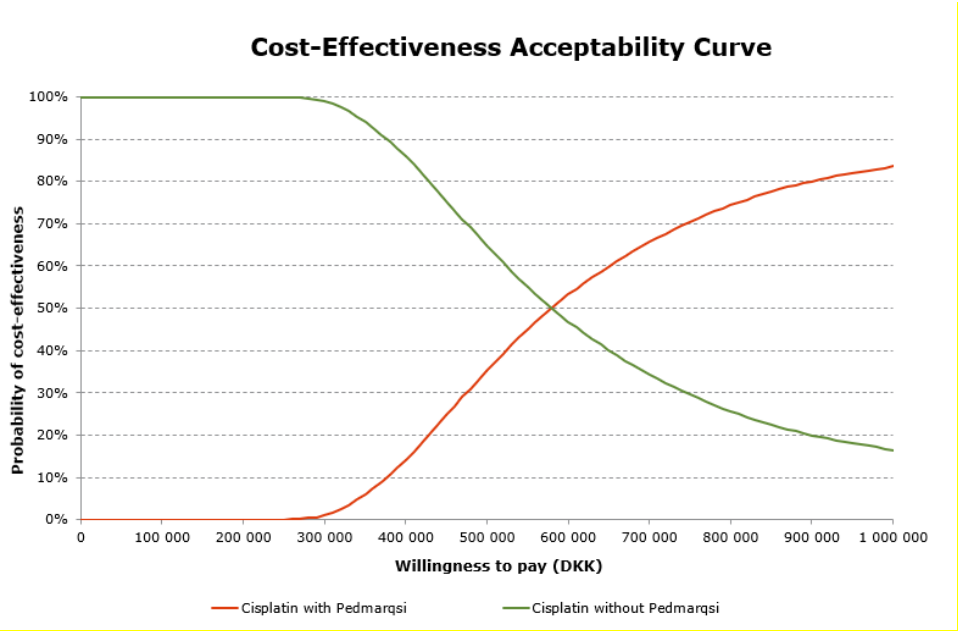


Figure 10 Cost-effective acceptability curve

Abbreviations: DKK: Danish krone

By varying these parameters simultaneously, it causes an artifact whereby in some iterations, the cisplatin without PEDMARQSI arm becomes more efficacious at preventing cisplatin-induced HL than the cisplatin with PEDMARQSI arm, which is implausible based on the available evidence.

12.2.2.1 Scenario analysis

To further explore uncertainty around the base case assumptions and to highlight additional value not captured in the base case, a set of scenario analyses were undertaken. Cisplatin-induced ototoxicity has a significant negative impact on diagnosed patients and caregivers. As such, in addition to direct costs, a scenario was explored to consider the societal impact of cisplatin-induced ototoxicity.

The loss of productivity due to HL was calculated from the age of 18 until the pension age of 67 years in Denmark, and was based on the expected relative reduction in working time for patients (sourced Dionne et al. (2012)), and the average full-time and part-time salary in Denmark. Part-time salary was assumed to be 50% of the full-time salary. The results of this societal scenario analysis are provided in Table 54. Data on percentage of people employed in the labour force (77.20%) was sourced from Statistics

Denmark and the number of individuals with a part-time employment was estimated to be 22.0% (Statistics Denmark 2024, Eurostat 2024).

Until the age of 18, there is a large accumulated societal cost based on the parent's need to accompany their children to health care visits. To avoid counting these costs twice, these costs are not applied as productivity loss, but as patient time costs and transportation costs described more in detail in Section 11.7. The largest deviation from the base case ICER came from changing the perspective from limited societal perspective to a societal perspective, excluding or lowering wastage costs, and changing the source for clinical efficacy as can be seen in Table 54.

The scenarios analyses performed in this section show that the base case settings should be considered conservative since the base case does not consider societal costs.

Table 54 Scenario analyses

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case					586,536
Discount rate: 0-39 years 4.00% 40-74 years 3.00% 75 year+ 2.00%	0%	Discount factor effect on ICER	788,452	3.481	226,507
	1%		815,013	2.585	315,252
	6%		866,064	0.966	896,235
Source for clinical efficacy: COG ACCL0431 efficacy population, Hearing loss was identified in 28.6% with PEDMARQSI and 56.4% without PEDMARQSI	SIOPEL-6 mITT	To explore efficacy source uncertainty	644,532	1.943	331,760
Source for HL severity:	SIOPEL-6	To explore severity distribution	840,911	1.255	670,082

Orgel et al. combined with Knight et al.		source uncertainty			
	Orgel et al. combined with SIOPEL-6	To explore severity distribution source uncertainty	824,355	1.451	567,995
The HRQoL in the base-case analysis is informed by Barton et al. (2006)	Gumbie et al, 2022	To explore QoL source uncertainty	849,931	1.179	721,146
Model cure assumption at year 10: No	Yes	Exploring mortality uncertainty in the model	847,005	1.553	545,509
Wastage: included	excluded	Explore impact of wastage assumptions	514,742	1.449	355,223
	New vial not costed for if less than 10% required		733,127	1.449	505,930
	New vial not costed for if less than 5% required		759,083	1.449	523,842
Cost of additional antiemetics: Included	Excluded		849,087	1.449	585,954
PEDMARQSI treatment-related serious AEs occurring in ≥2% of patients	Grade 3+ AEs occurring in ≥ 10% of patients in either arm		849,409	1.448	586,475

Limited societal perspective including patient time and transportation costs	Societal perspective	Large effects outside of Guideline framework not considered in base case	740,782	1.449	511,213

Abbreviations: AE: adverse event, HL: hearing loss, HRQoL: health-related quality of life, ICER: incremental cost-effectiveness ratio, mITT: modified intent-to-treat, DKK: Danish krone, QALY: quality-adjusted life year.

13. Budget impact analysis

The relevant population for the budget impact analysis are children between the ages of 1 month and <18 years with localised, solid tumours receiving cisplatin treatment. Since PEDMARQSI is taken in connection with cisplatin, to prevent ototoxicity induced HL, it automatically eliminates the prevalent population. Therefore, the eligible population is based on incidence statistics.

13.1 Eligible population calculation

PEDMARQSI is only administered alongside cisplatin, and the average time on treatment for children with localised cancer undergoing cisplatin chemotherapy is less than one year, irrespective of tumour type. This timeframe of cisplatin treatment was validated by clinician feedback and is also demonstrated by the duration of treatment in COG ACCL0431 (median of 15 weeks for patients across both treatment arms) (Food and Drug Administration 2022, Norgine 2025a). As such, the eligible population for PEDMARQSI is determined by estimating the annual number of incident paediatric cancer patients receiving cisplatin. The eligible Danish patient population for PEDMARQSI was estimated to be 22 patients. To adhere to DMC recommendation of outlining the calculation steps used to determine the final eligible population, this section presents the steps undertaken. Additionally, international epidemiological data applied to the Danish population is included to corroborate the results.

The calculations are based on cancer incidence data for children, teenagers, and young adults (CTYA) in the UK from 2012 to 2016, as well as peer-reviewed sources (N.H.S. England 2021a), which were then adapted to the Danish total population (see Table 55). These rates can be used to estimate the current incidence rates, since the report shows that the incidence rate of each tumour has remained stable over time. To calculate the incidence, the nine most common paediatric solid tumours treated with cisplatin were considered from the most recent CTYA data cut (2012-2016) (N.H.S. England 2021b).

The annual incidence rate of key paediatric solid cancers treatable with cisplatin was determined by dividing the number of patients in the target population (patients aged <18 years diagnosed with solid tumours as detailed in Table 55 notes [*]) by the number of years the data covers, expressed as a fraction of the total population of England and

Wales (N.H.S. England 2021a, Office of National Statistics 2023). The CTYA UK cancer incidence statistics are grouped by age categories of 0-19 years, meaning calculations were applied to reduce the population size to be reflective of only the population aged under 18 years in England and Wales, and is calculated to be 0.0008% of the total population. The percentage of patients with localised disease for each tumour type was sourced from peer-reviewed literature and averaged, resulting in an average of 64.6% (Youlden et al. 2019, Freyer et al. 2017, Chen et al. 2021, Meel et al. 2012). In the absence of published data for each paediatric localised tumour type, it was assumed that 70% of paediatric patients with localised cancers will receive a chemotherapy regimen containing cisplatin and therefore be eligible for PEDMARQSI (Table 55). The results were validated by a Danish clinical expert input [redacted]).

Table 55 Eligible population for PEDMARQSI

Stratification	Input value	Number of patients	Reference
Total population in Denmark	5,947,000		(Statistics Denmark 2025)
Annual incidence of key paediatric, solid cancers that can be treated with cisplatin*	0.0008%	49	(N.H.S. England 2021a) (Office of National Statistics 2023)
% with localised disease**	64.6%	31	(Youlden et al. 2019, Freyer et al. 2017, Chen et al. 2021, Meel et al. 2012, N.H.S. England 2021a)
% treated with cisplatin	70.0%	22	Based on the assumption that, across all cancer sub-types, 70% of patients are treated with cisplatin. This assumption was confirmed by a Danish clinical expert ([redacted].
Year 1 incident population eligible for treatment		**22**	

* Includes patients aged >18 years. Tumour types included are intracranial and intraspinal tumours, ependymomas, neuroblastomas, retinoblastomas, hepatoblastomas, osteosarcomas, malignant extracranial germ cell tumours, malignant gonadal germ cell tumours, and nasopharyngeal carcinoma.

** Regarding the tumour types described for the annual incidence of key paediatric cancers that can be treated with cisplatin.

Sources: (N.H.S. England 2021a, Youlden et al. 2019, Freyer et al. 2017, Chen et al. 2021, Statistics Denmark 2025)

Table 56 presents the expected number of paediatric patients eligible for PEDMARQSI over a 5-year period and the number of new patients expected to be treated over the next five-year period if the medicine is introduced (including assumptions of market

share). It is assumed that the eligible population will grow in each year of the model, in line with the growth rate of the Danish population at 0.74% (Trading Economics 2025). Life expectancy of the eligible population is variable dependent on the year of the model. In the first five years of the model, OS data from the COG ACCL0431 study is used.

Table 56 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
With PEDMARQSI	4.9	9.4	15.0	15.1	15.2
Without PEDMARQSI	17.1	12.8	7.3	7.4	7.4
			Non-recommendation		
With PEDMARQSI	0	0	0	0	0
Without PEDMARQSI	22.0	22.2	22.3	22.5	22.7

Table 57 presents the expected budget impact of introducing PEDMARQSI at the list price without indirect costs included. The budget impact in year five is 13.8 million DKK.

Table 57 Expected budget impact of recommending the medicine for the indication, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	4,801,793	9,014,862	14,285,672	14,473,644	14,660,497
The medicine under consideration is NOT recommended	318,613	454,000	586,334	727,076	865,310
Budget impact of the recommendation, DKK	4,483,180	8,560,862	13,699,338	13,746,569	13,795,187

Abbreviations: DKK: Danish krone

14. List of experts

Table 58 List of experts

Name	Job function	Work place
[redacted]	[redacted]	[redacted]

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Appendix A. Main characteristics of studies included

Table 59 Main characteristic of studies included

15.1	Trial name: Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy	NCT number: NCT00716976
Objective	The trial's objective was to evaluate effectivity and safety of PEDMARQSI for the prevention of cisplatin-induced ototoxicity in paediatric patients with solid tumours.	
Publications – title, author, journal, year	Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B, Pollock BH, Ramdas J, Lange B, Van Hoff D, VanSoelen ML, Wiernikowski J, Neuwelt EA, Sung L. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017 Jan;18(1):63-74. Orgel E, Villaluna D, Krailo MD, Esbenshade A, Sung L, Freyer DR. Sodium thiosulfate for prevention of cisplatin-induced hearing loss: updated survival from ACCL0431. Lancet Oncol. 2022 May;23(5):570-572. Orgel E, Knight KR, Villaluna D, Krailo M, Esbenshade AJ, Sung L, Freyer DR. Reevaluation of sodium thiosulfate otoprotection using the consensus International Society of Paediatric Oncology Ototoxicity Scale: A report from the Children's Oncology Group study ACCL0431. Pediatr Blood Cancer. 2023 Jul 7:e30550.	
Study type and design	The trial was a multicentre, randomised, open-label, phase 3 trial. Patients were randomly assigned 1:1. Allocation sequences were generated using a permuted block algorithm with balanced 2:2 randomizations per block. The randomisation was stratified by prior cranial irradiation (yes vs no); and for children without prior cranial irradiation, randomisation was further stratified by age (< 5 years vs ≥ 5 years) and duration of cisplatin infusion (< 2 hours vs ≥ 2 hours). Randomisation was blinded for central reviewers of audiometry data, but the study was open-label for children and treating physicians ([redacted], European Medicines Agency 2023b).	
Sample size (n)	125 eligible patients (out of 131 enrolled children)	
Main inclusion criteria	• Aged > 1 year and < 18 years • Newly diagnosed with any histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma,	

15.1	Trial name: Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy	NCT number: NCT00716976

	osteosarcoma, or other malignancy that was to be treated with cisplatin chemotherapy • Newly diagnosed with any histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy that was to be treated with cisplatin chemotherapy • Children not enrolled in any other COG study for their disease-specific treatment • Children who have not had previous platinum-based chemotherapy
Main exclusion criteria	• Females of child-bearing age must not have been pregnant. Females with germ cell tumours, which occasionally result in false-positive pregnancy tests, may have been enrolled, provided pregnancy was ruled out by other tests • Children must not have had any previous hypersensitivity to PEDMARQSI or other thiosulfate agents • Children must not have been enrolled in any COG therapeutic study for treatment of the underlying malignancy
Intervention	61 patients (treatment arm) received a 15-minute PEDMARQSI infusion which was administered 6 hours after each cisplatin treatment. Patients received an anti-emetic premedication 30 minutes prior to PEDMARQSI.
Comparator(s)	64 patients received cisplatin only treatment throughout their chemotherapeutic treatment protocol.
Follow-up time	Median follow-up of 3.5 years (range 1.4-4.5) Participating institutions were to follow all patients for 10 years from the date that the patient started the study, monitoring relapse, survival, and development of subsequent malignant neoplasm, regardless of protocol violation ([redacted], European Medicines Agency 2023b).
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	The primary endpoint was the incidence of HL. Although the trial was open-label due to the emergence of treatment-related side effects during infusion, blinded assessment of the primary endpoint was feasible and thus offsets any introduction of bias resulting from open-label trial status ([redacted], European Medicines Agency 2023b). Secondary endpoints were the change in hearing thresholds for key frequencies (500 hz, 1000 hz, 2000 hz, 4000 hz, 8000 hz), renal- and

15.1	Trial name: Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy	NCT number: NCT00716976

	haematological toxicity, event-free survival, overall survival, and HL among patients carrying/not-carrying two key gene mutations (TPMT and COMT). Results regarding HL among patients carrying/not-carrying two key gene mutations was not included in this application.
Method of analysis	The primary endpoint was development of HL according to ASHA criteria when the audiometric evaluation at enrolment ("baseline") was compared to the first evaluation conducted at least 4 weeks following the final dose of cisplatin ("post-treatment"). The magnitude of the association between STS assignment and HL was estimated using the odds ratio (OR), p-values for the test of OR=1, and corresponding 95% confidence interval (95%CI) derived using the Wald test for the parameter associated with the randomised treatment assignment from a logistic model. The logistic model was stratified according to the strata used for randomisation described above. Stratum-specific probabilities of HL were estimated by the observed proportion of evaluable participants in the particular stratum with HL; exact 95%CI were also calculated. For frequency-specific HL, the mean change for the randomisation group was determined and the hypothesis of no difference between groups was assessed using the Wilcoxon two sample test for non-parametric data. A one-sided p-value ≤ 0.05 was considered significant; no adjustment for multiple comparisons was made for this exploratory assessment. For renal and haematological toxicity, denominators represent the number of participants who completed the required toxicity assessment during each cycle. For both, the hypothesis of no difference in incidence was assessed using a χ^2 test of proportions. For OS and EFS, the probability of remaining event-free as a function of time post-enrolment was estimated by the method of Kaplan and Meier. Risk of event was compared across groups defined by randomised regimen using the log-rank statistic. Relative hazard ratios (RHR) and 95%CI were generated by fitting a RR regression model using partial likelihood where the model contained the characteristic of interest as the only variable. Survival estimates were computed as 3-year EFS and OS. All eligible participants were considered in the survival analyses. The outcome of each participant was associated with that participant's randomised treatment assignment (ITT).
Subgroup analyses	The COG ACCL0431 trial carried out a pre-specified subgroup analysis on the proportion of children with cisplatin-induced HL who were < 5 years of age compared with those ≥ 5 years of age. For the analysis comparing the proportional incidence of HL between both arms, HL was treated as a dichotomous variable (as defined by ASHA criteria via comparison of the baseline and 4-week follow-up evaluations). A logistic regression model was used to evaluate if there was any association between PEDMARQSI treatment and HL when adjusting for

15.1	Trial name: Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy	NCT number: NCT00716976
	the stratification variables. The odds ratio with associated 95% CI and p-value for the between-treatment comparison was estimated.	
Other relevant information	None.	

15.2	Trial name: Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III Childhood Liver Cancer (SIOPEL-6)	NCT number: NCT00652132
Objective	The trial's objective was to evaluate effectivity and safety of PEDMARQSI for the prevention of cisplatin-induced ototoxicity in paediatric patients with hepatoblastoma.	
Publications – title, author, journal, year	Brock PR, Maibach R, Childs M, Rajput K, Roebuck D, Sullivan MJ, Laithier V, Ronghe M, Dall'Igna P, Hiyama E, Brichard B, Skeen J, Mateos ME, Capra M, Rangaswami AA, Ansari M, Rechnitzer C, Veal GJ, Covezzoli A, Brugières L, Perilongo G, Czauderna P, Morland B, Neuwelt EA. Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. N Engl J Med. 2018 Jun 21;378(25):2376-2385.	
Study type and design	The trial was a multicenter, randomised, controlled, open-label study conducted by the International Childhood Liver Tumor Strategy Group (SIOPEL) to assess the efficacy and safety of PEDMARQSI in reducing ototoxicity in children receiving cisplatin chemotherapy for standard risk hepatoblastoma. Eligible study participants were children aged 1 month to <18 years with histologically confirmed newly diagnosed standard risk hepatoblastoma. During the screening phase, children were randomised 1:1 to receive PEDMARQSI after each cisplatin dose (cisplatin with PEDMARQSI arm) or to receive cisplatin without PEDMARQSI. This randomisation was stratified by country, median age (above vs below 15 months), and pre-treatment tumour extension (PRETEXT) classification (I and II vs III).	
Sample size (n)	109 patients. [A total of 129 children were registered, 114 of which were randomised in the study. (European Medicines Agency 2023b, [redacted]). Of the 114 children randomised, 5 were not treated (2 children were withdrawn due to parental consent, 2 children were reclassified as high-risk, and 1 child was ineligible for treatment).]	

15.2	Trial name: Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III Childhood Liver Cancer (SIOPEL-6)	NCT number: NCT00652132
Main inclusion criteria	• Aged > 1 month and < 18 years • Newly diagnosed, histologically confirmed hepatoblastoma • Standard-risk hepatoblastoma: PRETEXT I, II or III, serum AFP > 100 µg/L, no additional PRETEXT criteria	
Main exclusion criteria	• Hepatocellular carcinoma • Treatment starting more than 15 days from written biopsy report • High-risk hepatoblastoma • Abnormal renal function	
Intervention	57 patients (treatment arm) received a 15-minute PEDMARQSI infusion which was administered 6 hours after each cisplatin treatment. Patients received an anti-emetic premedication 30 minutes prior to PEDMARQSI.	
Comparator(s)	52 patients received cisplatin only treatment throughout their chemotherapeutic treatment protocol.	
Follow-up time	Median follow-up of 4.27 years (3.11 to 5.82 years) in the per-protocol population. The follow-up time was similar between the cisplatin with PEDMARQSI (4.55 years) and cisplatin without PEDMARQSI (4.17 years) arms. The follow-up time in the total population was 52 months.	
Is the study used in the health economic model?	No. Although the study supports the application with evidence about the effectiveness of PEDMARQSI in paediatric cancers, the study's focus on hepatoblastoma and its associated patient demographics would cause a shift of inputs towards this patient group.	
Primary, secondary and exploratory endpoints	The primary endpoint was the proportional incidence of HL, defined as Brock Grade ≥ 1 HL. Secondary end points were the response to preoperative chemotherapy, percentage of children per disease status, event-free survival, overall survival, toxic effects, long-term renal clearance or glomerular filtration rate, and the feasibility of central audiologic review. In this application, outcomes were included via scenario analyses.	
Method of analysis	The primary endpoint was the proportional incidence of HL, defined as Brock Grade ≥ 1 HL, determined of the better ear by PTA after the end of treatment or at age ≥ 3.5 years (whichever timepoint was later). As a method of censoring patients, children without a HL assessment were counted as a failure (i.e. had HL) in this analysis.	

15.2	Trial name: Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III Childhood Liver Cancer (SIOPEL-6)	NCT number: NCT00652132

	OS was calculated from the time of randomisation to death (relating to the underlying cancer). OS was graphically compared between the randomised groups by Kaplan-Meier plots. A stratified log-rank test was calculated and stratified by the stratification factors used for randomisation. The hazard ratio between the two groups was calculated by stratified Cox regression and was presented together with its asymmetrical 95% confidence interval (CI) ([redacted], European Medicines Agency 2023b). Event-free survival was calculated from the time of randomisation to the first of the following events: progression, relapse, second primary malignancy, or death (all relating to the underlying cancer). EFS was graphically compared between the randomised groups by Kaplan-Meier plots. A log-rank test was calculated, stratified by the 3 stratification factors used for randomisation. The hazard ratio between the 2 groups was calculated by stratified Cox regression and was presented together with its asymmetrical 95% CI. The percentage of children per disease status was measured for complete remission, partial remission, stable disease, progressive disease (all relating to the underlying cancer), and children who were not evaluable (presented overall and by randomised group). Long-term renal clearance was defined as a calculated creatinine clearance of ≥ 60 mL/min/1.73m^2 (a value less than this was considered as being of clinical concern). The log10 change in AFP from baseline to any later assessment as well as the change from nadir to a higher value (indicative of tumour progression) were evaluated on a per child level as a biomarker assessment of hepatoblastoma response and remission status.
Subgroup analyses	None
Other relevant information	None

Abbreviations: AFP: alpha-fetoprotein, ASHA: American Speech Language and Hearing Association, CI: confidence interval, EFS: event-free survival, HL: hearing loss, ITT: intent-to-treat, L: litre, m^2: square meter, min: minute, mITT: modified intent-to-treat, mL: millilitre, OR: odds ratio, OS: overall survival, PTA: pure-tone audiometry, RHR: relative hazard ratio, RR: relative risk

Sources: (Freyer et al. 2017, Orgel et al. 2022, Orgel et al. 2023, Brock et al. 2018, [redacted], European Medicines Agency 2023b)

Appendix B. Efficacy results per study

Results per study

Table 60 Results per study

Results of COG ACCL0431 (NCT00716976)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Incidence of hearing loss	Cisplatin with PEDMARQSI	49	14 (28.57%)	-17	NR	NR	RR: 0.516	0.318, 0.839	0.004	A logistic regression model was used to evaluate if there was any association between STS treatment and HL when adjusting for the stratification variables. The OR with associated 95% confidence interval (CI) and p-value for the between-treatment comparison was estimated based on the model.	(Freyer et al. 2017, [redacted] European Medicines Agency 2023b)
	Cisplatin without PEDMARQSI	55	31 (56.36%)								
Severity of hearing loss (Mean	Cisplatin with PEDMARQSI	Value s are displa	Values are displayed in Table 64	Values are displayed in Table 64	NR	Values are displayed in Table 64	NR	NR	NR	Linear regression analyses were used to assess whether STS treatment reduced the	(Freyer et al. 2017, [redacted]

Results of COG ACCL0431 (NCT00716976)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
change in hearing threshold)		yed in Table 64								mean change in hearing thresholds when adjusting for stratification variables. Analyses were performed individually for each key frequency; no multiple comparison adjustment was made for these analyses.	[redacted]
	Cisplatin without PEDMARQSI	Values are displayed in Table 64	Values are displayed in Table 64								
Overall survival	Cisplatin with PEDMARQSI	61	43 (70.5%)	-9	NR	NR	HR: 1.79	0.86, 3.72	0.1132	Kaplan-Meier curves (and corresponding 95% CI) of OS for the 2 arms were estimated. As exploratory analyses, OS between the 2 arms were compared using log-rank tests. These analyses were performed at each scheduled interim monitoring during accrual and in follow-up after accrual was	(Freyer et al. 2017, [redacted]
	Cisplatin without PEDMARQSI	64	52 (81.3%)								

Results of COG ACCL0431 (NCT00716976)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										completed. Exploratory analyses of OS outcomes using Cox models with randomization stratification as covariates were performed.	
Event-free survival	Cisplatin with PEDMARQSI	61	34 (55.7%) Min/Max. (years): 0.6/8.3	NR	NR	NR	HR: 1.27	0.73, 2.18	0.3964	Kaplan-Meier curves (and corresponding 95% CI) of EFS for the 2 arms were estimated. As exploratory analyses, EFS between the 2 arms were compared using log-rank tests. These analyses were performed at each scheduled interim monitoring during accrual and in follow-up after accrual was completed. Exploratory analyses of EFS outcomes using Cox models with randomization stratification as covariates were performed.	(Freyer et al. 2017, [redacted]
	Cisplatin without PEDMARQSI	64	39 (60.9%) Min/Max. (years): 0.8/7.9								

Results of SIOPEL-6 (NCT00652132)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Rate of Brock grade ≥ 1 hearing loss	Cisplatin with PEDMARQSI	57	20 (35.1%)	-15	NR	NR	RR: 0.521	0.349, 0.778	< 0.001	A non-stratified Chi-square test was chosen to avoid any loss of power incurred by a stratified analysis. However, a Cochran-Mantel-Haenszel test stratified by factors used for the randomization was also performed, as specified in the SAP. In addition, the RR of HL in the CIS+STS arm compared with the CIS Alone arm was also calculated, and shown with an exact 95% CI (2.5% confidence limit to 97.5% confidence limit).	(Brock et al. 2018, [redacted] European Medicines Agency 2023b)
	Cisplatin without PEDMARQSI	52	35 (67.3%)								
Severity of hearing loss	Cisplatin with PEDMARQSI	55	Brock grade 0: 37 (67%) Brock grade 1: 10 (18%)	Brock grade 0: 20 Brock grade 1: -2 Brock grade 2: -5	NR	NR	NR	NR	NR	NR	(Brock et al. 2018)

Results of SIOPEL-6 (NCT00652132)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
			Brock grade 2: 6 (11%) Brock grade 3: 1 (2%) Brock grade 4: 1 (2%)	Brock grade 3: -4 Brock grade 4: 0							
	Cisplatin without PEDMARQSI	46	Brock grade 0: 17 (37%) Brock grade 1: 12 (26%) Brock grade 2: 11 (24%) Brock grade 3: 5 (11%) Brock grade 4: 1 (2%)								
Overall survival	Cisplatin with PEDMARQSI	57	55 (96.5%)	7	NR	NR	HR: 0.44	0.08, 2.41	0.332	OS was graphically compared between the randomized	(Brock et al. 2018,

Results of SIOPEL-6 (NCT00652132)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	Cisplatin without PEDMARQSI	52	48 (92.3%)							groups by Kaplan-Meier plots. A stratified log-rank test was calculated, stratified by the stratification factors used for randomization. The hazard ratio between the 2 groups was calculated by stratified Cox regression and was presented together with its asymmetrical 95% CI.	[redacted]
Event-free survival	Cisplatin with PEDMARQSI	57	46 (80.7%)	5		NR	NR	HR: 0.89	0.39, 2.05	0.785	EFS was graphically compared between the randomized groups by Kaplan-Meier plots. A log-rank test was calculated, stratified by the 3 stratification factors used for randomization. The hazard ratio between the 2 groups was calculated by stratified Cox regression and was	(Brock et al. 2018, [redacted])
	Cisplatin without PEDMARQSI	52	41 (78.8%)								

Results of SIOPEL-6 (NCT00652132)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										presented together with its asymmetrical 95% CI.	

Abbreviations: CI: confidence interval, EFS: event-free survival, HL: hearing loss, HR: hazard ratio, Hz: hertz, min/max: minimum/maximum, NR: not reported, OS: overall survival, RR: relative risk

Sources: (Brock et al. 2018, Freyer et al. 2017, [redacted]

B.1 Outcomes in COG ACCL0431 – detailed description

B.1.1 Primary endpoint: proportional incidence of hearing loss

The primary efficacy endpoint was the proportional incidence of HL between the cisplatin with PEDMARQSI arm and the cisplatin without PEDMARQSI arm, measured in the efficacy population. Based on analyses in the efficacy population, following the last dose of cisplatin, the proportion of children in the cisplatin with PEDMARQSI arm with HL (14 children, 28.6%) was approximately one-half of the proportion in the cisplatin without PEDMARQSI arm (31 children, 56.4%). The odds of having HL as defined by ASHA criteria were statistically significantly lower in the cisplatin with PEDMARQSI arm compared with the cisplatin without PEDMARQSI arm, when adjusted for the stratification variables of prior cranial irradiation (yes vs no), age subgroup (< 5 years or ≥ 5 years), and duration of cisplatin infusion (< 2 vs ≥ 2 hours) (Table 61) (Freyer et al. 2017, [redacted].

Table 61 Summary of hearing loss (COG ACCL0431 efficacy population)

Results	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)
n	55	49
Yes, n (%)	31 (56.4)	14 (28.6)
No, n (%)	24 (43.6)	35 (71.4)
Relative risk (95% CI)[†]	0.516 (0.318, 0.839)	
P-value[†]	0.004	

[†]Based on logistic regression including treatment and stratification variables as covariates in the model.

Abbreviations: CI: confidence interval

Source: [redacted], Freyer et al. 2017, European Medicines Agency 2023b)

The results of a sensitivity analysis for HL conducted in the ITT population (Table 62) support the conclusion that PEDMARQSI is effective in preventing HL. These results therefore demonstrate that even when patients without 4-week follow-up data are included in the analysis (as patients with HL), the risk of having HL (as defined by the ASHA criteria) remained statistically significantly lower in the cisplatin with PEDMARQSI arm (26 children, 42.6%) compared with the cisplatin without PEDMARQSI arm (40 children, 62.5%) ([redacted], European Medicines Agency 2023b).

Table 62 Summary of hearing loss (COG ACCL0431 ITT population)

Results	Cisplatin without PEDMARQSI (N = 64)	Cisplatin with PEDMARQSI (N = 61)
n	64	61
Yes, n (%)	40 (62.5)	26 (42.6)
No, n (%)	24 (37.5)	35 (57.4)
Relative risk (95% CI)[†*]	0.65 (0.386, 0.954)	
P-value[†]	0.0234	

[†]Based on logistic regression including treatment and stratification variables as covariates in the model.

*Converted from Odds ratio.

Abbreviations: CI: confidence interval

Sources: ([redacted])

B.1.1.1 Subgroup-analysis

The COG ACCL0431 trial carried out a pre-planned subgroup analysis on the proportion of children with cisplatin-induced HL who were < 5 years of age compared with those ≥ 5 years of age; children under 5 years are more susceptible to HL, especially at high frequencies, since they have hearing that has not yet been subjected to normal age-related decline. The risk of having HL as defined by ASHA criteria were statistically significantly lower in the cisplatin with PEDMARQSI arm compared with the cisplatin without PEDMARQSI arm for children < 5 years of age, and were numerically lower for children ≥ 5 years of age (Table 63) ([redacted]).

It should be noted that although the results in older children did not reach statistical significance, considering the mechanism of action of PEDMARQSI and its localised effect in the inner ear, there is no plausible clinical reason why PEDMARQSI would not reduce HL in this older group of patients.

Table 63 Summary of hearing loss by age group (COG ACCL0431 efficacy population)

	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)	Relative risk (95% CI)[†*]	P-value[†]
All				
n	55	49		
Yes, n (%)	31 (56.4)	14 (28.6)		0.0049

No, n (%)	24 (43.6)	35 (71.4)	0.507 (0.267, 0.843)	
< 5 years				
n	15	14	0.292 (0.064, 0.821)	0.0082
Yes, n (%)	11 (73.3)	3 (21.4)		
No, n (%)	4 (26.7)	11 (78.6)		
> 5 years				
n	40	35	0.628 (0.302, 1.083)	0.1058
Yes, n (%)	20 (50.0)	11 (31.4)		
No, n (%)	20 (50.0)	24 (68.6)		

†Based on logistic regression including only treatment in the model.

*Converted from Odds ratio

Abbreviations: CI: confidence interval

Source: ([redacted], Freyer et al. 2017)

B.1.2 Secondary efficacy endpoint: mean change in hearing thresholds

Hearing data for secondary efficacy endpoint assessment were collected and reviewed by two different blinded central reviewers. For both the left and right ears, there were no significant differences across arms in the change in hearing threshold from baseline to 4 weeks after cisplatin treatment for frequencies ≤ 2000 Hz. Greater differences were observed in the cisplatin with PEDMARQSI arm compared with the cisplatin without PEDMARQSI arm at frequencies ≥ 4,000 Hz for both the left and right ears for both reviewers, with less HL observed for the cisplatin with PEDMARQSI arm (Table 64) ([redacted].

Table 64 Summary of mean change from baseline hearing loss (COG ACCL0431 efficacy population)

	Reviewer 1		Reviewer 2	
	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)
500 Hz – Left Ear, n	41	36	41	36
LS mean (SE)	0.3 (1.21)	0.9 (1.27)	0.3 (1.14)	0.5 (1.20)

	Reviewer 1		Reviewer 2	
	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)
LS mean treatment difference	–	0.7	–	0.1
P-value	–	0.6006	–	0.9327
500 Hz – Right Ear, n	41	36	41	36
LS mean (SE)	–0.0 (1.33)	–0.9 (1.40)	–0.3 (1.33)	–1.3 (1.39)
LS mean treatment difference	–	–0.8	–	–1.0
P-value	–	0.5657	–	0.4915
1,000 Hz – Left Ear, n	42	36	42	36
LS mean (SE)	–0.7 (1.86)	–0.8 (2.02)	–0.6 (1.85)	–1.3 (2.02)
LS mean treatment difference	–	–0.0	–	–0.7
P-value	–	0.9812	–	0.6768
1,000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	–0.2 (1.72)	–1.8 (1.87)	–0.1 (1.72)	–1.6 (1.87)
LS mean treatment difference	–	–1.6	–	–1.4
P-value	–	0.2799	–	0.3460
2000 Hz – Left Ear, n	43	36	43	36
LS mean (SE)	3.5 (3.03)	1.0 (3.35)	3.5 (3.02)	1.1 (3.35)
LS mean treatment difference	–	–2.5	–	–2.4
P-value	–	0.3588	–	0.3630

	Reviewer 1		Reviewer 2	
	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)
2000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	2.2 (2.64)	0.8 (2.91)	1.9 (2.61)	0.4 (2.88)
LS mean treatment difference	–	–1.4	–	–1.5
P-value	–	0.5440	–	0.5128
4,000 Hz – Left Ear, n	43	36	43	36
LS mean (SE)	10.7 (3.98)	3.5 (4.38)	11.2 (3.95)	3.2 (4.37)
LS mean treatment difference	–	–7.2	–	–8.0
P-value	–	0.0395	–	0.0221
4,000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	11.2 (4.24)	4.1 (4.70)	11.2 (4.24)	4.0 (4.71)
LS mean treatment difference	–	–7.0	–	–7.3
P-value	–	0.0625	–	0.0553
8,000 Hz – Left Ear, n	42	36	42	36
LS mean (SE)	31.4 (3.87)	22.1 (4.18)	31.2 (3.85)	22.5 (4.17)
LS mean treatment difference	–	–9.2	–	–8.7
P-value	–	0.0363	–	0.0488
8,000 Hz – Right Ear, n	42	36	42	36
LS mean (SE)	31.4 (4.05)	23.0 (4.34)	31.6 (4.06)	23.2 (4.35)

	Reviewer 1		Reviewer 2	
	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)	Cisplatin without PEDMARQSI (N = 55)	Cisplatin with PEDMARQSI (N = 49)
LS mean treatment difference	–	–8.5	–	–-8.4
P-value	–	0.0662	–	0.0707

Note: Linear regression was used. Covariates included baseline values, stratum, and treatment. Missing values were excluded from the model.

Abbreviations: CI: confidence interval, LS: least squares, SE: standard error

Source: ([redacted])

B.1.3 Secondary efficacy endpoint: overall survival

All 125 patients in the COG ACCL0431 ITT population were considered in the analysis of OS.

At the median 5.33-year follow-up, 18 children (29.5%) in the cisplatin with PEDMARQSI arm and 12 children (18.8%) in the cisplatin without PEDMARQSI arm died during the trial. There was no statistically significant difference in OS between the arms of the trial. The median OS could not be calculated because fewer than 50% of patients in either arm died (Table 65, Figure 11) ([redacted], European Medicines Agency 2023b).

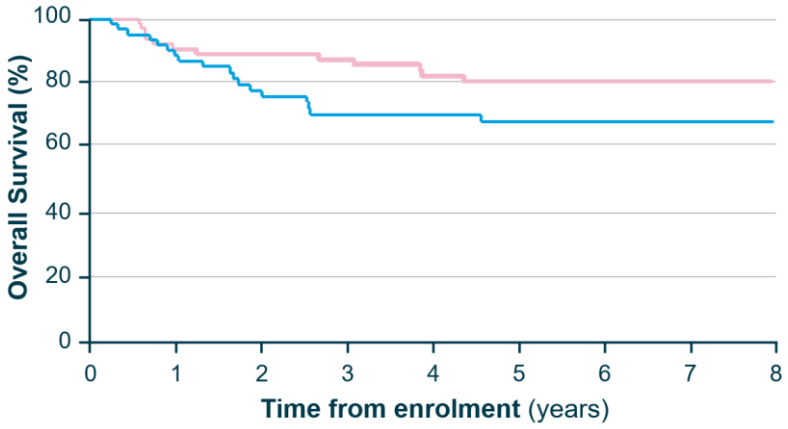
Table 65 Summary of overall survival (COG ACCL0431 ITT population)

Parameter Category/Statistic	Cisplatin without PEDMARQSI (N = 64)	Cisplatin with PEDMARQSI (N = 61)
Number of patients who died, n (%)	12 (18.8)	18 (29.5)
Number of patients censored, n (%)	52 (81.3)	43 (70.5)
Treatment comparison (cisplatin with PEDMARQSI vs cisplatin without PEDMARQSI)		
Hazard ratio (95% CI)	1.79 (0.86, 3.72)	
P-value (log-rank)	0.1132	

Abbreviations: CI: confidence interval, ITT: intent-to-treat

Source: ([redacted], European Medicines Agency 2023b)

Figure 11 Overall survival (COG ACCL0431 ITT population)



Abbreviations: ITT: intention-to-treat

Source: adapted from [redacted]

B.1.4 Secondary efficacy endpoint: event-free survival

As with the OS data, all 125 patients were considered in the EFS analysis. At the median 5.33-year follow-up, 27 children (44.3%) in the cisplatin with PEDMARQSI arm and 25 children (39.1%) in the cisplatin without PEDMARQSI arm experienced an event during this study. There was no statistically significant difference in EFS between the cisplatin with PEDMARQSI arm and the cisplatin without PEDMARQSI arm arm (Table 66, Figure 12) ([redacted], European Medicines Agency 2023b).

Table 66 Summary of event-free survival (median 5.33-year Follow-up) (COG ACCL0431 ITT population)

Parameter Category (Statistic)	Cisplatin without PEDMARQSI (N = 64)	Cisplatin with PEDMARQSI (N = 61)
Number of patients with event[†], n (%)	25 (39.1)	27 (44.3)
Number of patients censored, n (%)	39 (60.9)	34 (55.7)

EFS (years)		
Minimum	0.8	0.6
25% (95% CI)	1.5 (0.5, 2.7)	1.0 (0.6, 1.8)
Median[†] (95% CI)	NE (3.3, NE)	NE (1.8, NE)
75% (95% CI)	NE (NE, NE)	NE (NE, NE)
Maximum	7.9	8.3
Treatment comparison (cisplatin with PEDMARQSI vs cisplatin without PEDMARQSI)		
Hazard ratio	1.27	
95% CI of hazard ratio	(0.73, 2.18)	
Log-rank p-value	0.3964	

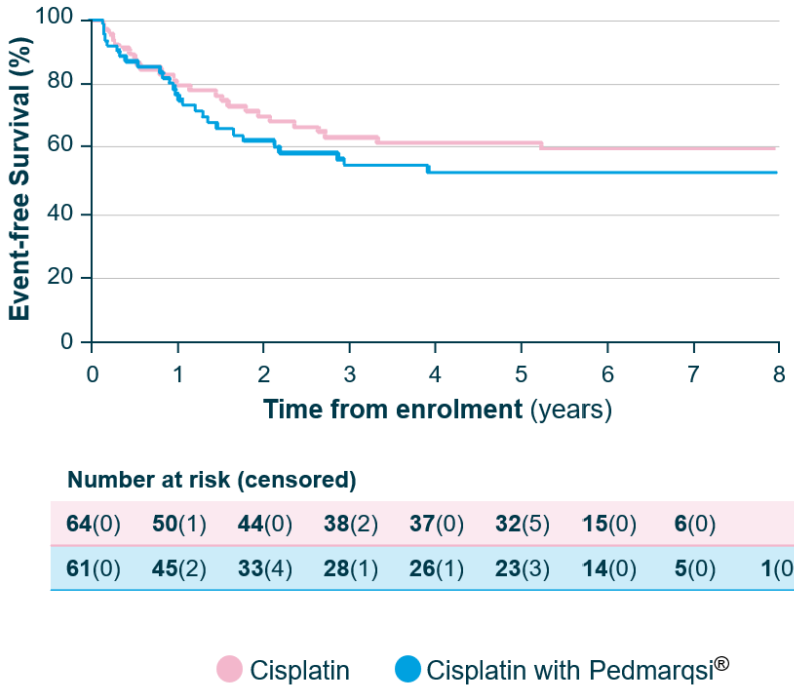
[†]The median and 75% estimates could not be calculated because fewer than 50% of patients in either arm experienced an event.

Abbreviations: CI: confidence interval, EFS: event-free survival, NE: not estimable.

Note: The time to event was defined as the time to the first reported relapse or progression. Patients without relapse or progression were censored at the date of the last survival follow-up.

Source: [redacted] European Medicines Agency 2023b)

Figure 12 Event-free survival (COG ACCL0431 ITT population)



Abbreviations: ITT: Intent-to-treat

Source: adapted from ([redacted])

B.1.5 Other secondary endpoints

Further to the key secondary endpoints discussed above, other secondary endpoints included the incidences of cisplatin-related Grades 3 and 4 nephrotoxicity and Grade 3 and 4 cytopenia, and the association of two key gene mutations (TPMT and COMT) with the development of chemotherapy induced HL. Due to an insufficient number of samples, analysis of the latter was not conducted; however, data pertaining to nephrotoxicity and cytopenia is available in the COG ACCL0431 CSR ([redacted]).

B.1.6 Post-hoc analysis of COG ACCL0431

As the COG ACCL0431 trial used the ASHA criteria to assess HL, Orgel et al. (2023) performed a secondary analysis of audiology data collected in the COG ACCL0431 clinical trial to provide benchmark data for PEDMARQSI efficacy using the more recent SIOP Ototoxicity Scale. The post-hoc analysis was performed by an audiologist investigator blinded to randomised allocation.

In this analysis, hearing endpoints from COG ACCL0431 were re-evaluated using HL at the end of cisplatin therapy and prior to autologous bone marrow transplantation. Hearing thresholds of SIOP Grade ≥ 2 and Grade ≥ 1 were evaluated.

Following repeat audiological central review, 121 of 125 (97%) of patients were evaluable for HL using the SIOP scale. After the end of cisplatin treatment, a lower incidence of Grade ≥ 2 cisplatin-induced HL occurred in the cisplatin with PEDMARQSI arm (4.0%) vs the cisplatin without PEDMARQSI arm (27.1%). In addition, it was concluded that the odds of developing SIOP Grade ≥ 2 were significantly lower for patients in the cisplatin with PEDMARQSI arm (OR: 0.10, 95% CI: 0.02, 0.50, p = 0.005). The same pattern was seen for SIOP Grade ≥ 1; a lower incidence of Grade ≥ 1 cisplatin-induced HL occurred in the cisplatin with PEDMARQSI arm vs the cisplatin without PEDMARQSI arm (18.0% vs 45.8%; OR: 0.25, 95% CI: 0.10, 0.64; p = 0.004) (Orgel et al. 2023).

Results from this re-analysis of hearing outcomes from the COG ACCL0431 trial confirm the otoprotective effects of PEDMARQSI using the SIOP Ototoxicity Scale. It was concluded that, compared with the cisplatin without PEDMARQSI arm, children receiving cisplatin with PEDMARQSI were approximately 90% less likely to develop Grade ≥ 2 cisplatin-induced HL at the end of cisplatin therapy (Orgel et al. 2023).

B.2 Outcomes in SIOPEL-6 – detailed description

B.2.1 Primary efficacy endpoint: proportional incidence of children with Brock Grade ≥ 1 hearing loss

The primary endpoint was the proportional incidence of HL, defined as Brock Grade ≥ 1 HL, determined of the better ear by pure-tone audiometry (PTA) after the end of treatment or at age ≥ 3.5 years (whichever timepoint was later). As a method of censoring patients, children without a HL assessment were counted as a failure (i.e. had HL) in this analysis [redacted], European Medicines Agency 2023b). The proportional incidence of children with Brock Grade ≥ 1 HL, measured by PTA after the end of cisplatin treatment or at ≥ 3.5 years of age (whichever was later), was approximately half as large in the cisplatin with PEDMARQSI treatment arm compared with cisplatin alone (Table 67) (European Medicines Agency 2023b, [redacted]).

Table 67 Summary of hearing loss (SIOPEL-6 ITT population)

Results – hearing loss	Cisplatin without PEDMARQSI (N = 52)	Cisplatin with PEDMARQSI (N = 57)
Yes, n (%)	35 (67.3)	20 (35.1)
No, n (%)	17 (32.7)	37 (64.9)
RR (95% CI)[†]	0.521 (0.349, 0.778)	
P-value[†]	< 0.001	
RR (95% CI)[‡]	0.519 (0.356, 0.755)	
P-value[‡]	< 0.001	

[†]P-value and relative risk from Chi-square test. [‡]P-value and relative risk from CMH test stratified by country group, PRETEXT group and age group.

Abbreviations: CI: confidence interval, CMH: Cochran-Mantel-Haenszel, ITT: intent-to-treat, PRETEXT: Pre-treatment Tumour Extension, RR: relative risk

Source: ([redacted], European Medicines Agency 2023b)

HL results were similar in the mITT population (reported in Brock et al. (2018)) the risk of experiencing HL was statistically significantly lower in the cisplatin with PEDMARQSI arm (32.7%) compared with the cisplatin without PEDMARQSI arm (63.0%), corresponding to a clinically meaningful 48% lower risk of HL after PEDMARQSI treatment (Table 68) (Brock et al. 2018, [redacted]).

Table 68 Summary of hearing loss (SIOPEL-6 mITT population)

Results	Cisplatin without PEDMARQSI (N = 46)	Cisplatin with PEDMARQSI (N = 55)
Yes, n (%)	29 (63.0)	18 (32.7)
No, n (%)	17 (37.0)	37 (67.3)
RR (95% CI)[†]	0.519 (0.335, 0.805)	
P-value[†]	0.002	
RR (95% CI)[‡]	0.516 (0.339, 0.787)	
P-value[‡]	0.002	

[†]P-value and relative risk from Chi-square test. [‡]P-value and relative risk from CMH test stratified by country group, PRETEXT group and age group.

Abbreviations: CI: confidence interval, CMH: Cochran-Mantel-Haenszel, ITT: intent-to-treat, PRETEXT: Pre-treatment Tumour Extension, RR: relative risk

Sources: ([redacted], Brock et al. 2018)

Furthermore, Figure 13 shows the centrally reviewed Brock grading with PTA that was performed at a minimum age of 3.5 years in the mITT population. Patients in the mITT population must have reached the primary endpoint of any HL (Brock Grade 1, 2, 3, or 4) and had this Brock Grade adjudicated by the audiology reviewer. This primary endpoint could be assessed in 101 children in the mITT (eight children had a missing hearing assessment and were recorded as “hearing impaired or failure”) (Brock et al. 2018).

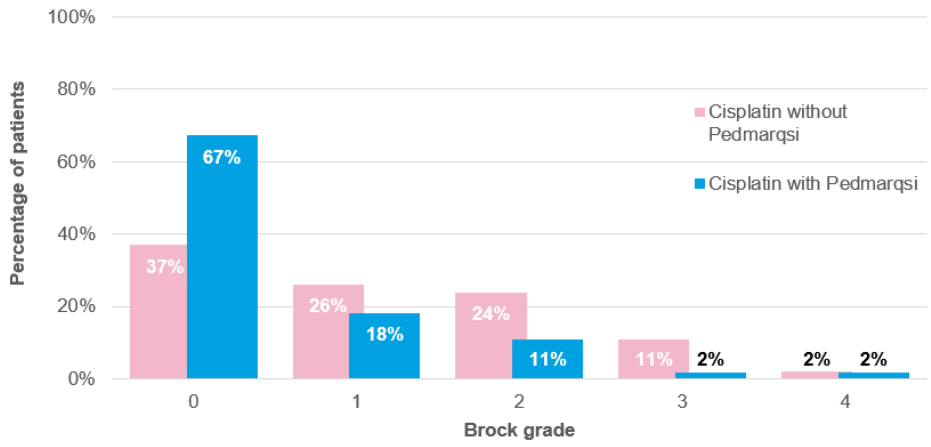


Figure 13 Percentages of children experiencing hearing loss (SIOPEL-6 mITT population)

Note: A Brock Grade of 0 indicates hearing at less than 40 dB at all frequencies and does not necessarily equate to completely normal hearing. Grades 1, 2, 3, and 4 indicate hearing levels at 40 dB or higher at 8 kHz, 4 kHz, 2 kHz, and 1 kHz and above, respectively. The Grade was determined according to the hearing level in the child’s better ear. Percentages rounded to nearest percent.

Abbreviations: dB: decibel

Source: (Brock et al. 2018)

By removing the children who did not experience HL (i.e. Brock Grade 0) from the analysis, it could be determined that not only were there fewer children with any HL in the cisplatin with PEDMARQSI group, but the HL these children experienced (i.e. Brock Grade > 1) was less severe than that of children in the cisplatin without PEDMARQSI arm (Figure 14).

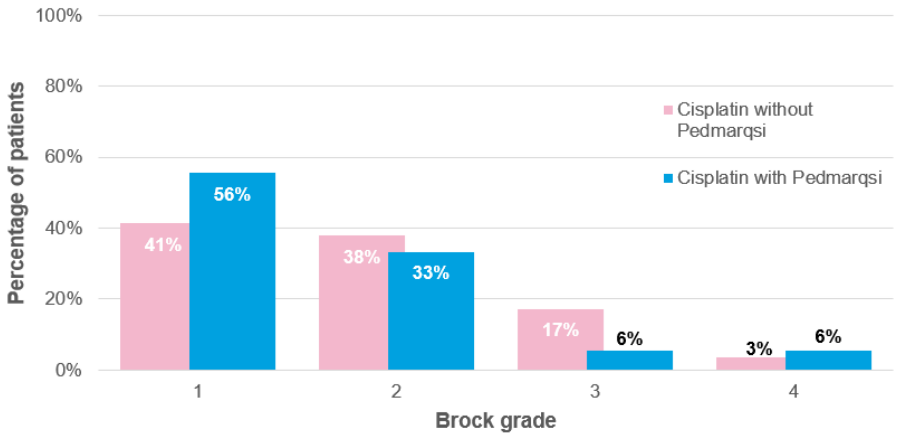


Figure 14 Percentage of children experiencing hearing loss of at least Brock Grade 1 (SIOPEL-6 mITT population)

Note: Percentages rounded to nearest percent

Abbreviations: mITT: modified intent-to-treat

Source: analysis based on Brock et al. (2018)

B.2.2 Secondary efficacy endpoint: overall survival

At a median follow-up of 52 months, there was no statistically significant difference between the proportion of children who died during the SIOPEL-6 trial in the cisplatin with PEDMARQSI arm (2 patients [3.5%]) and the cisplatin without PEDMARQSI arm (4 patients [7.7%]) [redacted]. A summary of OS results in the ITT population is presented in Table 69 and Figure 15.

Table 69 Summary of overall survival (SIOPEL-6 ITT population)

Parameter – Category/Statistic	Cisplatin without PEDMARQSI (N=52)	Cisplatin with PEDMARQSI (N=57)
Number of patients censored, n (%)	48 (92.3)	55 (96.5)
Number of patients who died, n (%)	4 (7.7)	2 (3.5)
Treatment comparison (cisplatin with PEDMARQSI vs cisplatin without PEDMARQSI)		
Hazard ratio (95% CI)	0.44 (0.08, 2.41)	

P-value (log-rank)	0.332

Time to event was calculated from the time of randomisation to death. Subjects alive were censored at the time of last known follow-up visit.

Abbreviations: CI: confidence interval, ITT: intent-to-treat

Source: [redacted]

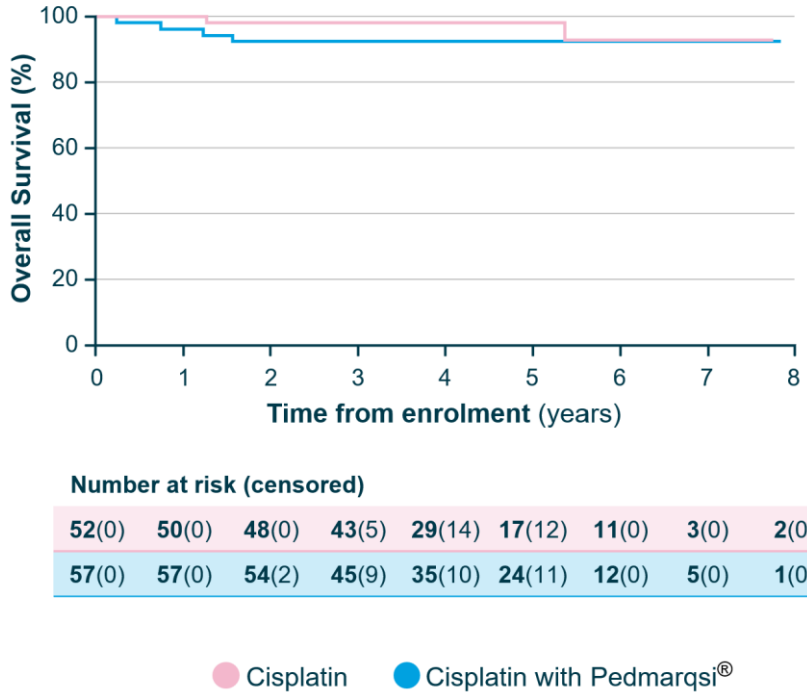


Figure 15 Overall survival (SIOPEL-6 ITT population)

Abbreviations: ITT: intent-to-treat

Source: adapted from SIOPEL-6 Figures [redacted] (as in Brock et al. (2018))

B.2.3 Secondary efficacy endpoint: event-free survival

At a median follow up of 52 months, there was no statistically significant difference between the proportion of children that were censored at the time of their last known Follow-up Visit (i.e. EFS) between the cisplatin with PEDMARQSI arm (80.7%) and the cisplatin without PEDMARQSI arm (78.8%) (Table 70, Figure 16) [redacted].

Table 70 Summary of event-free survival (SIOPEL-6 ITT population)

Parameter – Category/Statistic	Cisplatin without PEDMARQSI (N=52)	Cisplatin with PEDMARQSI (N=57)
Number of patients censored, n (%)	41 (78.8)	46 (80.7)

Number of patients with event, n (%)	11 (21.2)	11 (19.3)
Treatment comparison (cisplatin with PEDMARQSI vs cisplatin without PEDMARQSI)		
Hazard ratio (95% CI)	0.89 (0.39, 2.05)	
P-value (log-rank)	0.785	
Hazard ratio (95% CI) [a]	1.01 (0.43, 2.38)	
P-value (log-rank) [a]	0.673	

Abbreviations: CI: confidence interval, ITT: intent-to-treat, PRETEXT: Pre-treatment Tumor Extension

[a] Hazard ratio and 95% CI were based on Cox proportional hazards model and includes treatment and randomisation stratification of country group, PRETEXT group, and age group. The p-value was based on stratified log rank test.
Note: Time to event was calculated from the time of randomisation to the first of the following events: progression, relapse, second primary malignancy or death. Patients without an event were censored at the time of last known Follow-up Visit.

Source: [redacted]

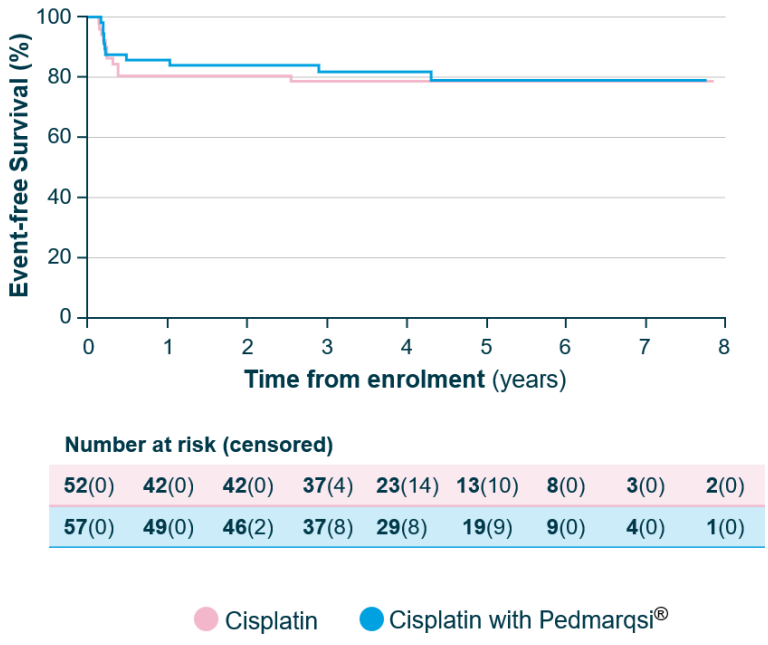


Figure 16 Event-free survival (SIOPEL-6 ITT population)

Abbreviations: ITT: intent-to-treat

Source: adapted from SIOPEL-6 ([redacted] (as in Brock et al. (2018))

B.2.4 Secondary efficacy endpoint: percentage of children per disease status

There was no statistically significant difference in the proportion of children with complete remission at the end of treatment (as reported by the Investigator) in the cisplatin with PEDMARQSI (91.2%) compared with the cisplatin without PEDMARQSI arm

(86.5%) (Table 71). The proportion of children in partial remission also similar between the arms. In the cisplatin with PEDMARQSI arm, no child had progressive disease, died from their disease, or died from other causes by the end of treatment. In the cisplatin without PEDMARQSI arm, 2 children (3.8%) had progressive disease, 1 child (1.9%) died from disease, and 1 child (1.9%) died from other causes (surgical complications) [redacted], European Medicines Agency 2023b).

The results of the complete remission assessment when performed by a Central Reviewer were generally similar for each category compared with those reported by the Investigator and also found no statistically significant difference between the 2 treatment arms [redacted], Brock et al. 2018).

Remission assessment results using the ITT population and the Safety population were similar to the Per Protocol (PP) population [redacted]).

Table 71 Summary of remission status at end of treatment (SIOPEL-6 ITT population)

Statistic	Cisplatin without PEDMARQSI (N=52)	Cisplatin with PEDMARQSI (N=57)
Status as Reported by Investigator, n (%)		
Complete remission	45 (86.5)	52 (91.2)
Partial remission	1 (1.9)	2 (3.5)
Progressive disease	2 (3.8)	0
Died from disease	1 (1.9)	0
Died from other causes	1 (1.9)	0
Withdrawn from protocol	2 (3.8)	3 (5.3)
Complete remission	45 (86.5)	52 (91.2)
Not complete remission	7 (13.5)	5 (8.8)
P-value[+]	-	0.545
Status as Assessed by Central Reviewer, n (%)		
Complete remission	44 (84.6)	52 (91.2)
Partial remission	4 (7.7)	5 (8.8)
Progressive disease	2 (3.8)	0
Not Evaluable	1 (1.9)	0

Statistic	Cisplatin without PEDMARQSI (N=52)	Cisplatin with PEDMARQSI (N=57)
Died from other causes	1 (1.9)	0
Complete remission	44 (84.6)	52 (91.2)
Not complete remission	8 (15.4)	5 (8.8)
P-value[†]	-	0.378

[†]P-value from Fisher's Exact Test.

Note: Treatment groups are treatments patients were randomised to receive and actually received.

Note: Patients that were withdrawn from the protocol switched from protocol-defined treatment to other treatments.

Source: ([redacted] Status as assessed by central reviewer as reported in Brock et al. (2018)

B.2.5 Secondary efficacy endpoint: long-term renal clearance

Long-term renal clearance was analysed in the ITT population. This was assessed at the end of treatment (6 to 12 weeks after stopping treatment) in some children, and some had additional assessments at follow-up (up to 5 years after treatment).

The proportion of children with a long-term glomerular filtration rate (GFR)/creatinine clearance ≥ 60 mL/min/1.73 m^2 was not statistically significantly different in the cisplatin with PEDMARQSI arm (Table 72) [redacted].

For the ITT population, the change from baseline in mean (SD) long-term GFR/creatinine clearance was not statistically significantly different in the cisplatin with PEDMARQSI arm compared with the cisplatin without PEDMARQSI arm (Table 72) [redacted].

The results for the PP population and the Safety population were similar to the results observed in the ITT population [redacted].

Table 72 Summary of long-term renal clearance (SIOPEL-6 ITT population)

Statistic	Cisplatin without PEDMARQSI N = 52	Cisplatin with PEDMARQSI N = 57
Category at last selected follow-up		
Number of patients with data	46	56

Statistic	Cisplatin without PEDMARQSI N = 52	Cisplatin with PEDMARQSI N = 57
GFR/creatinine clearance (≥ 60 mL/min/1.73 m^2), n (%)	41 (89.1)	54 (96.4)
GFR/creatinine clearance (< 60 mL/min/1.73 m^2), n (%)	5 (10.9)	2 (3.6)
P-Value†	-	0.239
Change from Baseline		
n	46	56
Mean (SD)	0.77 (71.017)	-1.33 (76.247)
Median (min, max)	0.00 (-254.7, 212.8)	-11.90 (-227.0, 225.0)
P-Value†	-	0.887

Abbreviations: GFR: glomerular filtration rate, max: maximum, min: minimum, SD: standard deviation

†P-value for categories was calculated from Fisher's Exact Test. The P-value for change from baseline was calculated from a t-test.

Note: The last collected GFR value was used if the patient also had a baseline value available. If not, the last collected calculated creatinine clearance value was used if the baseline value was available.

Source: [redacted]

B.2.6 Secondary efficacy endpoint: log_{10} change in AFP from baseline

Alpha-fetoprotein (AFP) values have been used as a tumour marker and are therefore included in the efficacy section. At baseline, the mean AFP log-transformed values were similar between the cisplatin with PEDMARQSI and the cisplatin without PEDMARQSI arms (4.999 ng/mL and 4.897 ng/mL, respectively). In both the cisplatin with PEDMARQSI and cisplatin without PEDMARQSI arms, the mean change from baseline in AFP values measured at different time points were similar and statistically significant reductions were observed in both (Table 73) [redacted].

AFP results in the PP population and the Safety population were similar to those in the ITT population [redacted]).

Table 73 Summary of change in log AFP from baseline to end of treatment and end of Follow-up (SIOPEL-6 ITT population)

Parameter - Category/Statistic	Cisplatin without PEDMARQSI (N = 52)	Cisplatin with PEDMARQSI (N = 57)
Baseline AFP (log-transformed, ng/mL)		
n	52	57
Mean (SD)	4.897 (1.071)	4.999 (1.076)
Median (min, max)	5.029 (2.11, 6.42)	5.347 (2.20, 6.50)
Post-Course 1+2 Change from Baseline AFP		
n	52	57
Mean (SD)	-0.817 (0.496)	-0.654 (0.640)
Median (min, max)	-0.740 (-2.05, 0.00)	-0.650 (-2.48, 1.04)
95% CI (lower, upper)	-0.955, -0.679	-0.824, -0.484
P-value[†]	<0.001	<0.001
Post-Course 3+4 Change from Baseline AFP		
n	50	55
Mean (SD)	-1.956 (1.035)	-1.487 (0.778)
Median (min, max)	-1.890 (-4.28, 1.17)	-1.547 (-3.56, 0.08)
95% CI (lower, upper)	-2.250, -1.661	-1.698, -1.277
P-value[†]	< 0.001	< 0.001
End of Treatment Change from Baseline AFP		
n	49	56
Mean (SD)	-3.714 (1.149)	-3.780 (1.088)
Median (min, max)	-4.070 (-5.39, -0.66)	-3.941 (-5.66, -1.14)
95% CI (lower, upper)	-4.044, -3.384	-4.071, -3.488

Parameter - Category/Statistic	Cisplatin without PEDMARQSI (N = 52)	Cisplatin with PEDMARQSI (N = 57)
P-value†	< 0.001	< 0.001

Abbreviations: AFP: alpha-fetoprotein, CI: confidence interval, max: maximum, min: minimum, PP: Per Protocol, SD: standard deviation

†P-value was from a paired t-test.

Source: [redacted]

Appendix C. Comparative analysis of efficacy

Not applicable for this application.

Table 74 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A: not applicable

Appendix D. Extrapolation

Appendix D is not applicable as the incidence of HL and severity of HL is not extrapolated in the mode, see Section 8.

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

Not applicable for this application.

D.1.2 Model

Not applicable for this application.

D.1.3 Proportional hazards

Not applicable for this application.

D.1.4 Evaluation of statistical fit (AIC and BIC)

Not applicable for this application.

D.1.5 Evaluation of visual fit

Not applicable for this application.

D.1.6 Evaluation of hazard functions

Not applicable for this application.

D.1.7 Validation and discussion of extrapolated curves

Not applicable for this application.

D.1.8 Adjustment of background mortality

Not applicable for this application.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable for this application.

D.1.10 Waning effect

Not applicable for this application.

D.1.11 Cure-point

Not applicable for this application.

D.2 Extrapolation of [effect measure 1]

Not applicable for this application.

Appendix E. Serious adverse events

All SAEs observed in COG ACCL0431 and SIOPEL-6 are presented below in Table 75 and Table 76, respectively.

Table 75 Summary of SAEs during the reporting period (COG ACCL0431 Safety Population)

Adverse event[a]	Cisplatin with PEDMARQSI (N=59) n (%)
Patients with at least 1 AE	21 (35.6)
Blood and lymphatic system disorders	14 (23.7)
Febrile neutropenia	12 (20.3)
Anaemia	7 (11.9)
Investigations	13 (22.0)
Neutrophil count decreased	10 (16.9)
Platelet count decreased	8 (13.6)
White blood cell count decreased	8 (13.6)
Lymphocyte count decreased	4 (6.8)
Alanine aminotransferase increased	3 (5.1)
Aspartate aminotransferase increased	1 (1.7)
Weight decreased	1 (1.7)
Gastrointestinal disorders	7 (11.9)
Stomatitis	5 (8.5)
Nausea	2 (3.4)
Colitis	2 (3.4)
Abdominal pain	1 (1.7)
Oral pain	1 (1.7)
Proctalgia	1 (1.7)

Vomiting	1 (1.7)
Infections and infestations	5 (8.5)
Urinary tract infection	2 (3.4)
Abdominal infection	1 (1.7)
Cellulitis staphylococcal	1 (1.7)
Conjunctivitis	1 (1.7)
Device related infection	1 (1.7)
Parainfluenza virus infection	1 (1.7)
Sepsis	1 (1.7)
Upper respiratory tract infection	1 (1.7)
Metabolism and nutrition disorders	5 (8.5)
Decreased appetite	2 (3.4)
Dehydration	2 (3.4)
Acidosis	1 (1.7)
Hypocalcaemia	1 (1.7)
Hypoglycaemia	1 (1.7)
Hypokalaemia	1 (1.7)
Hypomagnesemia	1 (1.7)
Hyponatremia	1 (1.7)
Tetany	1 (1.7)
Nervous system disorders	4 (6.8)
Syncope	2 (3.4)
Depressed level of consciousness	1 (1.7)
Extrapyramidal disorder	1 (1.7)
Posterior reversible encephalopathy syndrome	1 (1.7)
Cardiac disorders	1 (1.7)

Cardiac arrest	1 (1.7)
Immune system disorders	1 (1.7)
Anaphylactic reaction	1 (1.7)
Psychiatric disorders	1 (1.7)
Anxiety	1 (1.7)
Respiratory, thoracic, and mediastinal disorders	1 (1.7)
Pharyngeal stenosis	1 (1.7)
Vascular disorders	1 (1.7)
Hypotension	1 (1.7)

[a] Based on MedDRA Version 21.0.

Abbreviations: SAE: serious adverse event

Source: [redacted]

Table 76 Summary of SAEs during the treatment phase (SIOPEL-6 Safety Population)

Adverse event	Cisplatin with PEDMARQSI(N=56) n (%)	Cisplatin without PEDMARQSI (N=53) n (%)	Total (N=109) n (%)
Patients with at least 1 SAE	21 (39.6)	18 (32.1)	39 (35.8)
Infections and infestations	7 (13.2)	5 (8.9)	12 (11.0)
Infection	7 (13.2)	5 (8.9)	12 (11.0)
Investigations	6 (11.3)	3 (5.4)	9 (8.3)
Neutrophil count decreased	6 (11.3)	1 (1.8)	7 (6.4)
Haemoglobin decreased	1 (1.9)	1 (1.8)	2 (1.8)
aPTT prolonged	0	1 (1.8)	1 (0.9)
General disorders and administration site conditions	5 (9.4)	3 (5.4)	8 (7.3)
Pyrexia	5 (9.4)	3 (5.4)	8 (7.3)
Gastrointestinal disorders	2 (3.8)	2 (3.6)	4 (3.7)

Ascites	0	1 (1.8)	1 (0.9)
Colitis	1 (1.9)	0	1 (0.9)
Diarrhoea	1 (1.9)	0	1 (0.9)
Enteritis	0	1 (1.8)	1 (0.9)
Metabolism and nutrition disorders	2 (3.8)	2 (3.6)	4 (3.7)
Dehydration	0	1 (1.8)	1 (0.9)
Hypercholesterolemia	1 (1.9)	0	1 (0.9)
Hyperkalaemia	0	1 (1.8)	1 (0.9)
Hyponatraemia	1 (1.9)	0	1 (0.9)
Blood and lymphatic system disorders	1 (1.9)	2 (3.6)	3 (2.8)
Coagulopathy	1 (1.9)	0	1 (0.9)
Febrile neutropenia	0	1 (1.8)	1 (0.9)
Lymphatic disorder	0	1 (1.8)	1 (0.9)
Immune system disorders	1 (1.9)	1 (1.8)	2 (1.8)
Hypersensitivity	1 (1.9)	1 (1.8)	2 (1.8)
Injury, poisoning, and procedural complications	2 (3.8)	0	2 (1.8)
Procedural complication	2 (3.8)	0	2 (1.8)
Musculoskeletal and connective tissue disorders	1 (1.9)	0	1 (0.9)
Musculoskeletal disorder	1 (1.9)	0	1 (0.9)
Respiratory, thoracic, and mediastinal disorders	0	1 (1.8)	1 (0.9)
Dyspnoea	0	1 (1.8)	1 (0.9)
Skin and subcutaneous tissue disorders	0	1 (1.8)	1 (0.9)
Exfoliative rash	0	1 (1.8)	1 (0.9)

Vascular disorders	**0**	**1 (1.8)**	**1 (0.9)**
Thrombosis	0	1 (1.8)	1 (0.9)
Cardiac disorders	0	1 (1.8)	1 (0.9)
Cardiac arrest	0	1 (1.8)	1 (0.9)

Abbreviations: SAE: serious adverse event

Source: [redacted]

Appendix F. Health-related quality of life

Not applicable for this application.

Appendix G. Probabilistic sensitivity analyses

Table 77 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Age (years)	8.6	7	10	SE: 0.69 (Gamma)
% male	60.94%	36%	83%	Variation: 0.20 (Beta)
Percentage of patients experiencing hearing loss – Cisplatin with PEDMARQSI	28.57%	22.87%	34,28%	Variation: 0.20 (Beta)
Percentage of patients experiencing hearing loss – Cisplatin without PEDMARQSI	56.36%	45.09%	67.63%	Variation: 0.20 (Beta)
Percentage of hearing loss patients with Mild HL - Cisplatin with PEDMARQSI	77.78%	79.99%	75.60%	Dirichlet distribution
Percentage of hearing loss patients with Moderate HL - Cisplatin with PEDMARQSI	18.06%	17.14%	18.85%	Dirichlet distribution
Percentage of hearing loss patients with Marked HL - Cisplatin with PEDMARQSI	1.39%	0.84%	2.00%	Dirichlet distribution

Percentage of hearing loss patients with Severe HL - Cisplatin with PEDMARQSI	2.78%	2.04%	3.54%	Dirichlet distribution
Percentage of hearing loss patients with Mild HL - Cisplatin without PEDMARQSI	40.78%	41.37%	40.21%	Dirichlet distribution
Percentage of hearing loss patients with Moderate HL - Cisplatin without PEDMARQSI	48.12%	49.20%	47.09%	Dirichlet distribution
Percentage of hearing loss patients with Marked HL - Cisplatin without PEDMARQSI	3.70%	2.92%	4.47%	Dirichlet distribution
Percentage of hearing loss patients with Severe HL - Cisplatin without PEDMARQSI	7.40%	6.51%	8.23%	Dirichlet distribution
Mortality				
Mortality probability Year 1	7.85%	1%	20%	Variation: 0.20 (Beta)
Mortality probability Year 2	2.88%	2%	4%	Variation: 0.20 (Beta)
Mortality probability Year 3	3.23%	2%	5%	Variation: 0.20 (Beta)
Mortality probability Year 4	3.19%	2%	5%	Variation: 0.20 (Beta)

Mortality probability Year 5	1.99%	1%	3%	Variation: 0.20 (Beta)
Age-dependent post-cancer SMR – 5-19 years	19.90	19.21	20.61	SE: 0.36 (Gamma)
Age-dependent post-cancer SMR – 20-29 years	5.40	4.96	5.86	SE: 0.23 (Gamma)
Age-dependent post-cancer SMR – 30-39 years	4.20	3.81	4.61	SE: 0.20 (Gamma)
Age-dependent post-cancer SMR – 40-49 years	3.30	2.91	3.71	SE: 0.20 (Gamma)
Age-dependent post-cancer SMR – 50-59 years	2.40	1.97	2.87	SE: 0.23 (Gamma)
Age-dependent post-cancer SMR – 60+ years	2.30	1.26	3.65	SE: 0.61 (Gamma)
Adverse events (duration)				
Neutrophil count decreased	40.10	25.95	57.28	Variation: 0.20 (Gamma)
Haemoglobin decreased	42.90	27.76	61.28	Variation: 0.20 (Gamma)
Infection	182.50	118.10	260.68	Variation: 0.20 (Gamma)
Febrile neutropenia	7.00	4.53	10.00	Variation: 0.20 (Gamma)
White blood cell count decreased	42.90	27.76	61.28	Variation: 0.20 (Gamma)
Platelet count decreased	58.30	37.73	83.28	Variation: 0.20 (Gamma)

Alanine aminotransferase increased	28.00	18.12	40.00	Variation: 0.20 (Gamma)
Lymphocyte count decreased	4.10	2.65	5.86	Variation: 0.20 (Gamma)
Anaemia	42.90	27.76	61.28	Variation: 0.20 (Gamma)
Hypokalaemia	13.00	8.41	18.57	Variation: 0.20 (Gamma)
Hypophosphatemia	3.30	2.14	4.71	Variation: 0.20 (Gamma)
Hyponatremia	2.00	1.29	2.86	Variation: 0.20 (Gamma)
Stomatitis	14.00	9.06	20.00	Variation: 0.20 (Gamma)
Hypersensitivity	7.00	4.53	10.00	Variation: 0.20 (Gamma)
HSUV				
Minimal/no HL	0.92	0.91	0.93	SE: 0.00 (Beta)
Mild HL	0.80	N/A	N/A	Variation: 0.20 (Beta)
Moderate HL	0.68	N/A	N/A	Variation: 0.20 (Beta)
Marked HL	0.63	N/A	N/A	Variation: 0.20 (Beta)
Severe HL	0.52	N/A	N/A	Variation: 0.20 (Beta)
Cancer-related disutility, on treatment (year 1)	0.15	0.09	0.21	Variation: 0.20 (Beta)
Cancer-related disutility, off	0.07	0.04	0.10	Variation: 0.20 (Beta)

treatment (years 2+)				
Disutility				
Neutrophil count decreased	0.01	0.00	0.01	Variation: 0.20 (Beta)
Haemoglobin decreased	0.07	0.05	0.10	Variation: 0.20 (Beta)
Infection	0.04	0.03	0.06	Variation: 0.20 (Beta)
Febrile Neutropenia	0.09	0.06	0.13	Variation: 0.20 (Beta)
White blood cell count decreased	0.03	0.02	0.04	Variation: 0.20 (Beta)
Platelet count decreased	0.11	0.07	0.16	Variation: 0.20 (Beta)
Alanine aminotransferase increased	0.05	0.03	0.07	Variation: 0.20 (Beta)
Lymphocyte count decreased	0.20	0.13	0.28	Variation: 0.20 (Beta)
Anaemia	0.07	0.05	0.10	Variation: 0.20 (Beta)
Hypokalaemia	0.03	0.02	0.04	Variation: 0.20 (Beta)
Hypophosphatemia	0.08	0.05	0.11	Variation: 0.20 (Beta)
Hyponatremia	0.52	0.32	0.72	Variation: 0.20 (Beta)
Stomatitis	0.15	0.10	0.21	Variation: 0.20 (Beta)
Hypersensitivity	0.09	0.06	0.13	Variation: 0.20 (Beta)

Resource use				
Mean number of PEDMARQSI doses	[redacted]			Not varied
Mean 8 g vials per PEDMARQSI dose (assumes wastage)	[redacted]			Not varied
Nurse time to administer PEDMARQSI (hours)	0.50	N/A	N/A	Not varied
Percentage of patients with depression and anxiety – no hearing loss	14.89%	10%	21%	Variation: 0.20 (Beta)
Percentage of patients with depression and anxiety – hearing loss	25.58%	16%	36%	Variation: 0.20 (Beta)
% patients with Mild HL requiring hearing aids	50%	31%	69%	Variation: 0.20 (Beta)
% patients with Moderate HL requiring hearing aids	100%	100%	100%	Variation: 0.20 (Beta)
% patients with Marked HL requiring hearing aids	94%	18%	100%	Variation: 0.20 (Beta)
% patients with Severe HL requiring hearing aids	48%	29%	67%	Variation: 0.20 (Beta)
Replacement frequency for hearing aids (every X years)	4.00	2.59	5.71	Variation: 0.20 (Gamma)

% patients with Mild HL requiring cochlear implants	0%	0%	0%	Variation: 0.20 (Beta)
% patients with Moderate HL requiring cochlear implants	0%	0%	0%	Variation: 0.20 (Beta)
% patients with Marked HL requiring cochlear implants	6%	4%	9%	Variation: 0.20 (Beta)
% patients with Severe HL requiring cochlear implants	52%	32%	72%	Variation: 0.20 (Beta)
Replacement frequency for the external processor of the cochlear implants (every X years)	5.00	3.24	7.14	Variation: 0.20 (Gamma)
Length of warranty for external processor (years)	3.00	1.94	4.29	Variation: 0.20 (Gamma)
Length of warranty for internal electrode (years)	10.00	6.47	14.28	Variation: 0.20 (Gamma)
Frequency of audiology assessments for Mild HL and Moderate HL who are 0-5 years old (per year)	2.00	1.29	2.86	Variation: 0.20 (Gamma)
Frequency of audiology assessments for Marked HL and Severe HL who are 0-5 years old (per year)	3.00	1.94	4.29	Variation: 0.20 (Gamma)

Frequency of audiology assessments for patients who are 6-18 years old (per year)	1.00	0.65	1.43	Variation: 0.20 (Gamma)
Frequency of audiology assessments for patients who are over 18 years old (per year)	0.25	0.16	0.36	Variation: 0.20 (Gamma)
Number of speech and language therapy sessions for Mild HL patients – under 18 (per year)	0.00	0.00	0.00	Variation: 0.20 (Gamma)
Number of speech and language therapy sessions for Moderate HL patients – under 18 (per year)	0.00	0.00	0.00	Variation: 0.20 (Gamma)
Number of speech and language therapy sessions for Marked HL patients – under 18 (per year)	52.14	33.77	74.53	Variation: 0.20 (Gamma)
Number of speech and language therapy sessions for Severe HL patients – under 18 (per year)	52.14	33.77	74.53	Variation: 0.20 (Gamma)
Number of speech and language therapy sessions for Mild HL patients – 18+ (per year)	0.00	0.00	0.00	Variation: 0.20 (Gamma)
Number of speech and language therapy sessions	0.00	0.00	0.00	Variation: 0.20 (Gamma)

for Moderate HL patients – 18+ (per year)				
Number of speech and language therapy sessions for Marked HL patients – 18+ (per year)	0.00	0.00	0.00	Variation: 0.20 (Gamma)
Number of speech and language therapy sessions for Severe HL patients – 18+ (per year)	0.90	0.58	1.29	Variation: 0.20 (Gamma)
Costs				
Cost per 8 g vial	72,638	N/A	N/A	Not varied
Cost per hour of nurse time	468.35	N/A	N/A	Not varied
Cost of hearing assessments age 0-18 years old	289.26	187.19	413.18	Variation: 0.20 (Gamma)
Cost of depression per patient	26,633	17,236	38,043	Variation: 0.20 (Gamma)
Cost of hearing assessments age 18+ years old	289.26	187.19	413.18	Variation: 0.20 (Gamma)
Bilateral cochlear implants – initial pre-implantation cost, under 18 years old	0	N/A	N/A	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Initial cost of bilateral cochlear implant (including external processor), under 18 years old	228,746	148,032	326,742	Variation: 0.20 (Gamma)

Bilateral cochlear implants: Initial cost of fitting cochlear implants, under 18 years old	134,393	86,972	191,968	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Annual cost of maintenance and programming, under 18 years old	1,159	750	1656	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Replacement external processor cost, under 18 years old	134,393	86,972	191,968	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Replacement internal electrode cost, under 18 years old	0	0	0	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Replacement re-implantation cost, under 18 years old	134,393	86,972	191,968	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Annual cost of maintenance and programming, over 18 years old	1,159	750	1656	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Replacement external processor cost, over 18 years old	134,393	86,972	191,968	Variation: 0.20 (Gamma)
Bilateral cochlear implants: Replacement internal electrode	0	N/A	N/A	Variation: 0.20 (Gamma)

cost, over 18 years old				
Bilateral cochlear implants: Replacement re-implantation cost, over 18 years old	0	N/A	N/A	Variation: 0.20 (Gamma)
Hearing aids in patients 0-18 years: cost of hearing aid	17,980	11,636	25,683	Variation: 0.20 (Gamma)
Hearing aids in patients 0-18 years: cost of fitting hearing aid	1,286	832	1,837	Variation: 0.20 (Gamma)
Hearing aids in patients 0-18 years: cost of hearing aid follow-up	1,286	832	1,837	Variation: 0.20 (Gamma)
Hearing aids in patients over 18 years: cost of hearing aid	17,980	11,636	25,683	Variation: 0.20 (Gamma)
Hearing aids in patients over 18 years: cost of fitting hearing aid	1,286	832	1,837	Variation: 0.20 (Gamma)
Hearing aids in patients over 18 years: cost of hearing aid follow-up	1,286	832	1,837	Variation: 0.20 (Gamma)
Cost per speech and language therapy session – under 18	1,286	832	1,837	Variation: 0.20 (Gamma)
Cost per speech and language therapy session – 18+	1,286	832	1,837	Variation: 0.20 (Gamma)

Neutrophil count decreased	28,342	18,342	40,484	Variation: 0.20 (Gamma)
Haemoglobin decreased	28,342	18,342	40,484	Variation: 0.20 (Gamma)
Infection	14,298	9,253	20,423	Variation: 0.20 (Gamma)
Febrile neutropenia	28,342	18,342	40,484	Variation: 0.20 (Gamma)
White blood cell count decreased	28,342	18,342	40,484	Variation: 0.20 (Gamma)
Platelet count decreased	37,482	24,256	53,539	Variation: 0.20 (Gamma)
Alanine aminotransferase increased	70,675	45,737	100,953	Variation: 0.20 (Gamma)
Lymphocyte count decreased	20,988	13,582	29,979	Variation: 0.20 (Gamma)
Anaemia	28,342	18,342	40,484	Variation: 0.20 (Gamma)
Hypokalaemia	1,286	832	1,837	Variation: 0.20 (Gamma)
Hypophosphatemia	1,286	832	1,837	Variation: 0.20 (Gamma)
Hyponatremia	1,286	832	1,837	Variation: 0.20 (Gamma)
Stomatitis	2,060	1,333	2,943	Variation: 0.20 (Gamma)
Hypersensitivity	1,286	832	1,837	Variation: 0.20 (Gamma)

Abbreviations g: gram, HL: hearing loss, SE: standard error, PSA: probabilistic sensitivity analysis, SMR: standardised mortality ratio

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A thorough SLR was conducted in October 2023 to ensure a complete and updated understanding of PEDMARQSI for clinical assessment, focusing on its efficacy and safety for patients according to the indication. Furthermore, an updated SLR was performed in October 2024 to match the requirements of this application. The process followed established practices and was comprised of the following core stages: definition of scope and agreement of search terms, implementation of searches and abstract review to inform included papers, and extraction and quality assessment of data.

H.1.1 Scope and overview of the SLR

The scope of the SLR was defined in terms of criteria such as the Patient population, the Intervention, the Comparators, the Outcomes measures, and the Study design as described in Table 84 below.

In the original SLR, Comprehensive literature searches were undertaken in electronic databases on 31st October 2023. This list was updated and extended during the updated SLR search in 2024. The following electronic databases were searched (Table 78):

- Embase and Embase classic (using Embase.com)
- MEDLINE (using pubmed.ncbi.nlm.nih.gov)
- The Cochrane Library (using wiley.com), including:
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Cochrane Clinical Answers

In addition, supplementary searches of “grey” literature were performed in Google Scholar and through the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP), Cost-Effectiveness Analysis (CEA) registry, NICE website, Research papers in Economics (RePEc) website, EQ-5D website, Internation health technology assessment (INAHTA) database, clinicaltrials.gov and WHO websites (Table 79).

Furthermore, conference proceedings from the last three years were reviewed for any additional studies of interest published. The following conference proceedings were searched (Table 80):

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)

- International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer
- International Society for Paediatric Oncology

The database search strings identified included terms for free text and keywords (Medical Subject Heading [MESH] and Emtree terms) combined using Boolean combination techniques. Filters were used to ensure the search results were relevant for the review question.

Table 78 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	embase.com	1978 to present	31/10/2023 Updated: 14/10/2024
Embase Classic	embase.com	1947 to 1973	31/10/2023 Updated: 14/10/2024
Medline	pubmed.ncbi.nlm.nih.gov	1978 to present	31/10/2023 Updated: 14/10/2024
Cochrane Library (including CENTRAL)	wiley.com	1978 to present	31/10/2023 Updated: 14/10/2024

Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials

Source: (Norgine 2024c)

Table 79 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ICTRP	https://www.who.int/clinical-trials-registry-platform	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
NICE	www.nice.org.uk	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
CEA	https://cear.tuftsmedicalcenter.org/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024

Source name	Location/source	Search strategy	Date of search
RePEc	http://repec.org/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
EQ-5D	https://registration.euroqol.org/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
INAHTA	https://www.inahta.org/hta-database/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
WHO	https://www.who.int/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
Clinical trials	www.clinicaltrials.gov	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024

Abbreviations: CEA: Cost-Effectiveness Analysis registry, EQ-5D: EuroQol 5-dimensions, ICTRP: International Clinical Trials Registry Platform, INAHTA: Internation health technology assessment database, NICE: National Institute for Health and Care Excellence, RePEc: Research papers in Economics, WHO: World Health Organisation

Source: (Norgine 2024c)

Table 80 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	Conference proceedings	Manual search	Ototoxicity OR Deaf OR Hearing OR Auditory	Final search October 2024
American Society of Clinical Oncology (ASCO)	Conference proceedings	Manual search	Ototoxicity Deaf Hearing Auditory	Final search October 2024
European Society for Medical Oncology (ESMO)	Conference proceedings	Manual search	Ototoxicity Deaf Hearing Auditory	Final search October 2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer	Conference proceedings	Manual search	Ototoxicity Deaf Hearing Auditory	Final search October 2024
International Society for Paediatric Oncology	Conference proceedings	Manual search	Ototoxicity Deaf Hearing Auditory	Final search October 2024

Abbreviations: N/A: Not available

Source: (Norgine 2024c)

H.1.2 Search strategies

Table 81, Table 82, and Table 83 present the search strategies for Embase, MEDLINE and Embase Classic and CENTRAL databases, performed on the 14th of October 2024 and capturing publications from the 31st of October, 2023.

Table 81 Search strategy table for EMBASE, Medline, Medline (R) In-Process clinical search strategy (EMBASE interface) ([14/10/2024])

No.	Query	Results
#1	('paediatric'/exp OR 'paediatric' OR 'paediatric'/exp OR 'paediatric' OR 'child' OR 'children') AND 'cisplatin' AND ('ototoxicity' OR 'hearing' OR 'hearing'/exp)	1,560
#2	('clinical trial'/de OR 'randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'phase 3 clinical trial'/de OR 'phase 4 clinical trial'/de OR 'randomization'/exp OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial*':ti,ab OR 'randomi*ed trial*':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR ((allocated NEXT/2 random):ti,ab) OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR (((treble OR triple) NEXT/1 blind*):ti,ab) OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	3,039,446
#3	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic*	5,109,386

No.	Query	Results
	NEXT/1 (study OR studies)):ti,ab) OR (('cross sectional' NEXT/1 (study OR studies)):ti,ab)	
#4	#1 AND (#2 OR #3) AND [humans]/lim AND [31-10-2023]/sd AND [2023-2024]/py	29

Table 82 Search strategy table for CENTRAL database ([17/10/2024])

No.	Query	Results
#1	(*paediatric):ti,ab,kw OR (paediatric):ti,ab,kw (Word variations have been searched)	47,296
#2	(oncology OR cancer OR carcinoma):ti,ab,kw	235,695
#3	(cisplatin):ti,ab,kw	16,932
#4	(ototoxicity OR hearing):ti,ab,kw	9,947
#5	#1 AND #2 AND #3 AND #4 with Cochrane Library publication date Between October 2023 and 2024, in Trials, Clinical Answers	1

Table 83 Search strategy table for EMBASE, Medline, Medline (R) In-Process utility search strategy (EMBASE interface) ([15/10/2024])

No.	Query	Results
#5	('paediatric'/exp OR 'paediatric' OR 'paediatric'/exp OR 'paediatric' OR 'child' OR 'children') AND 'cisplatin' AND ('ototoxicity' OR 'hearing' OR 'hearing'/exp)	1,561
#6	('ototoxicity'/exp OR 'ototoxicity' OR 'ototoxic' OR (('hearing'/exp OR 'hearing') AND ('acquired' OR 'induced' OR 'developed')))	49,638
#7	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health*	1,358,122

No.	Query	Results
	year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti	
#8	(#5 OR #6) AND #7 AND [humans]/lim AND [31-10-2023]/sd AND [2023-2024]/py	138

H.1.3 Systematic selection of studies

The SLR was performed using a pre-defined search strategy described above to identify eligible studies. To determine the final set of studies eligible for review, explicit inclusion and exclusion criteria were applied to the literature search results. The inclusion and exclusion criteria (Population, Intervention, Comparator, Outcome, Study design [PICOS] criteria) for the 31st October 2023 searches are specified in Table 84.

Table 84 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Paediatric patients (≥1 month and <18 years old) with cisplatin-induced ototoxicity	• Studies that do not include patients of interest to the SLR. Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest.	No local adaptations required.
Intervention	Any	None	No local adaptations required.

Comparators	Any	None	No local adaptations required.

Outcomes	• Efficacy outcomes: Degree of ototoxicity assessed using a relevant instrument, including:
	  • The Brock scale
	  • The Boston scale
	  • CTCAE scale
	  • ASHA scale
	  • SIOP ototoxicity grading scale
	  • Chang scale
	• Safety outcomes:
	  • Adverse events
	• Discontinuation
	• Mortality
	Overall survival (only updated SLR search)
		• No reported outcomes of interest
		Outcomes reported only in studies with a mixed population
			No local adaptations required.

Study design/publication type	• RCTs • Non-RCTs • Observational studies (including patient registries) Cross-sectional studies	• Animal studies • In vitro/ex vivo studies Individual case study reports	No local adaptations required.
Language restrictions	Studies reported in English	Studies not reported in English	No local adaptations required.

Abbreviations: ASHA: American Speech Language and Hearing Association, CTCAE: Common Terminology Criteria for Adverse Events, RCT: randomised-controlled trial, SIOP: International Society for Paediatric Oncology, SLR: systematic literature review

After conducting the original database searches for clinical studies and removing duplicates, there were 546 unique references which underwent first pass screening. Of these, 520 did not meet the selection criteria and were consequently excluded, leaving 26 references to be considered for full text review.

Following review of the full texts, 20 references were excluded: 11 did not meet the population criteria, two did not meet the outcome criteria, two did not meet the intervention/comparator criteria, and five did not meet the publication type criteria (Table 84). Grey literature searches provided one additional reference that met the selection criteria. Overall, seven references from five unique randomised controlled trials (RCTs) and one observational study met the selection criteria following the first and second pass of the clinical studies review and were extracted (Figure 17).

In the updated database searches for clinical studies and after removing duplicates, there were 30 unique references which underwent first pass screening. Of these, 21 did

not meet the selection criteria and were consequently excluded, leaving nine references to be considered for full-text review.

Following review of the full-texts, six references were excluded: five did not meet the population criteria and one did not meet the intervention/comparator criteria (Table 84). Grey literature searches provided four additional references that met the selection criteria. Overall, seven references including one unique RCT, one single-arm clinical trial, and four observational studies met the selection criteria following the first and second pass of the clinical studies review and were extracted (Figure 18).

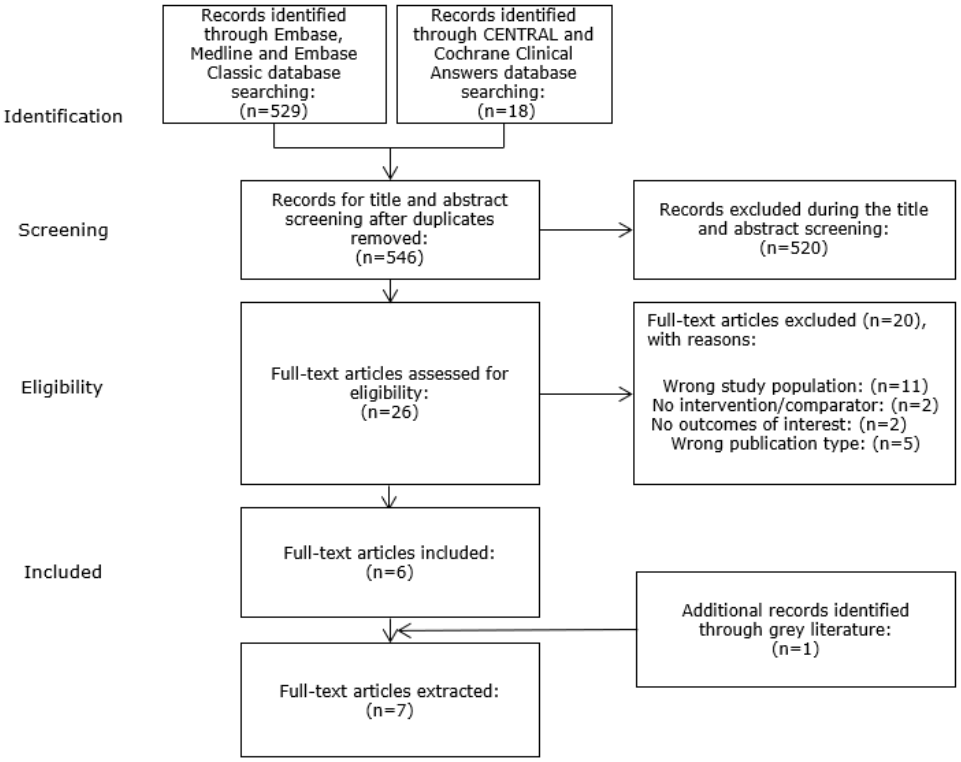


Figure 17 PRISMA flow diagram for the original Clinical Literature Search (31/10/2023)

Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials

Source: (Norgine 2024c)

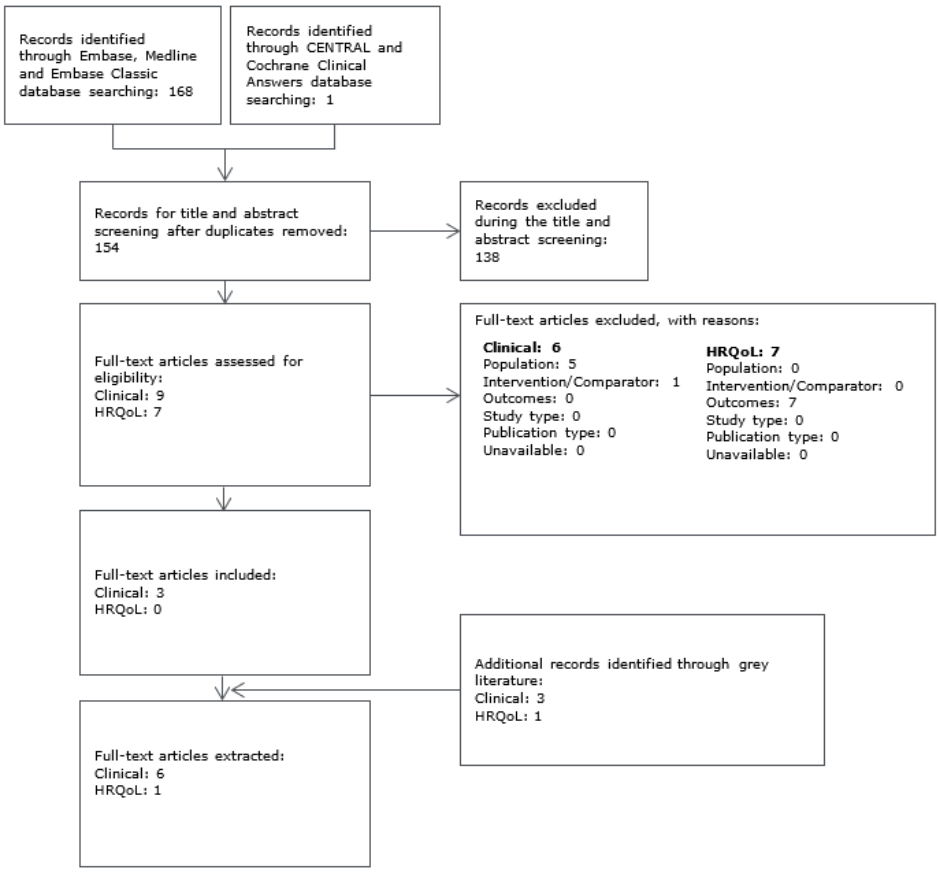


Figure 18 PRISMA flow diagram for the updated Clinical Literature Search (14/10/2024)

Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials, HRQoL: Health-related quality of life

Source: (Norgine 2024c)

Table 85 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
COG ACCL0431 **NCT00716976**	Evaluation of the safety and efficacy of PEDMARQSI in paediatric patients with solid tumours treated with cisplatin.	The trial was a multicentre, randomised, open-label, phase 3 trial. Patients were randomly assigned 1:1. Allocation sequences were generated using a permuted block algorithm with balanced 2:2 randomizations per block.	125 children with solid tumours between the age 1 and <18 years receiving cisplatin treatment (PEDMARQSI n=61, control n=65). The allocation sequence was generated for each stratum according to a permuted block algorithm, where each block of four contained two PEDMARQSI and two control randomisations.	Intervention (n=61): Patients received a 15-minute PEDMARQSI infusion which was administered 6 hours after each cisplatin treatment. Patients received an anti-emetic premedication 30 minutes prior to PEDMARQSI. Comparator (n=64): Patients received cisplatin only treatment throughout their chemotherapeutic	The primary endpoint was the incidence of hearing loss. HL was defined by comparing hearing sensitivity at the 4-weeks follow up evaluation relative to baseline measurements using ASHA criteria. The analysis was done in the efficacy population.	Important secondary endpoints were the change in hearing thresholds for key frequencies (500 hz, 1000 hz, 2000 hz, 4000 hz, 8000 hz), 4 weeks after the last dose of cisplatin; renal- and haematological toxicity, including a 4-weeks follow-up period; event-free

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
				treatment protocol.		survival and overall survival, with a median follow-up period of 5.33 years.
SIOPEL-6 **NCT00652132**	Evaluation of the safety and efficacy of PEDMARQSI in paediatric patients with hepatoblastoma	The trial was a multicenter, randomised, controlled, open-label study conducted by the International Childhood Liver Tumor Strategy Group (SIOPEL) to assess the efficacy and safety of PEDMARQSI in reducing ototoxicity in children receiving cisplatin chemotherapy	109 children with solid tumours who are to receive cisplatin treatment (PEDMARQSI n=57, no PEDMARQSI n=52) were stratified according to country, median age (<15 months vs ≥15 months), and PRETEXT tumour classification (I vs II vs III).	Intervention (n=57): Patients (treatment arm) received a 15-minute PEDMARQSI infusion which was administered 6 hours after each cisplatin treatment. Patients received an anti-emetic premedication 30 minutes prior to PEDMARQSI. Comparator (n=52): Patients received cisplatin only treatment	The primary endpoint was the rate of a Brock grade ≥1 on the Brock ototoxicity HL scale. The endpoint was determined at the end of the trial treatment or at an age of 3.5 years, whichever came later. The analysis was done in the intention-to-treat population.	Important secondary endpoints were the response to preoperative chemotherapy and complete resection, following completion of preoperative chemotherapy; complete remission at the end of the trial treatment; event-free survival, until

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
		for standard risk hepatoblastoma. Children were randomised 1:1 to receive PEDMARQSI after each cisplatin dose (cisplatin + PEDMARQSI arm) or cisplatin without subsequent PEDMARQSI (cisplatin alone arm).		throughout their chemotherapeutic treatment protocol.		first event or up to 5 years follow-up; overall survival, until event or up to 5 years follow-up; toxic effects, evaluated until 30 days post treatment; long-term renal clearance or glomerular filtration rate, until event or up to 5 years follow-up; and the feasibility of central audiologic review, at the end of trial treatment or at an age of 3.5 years,

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						whichever is later.

Abbreviations: ASHA: American Speech Language and Hearing Association, HL: hearing loss, Hz: hertz, PRETEXT: Pre-treatment Tumour Extension

Sources: (ClinicalTrials.gov 2018, ClinicalTrials.gov 2021, [redacted])

H.1.4 Excluded full text references

Table 86 depicts all excluded RCTs.

Table 86 Clinical SLR – excluded RCTs (N=20)

Author	Journal	Title	Reason for exclusion
Author	Journal	Title	Reason for exclusion
Original SLR			
Orgel *et al.* 2023	Clinical cancer research: an official journal of the American Association for Cancer Research	Intravenous N-Acetylcysteine to Prevent Cisplatin-Induced Hearing Loss in Children: A Nonrandomized Controlled Phase I Trial	Mixed population with no disaggregated results of interest
Oder *et al.* 2023	Paediatric Blood and Cancer	Platinum compound associated ototoxicity	Outcome not of interest
Brock *et al.* 2022	Paediatric Blood and Cancer	Named patient program use of Pedmark™ to reduce the risk of cisplatin-induced ototoxicity in paediatric patients with localized solid tumours	Mixed population with no disaggregated results of interest
Ellis *et al.* 2019	International Journal of Radiation Oncology Biology Physics	Reduction in Ototoxicity Using IMRT for Patients with Medulloblastoma/PNET	Not paediatric population
Levin *et al.* 2017	Paediatric Blood and Cancer	Cisplatin ototoxicity in patients with osteosarcoma treated with and without the organic cation transporter 2 inhibitor pantoprazole	Pre-2021 CA
Brock *et al.* 2016	Paediatric Blood and Cancer	Two year results of a randomised phase iii trial for standard risk hepatoblastoma (SR-HB) SIOPEL-6; cisplatin and sodium thiosulfate (STS) vs cisplatin alone	Pre-2021 CA
Paulino *et al.* 2016	Neuro-Oncology	Ototoxicity and cochlear sparing in children with medulloblastoma: Proton vs. photon radiotherapy	Pre-2021 CA
Brock *et al.* 2016	Journal of Clinical Oncology	Two-year results of clinical efficacy of cisplatin in combination with sodium thiosulfate (STS) vs cisplatin alone in a randomized phase III trial	Pre-2021 CA

		for standard risk hepatoblastoma (SR-HB): SIOPEL-6	
Am Zehnhoff-Dinnesen *et al.* 2015	Paediatric Blood and Cancer	Impact of gentamicin use on cisplatin-induced hearing loss in patients with osteosarcoma	Mixed population with no disaggregated results of interest
Clemens *et al.* 2015	Paediatric Blood and Cancer	The influence of co-medication on platinum-related ototoxicity in long-term survivors of childhood cancer: An observational dcog study	No intervention
Vieira *et al.* 2014	Radiation Oncology	Ototoxicity evaluation in medulloblastoma patients treated with involved field boost using intensity-modulated radiation therapy (IMRT): A retrospective review	Mixed population with no disaggregated results of interest
Neuwelt *et al.* 2018	Neuro-oncology	Hearing chemoprotection with sodium thiosulfate (STS) in children, adolescents and young adults with standard risk medulloblastoma	No intervention
Fouladi *et al.* 2008	Journal of Clinical Oncology	Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma	Mixed population with no disaggregated results of interest
Womack *et al.* 2014	Ear and hearing	Evaluation of ototoxicity in patients treated with hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin and sodium thiosulfate	Mixed population with no disaggregated results of interest
Ekborn *et al.* 2004	Laryngoscope	High-dose cisplatin with amifostine: Ototoxicity and pharmacokinetics	Not paediatric population
Fox *et al.* 2018	Oncologist	Pantoprazole, an Inhibitor of the Organic Cation Transporter 2, Does Not Ameliorate Cisplatin-Related Ototoxicity or Nephrotoxicity in Children and Adolescents with Newly Diagnosed Osteosarcoma Treated with Methotrexate, Doxorubicin, and Cisplatin	Mixed population with no disaggregated results of interest
Sarafraz *et al.* 2018	International Tinnitus Journal	Transtympanic injections of N-acetylcysteine and dexamethasone for prevention of cisplatin-induced ototoxicity: Double blind randomized clinical trial	Mixed population with no disaggregated results of interest

Takumida *et al.* 2000	Practica Otologica	Treatment of cisplatin ototoxicity by anti-oxidant drugs	Non-English publication
Petrilli *et al.* 2002	Journal of Paediatric Hematology/Oncology	Use of amifostine in the therapy of osteosarcoma in children and adolescents	Mixed population with no disaggregated results of interest
Orgel *et al.* 2022	Lancet Oncology	Sodium thiosulfate for prevention of cisplatin-induced hearing loss: updated survival from ACCL0431	Outcome not of interest
Updated SLR			
Abu-Arja *et al.* 2024	Neuro-Oncology	The cochlear dose and the age at radiotherapy predict severe hearing loss after passive scattering proton therapy and cisplatin in children with medulloblastoma	Not paediatric population
Becktell *et al.* 2024	Paediatric Blood and Cancer	Long-term outcomes among survivors of childhood osteosarcoma: A report from the Childhood Cancer Survivor Study (CCSS)	Not paediatric population
Elayadi *et al.* 2024	Neuro-Oncology	Toxicity profile of two chemotherapeutic regimens adopted from COG A9961 and ACNS0331 for standard-risk medulloblastoma, a comparative study	Not paediatric population
Coltin *et al.* 2024	Neuro-Oncology	Early severe hearing loss in Canadian children with central nervous system tumours: A population-based cohort study	Not cisplatin-induced toxicity
Robinson *et al.* 2024	Neuro-Oncology	Effect of reduced-dose craniospinal irradiation and reduced-dose adjuvant chemotherapy on children and adolescents with wingless (WNT) medulloblastoma without residual or metastatic disease: Results from the SJMB112 clinical trial	Not paediatric population
Temuroglu *et al.* 2023	Hematology, Transfusion and Cell Therapy	Long-term evaluation results of our patients diagnosed with nasopharyngeal carcinoma: A single centre experience	Not paediatric population

Source: (Norgine 2024c)

H.1.5 Quality assessment

Studies were selected by two independent reviewers based on title and abstract (first pass) and then full-text articles (second pass). Selected studies were then extracted by one reviewer and assessed for quality by a second reviewer. Disagreements were resolved by a third reviewer when required. Furthermore, a critical appraisal of the RCTs was performed. The questions were taken from the NICE user guide for Company evidence submission template (NICE 2022b).

The SLR methodology adhered to established, best-practice protocols, meeting the requirements outlined in the Centre for Reviews and Dissemination (CRD) guidance, which is considered robust for HTAs across Europe. The review included clinical and HRQoL studies, covering not only the clinical effectiveness of STS, including PEDMARQSI, in the prevention of cisplatin-induced ototoxicity, but also extending to HRQoL studies in patients with acquired HL. The quality assessment for the two trials COG ACCL0431 and SIOPEL-6 is depicted in Table 87.

Table 87 Randomised controlled trials quality assessment

Study identifier (trial acronym)	SIOPEL-6	COG ACCL0431
Was the method used to generate random allocations adequate? described in the Introduction or Methods section?	Y	Y
Comments	Randomisation was central via the CINECA remote data entry system; Described in supplement	Randomisation was centrally computer-generated by the COG trial management system; permuted blocks of four
Were the groups similar at the outset of the study in terms of prognostic factors, e.g., severity of disease? described in the Introduction or Methods section?	PN	NI

Comments	Cisplatin + STS arm had slightly lower PRETEXT score III than Cisplatin arm; In table 1	Similar between groups
Was the treatment allocation sequence adequately concealed? **in the study clearly described?**	PY	Y
Comments	Even though open-label, randomisation was central via the CINECA remote data entry system; Described in supplement	Allocation was electronically concealed to all investigators, clinicians, and participants
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	N	N
Comments	Only audiology central reviewer was blinded; Open-label study	Only audiology central reviewer was blinded; Open-label study
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? **each group of subjects to be compared clearly described?**	N	N
Comments	No unexpected imbalances in drop-outs	No unexpected imbalances in drop-outs

Is there any evidence to suggest that the authors measured more outcomes than they reported? described?	N	Y
Comments	Only outcomes from objective were reported	The study author did a post-hoc stratification of the sample by extent of disease at enrolment because of the possibility of an effect of STS on survival that emerged for the sample as a whole
Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? variability in the data for the main outcomes?	Y	Y
Comments	ITT; Appropriate methods used	ITT; Appropriate methods used

Abbreviations: ITT: intention to treat, N: no, NI: no information, PN: probably no, PRETEXT: Pre-treatment Tumour Extension, PY: probably yes, STS: sodium thiosulfate, Y: yes

H.1.6 Unpublished data

Not applicable.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

I.1.1 Overview of the SLR

A comprehensive SLR search was conducted in key biomedical electronic literature databases and supplemented with an updated SLR in October 2024. Searches for economic evaluation studies were conducted on 25th October 2023 in the following electronic databases:

- Embase and Embase classic (using Embase.com)
- MEDLINE (using pubmed.ncbi.nlm.nih.gov)
- CRD HTA Database
- CRD National Health Service (NHS) Economic Evaluation Database (EED)
- Sheffield Centre for Health and Related Research Health Utilities Database (ScHARRHUD)
- EuroQol database

An updated search was performed to adhere to Danish guidline regarding using searches that are younger than 6 months, The SLR was updated and conducted from the 14th of October 2024 to identify studies published since 31st October 2023.

In addition, Supplementary searches of “grey” literature were performed in Google Scholar and through the ICTRP, CEA registry, NICE, RePEc, EQ-5D, ScHARRHUD, CENTRAL, clinicaltrials.gov and WHO websites (see Table 88 and Table 89).

The database search strings identified included terms for free text and keywords (MESH and Emtree terms) combined using Boolean combination techniques. Filters were used to ensure the search results were relevant for the review question.

Where possible, data identified within the review was supplemented by data available (e.g., manufacturer submissions) on the following HTA body websites:

- NICE (England)
- Scottish Medicines Consortium (Scotland)
- All Wales Medicines Strategy Group (Wales)

I.1.2 Non-clinical SLR search expansion

It is noted that the clinical SLR is focused on identifying literature for the prevention or management of cisplatin-induced ototoxicity in paediatric patients, defined due to its alignment with the licence for PEDMARQSI (see Appendix H). However, given the

focused indication for PEDMARQSI, it was hypothesised, and later demonstrated through test runs, that few economic studies (cost-effectiveness, HRQoL, or cost and resource use) specific to this population would be available.

In order to overcome this problem, and subsequently identify a greater number of papers through the systematic review process, the patient population in the economic SLRs was expanded in the database searches to include the prevention/management of acquired HL in all age groups. It is considered that these population criteria are appropriate to include as the economic model captures patients across a lifetime horizon and not just in the paediatric setting. In addition, ototoxicity is a form of acquired HL (HL which develops after birth)(ASHA 2024) and it is assumed that patients with HL from birth are likely to cope with their condition differently to those who acquire it post-birth.

For the economic grey literature search, the search strategies included patients of all ages with HL of all causes (i.e. they were not limited to acquired HL). This strategy was applied for the grey literature search to reflect the broadest possible population.

In summary, given the focused licence for PEDMARQSI, it was expected that a limited number of literature sources would be identified for the economic SLRs. As a result, the population included in the data base searches was expanded to include the prevention/management of HL in all age groups with a focus on acquired causes of HL, while the grey literature included patients of all ages with HL of all causes. This search strategy reflects a comprehensive evidence base to inform this HTA submission and the same approach is used for the HRQoL and cost and resource use SLRs.

Table 88 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	embase.com	1978 to present	31/10/2023 Updated: 14/10/2024
Embase Classic	embase.com	1947 to 1973	31/10/2023 Updated: 14/10/2024
CRD	crd.york.ac.uk	1978 to present	31/10/2023 Updated: 14/10/2024
EED	crd.york.ac.uk	1978 to present	31/10/2023 Updated: 14/10/2024
ScHARRHUD	N/A	1978 to present	31/10/2023

Database	Platform	Relevant period for the search	Date of search completion
			Updated: 14/10/2024
EurpQpl	euroqol.org	1978 to present	31/10/2023 Updated: 14/10/2024

Abbreviations: CRD: Centre for Reviews and Dissemination health technology assessment database, EED: CRD, N/A: Not available, NHS Economic Evaluation Database, ScHARRHUD: Sheffield Centre for Health and Related Research Health Utilities Database

Source: (Norgine 2024c)

Table 89 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ICTRP	https://www.who.int/clinical-trials-registry-platform	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
NICE	www.nice.org.uk	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
CEA	https://cear.tuftsmedicalcenter.org/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
RePEc	http://repec.org/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
EQ-5D	https://registration.euroqol.org/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
WHO	https://www.who.int/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
Clinical trials	www.clinicaltrials.gov	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024

Source name	Location/source	Search strategy	Date of search
ScHARRHUD	N/A	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024
CENTRAL	www.cochranelibrary.com/central/	Searches for relevant literature using key words in website-based search function.	Final search conducted 14/10/2024

Abbreviations: CEA: Cost-Effectiveness Analysis registry, CENTRAL: Cochrane Central Register of Controlled Trials, EED: Economic Evaluation Database, EQ-5D: EuroQol 5-dimensions, ICTRP: International Clinical Trials Registry Platform, NICE: National Institute for Health and Care Excellence, RePEc: Research papers in Economics, WHO: World Health Organisation, ScHARRHUD: Sheffield Centre for Health and Related Research Health Utilities Database

Source: (Norgine 2024c)

No conference material was searched in the HRQoL-specific SLR.

I.1.3 Search strategies

Table 90 Search strategy for Embase, MEDLINE, CRD HTA and NHS EED

No.	Query	Results
#1	('pediatric'/exp OR 'pediatric' OR 'paediatric'/exp OR 'paediatric' OR 'child' OR 'children') AND 'cisplatin' AND ('ototoxicity' OR 'ototoxicity'/exp OR 'ototoxic' OR 'hearing' OR 'hearing'/exp)	1,476
#2	('ototoxicity'/exp OR 'ototoxicity' OR 'ototoxic' OR (('hearing'/exp OR 'hearing') AND ('acquired' OR 'induced' OR 'developed')))	45,550
#3	'socioeconomics'/de OR 'cost benefit analysis'/de OR 'cost effectiveness analysis'/de OR 'cost of illness'/de OR 'economic evaluation'/de OR 'cost utility analysis'/de OR 'cost control'/de OR 'economic aspect'/de OR 'financial management'/de OR 'health care cost'/de OR 'health care financing'/de OR 'health economics'/de OR 'hospital cost'/de OR fiscal:ab,ti OR financial:ab,ti OR finance:ab,ti OR funding:ab,ti OR 'cost minimization analysis'/de OR cost NEXT/1 estimate* OR cost NEXT/1 variable* OR unit NEXT/1 cost*	1,179,121
#4	'quality adjusted life year'/de OR 'value of life':ab,ti OR socioeconomics/de OR (qaly* OR qald* OR qale* OR qtime*):ab,ti OR (quality adjusted OR adjusted life year*):ab,ti OR 'disability adjusted life':ab,ti OR daly*:ab,ti OR ((index NEXT/3 wellbeing) OR (quality NEXT/3 wellbeing) OR qwb):ab,ti OR (multiattribute* OR multi attribute*):ab,ti OR (utility NEXT/3 (score* OR scoring OR valu* OR measur* OR evaluat* OR scale* OR instrument* OR weight OR weights OR weighting OR information OR data OR unit OR units OR health* OR life OR estimate* OR elicit* OR disease* OR mean OR cost* OR expenditure* OR gain OR	1,263,856

No.	Query	Results
	gains OR loss OR losses OR lost OR analysis OR index* OR indices OR overall OR reported OR calculate* OR range* OR increment* OR state OR states OR status)):ab,ti OR utility:ab,ti OR utilities:ab,ti OR disutili*:ab,ti OR (HSUV OR HSUVs):ab,ti OR 'health* year* equivalent*':ab,ti OR (hye OR hyes):ab,ti OR (hui OR hui1 OR hui2 OR hui3):ab,ti OR ('illness state*' OR health state*):ab,ti OR ('euro qual' OR 'euro qual5d' OR 'euro qol5d' OR eq-5d OR eq5-d OR eq5d OR euroqual OR euroqol OR euroqual5d OR euroqol5d):ab,ti OR (eq-sdq OR eqsdq):ab,ti OR (short form* OR shortform*):ab,ti OR (sf36* OR 'sf 36*' OR 'sf thirtysix' OR 'sf thirty six'):ab,ti OR (sf6 OR 'sf 6' OR sf6d OR 'sf 6d' OR 'sf six' OR sfsix OR sf8 OR 'sf 8' OR 'sf eight' OR sfeight):ab,ti OR (sf12 OR 'sf 12' OR 'sf twelve' OR sftwelve):ab,ti OR (sf16 OR 'sf 16' OR 'sf sixteen' OR sfsixteen):ab,ti OR (sf20 OR 'sf 20' OR 'sf twenty' OR sftwenty):ab,ti OR (15D OR 15-D OR '15 dimension'):ab,ti OR ('standard gamble*' OR sg):ab,ti OR ('time trade off*' OR 'time tradeoff*' OR tto OR timetradeoff*):ab,ti	
#5	burden:ti OR resource*:ti OR ((burden* NEXT/3 (illness* OR disease* OR sickness* OR treatment* OR therap*)):ab,ti) OR ((resource* NEXT/4 (use* OR usage OR utilit*)):ab,ti) OR 'office visits':ab,ti OR 'ambulatory care'/de OR visit:ab,ti OR visits:ab,ti OR visited:ab,ti OR appointment*:ab,ti OR 'hospitalization'/de OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR hospitalised:ab,ti OR hospitalized:ab,ti OR admission*:ab,ti OR readmission*:ab,ti OR admitted:ab,ti OR readmitted:ab,ti OR 'length of stay'/de OR 'hospital stay*':ab,ti OR ((bed NEXT/3 day*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 hospital*):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (stay OR stays OR stayed)):ab,ti) OR (((days OR time OR length OR duration*) NEXT/3 (discharge OR discharged OR home OR homes)):ab,ti)	2,286,499
#6	(#1 OR #2) AND (#3 OR #4 OR #5) AND [humans]/lim AND [1978-2023]/py	4,205

Table 91 Search strategy for CENTRAL

No.	Query	Results
#1	(*pediatric):ti,ab,kw OR (paediatric):ti,ab,kw (Word variations have been searched)	43,065
#2	(oncology OR cancer OR carcinoma):ti,ab,kw	219,215
#3	(cisplatin):ti,ab,kw	16,156
#4	(ototoxicity OR hearing):ti,ab,kw	9,041
#5	#1 AND #2 AND #3 AND #4 with Cochrane Library publication date Between Jan 1978 and Dec 2023, in Trials, Clinical Answers	18

I.1.4 Study selection

Potentially relevant publications were reviewed and assessed to collate a final set of studies that formed the main body of the economic evidence. To determine the final set of studies eligible for review, explicit PICOS inclusion and/or exclusion criteria were applied to the results of the literature search.

The study selection process was performed in the following two phases:

- Following the removal of duplicate records across the databases searched, two independent reviewers assessed the relevance of identified studies based on title and abstract (first pass) for inclusion using the review question and selection criteria (Table 92). A discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required to arbitrate disagreements.
- Following the completion of first pass, full text copies of all potentially relevant records were obtained and evaluated in more detail (second pass) against the pre-defined selection criteria (Table 92). A discussion was held between the two reviewers after 20% of the studies had been reviewed to ensure they were aligned on the selection criteria. Disagreements were discussed, and a third reviewer was involved where required to arbitrate disagreements. All papers excluded at this second stage of the screening process were documented along with the reasons for exclusion.

The PICOS inclusion and exclusion criteria for the HRQoL studies are specified in Table 92.

Table 92 Eligibility (PICOS) criteria for the HRQoL SLR

Selection criteria	Inclusion criteria	Exclusion criteria
Population (P)*	Patients with acquired HL	Studies that do not include patients of interest to the SLR. Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest.
Interventions (I)	Any	None
Comparators (C)	Any	None

Outcomes (O)	Cost-effectiveness results such as ICER and QALYs Cost-utility results Cost-minimisation results Cost-benefit results	No reported outcomes of interest
Study type (S)	Economic evaluations: Cost-effectiveness analysis Cost-utility analysis Cost-benefit analysis Cost-minimisation analysis Economic evaluations alongside clinical trials	Cost study Burden of disease study Resource use study Individual case study reports
Publication type	Article Conference abstract Conference paper Conference posters Article in press	Short surveys Letters Editorials Reviews Comment articles
Language	Studies reported in English	Studies not reported in English

*The population criteria in the HRQoL SLR database searches were expanded to include the prevention/management of acquired HL in all ages.

Abbreviations: BSC: best supportive care, HL: hearing loss, ICER: incremental cost-effectiveness ratio, QALY: quality-adjusted life year, SLR: systematic literature review

Source: (Norgine 2024c)

Following the review of 4,161 references against the selection criteria for the HRQoL SLR during the title and abstract screening, 94 references were considered for full text review.

Following review of the full texts, 75 references were excluded because they did not meet the selection criteria: three did not meet the population criteria, 56 did not meet the outcomes criteria, five did not meet the study type criteria, ten did not meet the publication type criteria and one was unavailable in English. A grey literature search provided an additional 18 QoL studies which met the inclusion criteria. Overall, 37 references met the selection criteria following the first and second pass of the HRQoL studies review and were extracted (Figure 19).

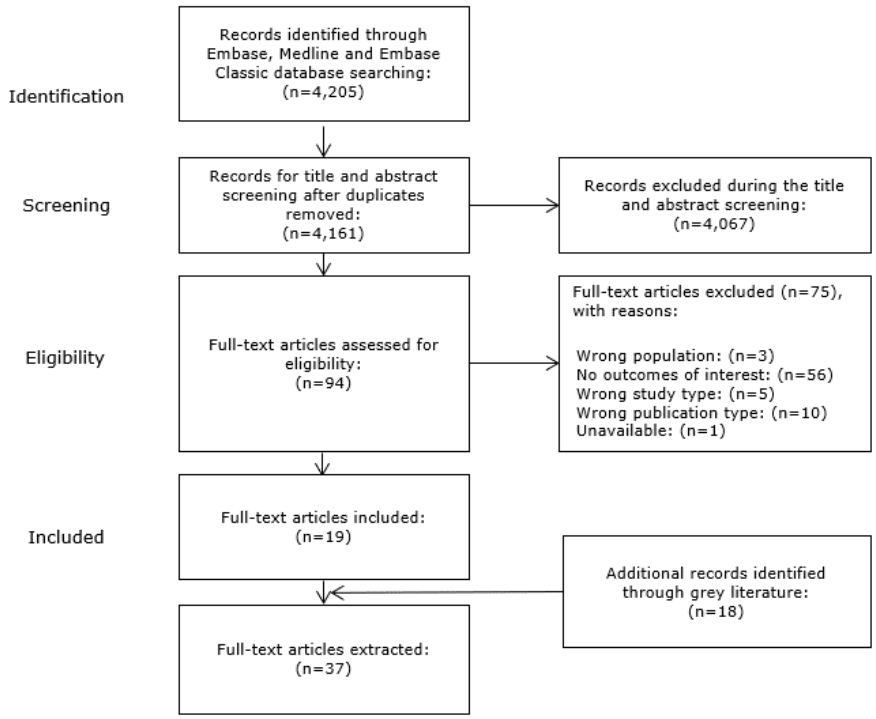


Figure 19 PRISMA flow chart – HRQoL evidence

As above mentioned, an updated SLR was performed to support this submission, so the search period was up to date.

The SLR was updated and conducted from the 14th of October 2024 to identify studies published since 31st October 2023, results are illustrated in Figure 20.

Following the review of 124 references against the selection criteria for review question 2 during the title and abstract screening, seven references were considered for full-text review.

Following review of the full-texts, six references were excluded because they did not meet the selection criteria: all six references did not meet the outcomes criteria. Furthermore, a grey literature search provided one additional study, an ongoing NICE TA, which met the inclusion criteria following first and second pass of the HRQoL studies review and was extracted.

In total, one HRQoL reference was identified as part of this SLR update, which was an ongoing NICE TA evaluating PEDMARQSI for the prevention of cisplatin-induced ototoxicity in the paediatric population. However, no results were reported.

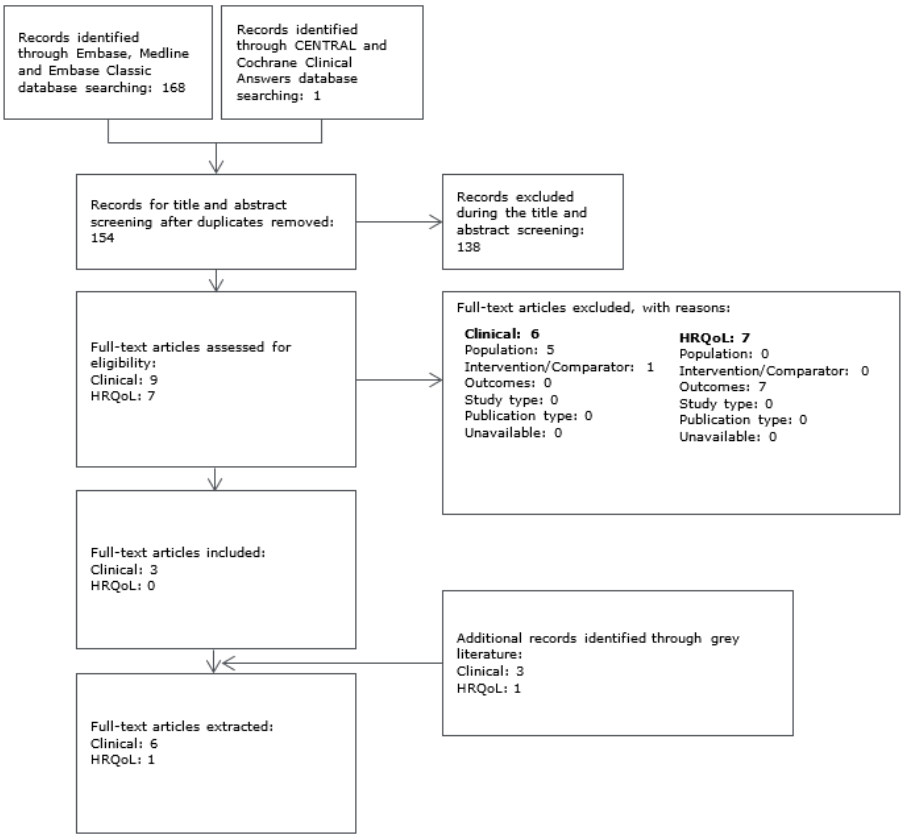


Figure 20 PRISMA flow diagram for the updated HRQoL Literature Search (14/10/2024)

Abbreviations: CENTRAL: Cochrane Central Register of Controlled Trials, HRQoL: Health-related quality of life

I.1.5 Results

A summary of included studies is presented in Table 93.

Table 93 HRQoL SLR – included studies (N=37)

Author	Treatment	Full citation
Palmer et al. 1999	Intervention: Multichannel cochlear implant Comparator: Non-implant recipients	Palmer et al. A prospective study of the cost-utility of the multichannel cochlear implant. Arch Otolaryngol Head Neck Surg. 1999;125(11):1221-1228.
McDool et al. 2021	NR	McDool et al. A Comparison of the SF-6Dv2 and SF-6D UK Utility Values in a Mixed Patient and Healthy Population. Pharmacoeconomics. 2021;39(8):929-940.
Mylanus et al. 2020	Intervention: Osia System	Mylanus et al. Multicentre Clinical Investigation of a New Active Osseo integrated Steady-State Implant System. Otol Neurotol. 2020;41(9):1249-1257.

Montes et al. 2017	Intervention: Cochlear Implant Comparator 1: Hearing Aids Comparator 2: No Treatment	Montes et al. Cochlear Implants Versus Hearing Aids in a Middle-Income Country: Costs, Productivity, and Quality of Life. Otol Neurotol. 2017;38(5):e26-e33
Krabbe et al. 2000	Intervention 1: Pre-cochlear Implant Intervention 2: Post-cochlear Implant Comparator: Control group	Krabbe et al. The effect of cochlear implant use in post lingually deaf adults. Int J Technol Assess Health Care. 2000;16(3):864-873.
Hirano et al. 2014	Intervention: Proton beam therapy with cochlear dose reduction Comparator: Conventional X-ray radiotherapy	Hirano et al. Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medulloblastoma in childhood. J Radiat Res. 2014;55(2):320-327.
Landry et al. 2022	Intervention: Novel hearing therapeutics	Landry et al. Early Health Economic Modelling of Novel Therapeutics in Age-Related Hearing Loss. Front Neurosci. 2022;16:769983. Published 2022 Mar 4.
James et al. 2021	NR	James et al. The Listening Network and Cochlear Implant Benefits in Hearing-Impaired Adults. Front Aging Neurosci. 2021;13:589296. Published 2021 Feb 25.
Culter et al. 2022	Intervention: Unilateral cochlear implants Comparator 1: Hearing aid Comparator 2: No hearing aid	Cutler et al. The cost-effectiveness of unilateral cochlear implants in UK adults. Eur J Health Econ. 2022;23(5):763-779.
Huang et al. 2021	NR	Huang et al. Cost-effectiveness of implementing routine hearing screening using a tablet audiometer for paediatric cystic fibrosis patients receiving high-dose IV aminoglycosides. J Manag Care Spec Pharm. 2021;27(2):157-165.
Gumbie et al. 2021	Intervention: Unilateral cochlear implant Comparator: Hearing aid	Gumbie et al. The cost-effectiveness of Cochlear implants in Swedish adults. BMC Health Serv Res. 2021;21(1):319.

Kosaner Kliess et al. 2017	Intervention: Vibrant Soundbridge implant Comparator: No surgical intervention	Kosaner Kliess et al. Cost-Utility of Partially Implantable Active Middle Ear Implants for Sensorineural Hearing Loss: A Decision Analysis. Value Health. 2017;20(8):1092-1099.
Hol et al. 2004	Intervention: Bone-anchored hearing aid Comparator: No treatment	Hol et al. The bone-anchored hearing aid: quality-of-life assessment. Arch Otolaryngol Head Neck Surg. 2004;130(4):394-399.
Lytle et al. 2023	NR	Lytle et al. Cost-effectiveness analysis of PCV20 to prevent pneumococcal disease in the Canadian paediatric population. Hum Vaccin Immunother. 2023;19(2):2257426.
Sevilla et al. 2022	NR	Sevilla et al. Cost-utility and cost-benefit analysis of paediatric PCV programs in Egypt. Hum Vaccin Immunother. 2022;18(6):2114252.
Veenstra et al. 2007	NR	Veenstra et al. Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes. Genet Med. 2007;9(10):695-704.
Gumbie et al. 2022	NR	Gumbie et al. Cost-Effectiveness of Screening Preschool Children for Hearing Loss in Australia. Ear Hear. 2022;43(3):1067-1078.
Verkleij et al. 2021	NR	Verkleij et al. Cost-Effectiveness of Neonatal Hearing Screening Programs: A Micro-Simulation Modeling Analysis. Ear Hear. 2021;42(4):909-916.
Lee et al. 2006	Intervention: Cochlear implant	Lee et al. Cost-utility analysis of cochlear implants in Korea using different measures of utility. Acta Otolaryngol. 2006;126(8):817-823.
Summerfield et al. 2018	Intervention: Cochlear implant	Summerfield et al. Sensitivity of EQ-5D-3L, HUI2, HUI3, and SF-6D to changes in speech reception and tinnitus associated with cochlear implantation. Qual Life Res. 2019;28(5):1145-1154.
Barton et al. 2004	Intervention: No hearing aid provision Comparator: Analogue or digital signal-processing hearing aid (or aids)	Barton et al. Comparing utility scores before and after hearing-aid provision : results according to the EQ-5D, HUI3 and SF-6D. Appl Health Econ Health Policy. 2004;3(2):103-105.

Hallin et al. 2023	Intervention: Cochlear implant	Hallin et al. Do Patients Aged 85 Years and above Benefit from Their Cochlear Implants?. Audiol Res. 2023;13(1):96-106. Published 2023 Jan 19.
Baek et al. 2016	NR	Baek et al. Health-Related Quality of Life in Korean Adults with Hearing Impairment: The Korea National Health and Nutrition Examination Survey 2010 to 2012. PLoS One. 2016;11(10):e0163999. Published 2016 Oct 6.
Maes et al. 2011	NR	Maes et al. Assessment of health state in patients with tinnitus: a comparison of the EQ-5D and HUI mark III. Ear Hear. 2011;32(4):428-435.
Mitchell et al. 2017	NR	Mitchell et al. Are Quality-Adjusted Life Years a Good Proxy Measure of Individual Capabilities?. Pharmacoeconomics. 2017;35(6):637-646. [published correction appears in Pharmacoeconomics. 2019 Jul;37(7):969].
Kwon et al. 2015	NR	Kwon et al. Sensory Impairment and Health-Related Quality of Life. Iran J Public Health. 2015;44(6):772-782.
Ramakers et al. 2016	Intervention: Simultaneous bilateral cochlear implantation Comparator: Unilateral cochlear implantation	Ramakers et al. Agreement between health utility instruments in cochlear implantation. Clin Otolaryngol. 2016;41(6):737-743.
Barton et al. 2005	NR	Barton et al. A comparison of the quality of life of hearing-impaired people as estimated by three different utility measures. Int J Audiol. 2005;44(3):157-163.
Joore et al. 2003	Intervention: Hearing aid	Joore et al. The cost-effectiveness of hearing-aid fitting in the Netherlands. Arch Otolaryngol Head Neck Surg. 2003;129(3):297-304. doi:10.1001/archotol.129.3.297
Grutters et al. 2007	Intervention: Direct hearing aid provision Comparator: Provision by referral	Grutters et al. Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. Qual Life Res. 2007;16(8):1439-1449.
Watson et al. 2021	Intervention: Active communication education + hearing aid provision (ACE) Comparator: Hearing aid	Watson et al. Randomised controlled feasibility trial of an active communication education programme plus hearing aid provision versus hearing aid provision alone (ACE To HEAR). BMJ Open. 2021;11(4):e043364. Published 2021 Apr 7.

	provision alone (TAU)	
Simpson et al. 2015	NR	Simpson et al. Health-related quality of life in older adults: Effects of hearing loss and common chronic conditions. Healthy Aging Res. 2015;4:4.
Kuthubutheen et al. 2014	Intervention: Bilateral cochlear implantation	Kuthubutheen et al. The effect of different utility measures on the cost-effectiveness of bilateral cochlear implantation. Laryngoscope. 2015;125(2):442-447.
Smulders et al. 2016	Intervention: Bilateral cochlear implantation Comparator: Unilateral cochlear implantation	Smulders et al. Cost-Utility of Bilateral Versus Unilateral Cochlear Implantation in Adults: A Randomized Controlled Trial. Otol Neurotol. 2016;37(1):38-45.
Oostenbrink et al. 2002	NR	Oostenbrink et al. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. J Clin Epidemiol. 2002;55(8):791-799. doi:10.1016/s0895-4356(02)00448-1
Joore et al. 2002	Intervention: Hearing aid	Joore et al. Development of a questionnaire to measure hearing-related health state preferences framed in an overall health perspective. International journal of technology assessment in health care, 18(3), 528–539.
Mailhot Vega et al. 2013	Intervention: Photon therapy Comparator: Proton therapy	Mailhot Vega RB et al. Cost-effectiveness of proton therapy compared with photon therapy in the management of paediatric medulloblastoma. Cancer. 2013;119(24):4299-4307.

Abbreviations: NR: Not reported

Of the 37 studies identified above, nine studies reported HRQoL data by HL severity level: McDool 2021; Montes 2017; Landry 2022; Gumbie 2022; Verkleij 2021; Baek 2016; Maes 2011; Simpson 2015; and Oostenbrink 2002. One study identified (Kuthubutheen 2014) reported utility values for professional carers of patients with severe to profound sensorineural HL. The HRQoL data reported in these studies are presented in Table 94.

Table 94 Details and results from included HRQoL studies

Author	N	Patient population	Elicitation method	Utilities with variance
Palmer et al. 1999	84	Adults 18 years or older who exhibited limited speech understanding with conventional (hearing aid) amplification. Severely to profoundly hearing-impaired adult recipients of a cochlear implant and adults eligible for the device who had not yet received it. No medical, surgical, or cognitive contraindications to implantation; and no prior cochlear implantation.	HUI.	HUI scores, mean (SD): At time of enrolment Implant group: 0.58 (0.17), Non-implant group: 0.58 (0.20). At 6 months Implant group: 0.76 (0.18) [P<0.001], Non-implant group: 0.57 (0.18). At 12 months Implant group: 0.78 (0.17) [P<0.01], Non-implant group: 0.58 (0.23), Increase in health utility for implant recipient, (range): 0.20 (0.20-0.20+0.5%).
McDool et al. 2021	831	Data from the Multi-Instrument Comparison (MIC) project were used. The Abbreviated Profile of Hearing Aid Benefit is used to assess hearing aid benefit and produces scores for aided and unaided performance for the HL sample.	SF-6D, SF-6Dv2.	Utilities, mean (SD): Hearing problems SF-6Dv2: 0.757 (0.228) [P= 0.152], SF-6D: 0.750 (0.119). Utilities, median [range]: Hearing problems SF-6Dv2: 0.820 [(-0.574)-1], SF-6D: 0.753 [0.334- 1]. Mild hearing problems, n=287 SF-6Dv2: 0.798 (0.185), SF-6D: 0.763 (0.110).

				Moderate hearing problem, n=225 SF-6Dv2: 0.734 (0.236), SF-6D: 0.708 (0.120). Severe hearing problem, n=104 SF-6Dv2: 0.680 (0.271), SF-6D: 0.708 (0.133).
Mylanus et al. 2020	51	Adult subjects with conductive HL or mixed HL in the ear to be implanted. Bone conduction thresholds with pure tone average [PTA4, mean of thresholds at 0.5, 1, 2, and 4 kHz] of ≤55 dB HL. Single-sided sensorineural deafness (air conduction thresholds with PTA4 [mean of thresholds at 0.5, 1, 2, and 3 kHz] ≤20 dB HL in the contralateral ear).	PROs collected at baseline, 3- and 12-months post-implantation using HUI3.	HUI3, mean change (SD) [range] [p-value]: Total population, n=42: 0.149 (0.30) [{-0.29}-0.71], [p=0.0026]. Mixed HL/conductive HL, n=30: 0.179 (0.317) [{-0.29}-0.710] [p=0.0046]. Single-sided sensorineural deafness, n=12: 0.073 (0.248), [{-0.29}-0.54] [p=0.31].
Montes et al. 2017	100	Patients with profound deafness. Data was obtained from audiometric tests of the 100 randomly selected cochlear implant pretreatment patients who were using hearing aids before being implanted with the cochlear implant, from 1998 to 2013 at Cochlear Implant Group of the Hospital Universitario de la Fundacio´n Santa Fe de Bogota.	NR	Disability weight: Mild (16-25 dB): -0.000, Moderate, treated (26-40 dB): -0.040, Moderate, untreated (41-65 dB): -0.120, Severe or profound, treated (66-95 dB): -0.120, Severe or profound, untreated (+96 dB): -0.333. Utility weight: Mild (16-25 dB): 0.000, Moderate, treated (26-40 dB): 0.960, Moderate, untreated (41-65 dB): 0.880,

		Data on years of education and wages for the CI approach were obtained from a survey conducted on 37 patients at the Cochlear Implant Group of the Hospital Universitario de la Fundacio´n Santa Fe de Bogota.		Severe or profound, treated (66-95 dB): 0.880, Severe or profound, untreated (+96 dB): 0.667.
Krabbe et al. 2000	91	Participants with post lingually deaf adult multichannel cochlear implant users and deaf candidates on the waiting list for a cochlear implant as control group.	HUI2.	HUI scores, mean (SD): Control group, n=46: 0.62 (0.16). Cochlear implants, n=45 Pre-cochlear implant: 0.55 (0.11), Post-cochlear implant: 0.82 (0.14), Change in pre-cochlear implant vs post-cochlear implant: 0.28 (0.15) [P<0.001].
Hirano et al. 2014	NR	Japanese cohort cohort of six-year old patients who underwent therapies for medulloblastomas.	EQ-5D, HUI3, SF-6D.	Utility values (range): Post-hearing aid use EQ-5D: 0.807 (0.784-0.830), HUI3: 0.644 (0.626-0.663), SF-6D: 0.792 (0.779-0.804).
Landry et al. 2022	NR	Adults patients (both men and women) comprising of five different age groups: 50-59, 60-69, 70-79 and 80-89 and 90 with age-related sensorineural HL.	HUI3.	HUI3, (SE): Health utilities Normal hearing: 0.95 (0.08), Functional impairment in normal hearing: 0.79, Mild HL: 0.80 (0.03), Functional impairment in mild HL: 0.74, Moderate HL: 0.73 (0.03), Functional impairment in moderate HL: 0.67, Severe HL: 0.73 (0.03), Functional impairment in severe HL: 0.67, Profound HL: 0.46 (0.21),

				Functional impairment in profound HL: 0.26. HL utilities with hearing aid: Mild HL with hearing aid: 0.89, Functional impairment in mild HL with hearing aid: 0.83, Moderate HL with hearing aid: 0.90, Functional impairment in moderate HL with hearing aid: 0.84, Severe HL with hearing aid: 0.90, Functional impairment in severe HL with hearing aid: 0.84, Profound HL with hearing aid: 0.64, Functional impairment in profound HL with hearing aid: 0.43, HL utilities with cochlear implant: Using a cochlear implant: 0.61 (0.19).
James et al. 2021	543	Patients with age >18 at time of implantation, unilateral cochlear implantation, and no second implant during the period of follow-up (maximum 3 years). Included patients were implanted between 2011 and 2019, and thus used Nucleus CP810 or CP900 series sound processors.	HUI.	HUI3 scores, mean [p-value]: Mean improvement from baseline to visit 1: 0.18 [P<0.001], Mean improvement from baseline to visit 3: 0.015 [P<0.001].
Culter et al. 2022	NR	UK adults assumed to have been diagnosed with severe to profound sensorineural HL in both ears.	Utility values.	Utility values: Severe and profound HL prior to a cochlear implant Traditional candidates: 0.410, Marginal hearing aid users: 0.494. Utility decrement from population utility norms for persons with severe and profound HL: Traditional candidates: 0.439,

				Marginal hearing aid users: 0.374. Utility increment associated with the intervention received: Traditional candidates: 0.214, Marginal hearing aid users: 0.151. Disutility values: Dysgeusia (taste disturbance): -0.020, Vertigo: -0.033, Tinnitus: -0.050, Wound infection: -0.042, Long-term adverse event, vertigo: -0.033.
Huang et al. 2021	NR	Paediatric patients with cystic fibrosis receiving high-dose intravenous aminoglycosides who developed HL.	HUI2/3.	Utilities: Undetected HL: 0.547, Prompt detected HL: 0.607, Delayed detected HL: 0.515.
Gumbie et al. 2021	38	Adults aged 19 years and older with severe to profound HL with an average age of 61 years.	HUI3.	Utilities: Severe and profound HL prior to a cochlear implant: 0.450, Utility decrement from population utility norms for persons with severe and profound HL: 0.391, Utility increment associated with receiving a unilateral cochlear implant: 0.210. Disutilities: Short term adverse events, 6 months: Dysgeusia (taste disturbance): -0.020, Vertigo: -0.033, Tinnitus: -0.050, Wound infection: -0.042,

				Long-term adverse events, lifetime: Vertigo: -0.033.
Kosaner Kliess et al. 2017	15	Male and female adults aged 18 to 75 years who had postlingual mild to severe sensorineural HL and could not use or benefit from hearing aids because of medical reasons.	NR	Utility, mean (SD): Aided: 0.66868 (0.24039), Unaided: 0.57514 (0.23816).
Hol et al. 2004	56	Fifty-six consecutive adult patients with acquired conductive or mixed HL and listed for bone-anchored hearing aid surgery participated in the prospective questionnaire study. 36 patients had been using an air conduction hearing aid and 20 patients a conventional bone conduction hearing aid.	EQ-5D.	Utility, mean (SD): Air conduction hearing aids Before bone-anchored hearing aid: 0.78 (0.17), After bone-anchored hearing aid: 0.77 (0.17). Conventional bone conduction hearing aid Before bone conduction hearing aid: 0.71 (0.23), After bone conduction hearing aid: 0.70 (0.19).
Lytle et al. 2023	NR	Canadian paediatric population aged <5 years divided into five groups (<1 year, 1-2 years, 2-3 years, 3-4 years, and 4-5 years) for prevention of pneumococcal disease. Direct and indirect medical cost per episode for complex and simple otitis media were of interest.	NR	Utility: Long-term deafness: -0.730. Complex otitis media <2 years: 0.998, 2-4 years: 0.998. Simple otitis media <2 years: 0.998, 2-4 years: 0.998.
Sevilla et al. 2022	NR	Patients with acute otitis media.	NR	Utility [range]: All ages (0-1 years, 2-4 years, 5-17 years, 18-34 years, 35-49 years, 50-64 years, and 65-100 years)

		Patients with HL due to acute otitis media and meningitis.		Acute otitis media: 0.9984 [0.9986-0.9982], HL after acute otitis media: 0.9984 [0.9986-0.9982], HL after meningitis: 0.5500 [0.6608-0.4392].
Veenstra et al. 2007	NR	Cystic fibrosis patients screened for A1555G variant with or without HL. Cystic fibrosis patients with HL were only of interest.	NR	Utility: Patient with cochlear implant: 0.80, Cystic fibrosis patient with mild HL: 0.91.
Gumbie et al. 2022	NR	Children aged 5 years with HL.	HUI3.	Utility (SE): Other hearing problems: 0.761 (-0.120), Other hearing problems with wireless remote microphone hearing device: 0.821 (0.121). Bilateral HL Mild HL: 0.839 (0.013), Moderate HL: 0.677 (0.013), Mild HL with hearing aids: 0.959 (0.025), Moderate HL with hearing aids: 0.797 (0.025). Unilateral HL Mild HL: 0.843 (0.154), Moderate HL: 0.685 (0.154), Severe/profound HL: 0.563 (0.127), Mild HL with hearing aids: 0.963 (0.155), Moderate HL with hearing aids: 0.805 (0.155), Severe/profound HL with hearing aids: 0.683 (0.129), Severe/profound HL with cochlear implant: 0.746 (0.130). Disutility: Other hearing problems: -0.239 (-0.120),

				Other hearing problems with wireless remote microphone hearing device: -0.179 (0.121). Bilateral HL Mild HL: -0.162 (0.013), Moderate HL: -0.323 (0.013), Mild HL with hearing aids: -0.042 (0.025), Moderate HL with hearing aids: -0.203 (0.025). Unilateral HL Mild HL: -0.157 (0.154), Moderate HL: -0.315 (0.154), Severe/profound HL: -0.437 (0.127), Mild HL with hearing aids: -0.037 (0.155), Moderate HL with hearing aids: -0.195 (0.155), Severe/profound HL with hearing aids: -0.317 (0.129), Severe/profound HL with cochlear implant: -0.254 (0.130). Utility gain associated with cochlear implants Children: 0.183 (95% CI, 0.126-0.239), Adult: 0.12 (95% CI, 0.082-0.166).
Verkleij et al. 2021	NR	Full term, well neonates excluding those admitted to the neonatal intensive care unit, screened for hearing impairment. Children with HL were of interest.	HUI3.	HUI3 scores: Unilateral mild (26-40 dB): 1.0, Unilateral moderate, severe, profound (>40 dB): 0.85, Bilateral mild (26-40 dB): 0.85, Bilateral moderate, severe (41-80 dB): 0.661, Bilateral profound (>81 dB): 0.467.
Lee et al. 2006	11	Twenty-six patients with postlingual HL who had received artificial cochlear implants between 1990 and 2002 and	QWB, HUI,	Pre-implantation, mean [range] EQ-5D: 0.52 (0.3-40.71), HUI: 0.29 (0.16-0.42),

		had used the devices for at least one year.	EQ-5D, TTO.	QWB: 0.45 (0.30-0.60). Post-implantation, mean [range] EQ-5D: 0.78 (0.58-0.98), HUI: 0.65 (0.55-0.76), QWB: 0.61 (0.47-0.75). TTO (transformed from VAS score): 0.61 (0.43-0.79).
Summerfield et al. 2018	147	Adults who met criteria of candidacy for implantation and received implants in any of 13 hospitals in the UK. Patients who had developed a severe to profound sensorineural HL in both ears after acquiring spoken language; had at least one patent cochlear nerve; could identify no more than 50% of the content words in pre-recorded sentences presented in quiet without lipreading when using hearing aids. Patients who had receive an implant in one ear in any of 13 hospitals in the UK between June 1997 and May 2000.	EQ-5D-5L, HUI2, HUI3, SF-6D.	Pre-operative utilities, mean: EQ-5D-5L: 0.788, HUI2: 0.640, HUI3: 0.433, SF-6D: 0.763. Post-operative utilities, mean: EQ-5D-5L: 0.827, HUI2: 0.775, HUI3: 0.629, SF-6D: 0.775.
Barton et al. 2004	609	Subset of subjects who were assessed in one of four UK audiology clinics between April 2000 and October 2002. Patients who had not previously worn a hearing aid; were provided with either an analogue or digital signal-processing hearing aid (or aids).	EQ-5D, HUI3, SF-6D.	Pre-intervention utilities, mean (95% CI) [range]: EQ-5D: 0.801 (0.783, 0.825) [{-0.074}-1], HUI3: 0.584 (0.566, 0.604) [{-0.249}-1], SF-6D: 0.778 (0.769, 0.787) [0.370-1]. Post intervention utilities, mean (95% CI) [range]: EQ-5D: 0.807 (0.784, 0.830) [{-0.077}-1],

		Completed all three measures of utility (EQ-5D, HUI3 and SF-6D) both pre and post intervention.		HUI3: 0.644 (0.626, 0.663) [{-0.211}-1], SF-6D: 0.792 (0.779, 0.804) [0.327-1].
Hallin et al. 2023	38	Elderly patients aged ≥85 years, getting cochlear implants at Akademiska University Hospital, Uppsala, Sweden or another clinic but did their follow-up checks at Akademiska University Hospital.	EQ-5D-3L.	Utility scores, mean: Women: 0.809, Men: 0.889, Total: 0.849.
Baek et al. 2016	Mild hearing impairment: 1,757 Moderate to severe hearing impairment: 890.	Participants aged >19 years, were chosen by proportional allocation-systematic sampling with multistage stratification (age, sex, and region) to complete the audiometric test, the health examination, and the quality of health questionnaire.	EQ-5D.	Utility scores with hearing impairment, unadjusted, mean (SE): Mild hearing impairment: 0.88 (0.00), Moderate to severe hearing impairment: 0.86 (0.01), p-value: < 0.001. Model 1 (adjusted for age and sex) Mild hearing impairment: 0.92 (0.00), Moderate to severe hearing impairment: 0.91 (0.01), p-value: < 0.001. Model 2 (adjusted for age {elderly}, sex, household income, education level, spouse, smoking status, alcohol intake, and regular exercise) Mild hearing impairment: 0.88 (0.01), Moderate to severe hearing impairment: 0.87 (0.02), p-value: 0.045. Model 3 (adjusted for age, sex, household income, education level, spouse, smoking status, alcohol intake, regular exercise, diabetes, hypertension, hypercholesterolemia, eGFR level, and stress level) Mild hearing impairment: 0.87 (0.01), Moderate to severe hearing impairment: 0.86 (0.02), p-value: 0.041.

				Model 4 (adjusted for age, sex, household income, education level, spouse, smoking status, alcohol intake, regular exercise, diabetes, hypertension, hypercholesterolemia, eGFR level, stress level, and tinnitus) Mild hearing impairment: 0.87 (0.01), Moderate to severe hearing impairment: 0.86 (0.02), p-value: 0.138.
Maes et al. 2011	At baseline: 428 At 3 months follow-up: 319.	All patients referred to the centre of audiology and communication (Adelante, Hoensbroek) because of tinnitus complaints were included. All patients were aged 18 years or older and being able to read and write in Dutch.	EQ-5D, HUI3.	Utility scores at baseline, mean (SD): EQ-5D: Mild, n=81: 0.87 (0.15), Moderate, n=112: 0.82 (0.17), Severe, n=235: 0.71 (0.24), Total, n=428: 0.77 (0.22). HUI3: Mild, n=81: 0.79 (0.18), Moderate, n=112: 0.82 (0.17), Severe, n=235: 0.55 (0.30), Total, n=428: 0.64 (0.28). Utility scores at baseline, median: EQ-5D: Mild, n=81: 0.79, Moderate, n=112: 0.80, Severe, n=235: 0.76, Total, n=428: 0.80. HUI3: Mild, n=81: 0.85, Moderate, n=112: 0.78, Severe, n=235: 0.55, Total, n=428: 0.70.

				Health utility scores at 3 months follow-up, mean (SD): EQ-5D: Mild, n=55: 0.86 (0.16), Moderate, n=86: 0.84 (0.18), Severe, n=178: 0.71 (0.25), Total, n=319: 0.77 (0.23). HUI3: Mild, n=55: 0.88 (0.18), Moderate, n=86: 0.73 (0.24), Severe, n=178: 0.54 (0.30), Total, n=319: 0.63 (0.28). Utility scores at 3 months follow-up, median: EQ-5D: Mild, n=55: 0.81, Moderate, n=86: 0.80, Severe, n=178: 0.73, Total, n=319: 0.80. HUI3: Mild, n=55: 0.84, Moderate, n=86: 0.79, Severe, n=178: 0.58, Total, n=319: 0.70.
Mitchell et al. 2017	581	Participants consisted of a healthy population (defined as reporting 70 or higher on a 0-100 VAS measuring overall health) and seven health condition groups where individuals	ICECAP-A, EQ-5D, SF-6D,	HL utility score, mean (SD): ICECAP-A: 0.855 (0.16), EQ-5D: 0.872 (0.14), SF-6D: 0.749 (0.12), AQoL-8D: 0.719 (0.20),

		reported having a primary condition of one of the following: asthma, arthritis, cancer, depression, diabetes mellitus, HL and heart disease, across six countries: Australia, Canada, Germany, Norway, UK, and US. Population with HL were of interest.	AQoL-8D, HUI3, 15D, QWB.	HUI3: 0.687 (0.23), 15D: 0.875 (0.10), QWB: 0.639 (0.12).
Kwon et al. 2015	568	Patients aged ≥60 years with sensory impairment in South Korea. Population with hearing impairment were of interest.	EQ-5D.	Hearing impairment utility score, mean (SD): Model 1 (age, sex adjusted): 0.88 (0.01), Model 2 (age, sex, smoking status, drinking, regular exercise, living place, economic status adjusted): 0.88 (0.01).
Ramakers et al. 2016	38	Adult patients with severe to profound bilateral postlingual sensorineural HL.	EQ-5D, HUI3, VAS hearing, VAS general.	Health utility score, median [range] (p-value): Pre-operative score EQ-5D: 1.00 [0.61-1.00], HUI3: 0.55 [0.26-0.85], VAS hearing: 0.10 [0.00-0.60], VAS general: 0.75 [0.25-1]. One year post-operative score EQ-5D: 1.00 [0.30-1.00] (p=NS), HUI3: 0.78 [0.22-0.85] (p=<0.001), VAS hearing: 0.70 [0.20-0.90] (p=<0.001), VAS general: 0.80 [0.45-0.99] (p=<0.027). Two years post-operative score EQ-5D: 1.00 [0.65-1.00] (p=NS), HUI3: 0.77 [0.42-0.85] (p=<0.001), VAS hearing: 0.70 [0.00-0.94] (p=<0.001), VAS general: 0.80 [0.55-1] (p=<0.012).

				Note: The VAS hearing was excluded from the analyses on agreement because it is not a general health utility instrument which can be used for a cost-utility analysis.
Barton et al. 2005	915	New referrals aged over 18, who gave consent to be included in the study within the modernising hearing aid services programme.	EQ-5D, HUI, SF-6D.	Hearing-impaired utility score, mean (95% CI) [range]: EQ-5D: 0.79 (0.78, 0.81) [{-0.18}-1], HUI3: 0.56 (0.55, 0.57) [{-0.25}-1], SF-6D: 0.77 (0.76, 0.77) [0.31-1].
Joore et al. 2003	126	Hearing-impaired persons 18 years and older were asked to enter the study when they received a prescription for a hearing aid from their ENT specialist or audiologist. Patients were recruited from February 1, 1998, to March 31, 1999.	EQ-5D, VAS.	Utility scores, mean (95% CI): Gain in generic quality of life: Patient score on the EQ-5D VAS: 0.02 ({-0.02}, 0.05), Population utility estimate EQ-5D: 0.03 ({-0.03}, 0.08). Gain in hearing-specific quality of life: Patient score on the hearing-specific VAS: 0.27 (0.22, 0.31).
Grutters et al. 2007	Baseline: 315 After hearing aid fitting: 70.	Patients with hearing complaints were recruited from three regions (Maastricht, Rotterdam and Amsterdam) in the Netherlands. Data were collected as part of a before-after study examining direct hearing aid provision vs provision by referral.	EQ-5D, HUI2, HUI3.	Utility scores in baseline population with hearing complaints, mean (SD) [p-value]: EQ-5D UK tariff: 0.83 (0.21) [P=<0.01], EQ-5D Dutch tariff: 0.86 (0.18) [P=<0.01], HUI2: 0.77 (0.14) [P=<0.01], HUI3: 0.61 (0.24) [P=<0.01]. Utility scores in baseline population with hearing complaints, median [range]{IQR} [p-value]: EQ-5D UK tariff: 0.85 [(-0.25)-1.00] {0.27} [P=<0.01], EQ-5D Dutch tariff: 0.86 [(-0.03)-1.00] {0.19} [P=< 0.01], HUI2: 0.79 [0.23-1.00] {0.15} [P=<0.01], HUI3: 0.62 [(-0.07)-1.00] {0.38} [P=<0.01].

				Change in health state utility after hearing aid fitting, mean (SD) [p-value]: EQ-5D UK tariff: 0.01 (0.13), EQ-5D Dutch tariff: 0.00 (0.12), HUI2: 0.07 (0.13) [P=<0.01], HUI3: 0.12 (0.18) [P=<0.01]. Change in health state utility after hearing aid fitting, median [range]{IQR} [p-value]: EQ-5D UK tariff: 0.00 [(-0.60)-0.27] {0.04}, EQ-5D Dutch tariff: 0.00 [(-0.60)-0.28] {0.04}, HUI2: 0.08 [(-0.50)-0.40] {0.12} [P=<0.01], HUI3: 0.13 [(-0.22)-0.60] {0.22} [P=<0.01].
Watson et al. 2021	ACE: 4 TAU: 4	Twelve hearing aid users aged 18 years or over who reported moderate or less than moderate benefit from their new hearing aid were recruited.	EQ-5D-5L.	EQ-5D-5L scores, mean (SD): Baseline ACE: 0.670 (0.333), TAU: 0.686 (0.411). 3 months post-randomisation ACE: 0.613 (0.512), TAU: 0.871 (0.133).
Simpson et al. 2015	Mild HL: 395 Moderate/severe HL: 26	Subjects aged between 60-90 years from the 2000 Medical Expenditure Panel Survey. Mild HL and moderate/severe HL population were of interest.	EQ-5D VAS.	EQ-5D VAS utility score, mean [p-value]: Mild HL: -0.015 [P<0.001], Moderate/severe HL: 0.079 [P<0.0001].
Kuthubutheen et al. 2014	142	Scenario-based population estimate with three scenarios:	HUI3, EQ-5D, VAS,	Utilities: HUI3 Scenario 1 Deaf: 0.51,

A patient with severe to profound sensorineural HL with no intervention (Scenario 1). Same patient with a unilateral cochlear implant with average or better performance (Scenario 2). Same patient with bilateral cochlear implant with average or better performance (Scenario 3).	TTO.	Unilateral cochlear implant: 0.57, Bilateral cochlear implant: 0.55, Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.54. Scenario 2 Deaf: 0.74, Unilateral cochlear implant: 0.78, Bilateral cochlear implant: 0.79 [P>0.05], Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.77. Scenario 3 Deaf: 0.77, Unilateral cochlear implant: 0.81, Bilateral cochlear implant: 0.79 [P>0.05], Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.79. EQ-5D Scenario 1 Deaf: 0.78, Unilateral cochlear implant: 0.78, Bilateral cochlear implant: 0.82, Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.79. Scenario 2 Deaf: 0.85 [P>0.05], Unilateral cochlear implant: 0.9, Bilateral cochlear implant: 0.94 [P>0.05], Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.89 [P>0.05]. Scenario 3 Deaf: 0.90 [P>0.05], Unilateral cochlear implant: 0.93,

Bilateral cochlear implant: 0.93 [P>0.05],
Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.92 [P>0.05].

VAS
Scenario 1
Deaf: 0.73,
Unilateral cochlear implant: 0.72,
Bilateral cochlear implant: 0.77,
Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.74.

Scenario 2
Deaf: 0.79,
Unilateral cochlear implant: 0.83,
Bilateral cochlear implant: 0.84,
Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.82.

Scenario 3
Deaf: 0.86,
Unilateral cochlear implant: 0.88,
Bilateral cochlear implant: 0.89,
Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.88.

TTO
Scenario 1
Deaf: 0.64,
Unilateral cochlear implant: 0.63,
Bilateral cochlear implant: 0.62,
Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.63.

Scenario 2
Deaf: 0.78,
Unilateral cochlear implant: 0.79,

Bilateral cochlear implant: 0.84,
Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.8.

Scenario 3
Deaf: 0.89,
Unilateral cochlear implant: 0.95,
Bilateral cochlear implant: 0.96,
Deaf + Unilateral cochlear implant + Bilateral cochlear implant: 0.93.

Incremental utility gain by second cochlear implant relative to total bilateral cochlear implant gain
HUI3: 0.035 (11.5%),
EQ-5D: 0.04 (22.2%),
VAS: 0.07 (35%),
TTO: 0.12 (41.4%).

Carer utilities:

Utility reported for professionals, mean

HUI

Scenario 1: 0.35,

Scenario 2: 0.75,

Scenario 3: 0.83.

EQ-5D

Scenario 1: 0.62,

Scenario 2: 0.87,

				Scenario 3: 0.95. TTO Scenario 1: 0.72, Scenario 2: 0.87, Scenario 3: 0.95.
Smulders et al. 2016	38	Thirty-eight post lingually deafened adults eligible for cochlear implantation.	HUI3, EQ-5D, VAS hearing, VAS general health.	HUI3, mean: Pre-operative Unilateral cochlear implant: 0.58, Bilateral cochlear implant: 0.56. 1 year post-operative Unilateral cochlear implant: 0.68, Bilateral cochlear implant: 0.71. 2 year post-operative Unilateral cochlear implant: 0.68, Bilateral cochlear implant: 0.72. HUI3, median: Pre-operative Unilateral cochlear implant: 0.57, Bilateral cochlear implant: 0.59. 1 year post-operative Unilateral cochlear implant: 0.78, Bilateral cochlear implant: 0.78. 2 year post-operative Unilateral cochlear implant: 0.74, Bilateral cochlear implant: 0.78. EQ-5D, mean:

Pre-operative
Unilateral cochlear implant: 0.95,
Bilateral cochlear implant: 0.93.
1 year post-operative
Unilateral cochlear implant: 0.93,
Bilateral cochlear implant: 0.90.
2 year post-operative
Unilateral cochlear implant: 0.94,
Bilateral cochlear implant: 0.92.

EQ-5D, median
Pre-operative
Unilateral cochlear implant: 1.00,
Bilateral cochlear implant: 1.00.
1 year post-operative
Unilateral cochlear implant: 1.00,
Bilateral cochlear implant: 1.00.
2 year post-operative
Unilateral cochlear implant: 1.00,
Bilateral cochlear implant: 1.00.

TTO, mean:
1 year post-operative
Unilateral cochlear implant: 0.91,
Bilateral cochlear implant: 0.99.
2 year post-operative
Unilateral cochlear implant: 0.90,
Bilateral cochlear implant: 0.99.

TTO, median:
1 year post-operative
Unilateral cochlear implant: 1.00,
Bilateral cochlear implant: 1.00.

2 year post-operative
Unilateral cochlear implant: 1.00,
Bilateral cochlear implant: 1.00.

VAS hearing, mean:
Pre-operative
Unilateral cochlear implant: 0.16,
Bilateral cochlear implant: 0.13.
1 year post-operative
Unilateral cochlear implant: 0.63,
Bilateral cochlear implant: 0.74.
2 year post-operative
Unilateral cochlear implant: 0.57,
Bilateral cochlear implant: 0.72.

VAS hearing, median:
Pre-operative
Unilateral cochlear implant: 0.10,
Bilateral cochlear implant: 0.10.
1 year post-operative
Unilateral cochlear implant: 0.65,
Bilateral cochlear implant: 0.80.
2 year post-operative
Unilateral cochlear implant: 0.66,
Bilateral cochlear implant: 0.75.

VAS general health, mean:
Pre-operative
Unilateral cochlear implant: 0.66,
Bilateral cochlear implant: 0.72.
1 year post-operative
Unilateral cochlear implant: 0.79,
Bilateral cochlear implant: 0.75.

				2 year post-operative Unilateral cochlear implant: 0.80, Bilateral cochlear implant: 0.78. VAS general health, median: Pre-operative Unilateral cochlear implant: 0.70, Bilateral cochlear implant: 0.80. 1 year post-operative Unilateral cochlear implant: 0.80, Bilateral cochlear implant: 0.80. 2 year post-operative Unilateral cochlear implant: 0.80, Bilateral cochlear implant: 0.80.
Oostenbrink et al. 2002	NR	A panel of paediatricians classified seven standardised descriptions of patients with permanent sequelae after bacterial meningitis. Data of mild HL and deafness as described by the paediatricians were of interest.	EQ-5D, HUI2, HUI3A (anchor points "pits" and "healthy"), HUI3B (anchor points "dead" and "healthy").	Utility score per case description, mean (SD): Deafness EQ-5D: 0.81 (0.15), HUI2: 0.79 (0.06), HUI3A: 0.47 (0.10), HUI3B: 0.28 (0.14). Mild HL EQ-5D: 0.91 (0.08), HUI2: 0.84 (0.07), HUI3A: 0.74 (0.11), HUI3B: 0.65 (0.14).
Joore et al. 2002	245	Patients aged 18 years or older, who lived in the Netherlands and received a prescription for a hearing aid at the ENT clinic of the Maastricht University	VAS, EQ-5D.	Utility score, mean (SD): Prior to hearing aid fitting Baseline, n=76: 0.51 (0.13), T1: 0.77 (0.11), T2: 0.78 (0.11).

		Hospital or the Hoensbroeck Audiological Centre. Patients who had not used a hearing aid for the past 5 years.		Marker state scores Baseline, n=77: 0.29 (0.20), T1, n=71: 0.33 (0.22), T2, n=72: 0.29 (0.17). EQ-5D VAS Baseline, n=77: 0.69 (0.17), T1: 0.71 (0.15), T2: 0.71 (0.15).
Mailhot Vega et al. 2013	NR	Paediatric medulloblastoma survivors aged 18 years was studied who had received treatment at age 5 years and who were at risk of developing 10 adverse events, such as growth hormone deficiency, coronary artery disease, ototoxicity, secondary malignant neoplasm, and death.	NR	Utility score: Deafness: 0.776.

Abbreviations: EQ-5D VAS: EuroQol visual analogue scale, HL: hearing loss, HUI: Health Utilities Index, NR: not reported, SD: standard deviation, SF-6Dv2: Short Form 6 Dimension version 2, TTO: time trade-off

Overall, 75 studies were excluded at full text screening, depicted in Table 95.

Table 95 Details and results from excluded HRQoL studies

Year	Author	Title	Publication title	Reason for exclusion
2020	Chen, K.; Zhong, Y.; Gu, Y.; Sharma, R.; Li, M.; Zhou, J.; Wu, Y.; Gao, Y.; Qin, G.	Estimated Cost-effectiveness of Newborn Screening for Congenital Cytomegalovirus Infection in China Using a Markov Model	JAMA Network Open	Population
2015	Choi, J.S.; Nieman, C.L.; Han, H.R.; Lin, F.R.	A community-based hearing intervention for older Korean americans	Otolaryngology - Head and Neck Surgery (United States)	No outcomes of interest
2017	Kim, H.; Song, S.O.; Jung, G.	A lateral paracarotid approach for ultrasound-guided stellate ganglion block with a linear probe	Journal of Anesthesia	No outcomes of interest
2017	Dritsakis, G.; van Besouw, R.M.; Kitterick, P.; Verschuur, C.A.	A Music-Related Quality of Life Measure to Guide Music Rehabilitation for Adult Cochlear Implant Users	American journal of audiology	No outcomes of interest
2021	Dentry, T.; Raj, S.; Savarirayan, R.	A pilot study investigating the health economics of achondroplasia in Australian children	Twin Research and Human Genetics	No outcomes of interest
2014	Öberg, M.; Bohn, T.; Larsson, U.; Hickson, L.	A preliminary evaluation of the active communication education program in a sample of 87-year-old hearing-impaired individuals	Journal of the American Academy of Audiology	No outcomes of interest
2014	Sharma, A.; Viets, R.; Parsons, M.S.; Reis, M.; Chrisinger, J.; Wippold II, F.J.	A two-tiered approach to MRI for HL: Incremental cost of a comprehensive MRI over high-resolution T2-weighted imaging	American Journal of Roentgenology	No outcomes of interest

2012	McMillan, G.P.; Konrad-Martin, D.; Dille, M.F.	Accuracy of distortion-product otoacoustic emissions-based ototoxicity monitoring using various primary frequency step-sizes	International Journal of Audiology	No outcomes of interest
2011	Liao, W.H.; Young, S.T.; Lien, C.F.; Wang, S.J.	An audiometer to monitor progressive hearing change in school-aged children.	Journal of medical screening	No outcomes of interest
2020	Hollander, C.; Joubert, K.; Schellack, N.	An Ototoxicity Grading System Within a Mobile App (OtoCalc) for a Resource-Limited Setting to Guide Grading and Management of Drug-Induced HL in Patients With Drug-Resistant Tuberculosis: Prospective, Cross-Sectional Case Series	JMIR mHealth and uHealth	No outcomes of interest
2012	Flores, F.; Armendariz, I.	Case series: 10 patients with cryptococcal meningitis, clinical parameters and treatment dose	Neurology	No outcomes of interest
2022	Wu, J.; He, X.; Chen, P.; Xie, S.; Li, X.; Hu, H.; Zhao, K.; Xie, F.	China Health Related Outcomes Measures (CHROME): Development of a New Generic Preference-Based Measure for the Chinese Population	PharmacoEconomics	No outcomes of interest
2019	Schwartz, S.R.; Almosnino, G.; Noonan, K.Y.; Banakis Hartl, R.M.; Zeitler, D.M.; Saunders, J.E.; Cass, S.P.	Comparison of Transmastoid and Middle Fossa Approaches for Superior Canal Dehiscence Repair: A Multi-institutional Study	Otolaryngology - Head and Neck Surgery (United States)	No outcomes of interest
2018	Dobie, R.A.	Cost-Effective Hearing Conservation: Regulatory and Research Priorities	Ear and hearing	Publication type not of interest

2018	Simonsz, H.; Carlton, J.; Griffith, H.; Horwood, A.; Uhlén, I.; Fronius, M.; Qirjazi, B.; Rajka, D.; Vladutiu, C.; Hoeve, H.; Heijnsdijk, E.; De Koning, H.	Cost-effectiveness comparison of childhood vision and hearing screening programmes throughout Europe (EUSCREEN Study)	Acta Ophthalmologica	No outcomes of interest
2000	Grimby, A.; Ringdahl, A.	Does having a job improve the quality of life among post-lingually deafened Swedish adults with severe-profound hearing impairment?	British Journal of Audiology	No outcomes of interest
2016	Alamgir, H.; Tucker, D.L.; Kim, S.-Y.; Betancourt, J.A.; Turner, C.A.; Gorrell, N.S.; Wong, N.J.; Sagiraju, H.K.; Cooper, S.P.; Douphrate, D.I.; Whitworth, K.W.; Marko, D.; Gimeno, D.; Cornell, J.; Hammill, T.L.; Senchak, A.J.; Packer, M.D.	Economic Burden of HL for the U.S. Military: A Proposed Framework for Estimation	Military medicine	Study type not of interest
2012	Dionne, F.; Mitton, C.; Rassekh, R.; Brooks, B.; Ross, C.; Hayden, M.; Carleton, B.	Economic impact of a genetic test for cisplatin-induced ototoxicity	Pharmacogenomics Journal	Study type not of interest
2017	Neitzel, R.L.; Swinburn, T.K.; Hammer, M.S.; Eisenberg, D.	Economic Impact of HL and Reduction of Noise-Induced HL in the United States	Journal of speech, language, and hearing research : JSLHR	No outcomes of interest

2005	McPherson, B.; Wong, E.T.L.	Effectiveness of an affordable hearing aid with elderly persons	Disability and Rehabilitation	No outcomes of interest
2022	Bonnafous, S.; Margier, J.; Bartier, S.; Tournegros, R.; Tringali, S.; Fieux, M.	Estimated Costs Associated with Management of Otosclerosis with Hearing Aids vs Surgery in Europe	JAMA Network Open	No outcomes of interest
2007	Patel, K.J.; Kedia, M.S.; Bajpai, D.; Mehta, S.S.; Kshirsagar, N.A.; Gogtay, N.J.	Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: A prospective study	BMC Clinical Pharmacology	No outcomes of interest
2010	Laplante-Lévesque, A.; Hickson, L.; Worrall, L.	Factors influencing rehabilitation decisions of adults with acquired hearing impairment	International Journal of Audiology	No outcomes of interest
2005	Horneman, G.; Folkesson, P.; Sintonen, H.; Von Wendt, L.; Emanuelson, I.	Health-related quality of life of adolescents and young adults 10 years after serious traumatic brain injury	International Journal of Rehabilitation Research	No outcomes of interest
1993	Fortnum, H.; Davis, A.	Hearing impairment in children after bacterial meningitis: Incidence and resource Implications	British Journal of Audiology	No outcomes of interest
2018	Mesaros, T.; Mesaros, S.	HTA Analysis of Cochlear Implant - Health Technology Assessment in Slovak Healthcare Environment	Value in Health	Publication type not of interest

2020	Leroi, I.; Simkin, Z.; Hooper, E.; Wolski, L.; Abrams, H.; Armitage, C.J.; Camacho, E.; Charalambous, A.P.; Collin, F.; Constantinidou, F.; Dawes, P.; Elliott, R.; Falkingham, S.; Frison, E.; Hann, M.; Helmer, C.; Himmelsbach, I.; Hussain, H.; Marié, S.; Montecelo, S.; Thodi, C.; Yeung, W.K.	Impact of an intervention to support hearing and vision in dementia: The SENSE-Cog Field Trial	International Journal of Geriatric Psychiatry	No outcomes of interest
2015	Ramos De Miguel, A.; Perez Zaballos, M.T.; Falcon Gonzalez, J.C.; Borkoski Barreiro, S.A.; Ramos Macías, A.	LifeQuestionnaire. A tool for continuous quality of life assessment for patients with HL [General]	International Archives of Otorhinolaryngology	No outcomes of interest
2021	Thum, C.; Langenfeld, R.; Flessa, S.	Lifetime Cost of Hearing AIDS in Germany	Laryngo- Rhino- Otologie	Not available in English
2008	Newman, C.W.; Sandridge, S.A.; Wodzisz, L.M.	Longitudinal benefit from and satisfaction with the Baha system for patients with acquired unilateral sensorineural HL.	Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	No outcomes of interest

2012	Gènova-Maleras, R.; Álvarez-Martín, E.; Morant-Ginestar, C.; Fernández de Larrea-Baz, N.; Catalá-López, F.	Measuring the burden of disease and injury in Spain using disability-adjusted life years: An updated and policy-oriented overview	Public Health	Publication type not of interest
2010	Tufts, J.B.; Weathersby, P.K.; Rodriguez, F.A.	Modeling the Unites States government's economic cost of noise-induced HL for a military population	Scandinavian Journal of Work, Environment and Health	Study type not of interest
2015	Porter, M.; Boothroyd, R.A.	Symptom severity, social supports, coping styles, and quality of life among individuals' diagnosed with Ménierè's disease	Chronic Illness	No outcomes of interest
2023	Cohen-Vaizer, M.; Dreyfuss, M.; Na'Ara, S.; Shinnawi, S.; Laske, R.	The Impact of Surgical Expertise on the Cost-Effectiveness of Stapes Surgery	Audiology and Neurotology	Population
2008	Ciorba, A.; Hatzopoulos, S.; Busi, M.; Guerrini, P.; Petruccelli, J.; Martini, A.	The universal newborn hearing screening program at the University Hospital of Ferrara: Focus on costs and software solutions	International Journal of Pediatric Otorhinolaryngology	Population
2022	Mohanty, M.; Kaur, R.; Gupta, S.K.; Tripathi, M.; Sharma, A.; Munjal, S.	Translation and Validation of Penn Acoustic Neuroma Quality of Life Scale for Hindi-Speaking Population	Neurology India	No outcomes of interest
2015	Fackrell, K.; Hall, D.A.; Barry, J.G.; Hoare, D.J.	UK validation of the Tinnitus Functional Index (TFI) in a large research population	Trials	No outcomes of interest

2018	Eichwald, J.; Scinicariello, F.; Telfer, J.L.; Carroll, Y.I.	Use of Personal Hearing Protection Devices at Loud Athletic or Entertainment Events Among Adults - United States, 2018	MMWR. Morbidity and mortality weekly report	No outcomes of interest
2004	Mo, F.; Choi, B.C.; Li, F.C.; Merrick, J.	Using Health Utility Index (HUI) for measuring the impact on health-related quality of Life (HRQL) among individuals with chronic diseases.	TheScientificWorldJournal	No outcomes of interest
1993	Maxon, A.B.; White, K.R.; Vohr, B.R.; Behrens, T.R.	Using transient evoked otoacoustic emissions for neonatal hearing screening	British Journal of Audiology	No outcomes of interest
2009	Roberts, R.A.; Abrams, H.; Sembach, M.K.; Lister, J.J.; Gans, R.E.; Chisolm, T.H.	Utility measures of health-related quality of life in patients treated for benign paroxysmal positional vertigo	Ear and Hearing	No outcomes of interest
2013	Engineer, N.D.; Rosellini, W.M.; Tyler, R.S.	Willingness to accept and pay for implantable tinnitus treatments: A survey	Neuromodulation	No outcomes of interest
2020	Tutar, B.; Saltürk, Z.; Berkiten, G.; Ekincioğlu, M.E.; Karaketir, S.; Arkan, E.; Akgün, M.F.; Yilmazer, A.B.; Kulak, E.; Bchinger, D.; Uyar, Y.	A novel Turkish instrument for assessing quality of life in chronic otitis media – translation and validation of zurich chronic middle ear inventory	Turkish Journal of Medical Sciences	No outcomes of interest
2021	Crocker, M.; Hutchinson, C.; Mpundu-Kaambwa, C.; Walker, R.; Chen, G.; Ratcliffe, J.	Assessing the relative importance of key quality of life dimensions for people with and without a disability: an empirical ranking comparison study	Health and Quality of Life Outcomes	No outcomes of interest

2016	Sorkin, D.L.; Buchman, C.A.	Cochlear Implant Access in Six Developed Countries	Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	No outcomes of interest
2017	Barnett, S.L.; Matthews, K.A.; Sutter, E.J.; DeWindt, L.A.; Pransky, J.A.; O'Hearn, A.M.; David, T.M.; Pollard, R.Q.; Samar, V.J.; Pearson, T.A.	Collaboration With Deaf Communities to Conduct Accessible Health Surveillance	American Journal of Preventive Medicine	No outcomes of interest
2015	Rao, V.B.	Conscious capitalism to help people with hearing disability in developing countries	International Journal on Disability and Human Development	Publication type not of interest
2000	Siegel, G.J.	Description of an office technique for laser ventilation of the ears	Ear, Nose and Throat Journal	No outcomes of interest
2020	Buchman, C.A.; Kaplan, B.A.	Developing international consensus on the use of unilateral cochlear implants for adults	Otolaryngology - Head and Neck Surgery	No outcomes of interest
2021	Aoki, H.; Kitano, T.; Kitagawa, D.	Disease burden of congenital cytomegalovirus infection in Japan	Journal of Infection and Chemotherapy	Publication type not of interest

2019	Simonsz, H.J.; Carlton, J.; Griffith, H.; Úhlen, I.; Vladutiu, C.; Ghititu, M.; Qirjazi, B.; Roshi, E.; Horwood, A.; Fronius, M.; Hoeve, H.; De Koning, H.	EUSCREEN study, stage 1: Data collection on vision and hearing screening programs in 40 European countries and Turkey, Israel, Russia, Malawi, Ruanda, Suth-Africa and India	Investigative Ophthalmology and Visual Science	Publication type not of interest
2022	Krabbe, P.; Zhang, X.	HSD94 A Novel Method to Measure Health	Value in Health	No outcomes of interest
2018	Mateer, E.J.; Huang, C.; Shehu, N.Y.; Paessler, S.	Lassa fever–induced sensorineural HL: A neglected public health and social burden	PLoS Neglected Tropical Diseases	No outcomes of interest
2021	Johnson, J.; Garcia, P.; Martin, K.; Randolph, L.M.; Rosenfeld, H.; Phillips, D.; Harmatz, P.	Long-term outcomes of patients with mucopolysaccharidosis type VI treated with galsulfase enzyme replacement therapy since infancy	Molecular Genetics and Metabolism	No outcomes of interest
1995	Feeny, D.; Furlong, W.; Boyle, M.; Torrance, G.W.	Multi-attribute health status classification systems. Health Utilities Index	PharmacoEconomics	No outcomes of interest
2015	Rismanchi, N.; Gold, J.J.; Sattar, S.; Glaser, C.; Sheriff, H.; Proudfoot, J.; Mower, A.; Nespeca, M.; Crawford, J.R.; Wang, S.G.	Neurological outcomes after presumed childhood encephalitis	Pediatric Neurology	No outcomes of interest
2005	Nelson, D.I.; Nelson, R.Y.; Concha-Barrientos, M.; Fingerhut, M.	The global burden of occupational noise-induced HL	American Journal of Industrial Medicine	No outcomes of interest

2004	Rouev, P.; Mumdzhiev, H.; Spiridonova, J.; Dimov, P.	Universal newborn hearing screening program in Bulgaria	International Journal of Pediatric Otorhinolaryngology	No outcomes of interest
2008	Glynn, F.; Osman, L.; Colreavy, M.; Rowley, H.; Dwyer, T.P.O.; Blayney, A.	Acute mastoiditis in children: Presentation and long term consequences	Journal of Laryngology and Otology	No outcomes of interest
2011	Botelho-Nevers, E.; Rovery, C.; Richet, H.; Raoult, D.	Analysis of risk factors for malignant mediterranean spotted fever indicates that fluoroquinolone treatment has a deleterious effect	Journal of Antimicrobial Chemotherapy	No outcomes of interest
2022	Schipmann, S.; Lohmann, S.; Al Barim, B.; Suero Molina, E.; Schwake, M.; Toksöz, Ö.A.; Stummer, W.	Applicability of contemporary quality indicators in vestibular surgery—do they accurately measure tumor inherent postoperative complications of vestibular schwannomas?	Acta Neurochirurgica	No outcomes of interest
2016	Manoj, M.P.	Bone Obliteration technique in recidivistic cholesteatoma	Journal of Laryngology and Otology	Publication type not of interest
2005	Henry, J.A.; Zaugg, T.L.; Schechter, M.A.	Clinical guide for audiologic tinnitus management II: Treatment	American Journal of Audiology	Publication type not of interest
2022	Massud, A.; Syed Sulaiman, S.A.; Ahmad, N.; Shafqat, M.; Chiau Ming, L.; Khan, A.H.	Frequency and Management of Adverse Drug Reactions Among Drug-Resistant Tuberculosis Patients: Analysis From a Prospective Study	Frontiers in Pharmacology	No outcomes of interest
1992	Benfield, P.; Chrisp, P.	Imipenem/cilastatin: a pharmacoeconomic appraisal of its use in intra-abdominal infections.	PharmacoEconomics	No outcomes of interest

2014	Kokong, D.D.; Bakari, A.; Ahmad, B.M.	Ototoxicity in Nigeria: Why it persists	Ear, Nose and Throat Journal	No outcomes of interest
2013	Maile, E.J.; Youngs, R.	Quality of life measures in otitis media	Journal of Laryngology and Otology	Publication type not of interest
2004	Shah, N.P.; Reddy, P.; Paladino, J.A.; McKinnon, P.S.; Klepser, M.E.; Pashos, C.L.	Direct medical costs associated with using vancomycin in methicillin-resistant Staphylococcus aureus infections: An economic model	Current Medical Research and Opinion	Study type not of interest
2012	Murray, C.J.L. et al.	Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010	The Lancet	No outcomes of interest
2017	Hay, S.I.et al.	Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016	The Lancet	No outcomes of interest
2010	Brännström, K.J.; Wennerström, I.	Hearing aid fitting outcome: Clinical application and psychometric properties of a Swedish translation of the international outcome inventory for hearing aids (IOI-HA)	Journal of the American Academy of Audiology	No outcomes of interest
2016	Yaneza, M.M.C.; Hunter, K.; Irwin, S.; Kubba, H.	Hearing in school-aged children with trisomy 21 – results of a longitudinal cohort study in children identified at birth	Clinical Otolaryngology	Study type not of interest

2021	Piromchai, P.; Tanamai, N.; Kiatthanabumrung, S.; Kaewsiri, S.; Thongyai, K.; Atchariyasathian, V.; Thanawirattananit, P.; Wacharasindhu, C.; Mukkun, T.; Isipradit, P.; Yimtae, K.	Multicentre cohort study of cochlear implantation outcomes in Thailand	BMJ Open	No outcomes of interest
2016	Portwine, C.; Rae, C.; Davis, J.; Teira, P.; Schechter, T.; Lewis, V.; Mitchell, D.; Wall, D.A.; Pullenayegum, E.; Barr, R.D.	Health-Related Quality of Life in Survivors of High-Risk Neuroblastoma After Stem Cell Transplant: A National Population-Based Perspective	Pediatric Blood and Cancer	No outcomes of interest
2010	Henderson, D.; Hayward, A.; Purdy, C.; Magar, R.	The potential economic benefits provided by combining Cisplatin with SRC inhibitor KX1-004 for cancer regimens	Value in Health	Pre-2021 CA

Review question 2 of the SLR update was carried out on the 15th of October 2024 and aimed to identify HRQoL data published from the 31st of October 2024 that were associated with acquired HL. Of in total 7 references at full-text screening, 6 HRQoL references were excluded and one HRQoL reference was identified as part of this SLR update, which was an ongoing NICE TA evaluating PEDMARQSI for the prevention of cisplatin-induced ototoxicity in the paediatric population (NICE 2024). However, no results were reported. A summary of this extracted study is presented in Table 96.

Table 96 SLR update summary of HRQoL publications (n=1)

Study	Reference	Intervention	Study design	Endpoints	Subgroups
NICE GID-TA10611	NICE GID-TA1061112	Cisplatin and PEDMARQSI	N/A	Frequency and severity of hearing loss Audiological outcomes (e.g., sound perception, speech recognition and sound localisation) Language and communication outcomes (e.g. intelligibility, sentence comprehension) Psychsocial development/adjustment Adverse effects of treatment including imapct on response to cisplatin and survival HRQoL	People aged 1 month to less than 18 years of age with localised, non-metastatic, solid tumours having cisplatin chemotherapy

Abbreviations: GID: general identification, HRQoL: health-related quality of life, N/A: not applicable, NICE: National Institute for Health and Care Excellence, TA: technology appraisal

I.1.6 Quality assessment and generalizability of estimates

Quality assessment and generalizability of estimates not available.

I.1.7 Unpublished data

Not applicable for this application.

I.1.8 Targeted literature review

To address the limited number of publications in the SLR that focus on paediatric patients and report utilities based on HL severity, a TLR for HRQoL in paediatric patients with HL was performed. Barton et al. (2006) was identified through this TLR. Although this study was not identified directly in the SLR, it was considered the most appropriate reference to inform health state utilities in the base case due to its close alignment with the population for which PEDMARQSI is indicated. (Barton et al. 2006) was a cost-effectiveness analysis of cochlear implants in children with bilateral hearing impairment in the UK and included utility values for HL categories by severity level (Barton et al. 2006). The utility values used in this study were elicited using the HUI3 utility measurement, which is an appropriate tool for assessing QoL in patients with HL (Borre et al. 2023). For the model base case, utility values were taken from Barton et al. (2006). Utility values from Barton et al. (2006) were also used in Bond et al. (2009), which was the basis of the economic evaluation within the UK HTA submission for cochlear implants for severe to profound deafness in both children and adults (NICE). The TLR search is in frame with the inclusion and exclusion criteria, as well as the search strategies described in Appendix I.1.3 and I.1.4.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

J.1.1 Overview of the SLR

A comprehensive SLR search was conducted in key biomedical electronic literature databases recommended by NICE. Searches for economic evaluation studies were conducted on 25th October 2023 in the following electronic databases (i.e. standard evidence sources used in the UK Health Technology Assessor (HTA)):

- Embase and Embase classic (using Embase.com)
- MEDLINE (using pubmed.ncbi.nlm.nih.gov)
- CRD HTA Database
- CRD NHS EED
- ScHARRHUD
- EuroQol database

In addition, Supplementary searches of "grey" literature were performed in Google Scholar and through the ICTRP, CEA registry, NICE, RePEc, EQ-5D, ScHARRHUD, CENTRAL, clinicaltrials.gov and WHO websites.

The database search strings identified included terms for free text and keywords (MESH and Emtree terms) combined using Boolean combination techniques. Filters were used to ensure the search results were relevant for the review question.

Where possible, data identified within the review was supplemented by data available (e.g., manufacturer submissions) on the following HTA body websites:

- NICE (England)
- Scottish Medicines Consortium (Scotland)
- All Wales Medicines Strategy Group (Wales)

Furthermore, an updated SLR was performed in October 2024.

J.1.2 Non-clinical SLR search expansion

For the non-clinical SLR search expansion, including sources used for the search, refer to Appendix I, Section I.1.2.

J.1.3 Search strategies

For search strategies, refer to Appendix I, Section I.1.3.

J.1.4 Study selection

Potentially relevant publications were reviewed and assessed to collate a final set of studies that formed the main body of the economic evidence as described in Appendix 0.

The PICOS inclusion and exclusion criteria for the cost and resource use studies are specified in Table 97 in terms of population, interventions, comparators, outcomes and other criteria.

Table 97 Eligibility (PICOS) criteria for the cost and resource use SLR

Selection criteria	Inclusion criteria	Exclusion criteria
Population (P)*	Patients with acquired HL	Studies that do not include patients of interest to the SLR. Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest.
Interventions (I)	Any	None
Comparators (C)	Any	None
Outcomes (O)	Any outcomes quantifying the costs and/or resource use requirements related to HL Any outcomes quantifying the costs and/or resource use associated with disease or treatment related adverse events Costs should be reported as incurred by the NHS in the UK	No reported outcomes of interest
Study type (S)	Cost and/or resource use studies Economic evaluations	None
Publication type	Primary publications Secondary publications Subgroup analysis Pooled data analysis	Letters Comment articles Publications that fail to present sufficient methodological detail or extractable results.

	Congress abstracts and papers corresponding to the above	
Language	Studies reported in English	Studies not reported in English

Abbreviations: HL: hearing loss, SLR: Systematic literature review

Following the review of 4,161 references against the selection criteria for the cost and resource use SLR during the title and abstract screening, 169 references were considered for full text review.

Following review of the full texts, 149 references were excluded because they did not meet the selection criteria: five did not meet the population criteria, 111 did not meet the outcomes criteria, nine did not meet the study type criteria, 18 did not meet the publication type criteria and six were unavailable in English. A grey literature search provided an additional seven cost and resource use studies which met the inclusion criteria. Overall, 27 references met the selection criteria following the first and second pass of the cost and resource use studies review and were extracted (Figure 21).

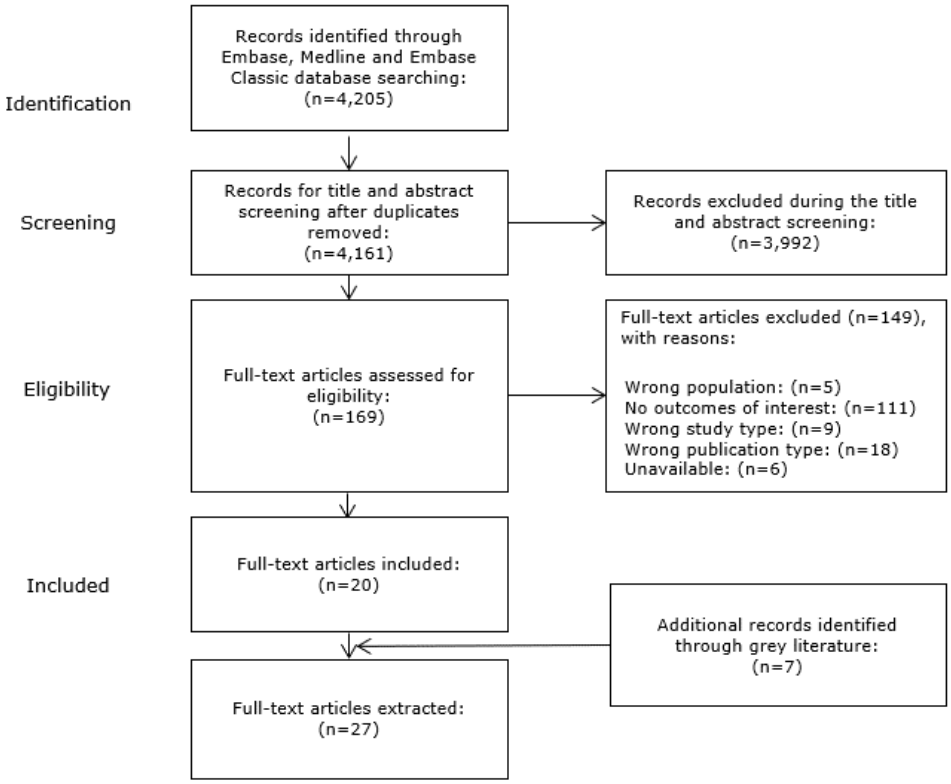


Figure 21 PRISMA flow chart – cost and resource use evidence

J.1.5 Example: Systematic search for […]

Not applicable for this application.

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

Abbreviations: N/A: not available

J.1.6 Example: Targeted literature search for [estimates]

Not applicable for this application.

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Abbreviations: N/A: not available

J.1.7 Results

A summary of included studies is presented in Table 98.

Table 98 Cost and resource use SLR – included studies (N=27)

Author	Full citation
Verkleij *et al.* 2021	Verkleij ML *et al.* Cost-Effectiveness of Neonatal Hearing Screening Programs: A Micro-Simulation Modeling Analysis. Ear Hear. 2021;42(4):909-916.
Kosaner Kliess *et al.* 2017	Kosaner Kliess M *et al.* Cost-Utility of Partially Implantable Active Middle Ear Implants for Sensorineural Hearing Loss: A Decision Analysis. Value Health. 2017;20(8):1092-1099.
Gumbie *et al.* 2022	Gumbie M *et al.* Cost-Effectiveness of Screening Preschool Children for Hearing Loss in Australia. Ear Hear. 2022;43(3):1067-1078.
Mohiuddin *et al.* 2014	Mohiuddin *et al.* A model-based cost-effectiveness analysis of a grommets-led care pathway for children with cleft palate affected by otitis media with effusion. Eur J Health Econ. 2015;16(6):573-587.
Dionne *et al.* 2011	Dionne F *et al.* Economic impact of a genetic test for cisplatin-induced ototoxicity Pharmacogenomics J. 2012;12(3):205-213.
Landry *et al.* 2022	Landry *et al.* Early Health Economic Modeling of Novel Therapeutics in Age-Related Hearing Loss. Front Neurosci. 2022;16:769983.
Cutler *et al.* 2022	Cutler *et al.* The cost-effectiveness of unilateral cochlear implants in UK adults. Eur J Health Econ. 2022;23(5):763-779.
Lytle *et al.* 2023	Lytle D *et al.* Cost-effectiveness analysis of PCV20 to prevent pneumococcal disease in the Canadian paediatric population. Hum Vaccin Immunother. 2023;19(2):2257426.
Ye *et al.* 2023	Ye *et al.* Direct Costs Attributable to Hearing Loss in China: Based on an Econometric Model. Ear Hear. 2023;44(2):330-337.

Montes *et al.* 2017	Montes *et al.* Cochlear Implants Versus Hearing Aids in a Middle-Income Country: Costs, Productivity, and Quality of Life. Otol Neurotol. 2017;38(5):e26-e33
Ordoñez *et al.* 2023a	Ordoñez *et al.* Cost-Utility Analysis of Pneumococcal Vaccines for Older Adults Available in Costa Rica. Value in Health. Volume 26, Issue 6, Supplement, 2023. Page S264. ISSN 1098-3015.
Bolaños-Díaz *et al.* 2022	Bolaños-Díaz R *et al.* Cost-effectiveness of the 13-valent pneumococcal conjugate vaccine compared to the 10-valent vaccine in children: predictive analysis in the Ecuadorian context. J Pharm Health Serv Res. 2022;13(4):341-350.
Sevilla *et al.* 2022	Sevilla JP *et al.* Cost-utility and cost-benefit analysis of paediatric PCV programs in Egypt. Hum Vaccin Immunother. 2022;18(6):2114252.
Ordoñez *et al.* 2023b	Ordoñez *et al.* Cost-Utility Analysis of Pneumococcal Vaccines for Older Adults Available in El Salvador. Value in Health,Volume 26, Issue 6, Supplement, 2023, Page S267,ISSN 1098-3015.
Hirano *et al.* 2014	Hirano *et al.* Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medulloblastoma in childhood. J Radiat Res. 2014;55(2):320-327.
Gumbie *et al.* 2021	Gumbie M *et al.* The cost-effectiveness of Cochlear implants in Swedish adults. BMC Health Serv Res. 2021;21(1):319.
Hol *et al.* 2004	Hol MK *et al.* The bone-anchored hearing aid: quality-of-life assessment. Arch Otolaryngol Head Neck Surg. 2004;130(4):394-399.
Joore *et al.* 2003	Joore *et al.* The cost-effectiveness of hearing-aid fitting in the Netherlands. *Arch Otolaryngol Head Neck Surg*. 2003;129(3):297-304. doi:10.1001/archotol.129.3.297
Smulders *et al.* 2016	Smulders *et al.* Cost-Utility of Bilateral Versus Unilateral Cochlear Implantation in Adults: A Randomized Controlled Trial. Otol Neurotol. 2016;37(1):38-45.
Tufts *et al.* 2010	Tufts *et al.* Modeling the Unites States government's economic cost of noise-induced hearing loss for a military population. Scand J Work Environ Health. 2010;36(3):242-249.
Yaneza *et al.* 2015	Yaneza MM *et al.* Hearing in school-aged children with trisomy 21 - results of a longitudinal cohort study in children identified at birth. Clin Otolaryngol. 2016;41(6):711-717.

Huang *et al.* 2021	Huang *et al.* Cost-effectiveness of implementing routine hearing screening using a tablet audiometer for paediatric cystic fibrosis patients receiving high-dose IV aminoglycosides. J Manag Care Spec Pharm. 2021;27(2):157-165.
Shah *et al.* 2004	Shah NP *et al.* Direct medical costs associated with using vancomycin in methicillin-resistant Staphylococcus aureus infections: an economic model. Curr Med Res Opin. 2004;20(6):779-790.
Veenstra *et al.* 2007	Veenstra D *et al.* Pharmacogenomic testing to prevent aminoglycoside-induced hearing loss in cystic fibrosis patients: potential impact on clinical, patient, and economic outcomes. Genet Med. 2007;9(10):695-704.
Neitzel *et al.* 2017	Neitzel RL *et al.* Economic Impact of Hearing Loss and Reduction of Noise-Induced Hearing Loss in the United States. J Speech Lang Hear Res. 2017;60(1):182-189.
Palmer *et al.* 1999	Palmer *et al.* A prospective study of the cost-utility of the multichannel cochlear implant. Arch Otolaryngol Head Neck Surg. 1999;125(11):1221-1228.
Mailhot Vega *et al.* 2013	Mailhot Vega RB *et al.* Cost-effectiveness of proton therapy compared with photon therapy in the management of paediatric medulloblastoma. Cancer. 2013;119(24):4299-4307.

A summary of excluded studies is presented in Table 99.

Table 99 Cost and resource use SLR – excluded studies (N=149)

Year	Author	Title	Publication title	Reason for exclusion
2020	Chen, K.; Zhong, Y.; Gu, Y.; Sharma, R.; Li, M.; Zhou, J.; Wu, Y.; Gao, Y.; Qin, G.	Estimated Cost-effectiveness of Newborn Screening for Congenital Cytomegalovirus Infection in China Using a Markov Model	JAMA Network Open	Population

2015	Choi, J.S.; Nieman, C.L.; Han, H.R.; Lin, F.R.	A community-based hearing intervention for older Korean americans	Otolaryngology - Head and Neck Surgery (United States)	No outcomes of interest
2017	Shields, G.E.; Rogers, K.D.; Young, A.; Buck, D.; Davies, L.M.	A COST-EFFECTIVENESS ANALYSIS OF IMPROVING ACCESS TO PSYCHOLOGICAL THERAPIES IN BRITISH SIGN LANGUAGE (BSL)	Journal of Epidemiology and Community Health	No outcomes of interest
2014	Sanderson, G.; Ariyaratne, T.V.; Wyss, J.; Looi, V.	A global patient outcomes registry: Cochlear paediatric implanted recipient observational study (Cochlear™ P-IROS)	BMC Ear, Nose and Throat Disorders	Study type not of interest
2020	Devis, T.; Manuel, M.	A low-complexity 3-level filter bank design for effective restoration of audibility in digital hearing aids	Biomedical Engineering Letters	No outcomes of interest
2017	Bhatt, G.; Erdeljac, H.P.; Owens, R.; Bittoni, A.M.; Custer, A.; Jones, D.; Rosko, A.	A multidisciplinary geriatric supportive care model for patients with hematologic malignancies	Supportive Care in Cancer	No outcomes of interest
2014	Sharma, A.; Viets, R.; Parsons, M.S.; Reis, M.; Chrisinger, J.; Wippold II, F.J.	A two-tiered approach to MRI for hearing loss: Incremental cost of a comprehensive MRI over high-resolution T2-weighted imaging	American Journal of Roentgenology	No outcomes of interest

2012	McMillan, G.P.; Konrad-Martin, D.; Dille, M.F.	Accuracy of distortion-product otoacoustic emissions-based ototoxicity monitoring using various primary frequency step-sizes	International Journal of Audiology	No outcomes of interest
2003	Ruiz, M.; Rejas Gutiérrez, J.; Soto, J.; Pardo, A.; Rebollo, I.	Adaptation and validation of the Health Utilities Index Mark 3 into Spanish and correction norms for Spanish population	Medicina Clinica	Not available in English
2011	Ng, S.L.; Meston, C.N.; Scollie, S.D.; Seewald, R.C.	Adaptation of the BKB-SIN test for use as a pediatric aided outcome measure	Journal of the American Academy of Audiology	No outcomes of interest
2009	Givens, D.J.; Karnell, L.H.; Gupta, A.K.; Clamon, G.H.; Pagedar, N.A.; Chang, K.E.; Van Daele, D.J.; Funk, G.F.	Adverse events associated with concurrent chemoradiation therapy in patients with head and neck cancer	Archives of Otolaryngology - Head and Neck Surgery	No outcomes of interest
2012	Hemraj, S.; James, S.J.	Age of suspicion and diagnosis of hearing impairment in children attending special schools	Australasian Medical Journal	No outcomes of interest
2010	Luo, X.; Shaw, J.W.; Pickard, A.S.; Walton, S.	An evaluation of the statistical efficiency of the us population median-based EQ-5D index using data from the medical expenditure panel survey	Value in Health	No outcomes of interest

2020	Tyler, R.; Perreauf, A.; Mohr, A.-M.; Ji, H.; Mancini, P.C.	An Exploratory Step Toward Measuring the Meaning of Life in Patients with Tinnitus and in Cochlear Implant Users	Journal of the American Academy of Audiology	No outcomes of interest
2016	Carroll, T.; Duncan, B.; Trujillo, F.	Arizona sonora border projects for inclusion (ARSOBO) a us-Mexico NGO collaboration, develops a sustainable social business to train, employ and assist individuals with disabilities	Annals of Global Health	No outcomes of interest
2019	Liu, C.; Marino, V.R.; Sheehan, O.C.; Huang, J.; Roth, D.L.; Haley, W.E.	Association between levels of caregiver engagement and rates of self-reported healthcare utilization after stroke: A mixed methods study	Circulation: Cardiovascular Quality and Outcomes	No outcomes of interest
2016	Zia Ur Rehman, M.; Shah, S.I.A.; Javaid, M.; Gilani, S.O.; Ansari, U.	Audio signal's test in designing a cost-effective hearing aid device using a microcontroller	International Journal of Biomedical Engineering and Technology	No outcomes of interest
2020	Favoreel, A.; Heuninck, E.; Mansbach, A.-L.	Audiological benefit and subjective satisfaction of children with the ADHEAR audio processor and adhesive adapter	International Journal of Pediatric Otorhinolaryngology	No outcomes of interest
2023	Chattaraj, A.; Syed, M.P.; Low, C.A.; Owonikoko, T.K.	Cisplatin-Induced Ototoxicity: A Concise Review of the Burden, Prevention, and Interception Strategies	JCO Oncology Practice	No outcomes of interest

2005	Bond, C.A.; Raehl, C.L.	Clinical and economic outcomes of pharmacist-managed aminoglycoside or vancomycin therapy	American Journal of Health-System Pharmacy	No outcomes of interest
2015	Huarte, A.; Manrique, R.; De Abajo, J.; Lezaun, R.; Martinez, P.	Cochlear implant in an adult active population [otology, neuro-otology and skull base surgery]	International Archives of Otorhinolaryngology	No outcomes of interest
2013	Sorkin, D.L.	Cochlear implantation in the world's largest medical device market: Utilization and awareness of cochlear implants in the United States	Cochlear Implants International	No outcomes of interest
2016	Kraaijenga, V.; Venekamp, R.; Grolman, W.	Cochlear implants	Huisarts en Wetenschap	Not available in English
1995	Zeng, F.-G.	Cochlear implants in China	Audiology	Publication type not of interest
2000	Berruecos, P.	Cochlear implants: An international perspective - Latin American countries and Spain	Audiology	No outcomes of interest
2023	Inglis-Jenson, M.; Robler, S.K.; Gallo, J.J.; Ivanoff, P.; Ryan, S.; Hofstetter, P.; Emmett, S.D.	Community Perspectives on Hearing Loss in Rural Alaska	Ear and hearing	No outcomes of interest

2016	Radi, S.; Benke, G.; Schaafsma, F.; Sim, M.	Compensation claims for occupational noise induced hearing loss between 1998 and 2008: yearly incidence rates and trends in older workers	Australian and New Zealand journal of public health	No outcomes of interest
1988	Melnick, W.	Compensation for hearing loss from occupational noise	Seminars in Hearing	Publication type not of interest
2006	Bertsche, P.K.; Mensah, E.; Stevens, T.	Complying with a corporate global noise health surveillance procedure--do the benefits outweigh the costs?	AAOHN journal : official journal of the American Association of Occupational Health Nurses	No outcomes of interest
1997	Carrier, D.A.; Arriaga, M.A.	Cost-effective evaluation of asymmetric sensorineural hearing loss with focused magnetic resonance imaging	Otolaryngology - Head and Neck Surgery	No outcomes of interest
2021	Verkleij, M.L.; Heijnsdijk, E.A.M.; Bussé, A.M.L.; Carr, G.; Goedegebure, A.; Mackey, A.R.; Qirjazi, B.; Uhlén, I.M.; Sloot, F.; Hoeve, H.L.J.; de Koning, H.J.	Cost-Effectiveness of Neonatal Hearing Screening Programs: A Micro-Simulation Modeling Analysis	Ear and hearing	No outcomes of interest
2018	Gumbie, M.; Parkinson, B.; Bowman, R.; Song, R.; Cutler, H.	Cost-Effectiveness of Screening a 5 Year Old Child for Hearing Loss Using Sound Scouts Compared with	Value in Health	Publication type not of interest

		no Screening: A Decision Model Analysis		
2021	Skarzynski, P.H.; Ciesla, K.; Lorens, A.; Wojcik, J.; Skarzynski, H.	Cost-utility analysis of bilateral cochlear implantation in adults in Poland	Otolaryngology - Head and Neck Surgery	No outcomes of interest
2021	Skarzynski, P.H.; Ciesla, K.; Lorens, A.; Wojcik, J.; Skarzynski, H.	Cost-Utility Analysis of Bilateral Cochlear Implantation in Adults With Severe to Profound Sensorineural Hearing Loss in Poland	Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	Study type not of interest
2021	Seebacher, J.; Muigg, F.; Kühn, H.; Weichbold, V.; Galvan, O.; Zorowka, P.; Schmutzhard, J.	Cost-utility Analysis of Cochlear Implantation in Adults With Single-sided Deafness: Austrian and German Perspective	Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	Study type not of interest
2018	Sayler, S.K.; Rabinowitz, P.M.; Cantley, L.F.; Galusha, D.; Neitzel, R.L.	Costs and effectiveness of hearing conservation programs at 14 US metal manufacturing facilities	International journal of audiology	No outcomes of interest
1989	Alleyne, B.C.; Dufresne, R.M.; Kanji, N.; Reesal, M.R.	Costs of workers' compensation claims for hearing loss	Journal of Occupational Medicine	No outcomes of interest

2013	Faivre, P.; Bénard, S.; Wright, C.; Voisine, J.; Gaudelus, J.	Counting the cost of meningococcal disease in France	Value in Health	Publication type not of interest
2018	Rebscher, S.; Zhou, D.D.; Zeng, F.-G.	Development and Clinical Introduction of the Nurotron Cochlear Implant Electrode Array	The journal of international advanced otology	No outcomes of interest
2021	Holzinger, D.; Binder, D.; Raus, D.; Palmisano, G.; Fellinger, J.	Development and implementation of a low-cost tracking system after newborn hearing screening in upper austria: Lessons learned from the perspective of an early intervention provider	Children	No outcomes of interest
2015	Stika, C.J.; Hays, R.D.	Development and psychometric evaluation of a health-related quality of life instrument for individuals with adult-onset hearing loss	International journal of audiology	No outcomes of interest
2013	Guthrie, D.M.; Poss, J.W.	Development of a case-mix funding system for adults with combined vision and hearing loss.	BMC health services research	Population
2011	Buhagiar, R.; Lutman, M.	Development of a quality-of-life measure for adult patients with sequential bilateral cochlear implants.	Cochlear implants international	No outcomes of interest

2012	Fraser, L.; Starritt, N.; Melia, L.; Kubba, H.	Development of a screening and splinting service for neonatal ear deformity	Clinical Otolaryngology	No outcomes of interest
2020	Hytönen, M.L.; Laakso, J.; Silvola, J.T.; Jero, J.; Sinkkonen, S.	Development of otology-specific health-related quality-of-life instrument: Ear outcome survey-16 (EOS-16)	Otolaryngology - Head and Neck Surgery	No outcomes of interest
2001	Jacobson, G.P.; Newman, C.W.; Fabry, D.A.; Sandridge, S.A.	Development of the three-clinic hearing aid selection profile (HASP)	Journal of the American Academy of Audiology	No outcomes of interest
2000	Grimby, A.; Ringdahl, A.	Does having a job improve the quality of life among post-lingually deafened Swedish adults with severe-profound hearing impairment?	British Journal of Audiology	No outcomes of interest
2016	Alamgir, H.; Tucker, D.L.; Kim, S.-Y.; Betancourt, J.A.; Turner, C.A.; Gorrell, N.S.; Wong, N.J.; Sagiraju, H.K.; Cooper, S.P.; Douphrate, D.I.; Whitworth, K.W.; Marko, D.; Gimeno, D.; Cornell, J.; Hammill, T.L.; Senchak, A.J.; Packer, M.D.	Economic Burden of Hearing Loss for the U.S. Military: A Proposed Framework for Estimation	Military medicine	Study type not of interest

2018	Medeulova, A.; Kosherbayeva, L.; Nurbakyt, A.	Economic evaluation of cochlear implantation for children in Kazakhstan	Drug Invention Today	Publication type not of interest
2017	Neitzel, R.L.; Swinburn, T.K.; Hammer, M.S.; Eisenberg, D.	Economic Impact of Hearing Loss and Reduction of Noise-Induced Hearing Loss in the United States	Journal of speech, language, and hearing research : JSLHR	No outcomes of interest
2022	Hoch, A.; Kiesewetter, K.; Dejaco, T.; Scandurra, F.; Rose-Eichberger, K.; Schwarz, Mag., C.; Urban, M.	EE157 Cost-Utility of Active Middle Ear Implants for Sensorineural Hearing Loss	Value in Health	Study type not of interest
2000	Krabbe, P.F.M.; Hinderink, J.B.; Van Den Broek, P.	Effect of cochlear implant use in postlingually deaf adults	International Journal of Technology Assessment in Health Care	Study type not of interest
2005	McPherson, B.; Wong, E.T.L.	Effectiveness of an affordable hearing aid with elderly persons	Disability and Rehabilitation	No outcomes of interest
2008	Thorne, P.R.; Ameratunga, S.N.; Stewart, J.; Reid, N.; Williams, W.; Purdy, S.C.; Dodd, G.; Wallaart, J.	Epidemiology of noise-induced hearing loss in New Zealand	New Zealand Medical Journal	Publication type not of interest
2020	Chen, K.; Zhong, Y.; Gu, Y.; Sharma, R.; Li, M.; Zhou, J.; Wu, Y.; Gao, Y.; Qin, G.	Estimated Cost-effectiveness of Newborn Screening for Congenital Cytomegalovirus Infection in China Using a Markov Model	JAMA Network Open	Study type not of interest

2022	Bonnafous, S.; Margier, J.; Bartier, S.; Tournegros, R.; Tringali, S.; Fieux, M.	Estimated Costs Associated with Management of Otosclerosis with Hearing Aids vs Surgery in Europe	JAMA Network Open	No outcomes of interest
2007	Patel, K.J.; Kedia, M.S.; Bajpai, D.; Mehta, S.S.; Kshirsagar, N.A.; Gogtay, N.J.	Evaluation of the prevalence and economic burden of adverse drug reactions presenting to the medical emergency department of a tertiary referral centre: A prospective study	BMC Clinical Pharmacology	No outcomes of interest
2001	Cox, L.Clarke; Toro, M.R.	Evolution of a universal infant hearing screening program in an inner city hospital	International Journal of Pediatric Otorhinolaryngology	No outcomes of interest
2010	Laplante-Lévesque, A.; Hickson, L.; Worrall, L.	Factors influencing rehabilitation decisions of adults with acquired hearing impairment	International Journal of Audiology	No outcomes of interest
2017	Khan, K.M.; Bielko, S.L.; Barnes, P.A.; Evans, S.S.; Main, A.L.K.	Feasibility of a low-cost hearing screening in rural Indiana	BMC public health	No outcomes of interest
2019	Elshahoubi, A.; Khattab, E.; Halalsheh, H.; Khaleifeh, K.; Bouffet, E.; Amayiri, N.	Feasibility of high-dose chemotherapy protocols to treat infants with malignant central nervous system tumors: Experience from a middle-income country	Pediatric Blood and Cancer	Population

2020	Lee, S.-Y.; Oh, D.-Y.; Han, J.H.; Kim, M.Y.; Kim, B.; Kim, B.J.; Song, J.-J.; Koo, J.-W.; Lee, J.H.; Oh, S.H.; Choi, B.Y.	Flexible Real-Time Polymerase Chain Reaction-Based Platforms for Detecting Deafness Mutations in Koreans: A Proposed Guideline for the Etiologic Diagnosis of Auditory Neuropathy Spectrum Disorder	Diagnostics	No outcomes of interest
2015	Emmett, S.D.; Tucci, D.L.; Smith, M.; Macharia, I.M.; Ndegwa, S.N.; Nakku, D.; Mukara, K.B.; Kaitesi, M.B.; Ibekwe, T.S.; Mulwafu, W.; Gong, W.; Francis, H.W.; Saunders, J.E.	GDP Matters: Cost Effectiveness of Cochlear Implantation and Deaf Education in Sub-Saharan Africa	Otology & neurotology: official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	Population
2019	Rochat, R.H.; Demmler-Harrison, G.J.	Health outcomes in congenital cytomegalovirus, a systematized and unbiased approach in the electronic medical record era	Open Forum Infectious Diseases	No outcomes of interest
2004	Quinn, G.E.; Dobson, V.; Saigal, S.; Phelps, D.L.; Hardy, R.J.; Tung, B.; Summers, C.G.; Palmer, E.A.	Health-related quality of life at age 10 years in very low-birth-weight children with and without threshold retinopathy of prematurity	Archives of Ophthalmology	No outcomes of interest

2012	Gopinath, B.; Schneider, J.; Hickson, L.; McMahon, C.M.; Burlutsky, G.; Leeder, S.R.; Mitchell, P.	Hearing handicap, rather than measured hearing impairment, predicts poorer quality of life over 10 years in older adults	Maturitas	No outcomes of interest
2023	Ordoñez, J.; Baldi Castro, J.J.	HTA31 Cost-Utility Analysis of Pneumococcal Vaccines for Older Adults Available in Costa Rica	Value in Health	No outcomes of interest
2023	Ordoñez, J.; Baldi Castro, J.J.	HTA49 Cost-Utility Analysis of Pneumococcal Vaccines for Older Adults Available in El Salvador	Value in Health	No outcomes of interest
2019	Alvarenga Reis, R.; Bullinger, M.; Borozan, O.; Brutt, A.; Meiss, M.; Rohlfs, K.; Fegadolli, C.; Santos, C.	Identification of attributes of quality of life among children and adolescents with hearing loss	Quality of Life Research	No outcomes of interest
2018	Miaskowski, C.; Mastick, J.; Paul, S.M.; Abrams, G.; Cheung, S.; Sabes, J.H.; Kober, K.M.; Schumacher, M.; Conley, Y.P.; Topp, K.; Smoot, B.; Mausisa, G.; Mazor, M.; Wallhagen, M.; Levine, J.D.	Impact of chemotherapy-induced neurotoxicities on adult cancer survivors' symptom burden and quality of life	Journal of cancer survivorship : research and practice	No outcomes of interest
2021	Thum, C.; Langenfeld, R.; Flessa, S.	Lifetime Cost of Hearing AIDS in Germany	Laryngo- Rhino- Otologie	Not available in English

2018	McDowell, L.J.; Rock, K.; Xu, W.; Chan, B.; Waldron, J.; Lu, L.; Ezzat, S.; Pothier, D.; Bernstein, L.J.; So, N.; Huang, S.H.; Giuliani, M.; Hope, A.; O'Sullivan, B.; Bratman, S.V.; Cho, J.; Kim, J.; Jang, R.; Bayley, A.; Ringash, J.	Long-Term Late Toxicity, Quality of Life, and Emotional Distress in Patients With Nasopharyngeal Carcinoma Treated With Intensity Modulated Radiation Therapy	International Journal of Radiation Oncology Biology Physics	No outcomes of interest
2008	Newman, C.W.; Sandridge, S.A.; Wodzisz, L.M.	Longitudinal benefit from and satisfaction with the Baha system for patients with acquired unilateral sensorineural hearing loss.	Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	No outcomes of interest
2022	Nathan, A.S.; Hubbell, R.D.; Levi, J.R.	Management of children with co-occurring sleep disordered breathing and hearing loss	International Journal of Pediatric Otorhinolaryngology	No outcomes of interest
2011	Gènova-Maleras, R.; Álvarez-Martín, E.; Morant-Ginestar, C.; Fernández De Larrea, N.; Catalá-López, F.	Measuring the burden of disease and injury in Spain using disability-adjusted life years: A population-based study	Value in Health	No outcomes of interest

2012	Gènova-Maleras, R.; Álvarez-Martín, E.; Morant-Ginestar, C.; Fernández de Larrea-Baz, N.; Catalá-López, F.	Measuring the burden of disease and injury in Spain using disability-adjusted life years: An updated and policy-oriented overview	Public Health	Publication type not of interest
2022	Kiesewetter, K.; Dejaco, T.; Scandurra, F.; Rose-Eichberger, K.; Hoch, A.; Schwarz, Mag., C.; Urban, M.	MT9 Cost-Utility of Bone Conduction Implants for Conductive or Mixed Hearing Loss or Single-Sided Deafness: A Decision Analysis	Value in Health	Study type not of interest
2015	Kopec, J.A.; Sayre, E.C.; Rogers, P.; Davis, A.M.; Badley, E.M.; Anis, A.H.; Abrahamowicz, M.; Russell, L.; Rahman, M.M.; Esdaile, J.M.	Multiattribute health utility scoring for the computerized adaptive measure CAT-5D-QOL was developed and validated	Journal of Clinical Epidemiology	No outcomes of interest
2020	Mylanus, E.A.M.; Hua, H.; Wigren, S.; Arndt, S.; Skarzynski, P.H.; Telian, S.A.; Briggs, R.J.S.	Multicenter Clinical Investigation of a New Active Osseointegrated Steady-State Implant System	Otology & neurotology : official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	No outcomes of interest
1998	Daniell, W.E.; Fulton-Kehoe, D.; Smith-Weller, T.; Franklin, G.M.	Occupational hearing loss in Washington State, 1984-1991: II. Morbidity and associated costs	American Journal of Industrial Medicine	No outcomes of interest

2015	Girard, S.-A.; Leroux, T.; Courteau, M.; Picard, M.; Turcotte, F.; Richer, O.	Occupational noise exposure and noise-induced hearing loss are associated with work-related injuries leading to admission to hospital	Injury prevention: journal of the International Society for Child and Adolescent Injury Prevention	No outcomes of interest
2008	Muluk, N.B.; Oğuztürk, Ö.	Occupational noise-induced tinnitus: Does it affect workers' quality of life?	Journal of Otolaryngology - Head and Neck Surgery	No outcomes of interest
2017	Wong, L.-Y.; Espinoza, F.; Alvarez, K.M.; Molter, D.; Saunders, J.E.	Otoacoustic Emissions in Rural Nicaragua: Cost Analysis and Implications for Newborn Hearing Screening	Otolaryngology - Head and Neck Surgery (United States)	Population
2022	Ten Tije, F.A.; Pauw, R.J.; Bom, S.J.H.; Stam, M.; Kramer, S.E.; Lissenberg-Witte, B.I.; Merkus, P.	Postoperative Patient Reported Outcomes After Cholesteatoma Surgery	Otology & neurotology: official publication of the American Otological Society, American Neurotology Society [and] European Academy of Otology and Neurotology	No outcomes of interest
2020	Si, S.; Lewkowski, K.; Fritschi, L.; Heyworth, J.; Liew, D.; Li, I.	Productivity burden of occupational noise-induced hearing loss in australia: A life table modelling study	International Journal of Environmental Research and Public Health	No outcomes of interest
2022	Mohamed-Noriega, J.; Munoa, S.A.; Lazaridis, G.; Praditsuktavorn, P.; Garway-Heath, D.F.	Prospective observational study of disc haemorrhages (POSH). Comparison of ocular and systemic	Investigative Ophthalmology and Visual Science	No outcomes of interest

		variables between visits with and without disc haemorrhages.		
2019	Cutler, H.; Gumbie, M.; Olin, E.; Parkinson, B.; Bowman, R.; Quadri, H.; Gonzalo, F.	PSS1 THE COST-EFFECTIVENESS OF COCHLEAR IMPLANTS IN UK ADULTS	Value in Health	Publication type not of interest
2000	Fugain, C.; Ouayoun, M.; Meyer, B.; Chouard, C.H.	Q.A.L.Y. index and assessment of cost efficiency of the cochlear implant in acquired profound deafness	Annales d'oto-laryngologie et de chirurgie cervico faciale : bulletin de la Société d'oto-laryngologie des hôpitaux de Paris	Not available in English
2016	Er, O.; Arslan, F.; Celik, M.; Etli, T.	Quality of life in patients with unilateral sensorineural hearing loss	Klinik Psikofarmakoloji Bulteni	Publication type not of interest
2021	Zhou, H.; Zhou, Y.; Zhang, H.; Yu, A.; Zhu, B.; Zhang, L.	Socio-economic disparity in the global burden of occupational noise-induced hearing loss: An analysis for 2017 and the trend since 1990	Occupational and Environmental Medicine	No outcomes of interest
2015	Porter, M.; Boothroyd, R.A.	Symptom severity, social supports, coping styles, and quality of life among individuals' diagnosed with Ménierè's disease	Chronic Illness	No outcomes of interest

2015	Carlson, M.L.; Tveiten, Ø.V.; Yost, K.J.; Lohse, C.M.; Lund-Johansen, M.; Link, M.J.	The Minimal Clinically Important Difference in Vestibular Schwannoma Quality-of-Life Assessment: An Important Step beyond P <.05	Otolaryngology - Head and Neck Surgery (United States)	No outcomes of interest
2005	Chisolm, T.H.; Abrams, H.B.; McArdle, R.; Wilson, R.H.; Doyle, P.J.	The WHO-DAS II: Psychometric properties in the measurement of functional health status in adults with acquired hearing loss	Trends in Amplification	No outcomes of interest
2015	Kopec, J.A.; Sayre, E.C.; Fines, P.; Okhmatovskaia, A.; Flanagan, W.M.; Wolfson, M.C.	Time Trends in the Health Utilities Index Mark 3 attributes in the general population of Canada, 2000-2010	Quality of Life Research	No outcomes of interest
2016	Rogers, K.D.; Pilling, M.; Davies, L.; Belk, R.; Nassimi-Green, C.; Young, A.	Translation, validity and reliability of the British Sign Language (BSL) version of the EQ-5D-5L	Quality of Life Research	No outcomes of interest
2018	Eichwald, J.; Scinicariello, F.; Telfer, J.L.; Carroll, Y.I.	Use of Personal Hearing Protection Devices at Loud Athletic or Entertainment Events Among Adults - United States, 2018	MMWR. Morbidity and mortality weekly report	No outcomes of interest
2004	Mo, F.; Choi, B.C.; Li, F.C.; Merrick, J.	Using Health Utility Index (HUI) for measuring the impact on health-related quality of Life (HRQL) among individuals with chronic diseases.	TheScientificWorldJournal	No outcomes of interest

1993	Maxon, A.B.; White, K.R.; Vohr, B.R.; Behrens, T.R.	Using transient evoked otoacoustic emissions for neonatal hearing screening	British Journal of Audiology	No outcomes of interest
2021	McRackan, T.R.; Hand, B.N.; Velozo, C.A.; Dubno, J.R.	Validity and reliability of the Cochlear Implant Quality of Life (CIQOL)-35 Profile and CIQOL-10 Global instruments in comparison to legacy instruments	Ear and hearing	No outcomes of interest
2016	Raine, C.; Atkinson, H.; Strachan, D.R.; Martin, J.M.	Access to cochlear implants: Time to reflect	Cochlear implants international	No outcomes of interest
2010	Bobay, K.L.; Jerofke, T.A.; Weiss, M.E.; Yakusheva, O.	Age-related differences in perception of quality of discharge teaching and readiness for hospital discharge	Geriatric Nursing	No outcomes of interest
1983	Grove, S.J.; Fisk, R.P.	An analysis of the health care needs of the hearing impaired: From hearing aids to microcomputers	Journal of Health Care Marketing	Publication type not of interest
2019	Baum, A.; Mulwafu, W.; Phiri, M.; Polack, S.; Bright, T.	An intervention to improve uptake of referrals for children with ear disease or hearing loss in Thyolo district, Malawi: Acceptability and feasibility	International Journal of Environmental Research and Public Health	No outcomes of interest

2009	Wu, C.-C.; Lu, Y.-C.; Chen, P.-J.; Liu, A.Y.-Z.; Hwu, W.-L.; Hsu, C.-J.	Application of SNaPshot multiplex assays for simultaneous multigene mutation screening in patients with idiopathic sensorineural hearing impairment	Laryngoscope	No outcomes of interest
2018	Guan, Q.; Balciuniene, J.; Cao, K.; Fan, Z.; Biswas, S.; Wilkens, A.; Gallo, D.J.; Bedoukian, E.; Tarpinian, J.; Jayaraman, P.; Sarmady, M.; Dulik, M.; Santani, A.; Spinner, N.; Abou Tayoun, A.N.; Krantz, I.D.; Conlin, L.K.; Luo, M.	AUDIOME: a tiered exome sequencing–based comprehensive gene panel for the diagnosis of heterogeneous nonsyndromic sensorineural hearing loss	Genetics in Medicine	No outcomes of interest
2017	Zeng, F.-G.	Challenges in improving cochlear implant performance and accessibility	IEEE Transactions on Biomedical Engineering	No outcomes of interest
2016	Crowson, M.G.; Ramprasad, V.H.; Chapurin, N.; Cunningham, C.D.; Kaylie, D.M.	Cost analysis and outcomes of a second-look tympanoplasty-mastoidectomy strategy for cholesteatoma	Laryngoscope	No outcomes of interest
2018	Ordoñez Molina, J.E.; Ordóñez, A.	COST-EFFECTIVENESS OF PNEUMOCOCCAL CONJUGATE	Value in Health	No outcomes of interest

2014	Ko, Y.; Gwee, Y.-S.; Huang, Y.-C.; Chiang, J.; Chan, A.	Costs and length of stay of drug-related hospital admissions in cancer patients	Clinical Therapeutics	No outcomes of interest
2000	Siegel, G.J.	Description of an office technique for laser ventilation of the ears	Ear, Nose and Throat Journal	No outcomes of interest
2013	Caporali, S.A.; Schmidt, E.; Eriksson, Å.; Sköld, B.; Popecki, B.; Larsson, J.; Auriemmo, J.	Evaluating the physical fit of receiver-in-the-ear hearing aids in infants	Journal of the American Academy of Audiology	No outcomes of interest
2004	Palti, H.; Gofin, R.; Adler, B.	Evaluation of utilization of preventive services for infants in Israel - Personal and organizational determinants	Harefuah	Not available in English
2022	Távora-Vieira, D.; Voola, M.; Majteles, L.; Timms, L.; Acharya, A.; Kuthubutheen, J.	Extended scope of practice audiology in the ENT outpatient clinic - a pilot study	International journal of audiology	No outcomes of interest
1998	Uimonen, S.; Mäki-Torkko, E.; Sorri, M.	Hearing and occupation.	International journal of circumpolar health	Publication type not of interest

2023	Hotton, M.; Prud'Homme, V.; Richard, L.; Cormier, L.; Simoneau, K.; Lefebvre-Demers, M.; Vincent, C.; Boucher, N.	Impacts and Identification of Hearing Aid Refurbishing Programs for People with Hearing Loss: A Scoping Review	Audiology Research	No outcomes of interest
2021	Patro, A.; Haynes, D.S.; Perkins, E.L.	Implementation and barriers to same-day patient consultation and cochlear implantation	Otolaryngology - Head and Neck Surgery	No outcomes of interest
2002	Daniell, W.E.; Fulton-Kehoe, D.; Cohen, M.; Swan, S.S.; Franklin, G.M.	Increased reporting of occupational hearing loss: Workers' compensation in Washington State, 1984-1998	American Journal of Industrial Medicine	No outcomes of interest
2008	Goto, F.; Yabe, H.; Kunihiro, T.; Ogawa, K.	Meniere's disease in the elderly in Japan	Equilibrium Research	Not available in English
1995	Feeny, D.; Furlong, W.; Boyle, M.; Torrance, G.W.	Multi-attribute health status classification systems. Health Utilities Index	PharmacoEconomics	No outcomes of interest
2019	Phillips, A.; Cooney, R.; Harris, Z.; Myrtil, D.; Hodgson, M.	Noise and Occupational Medicine: Common Practice Problems	Journal of Occupational and Environmental Medicine	No outcomes of interest
1996	Moore, A.A.; Siu, A.L.	Screening for common problems in ambulatory elderly: Clinical confirmation of a screening instrument	American Journal of Medicine	No outcomes of interest

2017	Li, Y.; Zhu, Y.; Zhong, Q.; Zhang, X.; Shu, M.; Wan, C.	Serious Adverse Reactions from Anti-tuberculosis Drugs among 599 Children Hospitalized for Tuberculosis	Pediatric Infectious Disease Journal	No outcomes of interest
2018	Driscoll, T.	The 2016 global burden of disease arising from occupational exposures	Occupational and Environmental Medicine	No outcomes of interest
2011	Tumwikirize, W.A.; Ogwal-Okeng, J.W.; Vernby, A.; Anokbonggo, W.W.; Gustafsson, L.L.; Lundborg, S.C.	Adverse drug reactions in patients admitted on Internal Medicine wards in a district and Regional Hospital in Uganda	African Health Sciences	No outcomes of interest
2011	Botelho-Nevers, E.; Rovery, C.; Richet, H.; Raoult, D.	Analysis of risk factors for malignant mediterranean spotted fever indicates that fluoroquinolone treatment has a deleterious effect	Journal of Antimicrobial Chemotherapy	No outcomes of interest
2022	Schipmann, S.; Lohmann, S.; Al Barim, B.; Suero Molina, E.; Schwake, M.; Toksöz, Ö.A.; Stummer, W.	Applicability of contemporary quality indicators in vestibular surgery—do they accurately measure tumor inherent postoperative complications of vestibular schwannomas?	Acta Neurochirurgica	No outcomes of interest
2016	Manoj, M.P.	Bone Obliteration technique in recidivistic cholesteatoma	Journal of Laryngology and Otology	Publication type not of interest

2005	Henry, J.A.; Zaugg, T.L.; Schechter, M.A.	Clinical guide for audiologic tinnitus management II: Treatment	American Journal of Audiology	Publication type not of interest
1988	Wright, P.F.; Sell, S.H.; McConnell, K.B.; Sitton, A.B.; Thompson, J.; Vaughn, W.K.; Bess, F.H.	Impact of recurrent otitis media on middle ear function, hearing, and language	Journal of Pediatrics	No outcomes of interest
2016	Vos, T. et al.	Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015	The Lancet	No outcomes of interest
1998	Robertson, C.M.T.; Cheung, P.-Y.; Magathan Haluschak, M.; Elliott, C.A.; Leonard, N.J.; Sauve, R.S.; Whitfield, M.F.; Belgaumkar, T.K.; Casiro, O.G.; Saunders, M.A.; Mueller, G.; Ng, P.	High prevalence of sensorineural hearing loss among survivors of neonatal congenital diaphragmatic hernia	American Journal of Otology	No outcomes of interest
2014	Girard, S.A.; Leroux, T.; Verreault, R.; Courteau, M.; Picard, M.; Turcotte, F.; Baril, J.	Falls risk and hospitalization among retired workers with occupational noise-induced hearing loss.	Canadian journal on aging = La revue canadienne du vieillissement	No outcomes of interest

2023	Cohen-Cutler, S.; Kaplan, C.; Olch, A.; Wong, K.; Malvar, J.; Constine, L.S.; Freyer, D.R.	Impact of Volumetric Dosimetry on the Projected Cost of Radiation-Related Late Effects Screening After Childhood Cancer: A Real-World Cohort Analysis	Oncologist	Outcome not of interest
2023	Zitelli, L.; Palmer, C.; Mamula, E.; Johnson, J.; Rauterkus, G.; Nilsen, M.L.	Hearing screening and amplifier uptake results in a multidisciplinary head and neck cancer survivorship clinic	Journal of cancer survivorship : research and practice	Outcome not of interest
2023	Coltin, H.; Pequeno, P.; Liu, N.; Tsang, D.S.; Gupta, S.; Taylor, M.D.; Bouffet, E.; Nathan, P.C.; Ramaswamy, V.	The Burden of Surviving Childhood Medulloblastoma: A Population-Based, Matched Cohort Study in Ontario, Canada	Journal of Clinical Oncology	Outcome not of interest
2022	Dillard, L.K.; Lopez-Perez, L.; Martinez, R.X.; Fullerton, A.M.; Chadha, S.; McMahon, C.M.	Global burden of ototoxic hearing loss associated with platinum-based cancer treatment: A systematic review and meta-analysis	Cancer Epidemiology	Outcome not of interest
2021	Piromchai, P.; Tanamai, N.; Kiatthanabumrung, S.; Kaewsiri, S.; Thongyai, K.; Atchariyasathian, V.; Thanawirattananit, P.; Wacharasindhu, C.; Mukkun, T.; Isipradit, P.; Yimtae, K.	Multicentre cohort study of cochlear implantation outcomes in Thailand	BMJ Open	Outcome not of interest

2020	Page, B.R.; Fernandez, K.; Garrett, J.; Marcia, M.; Clements, A.; Schmitt, N.C.; Cunningham, L.L.	Feasibility of Portable Audiometry for Ototoxicity Monitoring in a Radiation Oncology Clinic for Head and Neck Cancer Patients Receiving Cisplatin-Based Chemoradiotherapy	International Journal of Radiation Oncology Biology Physics	Outcome not of interest
2020	Khan, A.; Mubdi, N.; Budnick, A.; Feldman, D.R.; Williams, S.W.; Patel, S.; Tonorezos, E.S.	The experience of hearing loss in adult survivors of childhood and young adult cancer: A qualitative study	Cancer	Outcome not of interest
2020	Pasternak, P.; Frąckiewicz, M.; Zawadzka-Glos, L.	Gentamicin and its ototoxicity	New Medicine	Outcome not of interest
2019	Hunter, L.L.; Blankenship, C.; Feeney, P.; Garinis, A.C.; Vinks, A.; McPhail, G.L.	Impact of hearing loss in children and teens with CF treated with IV antibiotics	Pediatric Pulmonology	Pre-2021 CA
2018	Kruseova, J.; Perníková, I.; Valvoda, J.; Císařová, E.; Kováčová, A.S.; Sumerauer, D.; Lukš, A.; Čapek, V.; Langer, T.; Zehnhoff-Dinnesen, A.; Kynčl, M.; Starý, J.	Influence of cisplatin-based chemotherapy on hearing impairment, neurological outcome and education in CNS survivors	Pediatric Blood and Cancer	Outcome not of interest

2018	Ionescu, A.; Agnarson, M.A.; Kambili, C.; Kfoury, J.; Steven, W.; Singh, V.; Williams, A.; Thomas, A.	COST-EFFECTIVENESS OF BEDAQUILINE VERSUS INJECTABLE STANDARD-OF-CARE AGENTS FOR THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS (DR-TB) IN RUSSIA, INDIA, AND SOUTH AFRICA: BREAKTHROUGH INNOVATION DRIVING DOWN COST OF TREATMENT SUCCESS	Value in Health	Outcome not of interest
2014	Bagatell, R.; Fisher, B.; Seif, A.E.; Huang, Y.-S.; Li, Y.; Desai, A.V.; London, W.B.; Van Ryn, C.; Park, J.R.; Richardson, T.; Hall, M.; Aplenc, R.	Evaluation of resources used during care of children with high-risk neuroblastoma (HR NBL) via merging of cooperative group trial data and administrative data	Journal of Clinical Oncology	Pre-2021 CA
2013	Rodriguez, C.P.; Adelstein, D.J.; Rybicki, L.A.; Savvides, P.; Saxton, J.P.; Koyfman, S.A.; Greskovich, J.; Yao, M.; Scharpf, J.; Lavertu, P.; Wood, B.J.; Burkey, B.; Lorenz, R.; Rezaee, R.; Zender, C.; Ives, D.I.	A phase III randomized trial of two cisplatin-based concurrent chemoradiation (CCRT) regimens for locally advanced head and neck squamous cell carcinoma (LAHNSCC)	Journal of Clinical Oncology	Pre-2021 CA

2012	Burnham, N.B.; Ittenbach, R.F.; Knightly, C.; Solot, C.B.; Gerdes, M.; Bernbaum, J.C.; Wernovsky, G.; Spray, T.L.; Nicolson, S.C.; Clancy, R.R.; Licht, D.J.; Zackai, E.; Gaynor, J.W.	Hearing loss is common and often unrecognized in preschool children following cardiac surgery in infancy	Congenital Heart Disease	Pre-2021 CA
2010	Henderson, D.; Hayward, A.; Purdy, C.; Magar, R.	The potential economic benefits provided by combining Cisplatin with SRC inhibitor KX1-004 for cancer regimens	Value in Health	Pre-2021 CA
2006	Vaile, L.; Williamson, T.; Waddell, A.; Taylor, G.	Interventions for ear discharge associated with grommets (ventilation tubes).	Cochrane database of systematic reviews (Online)	Study type not of interest
2004	Mawman, D.J.; Bhatt, Y.M.; Green, K.M.J.; O'Driscoll, M.P.; Saeed, S.R.; Ramsden, R.T.	Trends and outcomes in the Manchester adult cochlear implant series	Clinical Otolaryngology and Allied Sciences	Outcome not of interest

J.1.8 Cost and resource use studies

Four cost and resource use studies identified in the SLR reported results for UK patient populations. Of these, no studies were identified which report costs or resource use specifically in patients with cisplatin-induced ototoxicity, however, costs and resource use data were reported for other causes of HL.

Mohiuddin et al. (2015) reported hearing aid-related costs and resource use, diagnostic and evaluation costs and resource use and the costs of medication for patients under the age of 12 years with persistent otitis media with effusion. Landry et al. (2022) reported medication costs, hearing aid and cochlear implant costs, diagnostic and evaluation costs, hearing device and maintenance costs and AE costs for adult patients with age-related sensorineural HL. Cutler et al. (2022) reported diagnostic and evaluation costs and resource use, cochlear implant and hearing aid-related costs and resource use, device programming and maintenance costs and resource use, sound processor replacement/upgrade costs and resource use and AE costs and resource use for UK adults diagnosed with severe to profound sensorineural HL in both ears. Yaneza et al. (2016) reported hearing aid-related resource use in school age children with trisomy 21 and abnormal hearing or middle ear pathology. The results of these studies are presented in Table 100. Of the remaining 23 cost and resource use studies identified in the SLR which reported non-UK costs and resource use data, one study (Dionne et al. 2012) reported hearing aid-related costs, overall costs, device programming and maintenance costs and indirect costs in a Canadian population of paediatric patients at risk of cisplatin-induced HL. A further three US studies reported disease management costs for other forms of drug-induced ototoxicity (Huang et al. (2021) [cystic fibrosis patients receiving aminoglycosides who developed HL]; Shah et al. (2004)) [adult patients with ototoxicity caused by vancomycin treatment for bacterial infections]; and Veenstra et al. (2007) [cystic fibrosis patients receiving aminoglycosides who developed HL]). One US study reported the annual cost of deafness as an AE in patients who survived paediatric medulloblastoma (Mailhot Vega et al. 2013). The remaining studies reported costs and resource use data for other causes of acquired HL.

Table 100 Details and results from included cost and resource use studies

Author	Year	Country	Resource use/costs considered	Results
Verkleij *et al.* 2021	2021	Albania	Hearing aid-related cost, Device programming and maintenance costs, Overall/total costs.	Costs, mean: Hearing aid (per side): €110, Fitting hearing aids (per side): €290, Repair of hearing aids (yearly): €23. Extra costs due to late treatment (age 1-16): Unilateral >80 dB loss: €500, Bilateral 41-80 dB loss: €1,000, Bilateral >80 dB loss: €1,500.
Kosaner Kliess *et al.* 2017	2017	Australia	Medication cost, Diagnostic and evaluation costs, Implant cost, Device programming and maintenance costs, Diagnostic and evaluation resource use, Device programming and maintenance costs.	Unit costs: Otitis externa treatment: AUD 109.9, Exostosis treatment: AUD 928, Syringing (general practitioner assisted): AUD 37.05, Candidacy assessment: AUD 511.1, Vibrant Soundbridge provision, first cycle: AUD 19,014.75, Revision surgery: AUD 1,089.9,

				Device explantation: AUD 4,143.6, Device reimplantation: AUD 12,514.75.
Gumbie *et al.* 2022	2022	Australia	Hearing aid-related cost, Diagnostic and evaluation cost, Cochlear implant cost, Hearing aid-related resource use, Diagnostic and evaluation resource use, Cochlear implant resource use.	Costs associated with management of HL: Annual audiologist review: AUD 138. Non-surgical intervention: Follow-up audiologist review: AUD 43.80, Hearing aid device (unilateral): AUD 234.45, Hearing aid device (bilateral): AUD 468.90, Hearing aid batteries (unilateral): AUD 71.15, Hearing aid batteries (bilateral): AUD 188.45, Hearing aid fitting, rehabilitation unilateral (by audiologist): AUD 428.35, Hearing aid fitting, rehabilitation bilateral (by audiologist): AUD 513.80. Surgical intervention: ENT specialist visit: AUD 85.55, Follow-up ENT visit: AUD 62.25, Annual audiology assessment: AUD 43.80, Cochlear operation: AUD 1,895.20,

Cochlear implant or cochlear hybrid implant (unilateral): AUD 13,570.00.

Other hearing problems:

Other hearing problems assessment: AUD 576,

Other hearing problems remediation support: AUD 280,

Audiologist review: AUD 87.95,

Frequency modulation system: AUD 1,855.

Resource use associated with HL (SE):

No intervention:

Annual audiologist review: 1 (0.500).

Non-surgical intervention:

Audiologist review: 1 (0.500),

Hearing aid device: 1 (0.500),

Hearing aid batteries: 1 (0.500),

Hearing aid fitting (audiologist): 1 (0.500).

Surgical intervention:

ENT specialist visit: 2 (1.000),

Audiologist review: 1 (0.500),

				Cochlear operation: 1 (0.500), Cochlear implant or cochlear hybrid implant: 1 (0.500), Annual audiology assessment: 1 (0.500).
Mohiuddin *et al.* 2014	2014	UK	Hearing aid-related costs, Diagnostic and evaluation costs, Cost of medication, Hearing aid-related resource use, Diagnostic and evaluation resource use.	Cost, mean (per child): Hearing aid: £80, Ear mould: £17, Hearing aid care kit: £20.88, Hearing aid battery: £0.49, Hearing aid fitting: £76, GP visit: £41, Antibiotic medication: £11, Audiological review: £48, ENT specialist visit: £91.72. Resource use, mean (per child): Hearing aid: 2, Ear mould: 8/year, Hearing aid care kit: 1,

				Hearing aid battery: 26/year, Hearing aid fitting: 1 procedure. GP visit/antibiotic medication: Hearing aid strategy: 2.8 times. Audiological review: Hearing aid strategy: 1 + 1.5/year. ENT specialist visit: Hearing aid strategy: 1.5/year.
Dionne *et al.* 2011	2011	Canada	Hearing aid-related costs, Overall/total costs, Device programming and maintenance costs, Indirect costs.	Unit cost per year: Hearing aid, 2 ears: $600, Batteries: $144, Earmolds, <6 years old: $270, Earmolds, 6 years old or greater: $90, Total hearing aid cost: Age 0-6 years: $1,014, Age >6years: $834, Binaural frequency modulation system: $640,

Microphone replacement: $60,

Maintenance/repairs: $160,

Total frequency modulation cost, per year: $860,

Annual cost associated with ototoxicity (Children age group):

Grade 1 or lesser HL:

0 to 5, 2.5 times/year: $138,

6 to 11, 1 time/year: $55,

12 to 18, 1 time/year: $55.

Grade 2 HL:

0 to 5, 3 times/year: $165,

6 to 11, 1.5 times/year: $83,

12 to 18, 1 time/year: $55.

Grade 3 or 4 HL:

0 to 5, 3 times/year: $165,

6 to 11, 2 times/year: $110,

12 to 18, 1 time/year: $55.

Equipment:

Grade 2 HL:

0 to 5, frequency modulation system for half the children: $430 (half the total annual cost of $860),

6 to 11, frequency modulation system: $860,

1 to 18, frequency modulation system: $860.

Grade 3 or 4 HL:

0 to 5, Hearing aids: $1,014,

6 to 11, Hearing aids: $834,

6 to 11, frequency modulation system: $860,

12 to 18, Hearing aids: $834,

12 to 18, frequency modulation system: $860.

Therapy/supports, Grade 3 or 4 HL:

0 to 5 (Speech therapy weekly, specialised early intervention services, special preschool placement): $6,600,

6 to 11 (Hearing resource teacher weekly; speech language pathologist as needed): $18,300,

12 to 18 (Hearing resource teacher weekly; note taking, captioning as needed): $18,300.

Estimated annual loss of productivity:

18 to 44 years: $13,265,

45 to 65 years: $5,226.

Average annual earnings, 2010 dollars*:

Men: $46,575,

Women: $30,631,

Annual estimated health care cost for ages 18-65 years: $766.50,

Total health care costs, Range:

Grade 2 HL: $298-$1,269,

Grade 3 or 4 HL: $21,018-$39,176.

Total societal costs, Range:

Grade 2 HL: $3,465-$11,626,

Grade 3 or 4 HL: $445,446-$562,198.

Total present value lifetime costs related to ototoxicity by type of cancer:

Brain tumour under 4:

Minimal HL: $992,

Grade 2: $11,386,

Grade 3 or 4: $454,156.

Brain tumour 4 and over:

Minimal HL: $523,

Grade 2: $8,128,

Grade 3 or 4: $445,446.

Neuroblastoma:

Minimal HL: $749,

Grade 2: $10,228,

Grade 3 or 4: $458,827.

Osteosarcoma:

Minimal HL: $256,

Grade 2: $3,465,

Grade 3 or 4: $562,198.

Hepatoblastoma:

Minimal HL: $1,034,

Grade 2: $11,626,

Grade 3 or 4: $468,695.

Germ cell tumours:

Minimal HL: $1,020,

Grade 2: $11,567,

				Grade 3 or 4: $455,712. Note: *2007 figures adjusted to 2010 using core Consumer Price Index increases from Bank of Canada
Landry *et al.* 2022	2022	UK	Medication cost, Hearing aid-related costs, Diagnostic and evaluation costs, Cochlear implant costs, Device programming and maintenance costs, Adverse event costs.	Direct medical costs: Novel therapeutic cost: £0. Cost of hearing aids: Monaural pathway: £275, Binaural pathway: £380, Cost hearing aid aftercare: £26, Cost of hearing evaluation for hearing aid: £54. Cost of cochlear implant: Unilateral cochlear implant cost: £22, 919, Presurgical cochlear implant candidacy costs: £5,308. Post-implantation costs: Maintenance costs in year 1: £6,617, Maintenance costs in year 2+: £945, Processor upgrade every 5 years: £5,445, Cost of major complication: £10,292.

Culter *et al.* 2022	2022	UK	Diagnostic and evaluation costs, Cochlear implant costs, Hearing aid-related costs, Device programming and maintenance costs, Sound processor replacement/upgrade costs, Adverse event costs, Diagnostic and evaluation resource use, Cochlear implant resource use, Hearing aid-related resource use, Device programming and maintenance resource use, Sound processor replacement/upgrade resource use, Adverse events resource use.	Cost of pre-implant assessment: Referral: Audiologist: £84, Removing earwax: £106. Stage 1: Initial assessment: Audiologist: £84. Stage 2: testing: Vestibular assessment and tests: £86, Radiologist: £74, MRI scan: £138, CT scan: £88. Stage 3: electrophysiology: Audio scientist: £84, Electrophysiology assessment: £70. Stage 4: medical assessment: Audiologist pre-operative assessment: £84, ENT surgeon consultation: £104,

Anaesthetist consultation: £130,

General practitioner consultation for meningitis vaccination: £31,

Meningitis vaccination: £60.

Stage 5: pre-procedural assessment outcome discussion:

Cochlear implant surgery coordinator: £44.

Surgery cost:

Unilateral cochlear implant operation-surgical cost: £5,956,

Unilateral cochlear implant operation-device cost: £16,964.

Cost of unilateral cochlear implant:

One hearing aid cost: £166,

Pair of hearing aids: £332,

Device programming and rehabilitation cost:

Initial care-Year 1:

General practitioner medical check: £31.

Cochlear implant programming:

Audiologist: £84.

Follow-up care-Year 2 and beyond:

Audiologist: £84,

Annual equipment maintenance (batteries, cables, coils and sound processor repairs): £328,

Cochlear implant annual administration: £44.

Sound processor replacement / upgrade, explant and re-implant cost:

Sound processor replacement/upgrade:

External component: £5,000,

Audiologist: £84.

Explant:

Audiologist (assessment): £84,

Explant 1 Visit: £4,253.

Re-implant:

Audiologist pre-operative assessment: £84,

ENT surgeon consultation: £104,

Anaesthetist consultation: £130,

Cochlear implant surgery coordinator: £44,

Unilateral cochlear implant operation-surgical cost: £5,956,

General practitioner medical check: £31.

Cost of short term and long-term adverse events cost

Short term adverse events, taste disturbances, Vertigo, Tinnitus:

General practitioner medical check: £31.

Infection:

Antibiotics: £10.

Long-term adverse events, vertigo:

General practitioner medical check: £31.

Resource use:

Pre-implant assessment resource use, per visit:

Referral:

Audiologist: 1 consultation,

Removing earwax: 1 Hour.

Stage 1: initial assessment:

Audiologist: 1.5 Hours.

Stage 2: testing:

Vestibular assessment and tests: 1.5 Hours,

Radiologist: 1 Hour,

MRI scan: 1 Hour,

CT scan: 1 Hour,

Stage 3: electrophysiology:

Audio scientist: 1 Hour,

Electrophysiology assessment: 1 Hour,

Stage 4: medical assessment:

Audiologist pre-operative assessment: 1.5 Hours,

ENT surgeon consultation: 1 Hour,

Anaesthetist consultation: 1 Hour,

General practitioner consultation for meningitis vaccination: 1 Consultation,

Meningitis vaccination: 1 Unit.

Stage 5: pre-procedural assessment outcome discussion:

Cochlear implant surgery coordinator: 1 Hour.

Surgery resource use, per visit:

Hospital ward:

Unilateral cochlear implant operation-surgical cost: 1 Visit,

Unilateral cochlear implant operation-device cost: 1 Implant.

Hearing aid resource use, per visit:

One hearing aid: 1 Unit,

Pair of hearing aids: 1 Unit.

Device programming and rehabilitation resource use, per visit:

Initial care-Year 1:

General practitioner medical check: 1 consultation.

Follow-up care-Year 2 and beyond:

Audiologist (tuning visit): 1 Hour,

Annual equipment maintenance (batteries, cables, coils and sound processor repairs): 1 Units,

Cochlear implant annual administration: 1 Hour.

Cochlear implant programming:

Audiologist 6 visits: 1.5 Hours.

Sound processor replacement / upgrade, explant and re-implant resource use, per visit:

Sound processor replacement/upgrade:

External component: 1 Unit,

Audiologist (tuning visit): 1.5 Hours.

Explant:

Audiologist (assessment): 1.5 Hours,

				Explant: 1 visit. Re-implant: Audiologist pre-operative assessment: 1.5 Hours, ENT surgeon consultation: 1 Hour, Anaesthetist consultation: 1 Hour, Cochlear implant surgery coordinator: 1 Hour, Unilateral cochlear implant operation-surgical cost: 1 Visit, General practitioner medical check: 1 Consultation. Short term and long-term adverse events, per visit: Short term adverse events, taste disturbances, Vertigo, Tinnitus: General practitioner visit: 1 Consultation. Infection: General practitioner visit: 1 Consultation, Antibiotics: 1 Course. Long-term adverse events, Vertigo: General practitioner visit: 1 Consultation.
Lytle *et al.* 2023	2023	Canada	Overall/total costs.	Direct medical cost, per episode:

Complex otitis media:

<2 years: $3,873,

2-4 years: $3,284.

Simple otitis media:

<2 years: $484,

2-4 years: $356.

Lifetime direct medical costs per episode:

Deafness sequelae of Meningitis:

<2 years: $182,135,

2-4 years: $182,135,

5-17 years: $172,491,

18-49 years: $138,423,

50-64 years: $91,144,

≥65 years: $66,353.

Indirect non-medical cost per episode
Complex otitis media:

<2 years: $246,

2-4 years: $246.

				Simple otitis media: <2 years: $246, 2-4 years: $246.
Ye *et al.* 2023	2023	China	Overall/total costs.	Total direct costs attributable to HL among adults aged 45 and above in China from 2011 to 2015: Year 2011: Outpatient costs: $41,130,589,956, Inpatient costs: $9,568,207,113, Total direct costs: $50,698,797,069, Per capita outpatient costs: $89.192, Per capita inpatient costs: $20.749, Per capita total direct costs: $109.941. Year 2013: Outpatient costs: $63,817,794,269, Inpatient costs: $17,965,937,071, Total direct costs: $81,783,731,339, Per capita outpatient costs: $129.558, Per capita inpatient costs: $36.473,

Per capita total direct costs: $166.031.

Year 2015:

Outpatient costs: $80,884,440,880,

Inpatient costs: $25,892,549,145,

Total direct costs: $106,776,990,025,

Per capita outpatient costs: $153.472,

Per capita inpatient costs: $49.129,

Per capita total direct costs: $202.601.

Patients without self-reported HL, 2011-2015, mean (SD):

Outpatient costs: $2,989.72 (401.68),

Inpatient costs: $1,192.57 (43.95).

Patients with self-reported HL, 2011-2015, mean (SD):

Outpatient costs: $2,830.04 (221.38),

Inpatient costs: $1,642.61 (122.99).

Direct costs per capita attributable to HL for outpatient and inpatient services:

Male:

Urban, 45-59 years old:

Year 2011:

Outpatient cost: $30,

Inpatient cost: $36.

Year 2013:

Outpatient cost: $56,

Inpatient cost: $51.

Year 2015:

Outpatient cost: $44,

Inpatient cost: $54.

Urban, 60+ years old:

Year 2011:

Outpatient cost: $94,

Inpatient cost: $27.

Year 2013:

Outpatient cost: $198,

Inpatient cost: $35.

Year 2015:

Outpatient cost: $227,

Inpatient cost: $39.

Rural, 45-59 years old:

Year 2011:

Outpatient cost: $0,

Inpatient cost: $0.

Year 2013:

Outpatient cost: $0,

Inpatient cost: $0.

Year 2015:

Outpatient cost: $0,

Inpatient cost: $0.

Rural, 60+ years old:

Year 2011:

Outpatient cost: $18,

Inpatient cost: $17.

Year 2013:

Outpatient cost: $42,

Inpatient cost: $21.

Year 2015:

Outpatient cost: $68,

Inpatient cost: $27.

Female:

Urban, 45-59 years old:

Year 2011:

Outpatient cost: $110,

Inpatient cost: $33.

Year 2013:

Outpatient cost: $30,

Inpatient cost: $86.

Year 2015:

Outpatient cost: $110,

Inpatient cost: $33.

Urban, 60+ years old:

Year 2011:

Outpatient cost: $176,

Inpatient cost: $72.

Year 2013:

Outpatient cost: $86,

Inpatient cost: $244.

Year 2015:

Outpatient cost: $176,

Inpatient cost: $72.

Rural, 45-59 years old:

Year 2011:

Outpatient cost: $0,

Inpatient cost: $3.

Year 2013:

Outpatient cost: $5,

Inpatient cost: $0.

Year 2015:

Outpatient cost: $0,

Inpatient cost: $3.

Rural:

60+ years old:

Year 2011:

Outpatient cost: $36,

Inpatient cost: $30.

Year 2013:

Outpatient cost: $40,

Inpatient cost : $116.

Year 2015:

Outpatient cost: $36,

Inpatient cost : $30.

Total direct costs attributable to HL for outpatient and inpatient services:

Male:

Urban, 45-59 years old:

Year 2011:

Outpatient cost: $1,959,024,328,

Inpatient cost: $1,112,175,097.

Year 2013:

Outpatient cost: $4,518,423,261,

Inpatient cost: $2,343,782,192.

Year 2015:

Outpatient cost: $4,064,986,810,

Inpatient cost: $3,009,808,820.

Urban, 60+ years old:

Year 2011:

Outpatient cost: $6,957,577,491,

Inpatient cost: $1,513,741,720.

Year 2013:

Outpatient cost: $19,301,091,028,

Inpatient cost: $3,260,324,990.

Year 2015:

Outpatient cost: $22,834,678,677,

Inpatient cost: $3,802,916,416.

Rural, 45-59 years old:

Year 2011:

Outpatient cost: $0,

Inpatient cost: $0.

Year 2013:

Outpatient cost: $0,

Inpatient cost: $0.

Year 2015:

Outpatient cost: $0,

Inpatient cost: $0.

Rural, 60+ years old:

Year 2011:

Outpatient cost: $1,664,479,905,

Inpatient cost: $793,228,790.

Year 2013:

Outpatient cost: $4,222,143,756,

Inpatient cost: $1,457,404,707.

Year 2015:

Outpatient cost: $6,863,833,099,

Inpatient cost: $2,347,930,874.

Female:

Urban, 45-59 years old:

Year 2011:

Outpatient cost: $9,656,067,436,

Inpatient cost: $1,166,870,302.

Year 2013:

Outpatient cost: $1,625,850,900,

Inpatient cost: $9,212,460,270.

Year 2015:

Outpatient cost: $9,656,067,436,

Inpatient cost: $1,166,870,302.

Urban, 60+ years old:

Year 2011:

Outpatient cost: $17,153,753,177,

Inpatient cost: $3,479,885,715.

Year 2013:

Outpatient cost: $6,437,600,089,

Inpatient cost: $24,565,310,758.

Year 2015:

Outpatient cost: $17,153,753,177,

Inpatient cost: $347,988,5715.

Rural, 45-59 years old:

Year 2011:

Outpatient cost: $0,

Inpatient cost: $103,729,503.

Year 2013:

Outpatient cost: $243,752,524,

Inpatient cost: $0.

Year 2015:

Outpatient cost: $0,

Inpatient cost: $103,729,503.

Rural:

60+ years old:

Year 2011:

Outpatient cost: $3,739,687,619,

Inpatient cost: $1,398,575,986.

Year 2013:

Outpatient cost: $2,597,221,669,

				Inpatient cost : $13,343,171,267. Year 2015: Outpatient cost: $3,739,687,619, Inpatient cost : $1,398,575,986.
Montes *et al.* 2017	2017	Colombia	Hearing aid-related costs, Diagnostic and evaluation costs, Education-related costs, Annual costs in cochlear implant patients, Annual costs in hearing aids patients, Annual costs in no treatment patients.	Annual costs in cochlear implant patients: Medical visits for assessments (once in lifetime cost): $7, Surgery kit (once in lifetime cost): $21,510, Audiological rehabilitation: $119, Language rehabilitation: $2,575, Wires: $106, Batteries: $817, Health coverage: $310, Preschool: $622, Elementary school: $598, High school: $754, Undergraduate: $3,971, Graduate: $5,791.

Annual costs in hearing aids patients:

Medical visits for assessments (once in lifetime cost): $7,

Hearing aids (once in lifetime cost): $1,311,

Language rehabilitation: $2,575,

Batteries: $131,

Accessories: $459,

Health coverage: $310,

Preschool: $622,

Elementary school: $598,

High school: $754,

Undergraduate: $3,971,

Graduate: $5,791.

Annual costs in no treatment patients:

Health coverage: $310,

Preschool: $7,705,

Elementary school: $7,681,

High school: $7,837,

Undergraduate: $14,298,

				Graduate: $17,864.
Ordoñez *et al.* 2023a	2023	Costa Rica	Overall/total costs.	Cost of HL: $550.
Bolaños-Díaz *et al.* 2022	2022	Ecuador	Overall/total costs.	Unit costs: Acute otitis media: $29, Deafness: $2,214, Deafness (first year): $2,045, Deafness (third year): $500.
Sevilla *et al.* 2022	2022	Egypt	Overall/total costs.	Direct medical cost, per care episode [range]: Acute otitis media: $1.816 [$1.569-$2.119].
Ordoñez *et al.* 2023b	2023	El Salvador	Overall/total costs.	Cost of HL: $326.
Hirano *et al.* 2014	2014	Japan	Hearing aid-related costs, Diagnostic and evaluation costs.	Cost, (range): Hearing test: $65.4, Hearing aid fitting test: $121.5, Hearing aid: $2,086.9 ($1,565.2-$2,608.6).

Gumbie *et al.* 2021	2021	Sweden	Hearing aid-related cost, Diagnostic and evaluation cost, Cochlear implant cost, Medication cost, Device programming and maintenance cost, Sound processor replacement/upgrade cost, Adverse event cost, Hearing aid-related resource use, Diagnostic and evaluation resource use, Cochlear implant resource use, Medication resource use, Device programming and maintenance resource use, Sound processor replacement/upgrade resource use, Adverse events resource use.	Pre-implant assessment unit costs: Initial assessments: Medical doctor appointment: SEK 1,406, Fitting of hearing aid: SEK 1,704, Audiological Assessment: SEK 1,476, Vestibular assessment and tests: SEK 1,476, Hearing counsellor: SEK 2,215, MRI Scan: SEK 2,328, CT Scan: SEK 2,328. Step 1: Multidisciplinary team meeting: SEK 3,237, Audiologist: SEK 1,476, ENT surgeon consultation: SEK 2,612, Social worker assessment: SEK 2,215. Step 2: ENT surgeon consultation: SEK 2,612, Audiologist: SEK 2,215,

Multidisciplinary team meeting: SEK 3,237,

Meningitis vaccination: SEK 1,406.

Surgery, device and device programming and rehabilitation unit costs:

Unilateral cochlear implant operation-Surgical cost: SEK 69,744,

Unilateral cochlear implant operation-Device cost: SEK 145,000,

One hearing aid: SEK 3,404

Pair of hearing aids: SEK 6,807.

Initial care-Year 1:

Medical check: SEK 1,406,

Audiologist: SEK 1,476,

Engineer: SEK 1,987,

ENT specialist: SEK 2,612,

Hearing counsellor: SEK 2,2145,

Social worker: SEK 2,215.

Maintenance and programming, cochlear implant (Year 2 and beyond):

Processor upgrade: SEK 60,000,

Audiologist (year 2 and beyond): SEK 1,476,

Cochlear implant annual administration: SEK 520.

Sound processor replacement, adverse events, explantation and reimplantation unit costs:

Sound processor replacement:

External component: SEK 60,000,

Audiologist (tuning visit): SEK 1,476,

Engineer (tuning visit): SEK 1,987.

Short term adverse event: Taste disturbances, Vertigo, Tinnitus:

Medical doctor visit: SEK 1,406.

Infection:

Medical doctor visit: SEK 1,406,

Surgery: SEK 276,227.

Long-term adverse event: Vertigo:

Medical doctor visit: SEK 1,406.

Explantation:

Audiologist (assessment): SEK 1,476,

Explantation: SEK 55,614.

Reimplantation:

Audiologist pre-operative assessment: SEK 1,476,

ENT surgeon consultation: SEK 2,612,

Multidisciplinary team meeting: SEK 3,237,

Unilateral cochlear implant operation-Surgical cost: SEK 55,613.6,

Medical check: SEK 1,406.

No. Of visit of pre-implant assessment resource use:

Initial assessments, per consultation:

Medical doctor appointment: 1,

Fitting of hearing aid: 1,

Audiological assessment: 1,

Vestibular assessment and tests: 1,

Hearing counsellor: 1,

Multidisciplinary team meeting: 1,

Audiologist: 1.

Initial assessments, per test:

MRI Scan: 1,

CT Scan: 1.

Step 1, per consultation:

Multidisciplinary team meeting: 1,

Audiologist: 1,

ENT surgeon consultation: 1,

Social worker assessment: 1.

Step 2, per consultation:

ENT surgeon consultation: 1,

Audiologist: 1,

Multidisciplinary team meeting: 1,

Meningitis vaccination: 1.

No. Of visit of surgery, device and device programming and rehabilitation resource use:

Unilateral cochlear implant operation-Surgical cost per visit: 1,

Unilateral cochlear implant operation-Device cost per unit: 1,

One hearing aid per unit: 1,

Pair of hearing aids per unit: 1.

Initial care-Year 1, per consultation:

Medical check: 1,

Audiologist: 5,

Engineer: 7,

ENT specialist: 1,

Hearing counsellor: 1,

Social worker: 3.

Maintenance and programming, cochlear implant (year 2 and beyond):

Processor upgrade per unit:

Audiologist (Year 2 and beyond) per consultation: 3.

Cochlear implant annual administration per unit:

Sound processor replacement, adverse events, explantation and reimplantation resource use per visit:

Sound processor replacement:

External component: 1 unit,

Audiologist (tuning visit): 1.5 hours,

Engineer (tuning visit): 1.5 hours.

Short term adverse event: Taste disturbances, Vertigo, Tinnitus:

Medical doctor visit: 1 consultation.

Infection:

Medical doctor visit: 1 consultation,

Surgery: 1 procedure.

				Long-term adverse event: Vertigo: Medical doctor visit: 1 consultation. Explantation: Audiologist (assessment): 1.5 hours, Explantation: 1 unit. Reimplantation: Audiologist pre-operative assessment: 1.5, hours ENT surgeon consultation: 1 hours, Multidisciplinary team meeting: 1 hours, Unilateral cochlear implant operation-surgical cost: 1 unit, Medical check: 1 consultation.
Hol *et al.* 2004	2004	The Netherlands	Diagnostic and evaluation resource use.	Number of otolaryngology visits by patients classified according to previous hearing aid before and after receiving a bone-anchored hearing aid: Air conduction hearing aids group, mean (SD) [range]: Before bone-anchored hearing aid, n=32: 12.7 (10.5) [0-30], After bone-anchored hearing aid, n=33: 3.3 (4.8) [0-25]. Conventional bone conduction hearing aid group, mean (SD) [range]:

				Before bone-anchored hearing aid, n=19: 5.4 (4.9) [0-20], After bone-anchored hearing aid, n=20: 1.5 (2.1) [0-6]. Total, mean (SD) [range]: Before bone-anchored hearing aid, n=51: 9.96 (9.5) [0-30], After bone-anchored hearing aid, n=53: 2.66 (4.1) [0-25].
Joore *et al.* 2003	2003	The Netherlands	Overall/total costs, Diagnostic and evaluation costs, Device programming and maintenance costs, Hearing aid related costs.	Mean cost [range]: General practitioner consultations: €24.40, Audiological centre: €216.09, Hearing aid: €670.69 [€350-€1,000], Dispenser negative trial per hearing aid: €261.69 [€137-€390], Hearing aid battery costs for satisfied hearing aid users: €34.31, Hearing aid battery costs for dissatisfied hearing aid users: €10.04, Hearing aid repair costs for satisfied hearing aid users: €18.75 [€9.80-€28.00], Hearing aid repair costs for dissatisfied hearing aid users: €9.38 [€4.90-€14.00], Tone audiometry: €29.55, Total cost per each successful hearing aid fitting: €242.92.

				ENT clinic: First consultation: €121.46 [€121.46-€177.99], Follow-up consultation after successful trial at the dispenser: €121.46 [€121.46-€177.99], Follow-up consultation after negative trial result at the dispenser: €28.26 [€28.26-€84.79].
Smulders *et al.* 2016	2016	The Netherlands	Cochlear implant costs, Overall/total costs, Diagnostic and evaluation costs, Device programming and maintenance costs, Diagnostic and evaluation resource use,	Cost per person per year, mean (SD): Unilateral cochlear implant: Direct healthcare costs: Cochlear implantation: €43,883 (€11,513), Annual follow-up costs: €3,435 (€1,085), Electronystagmography: €654 (€212). Direct non-healthcare costs: Pre-operative travel expenses: €70.57 (€47.15), First year after surgery travel expenses: €168.62 (€123.75), Second year after surgery travel expenses: €56.08 (€39.06). Bilateral cochlear implant: Direct healthcare costs:

Cochlear implantation: €87,765 (€23,027),

Annual follow-up costs: €6,871 (€2,169),

Electronystagmography: €654 (€212).

Direct non-healthcare costs:

Pre-operative travel expenses: €77.10 (€50.94),

First year after surgery travel expenses: €197.70 (€170.26),

Second year after surgery travel expenses: €56.43 (€55.45),

Cochlear implant maintenances, possible processor replacement: €3,435 (€1,085),

Hospital visits: €6,871 (€2,169).

Number of visits per person per year, mean (SD):

Pre-operative:

Unilateral cochlear implant:

Otolaryngologist: 3.4 (1.0),

Audiologist: 2.6 (1.9),

Speech therapist: 1.2 (0.8),

Social worker/psychologist: 1.5 (0.5),

Audiometry: 2.8 (1.4),

Electronystagmography: 0.4 (0.5),

CT scan: 1.0 (0.4),

MRI scan: 0.3 (0.5).

Bilateral cochlear implant:

Otolaryngologist: 3.2 (1.0),

Audiologist: 3.0 (2.0),

Speech therapist: 0.9 (0.7),

Social worker/psychologist: 1.4 (0.6),

Audiometry: 2.6 (1.0),

Electronystagmography: 0.5 (0.5),

CT scan: 1.0 (1.1),

MRI scan: 0.2 (0.4).

First year after surgery:

Unilateral cochlear implant:

Otolaryngologist: 2.5 (1.5),

Audiologist: 8.6 (2.0),

Speech therapist: 8.8 (4.4),

Social worker/psychologist: 1.6 (1.6),

Audiometry: 2.3 (1.6).

Bilateral cochlear implant:

Otolaryngologist: 2.3 (1.7),

Audiologist: 10.2 (4.4),

Speech therapist: 10.1 (4.9),

Social worker/psychologist: 1.8 (2.3),

Audiometry: 2.4 (2.4).

Second year after surgery:

Unilateral cochlear implant:

Otolaryngologist: 0.7 (0.8),

Audiologist: 1.6 (1.8),

Speech therapist: 0.8 (0.6),

Social worker/psychologist: 0.3 (0.6),

Audiometry: 1.2 (0.9).

Bilateral cochlear implant:

Otolaryngologist: 0.7 (1.1),

Audiologist: 2.9 (2.8),

Speech therapist: 1.2 (0.5),

				Social worker/psychologist: 0.6 (0.8), Audiometry: 1.1 (1.6).
Tufts *et al.* 2010	2010	US	Hearing aid-related costs, Diagnostic and evaluation costs.	Unit costs: Annual monitoring audiogram: $91.25, Cost of audiometric technician salary: $7.30, Cost of patient time (1.5 hours for mid-grade enlisted): $44.87, Cost of earplugs: $20, Cost of audiogram at standard reimbursement rate: $19.08), The annual cost of prescribing hearing aid, averaged over the five-year life of the hearing aids: $440.03. Annual monitoring audiogram, expected annual cost: With standard threshold shift: $65.70, Without standard threshold shift: $65.70.
Yaneza *et al.* 2015	2015	UK	Hearing aid-related resource use.	Management of HL, n: Persistent otitis media with effusion, N=15: Conservative management: 2, Ventilation tube insertion: 4,

Hearing aid: 2,

Hearing aid + ventilation tube insertion: 5,

Hearing aid use intolerant: 2.

Fluctuating otitis media with effusion, N=26:

Conservative management: 14,

Ventilation tube insertion: 1,

Hearing aid: 4,

Hearing aid + ventilation tube insertion: 1,

Bone-anchored hearing aid: 1.

Mixed HL, N=7:

Hearing aid: 2,

Hearing aid + ventilation tube insertion: 2.

Abnormal hearing or middle ear pathology, N=48:

Hearing aid: 19,

Bone conducting hearing aid: 1,

Bone-anchored hearing aid: 1,

Hearing aid + ventilation tube insertion: 6,

Ventilation tube insertion: 5.

Huang *et al.* 2021	2021	US	Hearing aid-related costs, Diagnostic and evaluation costs.	Unit costs: Hearing aid new user cost: $2,325, Hearing aid maintenance cost: $574, Pure tone audiometry test: $105, Audiology visit: $136, Otoacoustic emissions, tympanometry, play audiometry: $189.68.
Shah *et al.* 2004	2004	US	Diagnostic and evaluation cost.	Unit cost: Audiogram: $16.60, Staff time for evaluating audiogram, 15 mins: $8.34.
Veenstra *et al.* 2007	2007	US	Cochlear implant costs. Device programming and maintenance costs. Overall cost.	Unit costs: Cochlear implant: $81,000, Annual maintenance of cochlear implant: $2,170, Mild or moderate HL: $680.
Neitzel *et al.* 2017	2017	US	Overall/total costs.	2013 wages associated with HL: Mean (median): $35,386 ($26,314). Total earned: $295,000,000,000.

Palmer *et al.* 1999	1999	US and Canada	Hearing aid-related costs, Diagnostic and evaluation costs, Implant-related and 1 year follow-up charges per patient.	Implant-related and 1 year follow-up charges per patients, mean (range): Pre-operative assessment: $1,200, Audiologic assessment: $1,027, Surgical assessment: $150, Anaesthesiologist, n=23: $1,110 ($246-$1,616), Surgeon, n=24: $4,492 ($2,410-$5,875), Inpatient or day-surgery stay, n=23: $5,758 ($1,274-$11,094), Implant device, n=23: $22,516 ($14,027-$37,572), Follow-up (1 year), n=27: $1,152 ($56-$4,215), Annual insurance and batteries only: $443 ($145-$443), Loss/damage insurance for the external device components: $135, Extended warranty after year 3: $248, Rechargeable battery replacement: $10. Imputed charges, mean: Anaesthesiologist, n=24: $1,051, Surgeon, n=23: $4,694, Inpatient or day-surgery stay, n=23: $5,666,

				Implant device, n=23: $21,598, Follow-up (1-year), n=27: $1,451. Total cost: Mean charges: $37,405, Mean imputed charges: $34,460, Mean charge with imputation of missing charges: $36,837.
Mailhot Vega *et al.* 2013	2013	US	Overall/total costs.	Cost of deafness: $1,038.

Abbreviations: AUD: Australian Dollar, CI: cochlear implant, CT: computed tomography, dB: dfecibel, ENT: ear, nose and throat, GP: general practitioner, HL: hearing loss, MRI: magnetic resonance imaging, SD: standard deviation, SE: standard error, SEK: Swedish krona, UK: United Kingdom, US: United States

Appendix K. Description of scenario analyses in the health economic model

The data used to inform the scenario analyses performed in the health economic model is described below.

K.1 Source for clinical efficacy

K.1.1 Incidence of hearing loss

Results from the SIOPEL-6 mITT population and the Orgel et al. (2023) re-analysis of COG ACCL0431 are considered in scenario analyse to explore incidence of HL. The efficacy inputs for the base case and scenarios are presented in Table 101.

Table 101 Number and percentage of patients experiencing hearing loss – scenario analyses

Percentage of patients	SIOPEL-6 mITT		Orgel et al. (2023) re-analysis of COG ACCL0431	
	Cisplatin without PEDMARQSI	Cisplatin with PEDMARQSI	Cisplatin without PEDMARQSI	Cisplatin with PEDMARQSI
With HL	29 (63.04%)	18 (32.73%)	27 (45.76%)	9 (18.00%)
Without HL	17 (36.96%)	37 (67.27%)	32 (54.24%)	41 (82.00%)

Abbreviations: HL: hearing loss, mITT: Modified intention-to-treat

Sources: (Orgel et al. 2023, [redacted])

K.1.2 Severity of hearing loss

The distribution of HL severity in the two scenarios is presented in Table 102.

Table 102 Severity of hearing loss (as a proportion of those with hearing loss) – scenario analyses

Percentage of patients	SIOPEL-6		Orgel et al. (2023) and SIOPEL-6	
	Cisplatin without PEDMARQSI	Cisplatin with PEDMARQSI	Cisplatin without PEDMARQSI	Cisplatin with PEDMARQSI

Mild HL	41.38%	55.56%	40.78%	77.78%
Moderate HL	37.93%	33.33%	38.32%	16.67%
Marked HL	17.24%	5.56%	17.42%	2.78%
Severe HL	3.45%	5.56%	3.48%	2.78%

Abbreviations: HL: hearing loss

Sources: (Orgel et al. 2023, [redacted])

K.2 HSUV

Disutility values for the bilateral mild HL (-0.161), bilateral moderate HL (-0.323) and unilateral severe/profound HL (-0.437) were used for the Mild HL, Moderate HL, and Severe HL health states. The utility value of 0.920 for the Minimal/no HL health state wase used as reference when subtracting the disutility values. The Marked HL health state was calculated as an average of the Moderate HL and Severe HL health states. In the scenario analysis, only HSUV for Mild HL, Moderate HL, Marked HL and Severe HL was adjusted, as seen in Table 103. All other inputs for HRQoL remained fixed as outlined in Section 10.3.3.

A scenario analysis considering utility values from Gumbie et al. was conducted (Gumbie et al. 2022). Gumbie et al was identified in the SLR described more in detail in Appendix I. It was decided to only include utilities from Gumbie et al. as a scenario (rather than in the base case) due to limitations the following limitations (Gumbie et al. 2022). Firstly, this study assumes that the 'Minimal/no HL' health state has a utility value of 1 (i.e. perfect health), this assumption is not appropriate, even for a population without a health condition (Ara and Wailoo 2011). Secondly, it is believed to be inappropriate to apply a utility gain associated with hearing aid use as this will lead to double counting of hearing aid utility. Thirdly, the utility gain associated with hearing aids was sourced from adults due to a lack of data available in children, further adding to the uncertainty of the hearing aid utility value applied. In addition, (Gumbie et al. 2022) combines data from multiple sources (Barton et al. (2006), Grutters et al. (2007), de Wolf et al. (2011), and Bond et al. (2009)) and in some cases, the methods are not transparent. For example, it states that the moderate unilateral HL utility value is "calculated based on applying the ratio of [unilateral] and [bilateral] in de Wolf et al. (2011) and applying to Barton et al. (2006)", yet Barton et al. does not report a separate utility for unilateral and bilateral HL (de Wolf et al. 2011, Barton et al. 2006). For these reasons, it is believed that using the primary source of data (i.e.Barton et al. (2006)) reduces uncertainty and is a fairer representation of the health state utility values in the relevant population.

Table 103 Overview of literature-based health state utility values – scenario analyses

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Scenario- Gumbie et al 2022				
Mild HL	0.82 [NR]	HUI3		Gumbie et al. 2022 was identified in the SLR but deemed inappropriate to use in the base case as outlined above. Hence, it was deemed better to analyse it in a scenario analysis
Moderate HL	0.72 [NR]			
Marked HL	0.66 [NR]			
Severe HL	0.64 [NR]			

Abbreviations: HL: hearing loss, HUI3: Health Utilities Index Mark 3, NR: Not reported

Sources: (Gumbie et al. 2022)

K.3 Adverse events

As described in the Section 9, the base case includes PEDMARQSI treatment-related SAEs occurring in ≥2% of patients sourced from COG ACCL0431, but no AEs met this criterion. The table below lists the costs of all AEs included in scenario analyses (PEDMARQSI treatment-related SAEs occurring in ≥2% sourced from SIOPEL-6, and AEs graded CTCAE Grade ≥3 and occurring in ≥10% in either arm sourced from COG ACCL0431). Section K.3.1 and K.3.2 describes the disutilities and cost associated with the AEs included in the scenario analysis.

K.3.1 Disutilities associated with adverse events

AE disutilities were sourced from published literature and were adjusted according to the duration that they typically last for (also sourced from published literature). As detailed in Section 4.2 section, all key paediatric cancer types are treated with cisplatin (and therefore Pedmarqsi) for no more than one year. Therefore, disutilities were applied to the percentage of patients experiencing each AE in the first year of the cost-effectiveness model only.

Table 104 includes the list of AE disutilities and durations included in the model. The incidence of AEs was obtained from the COG ACCL0431 clinical trial in the base case, and as none of the treatment-related SAEs met the threshold for inclusion, AE disutilities have no impact on the base case results. Therefore, the AE inputs listed in Table 104 only have an impact on model results in a scenario analysis.

Table 104 Disutilities associated with adverse events – scenario analyses

Adverse event	Utility decrement	Duration (days)	Source (disutility)	Source (duration)
Neutrophil count decreased	-0.01	40.10	Hudgens (2014)	TA704 and TA862
Haemoglobin decreased	-0.07	42.90	Assumed to be equal to anaemia	
Infection	-0.04	182.50	Cutler (2022)	
Febrile neutropenia	-0.09	7.00	Nafees (2008)	AJMC (2017)
White blood cell count decreased	-0.03	42.90	Hudgens (2014)	TA704 and TA862
Platelet count decreased	-0.11	58.30	Shao (2022)	TA862
Alanine aminotransferase increased	-0.05	28.00	Telford (2019)	Assumed due to lack of data
Lymphocyte count decreased	-0.20	4.10	Shao (2022)	McNamara (2008)
Anaemia	-0.07	42.90	Shao (2022)	TA704 and TA862
Hypokalaemia	-0.03	13.00	Shao (2022)	Schlögl (2021)
Hypophosphatemia	-0.08	3.30	HST843	Corona (2016)
Hyponatremia	-0.52	2.00	Szymanski (2020)	Assumption from Lee (2014) (<48 hours is acute hyponatremia)
Stomatitis	-0.15	14.00	Lloyd (2006)	Plewa (2023) (Assumed RAS)

Abbreviations: AJMC : American Journal of Managed Care, HST: Highly Specialised Technology, RAS: recurrent aphthous stomatitis; TA: Technology Appraisal.

Sources: (Hudgens et al. 2014, Cutler et al. 2022, Nafees et al. 2008, Lloyd et al. 2006, Shao et al. 2022, Telford et al. 2019, Szymanski 2020, NICE 2023, Neutropenia 2017, McNamara et al. 2008, Schlögl et al. 2021, Corona et al. 2016, Lee et al. 2014, Plewa and Chatterjee 2024, NICE 2021)

K.3.2 Costs associated with adverse events

The unit costs associated with the management of AEs were sourced from Diagnosis Related Group (DRG) and published literature. Table 105 summarises the costs associated with each AE. The unit cost of each AE is applied to the incidence rate within each treatment arm. The total weighted cost per treatment arm was calculated and

applied as a one-off cost within the first cycle of the economic model based on the assumption that all key paediatric cancer types are treated with cisplatin (and therefore PEDMARQSI) for no more than one year.

Table 105 Cost associated with management of adverse events (scenario analysis)

	DRG code	Unit cost/DRG tariff
Neutrophil count decreased	DRG Takster 2025. 16MA10 Øvrige sygdomme I blod og bloddannende organer	28,342 DKK
Haemoglobin decreased	DRG Takster 2025. 16MA10 Øvrige sygdomme I blod og bloddannende organer	28,342 DKK
Infection	DRG Takster 2025. 18MA07 Virussygdomme og feber ad ukendt årsag, pat. 0-17 år.	14,298 DKK
Febrile neutropenia	DRG Takster 2025. 16MA10 Øvrige sygdomme I blod og bloddannende organer	28,342 DKK
White blood cell count decreased	DRG Takster 2025. 16MA10 Øvrige sygdomme I blod og bloddannende organer	28,342 DKK
Platelet count decreased	DRG Takster 2025. 16MA03 Granulo- og trombocytopeni	37,482 DKK
Alanine aminotransferase increased	DRG Takster 2025. 07MP03 Diagnostiske og terapeutiske indgreb på lever og galdeveje	70,675 DKK
Lymphocyte count decreased	DRG Takster 2025. 49PR07 Immundefekt	20,988 DKK
Anaemia	DRG Takster 2025. 16MA10 Øvrige sygdomme I blod og bloddannende organer	28,988 DKK
Hypokalaemia	Interaktiv DRG Takster 2025. 03MA09 Andre sygdomme i øre, næse, mund og hals. Diagnose: DH906: Dobbeltsidigt blandet konduktivt og perceptivt høretab: DE876: Hypokaliæmi	1,286 DKK
Hypophosphatemia	Interaktiv DRG Takster 2025. 03MA09 Andre sygdomme i øre, næse, mund og hals. Diagnose: DH906: Dobbeltsidigt blandet	1,286 DKK

	DRG code	Unit cost/DRG tariff
	konduktivt og perceptivt høretab: DE833A: Hypofosfatæmi	
Hyponatremia	Interaktiv DRG Takster 2025. 03MA09 Andre sygdomme i øre, næse, mund og hals. Diagnose: DH906: Dobbeltsidigt blandet konduktivt og perceptivt høretab: DE871A: Hyponatriæmi	1,286 DKK
Stomatitis	Interaktiv DRG Takster 2025. 03MA98 MDC03 1-dagsgruppe, pat. mindst 7 år. Diagnose: DK121B: Stomatitis UNS	2,060 DKK
Hypersensitivity	Interaktiv DRG Takster 2025. 03MA09 Andre sygdomme i øre, næse, mund og hals. Diagnose: DH906: Dobbeltsidigt blandet konduktivt og perceptivt høretab: DT887A: Lægemiddelallergi UNS	1,286 DKK

Abbreviations: DKK: Danish krone, DRG: Diagnosis Related Group

Source: (Sundhedsdatastyrelsen 2025)

Appendix L. Disease management costs justifications

L.1 Hearing assessment

The frequency of audiology assessment per health state for children aged 6-17 were sourced from Dionne et al. (2012), a study which assessed the economic impact of a test to determine if a cisplatin-treated paediatric patient would develop ototoxicity, which aligns with the licensed population being considered in this cost-effectiveness analysis. Interviews with 10 audiologists conducted in 2018 confirmed these inputs, and provided a consensus on the frequency of assessments for patients aged under five years old and over 18 years old [redacted]). The unit costs of 286.69 DKK were sourced from the Danish tariff card for Nose, and Throat Specialty physician performing hearing test for children ((Laeger.dk 2024)).

Table 106 Hearing assessment resource use included in the model

Resource	Frequency (per person, per cycle)			Unit cost DKK		Frequency source	Cost source
	0-5 years	6-17 years	>18 years	1 month to <18 years	≥18 years		
Audiology assessment	Mild HL: 2 Moderate HL: 2 Marked HL: 3 Severe HL: 3	Mild HL: 1.00 Moderate HL: 1 Marked HL: 1 Severe HL: 1	Mild HL: 0.25 Moderate HL: 0.25 Marked HL: 0.25 Severe HL: 0.25	289	289	6-17 years old: Dionne et al. and verified by interviews with audiologists in 2018 0-5 and >18 years old: Assumption verified by interviews with audiologists in 2018	Takstkort 11A, Øre-, næse- og halsspecialet, Legeaudiometri (høreprøve for børn)

Abbreviations: DKK: Danish krone, DRG: Diagnosis Related Group, HL: hearing loss

Sources: (Dionne et al. 2012, [redacted] Laeger.dk 2024)

L.2 Hearing loss management

The costs and resource use corresponding to hearing aids, cochlear implants are summarised in Table 107. Data for the percentage of patients requiring these management strategies were sourced from published literature (Dionne et al. 2012, Chorozoglou et al. 2018) and interviews with audiologists in 2018 [redacted].

The costs of cochlear implants are applied to the more severe HL health states only ('Marked HL' and 'Severe HL'). The proportion of patients receiving cochlear implants in these health states was based on Chorozoglou et al. (2018). In terms of hearing aids, the proportion of patients with 'Mild HL' and 'Moderate HL' receiving these devices is derived from the audiologist market research report, which states that "all moderate HL patients would be fitted with a hearing aid", and that "a proportion of children (50%) of those with mild HL would also have hearing aids" ([redacted]). For more severe HL health states ('Marked HL' and 'Severe HL'), the percentage of patients receiving hearing aids was calculated as one minus the percentage of patients receiving cochlear implants.

Published literature shows that on average, hearing aids are replaced every four years (Dionne et al. 2012). Therefore, from year two onwards in the model, an average annual cost is calculated for hearing aids based on the replacement frequency and applied to the percentage of patients requiring these management strategies in each health state.

Bond et al. reported that the external component of a cochlear implant is under warranty for free repairs/replacements for three years (Bond et al. 2009). Therefore, the model does not account for external processor replacement costs during the first three years from initial implantation, and only the annual maintenance and programming cost is applied. A report from the NHS England cochlear implantation services states that the external processor of a cochlear implant is replaced on average every five years to ensure the technology is kept up to date (N. H. S. England 2023).

Table 107 Hearing loss management unit costs and resource use included in the model

Resource	% patients requiring treatment	Unit cost (DKK)		Frequency source	Cost source
		1 month to <18 years	≥18 years		
Hearing aid	Mild HL: 50% Moderate HL: 100% Marked HL: 94% Severe HL: 48% Replacement frequency: 4 years	**Hearing aid:** 17,980 (Double sided) **Fitting:** 1,286 **Follow-up:** 1,286	**Hearing aid:** 17,980 (Double sided) **Fitting:** 1,286 **Follow-up:** 1,286	**Mild HL:** Audiologist report 2018 **Moderate HL, Marked HL & Severe HL:** Calculation based on one minus the percentage receiving cochlear implants in these health states **Replacement frequency:** Dionne et al. 2012 and validated in interviews with audiologists in 2018	**Hearing aid:** AudioNova (2025) **Fitting**: Interaktiv DRG: Diagnose: DH919: Høretab UNS. Procedure: BDDD6: Tilpasning af høreapparat **Follow-up:** Interaktiv DRG: Diagnose: DH919: Høretab UNS. Procedure: BDDD6: Tilpasning af høreapparat
Cochlear implant	Mild HL: 0% Moderate HL: 0% Marked HL: 6% Severe HL: 52% Replacement frequency for the external processor**: 5 years Replacement frequency for the internal electrode: based on survival curve)	**Initial pre-implantation**: assumed to be included in DRG for Cochlear implant costs **Initial bilateral cochlear implant (including external processor):** 228,746 (double sided)	**Maintenance and programming:** 1,159 **Replacement external processor:** 134,393 **Replacement internal electrode:** 0	**Mild HL & Moderate HL:** Assumption **Marked HL & Severe HL:** Chorozoglou et al. 2018 **Replacement frequency:** NHS England cochlear implantation services and Bond et al. 2009	**Initial bilateral cochlear implant:** Interaktiv DRG: Diagnose: DH919. Takst 114,373 Procedure: KDFE00: Indsættelse af implantat i cochlea In the model the cost is doubled to account for implant in both ears. **Initial cost of fitting bilateral cochlear implant:** DRG: 03PR07, Takst 134,393 Udskiftning af processor i cochlear implantat, dobbeltsidigt

Initial fitting: 134,393

Annual maintenance and programming: 1,159

Replacement external processor: 134,393

Replacement internal electrode: 0

Re-implantation of internal electrode: 0

Re-implantation of internal electrode: 0

Annual maintenance and programming: Interaktiv DRG: DH919: Høretab UNS. Procedure: BDDD62: Indstilling og justering af cochlea-implantat

Replacement external processor cost: DRG: 03PR07, Takst 134,393 Udskiftning af processor i cochlear implantat, dobbeltsidigt

*Hearing aid costs extracted from DRG. Hearing aid costs are therefore doubled for bilateral HL.

**It is assumed that only the external processor of the cochlear implant is replaced

Abbreviations: DKK: Danish krone, DRG: Diagnosis Related Group, HL: hearing loss

Sources: ([redacted], Dionne et al. 2012, Bond et al. 2009, Chorozoglou et al. 2018, N.H.S England, Sundhedsdatastyrelsen 2025)

L.3 Speech and language therapy

The costs and resource use associated with speech and language therapy are presented in Table 108. The number of sessions per person, per cycle, were sourced from Dionne et al. (2012) and Smulders et al. (2016) whilst the unit cost per session was obtained from Sundhedsdatastyrelsen interactive DRG sourcing database, to a unit cost of 1,286 DKK based on DRG: 03MA09 shown in Table 108.

Dionne et al. (2012) estimated the economic impact of a test to determine if a cisplatin-treated paediatric patient would develop ototoxicity, and therefore the study population aligns with the licensed population being considered in this cost-effectiveness analysis. Smulders et al. (2016) focused on adult patients receiving cochlear implants, so provides a better estimate of speech and language therapy resource use for patients when they reach adulthood. Based on this, the value from Dionne et al. (2012) is used for patients 0-18 years, while the value from Smulders et al. (2016) is used for patients over 18 years old.

Table 108 Speech and language therapy unit costs and resource use included in the model

Resource	Frequency (per person, per cycle)		Unit cost DKK		Frequency source	Cost source
	1 month to <18 years	≥18 years	1 month to <18 years	≥18 years		
Speech and language therapy	Mild HL: 0.00 Moderate HL: 0.00 Marked HL: 52.14 Severe HL: 52.14	Mild HL: 0.00 Moderate HL: 0.00 Marked HL: 0.00 Severe HL: 0.90	1,286	1,286	Dionne et al. 2012 Smulders et al. 2016	Interaktiv DRG: Diagnose: DH906: Dobbeltsidigt blandet konduktivt og perceptivt høreta b. Procedure: ZZ0190E: Tværfaglig logopædisk konference med patienten til stede

Abbreviations: HL: hearing loss, DKK: Danish krone, DRG: Diagnosis Related Group

Sources: (Dionne et al. 2012, Smulders et al. 2016, N.H.S England, Sundhedsdatastyrelsen 2025)

L.4 Depression and anxiety

HL can contribute to anxiety and depressive symptoms amongst cancer survivors (Bass et al. 2016, Khan et al. 2020). As such, the costs associated with depression and anxiety within each health state are included in the model and are presented in Table 109. A TLR using key search terms for depression and anxiety related to HL was conducted.

The TLR process identified Gurney et al. (2007), a report from the COG assessing the HL, QoL, and academic problems in childhood neuroblastoma survivors. This publication was

deemed an appropriate source to inform depression and anxiety costs in the model as it considered children (mean age of 12.1 years) with neuroblastoma. The inclusion of these costs within the economic model are important, as the literature indicates that HL can contribute to anxiety and depressive symptoms amongst cancer survivors (Bass et al. 2016, Khan et al. 2020). The model does not include a disutility for depression or anxiety to avoid overestimating the reduction in QoL associated with HL. The study results are considered highly transferable to a Danish setting.

The unit cost for depression and anxiety is sourced from Sundhedsdatastyrelsen, Takstvejledning 2025, DRG code 19MA08 nervous disorders in children (Sindslidelser hos børn) with an annual cost of 26,633 DKK.

Table 109 Depression and anxiety unit costs and resource use included in the model

Resource	% of patients experiencing depression	Unit cost DKK	Frequency source	Cost source
Depression and anxiety	Minimal/no HL: 14.89% Mild HL: 25.58% Moderate HL: 25.58% Marked HL: 25.58% Severe HL: 25.58%	26,633	Gurney et al. (2007)	DRG Takster 2025: 19MA08: Sindslidelser hos børn

Abbreviations: HL: hearing loss; DKK: Danish krone, DRG: Diagnosis Related Group

Sources: (Gurney et al. 2007, NICE 2015, Sundhedsdatastyrelsen 2025)

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