NHS England Evidence Review:

Allogeneic haematopoietic stem cell transplantation for X-linked cerebral adrenoleukodystrophy in adult males

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Allogeneic haematopoietic stem cell transplantation for X-linked cerebral adrenoleukodystrophy in adult males

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of allogeneic haematopoietic stem cell transplantation (HSCT) compared to standard care for the treatment of X-linked cerebral adrenoleukodystrophy (C-ALD) in adult males.

Allogeneic HSCT is the transplant of multipotent hematopoietic stem cells, usually derived from the bone marrow or peripheral blood of a donor. It involves five distinct stages; conditioning, transplant, neutropenic, engraftment and post-engraftment stage. Any conditioning and transplant regimen is eligible for inclusion in this review.

Current standard care for adult males with X-linked C-ALD is supportive care for the physical and neurological symptoms as they develop, which may include palliative care as symptoms progress.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from HSCT more than others and the criteria used by the included studies to define those patients with X-linked C-ALD who are eligible to receive HSCT.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of allogeneic haematopoietic stem cell transplantation (HSCT) compared to standard care for the treatment of X-linked cerebral adrenoleukodystrophy (C-ALD) in adult males. The searches for evidence published since January 2012 were conducted on 17th May 2022 and identified 221 potential references. These were screened using their titles and abstracts and 10 full text papers potentially relating to the use of HSCT for X-linked C-ALD in adult males were obtained and assessed for relevance.

Three papers were identified for inclusion, one prospective cohort study (Matsukawa et al 2020) and two retrospective case series (Kühl et al 2017, Waldhüter et al 2019). The prospective cohort study was conducted at one centre in Japan and included male patients with adult-onset cerebral form/ cerebello-brainstem form ALD who either received HSCT (n=12) or were considered for, but did not receive, HSCT (n=8). Patients who received HSCT were followed-up for a median of 28.6 months and patients who did not receive HSCT for a median of 69.1 months. The retrospective case series by Kühl et al (2017) included adult males with C-ALD (n=14) who received HSCT at four European centres, including one UK centre. Patients were followed-up for a median of 65 months. The retrospective case series by Waldhüter et al (2019) included adult males with C-ALD (n=15) who received HSCT at one centre in Germany with a median follow-up of 56 months. Eight patients included in Waldhüter et al (2019) were also included in Kühl et al (2017).

In terms of clinical effectiveness[1]:

- **Stabilisation or improvement in MRI findings of C-ALD (critical outcome).**
  - *For HSCT vs no HSCT:* One prospective cohort study provided very low certainty evidence that median **Loes score**[2] improved from before HSCT to a median of 1.55 years after HSCT. For 'no HSCT' patients, the median Loes score worsened over time. No statistical comparison was reported. The same prospective cohort study also provided very low certainty evidence that **Gd enhancement** was 'not enhanced' or 'obscure' after HSCT for all patients, with follow-up ranging from one to 80 months, and that **white matter lesions** stabilised or reduced in size for all patients who received HSCT (within 12 months) and continued to enlarge for all 'no HSCT' patients.
  - *For HSCT (no comparator):* One retrospective case series provided very low certainty evidence that median **Loes score** worsened during the first year after HSCT but then improved beyond 12 months after HSCT, whilst remaining higher than the before HSCT median score. No statistical comparison was reported. The same retrospective case series also provided very low certainty evidence that no patients examined more than six months after HSCT showed further **Gd enhancement** of cerebral demyelinating lesions.

[1] For the critical outcomes of stabilisation or improvement in MRI findings of C-ALD and cognitive function, and the important outcomes of progression free survival, activities of daily living and quality of life, the PICO specified that longer term outcomes (>12 months after HSCT) would be of critical importance to patients (as the intervention takes time to stabilise the disease). Given the progressive nature of the disease an individual is not expected to return to their baseline pre-intervention level

[2] Loes MRI severity score is a 34-point scale that assigns a score to a MRI based on the extent of white matter lesions. Higher scores indicate more significant ALD involvement. Loes score minimum of 1 is used to be considered for HSCT and shows evidence of MRI Gd enhancement around a consistent lesion

- **Survival (critical outcome).**
  - *For HSCT vs no HSCT:* One prospective cohort study provided very low certainty evidence of statistically significantly higher survival probability in patients who received HSCT compared to 'no HSCT' patients, with median follow-up of 29 months for HSCT patients and 69 months for 'no HSCT' patients.
  - *For* HSCT *(no comparator):* Two retrospective case series provided very low certainty evidence of 57% survival at a median follow-up of 65 months and 73% at a median follow-up of 56 months after HSCT respectively.

- **Cognitive function (critical outcome).**
  - No comparative evidence was available for cognitive function.
  - *For HSCT (no comparator):* One retrospective case series provided very low certainty evidence of an improvement in median AACS cortical subdomain[3] score from before HSCT up to a median of approximately five years, after HSCT. No statistical comparison was reported. This same case series reported that cognitive function for nine patients with more than 24 months follow-up was improved for 22%, stable for 56%[4] and deteriorated for 22%. A second retrospective case series provided very low certainty evidence that for eight surviving patients, cognitive function remained stable for 63% and had moderately deteriorated for 38% at a median of approximately five years after HSCT.

- **Progression free survival (important outcome).**
  - *For HSCT vs no HSCT:* One prospective cohort study provided very low certainty evidence of a worsening in median **EDSS[5] score** from before HSCT to a median follow-up of 14 months after HSCT. Neurological outcomes were described as 'stable' for all patients at a median of 2.4 years after HSCT. For 'no HSCT' patients, the median EDSS score worsened over time. No statistical comparison between groups or over time was reported.
  - *For HSCT (no comparator):*
    - One retrospective case series provided very low certainty evidence that **event-free survival** was 36% at a median of approximately five years after HSCT.
    - One retrospective case series provided very low certainty evidence that median **EDSS score** worsened in the six months after HSCT but was improved 24 months after HSCT, whilst remaining higher than the before HSCT median score. A second retrospective case series provided very low certainty evidence that median EDSS score worsened from before HSCT up to a median of approximately five years after HSCT. No statistical comparison was reported in either study. The second retrospective case series also provided very low certainty evidence that 36% of 11 surviving patients experienced no change in EDSS score from before HSCT to 24 months follow-up. For other surviving patients EDSS score worsened by either 0.5 points (36%) or 2 points (27%).
    - One retrospective case series provided very low certainty evidence that median **AACS[6] score** worsened from before HSCT to 24 months after HSCT but had returned to the before HSCT value at a median of five years after HSCT. No

[3] The AACS cortical subdomain is one of 4 subdomains of the Adult ALD Clinical Score (AACS). The cortical subdomain is scored from 0 to 12 with higher scores indicating higher dysfunction. A score of >3 points in the cortical domain is defined as moderate cerebral dysfunction

[4] The number of patients that had stable cognitive function is described differently in different sections of the paper. The descriptions and numbers presented in the paper's table of results have been extracted

[5] The EDSS is a clinical scoring system. Scores range from 0 to 10 points where 0 = no deficits, 6 = inability to walk without assistance and 10 = death

[6] The AACS is a composite score of motor (0-6 points), bladder (0-3 points), sensory (0-3 points) and cortical (0-12 points). Composite scores range from 0 points (normal) to 24 (maximum dysfunction)

statistical comparison was reported. This same retrospective case series also provided very low certainty evidence that for 11 surviving patients, AACS score at 24 months after HSCT had improved (for 9%) or remained the same (for 36%). For other patients, AACS score worsened from before HSCT to 24 months by between one and six points (clinical significance unknown).

- One retrospective case series provided very low certainty evidence that **motor function status** at more than 36 months follow-up was improved for 50% of eight patients, stable for 25% and had deteriorated for 25%. A second retrospective case series provided very low certainty evidence that motor function status at a median follow-up of approximately five years was improved for 22% of nine patients, stable for 67% and mildly deteriorated for one patient (11%).

- **Activities of daily living (important outcome).**
  - *For HSCT vs no HSCT:*
    - One prospective cohort study provided very low certainty evidence of a worsening in median **Barthel Index[7] score** from before HSCT to a median follow-up of 14 months after HSCT. For 'no HSCT' patients, the median Barthel Index score worsened over time. No statistical comparison between groups or over time was reported.
    - One prospective cohort study provided very low certainty evidence that the median **ALD-Disability Rating Scale[8] score** was the same before and a median of 14 months after HSCT. For 'no HSCT' patients, the median ALD-Disability Rating Scale score worsened over time. No statistical comparison between groups or over time was reported.
    - One prospective cohort study described **status at last follow-up** (median approximately two years) and provided very low certainty evidence that 50% of 12 HSCT patients were working or studying after HSCT. The remaining patients had received HSCT recently (33%) or remained at home (17%). The two surviving patients who did not receive HSCT were 'wheelchair bound due to disease progression'.
  - *For HSCT (no comparator):* One retrospective case series described **status 24 months after HSCT** for 11 patients and provided very low certainty evidence that six were employed or retired but fully active. Two patients needed support in ADL and two were restricted in ADL. The remaining patient had developed a 'depressive mood disorder' (no further detail on ADL). A second retrospective case series provided very low certainty evidence that for five patients who maintained their occupational status prior to HSCT, two had continued as students, one was unable to resume work and two had died following HSCT.

- **Quality of life (important outcome).**
  - No comparative evidence was available for quality of life.
  - *For HSCT (no comparator):* One retrospective case series provided very low certainty evidence that eight surviving patients had a good (50%) or excellent (12.5%) quality of

[7] The Barthel Index consists of 10 items that measure a person's daily functioning including feeding, transfers from bed to wheelchair and to and from a toilet, grooming, walking on a level surface, going up and down stairs, dressing, continence of bowels and bladder. Scores from the 10 items are added to give a total score ranging from 0 (totally dependent) to 100 (completely independent)

[8] The ALD-Disability Rating Scale assesses function level as a composite score. Scores range from 0 to IV representing increasing disability. A score of 0 = no difficulties; I = mild learning or coordination difficulties from ALD not requiring support or intervention; II = moderate learning, sensory and/ or neurologic abnormality requiring support or intervention in a few areas; III = severe learning, sensory and/ or neurologic abnormality requiring support or intervention in many areas; IV = loss of cognitive ability and disorientation, patient requires constant supervision

life at between 38 and 116 months follow-up. The three remaining surviving patients were described as having a low quality of life or with depression that had improved or deteriorated respectively, with no further comment on quality of life.

In terms of safety:

- No comparative evidence was available for safety outcomes.
- Two retrospective case series provided very low certainty evidence of **transplant-related mortality** in approximately 20% of patients.
- One retrospective case series provided very low certainty evidence of fatal **infections** in 27% of patients within one year of HSCT. A second retrospective case series provided very low certainty evidence of fatal, life-threatening and severe infections in 14%, 29% and 21% of patients respectively. 36% of patients in this study had no significant infections with a median follow-up of 65 months.
- One prospective cohort study provided very low certainty evidence of **adverse events** in 25% of patients (grade not stated) at approximately two years median follow-up. This study also reported no Grade IV infections or other serious complications. Two retrospective case series provided very low certainty evidence of significant transplant adverse events in 43% and 73% of patients respectively at approximately five years median follow-up.
- One prospective cohort study and two retrospective case series provided very low certainty evidence of acute **GvHD** Grade I in between 27% and 36% of patients, and acute GvHD ≥ Grade II in between 7% and 13% of patients. These studies also reported chronic GvHD in between 17% and 33% of patients. Median follow-up was approximately two years in the prospective cohort study and approximately five years in both case series.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- One retrospective case series reported no statistically significant difference in **stabilisation or improvement in MRI findings of C-ALD** between subgroups of patients, or before and after HSCT for the different subgroups. The subgroups were based on EDSS score before HSCT and whether they had transplant complications.
- One retrospective case series reported that superior **survival** was statistically significantly associated with an EDSS score of <6 before HSCT and also with an EDSS score of <6 without transplant complications. A second retrospective case series reported that higher overall survival was statistically significantly associated with no or mild cerebral symptoms before HSCT and also with an EDSS score of <6 without cerebellum or thalamus involvement. There was no statistically significant difference in survival based on whether the EDSS score before HSCT was above or below six alone.
- One retrospective case series reported that higher **survival with stable cognition** was statistically significantly associated with an EDSS score of <6 without cerebellum or thalamus involvement and also with no or mild cerebral symptoms before HSCT. There was no statistically significant difference in survival with stable cognition based on whether the EDSS score before HSCT was above or below six alone.
- One retrospective case series reported a statistically significant association between fewer patients with **neurological symptoms** in the six months following HSCT and an EDSS score of <6 before HSCT. The same retrospective case series reported that **EDSS score** and **AACS score** both statistically significantly worsened to ~24 months

for patients who had an EDSS score of ≥6 before HSCT or early transplant complications, but that there was no statistically significant change in these scores after ~24 months for patients with an EDSS <6 before HSCT and without transplant complications. In a comparison between subgroups, better EDSS and AACS scores after HSCT were statistically significantly associated with lower EDSS score before HSCT (<6) in combination with the absence of early transplant complications. A second retrospective case series reported that higher **event-free survival** was statistically significantly associated with an EDSS score of <6 without cerebellum or thalamus involvement and also with no or mild cerebral symptoms before HSCT. There was no statistically significant difference in event free survival based on whether the EDSS score before HSCT was above or below six alone.

- One retrospective case series reported that **Modified Rankin[9] score** was statistically significantly worse at ~24 months, compared to before HSCT, for patients with an EDSS score of ≥6 before HSCT or early transplant complications. However, there was no statistically significant change from before HSCT to ~24 months for patients with an EDSS <6 before HSCT and without transplant complications. There was no statistically significant difference in a comparison between these subgroups at ~24 months after HSCT.

Criteria used to define patients with X-linked C-ALD eligible to receive HSCT:

- In one prospective cohort study, the indications for receiving HSCT included cerebral form of ALD or cerebello-brainstem form of ALD with Loes scores up to 13, the presence of progressively enlarging white matter lesions and/ or lesions with gadolinium enhancement on brain MRI. This study excluded patients with severe neuropsychiatric symptoms that made coordinated treatment during HSCT difficult.
- One retrospective case series stated that patients were offered HSCT on an individually selected compassionate basis in accordance with the practice guidelines of the Working Party on Inborn Errors of the European Group for Blood and Marrow Transplantation[10]
- A second retrospective case series stated that patients were offered HSCT on an individually selected compassionate basis. No further detail was provided.

Please see the results table (section 5) in the review for further details of outcomes.

Limitations:

Limitations reducing certainty outcomes reported in the prospective cohort study included differences between the groups at baseline, lack of adjustment for potential confounding factors and variable duration of follow-up of patients. Limitations reducing certainty in the outcomes reported in the two retrospective case series included uncertainty about whether the inclusion of participants was complete or consecutive. Lack of statistical analysis was also a limitation across all three studies for some outcomes.

Conclusion:

This evidence review includes one prospective cohort study and two retrospective case series. The prospective cohort study compared HSCT to no HSCT. The populations of all

[9] The Modified Rankin Score describes disability status in daily activities. It is scored from 0 to 6 with higher scores indicating greater disability. A score of 0 = no symptoms, 1 = no significant disability despite symptoms, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, 6= dead

[10] Peters C, Steward CG. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. Bone Marrow Transplant 2003; 31: 229–39

three studies were adult males with X-linked C-ALD. Some patients (n=8) were included in the populations of both the retrospective case series.

The prospective cohort study provided data contrasting HSCT to no HSCT and reported more positive results with HSCT for the critical outcomes of stabilisation or improvement in MRI findings of C-ALD and survival. The cohort study also reported results for the important outcomes of progression free survival and activities of daily living, with some evidence that HSCT may stabilise disease compared to no HSCT, but with a shorter follow-up time for HSCT patients. Comparisons between these groups should be interpreted with caution as the patients in the two groups were not similar at baseline in terms of meeting the study's inclusion criteria to receive HSCT. Non-comparative data were available for all the outcomes of interest. Due to the progressive nature of the disease, it is expected that patients may not return to their pre-treatment baseline scores after treatment. The outcomes reported generally provided evidence that HSCT can stabilise disease over time after an initial decline in the period after HSCT as might be expected in this context. Longer term outcomes (>12 months) after HSCT were of particular interest. The duration of the follow-up period was sufficient for the outcomes assessed for some, but not all, patients and it was not always clear how clinically significant the smaller changes in score observed on some scales were. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered. The results also suggest variability in the outcomes achieved by individual patients, for example, in outcomes around function and quality of life.

Safety outcomes were reported for patients who received HSCT. These suggested that severe adverse events can be associated with HSCT with this affecting around a quarter of patients in the studies, although this proportion was higher in one study. Conversely some patients did not experience any severe adverse events.

There was some evidence that patients with an EDSS score of less than six before HSCT may benefit more from HSCT than the wider population of interest. However, this was usually when in combination with another characteristic such as the absence of cerebellum or thalamus involvement or the absence of transplant complications. There was also evidence that patients with no or mild cerebral symptoms before HSCT had better outcomes than patients with moderate or severe cerebral symptoms.

No evidence on cost effectiveness was identified.

The studies identified for this review therefore provide very low certainty evidence suggesting positive results associated with allogeneic HSCT for adult males with X-linked C-ALD. There was some evidence that patients with no or mild cerebral symptoms prior to HSCT or an EDSS score <6 in combination with other factors may benefit more than the wider population of interest.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In adult males with X-linked C-ALD, what is the clinical effectiveness of allogeneic HSCT compared with standard of care?

2. In adult males with X-linked C-ALD, what is the safety of allogeneic HSCT compared with standard of care?

3. In adult males with X-linked C-ALD, what is the cost effectiveness of allogeneic HSCT compared with standard of care?

4. From the evidence selected, are there any subgroups of patients that may benefit from HSCT more than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define those patients with X-linked C-ALD who are eligible to receive HSCT?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Services Commissioning Products' (2020).

The searches for evidence were informed by the PICO document and were conducted on 17th May 2022.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Three studies were identified for inclusion. One prospective cohort study compared HSCT to no HSCT in adult-onset cerebral form/ cerebello-brainstem form ALD (Matsukawa et al 2020). Two retrospective case series included adult males with C-ALD who received HSCT (Kühl et al 2017, Waldhüter et al 2019).

Table 1 provides a summary of the included studies and full details are given in Appendix E.

No cost effectiveness studies were identified.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Kühl et al 2017
 	
Retrospective case series
 	
4 centres in Germany, France and the UK
	14 adult males with C-ALD[a]
	
	Median (range) age at HSCT: 34 years (21 to 48)
	
	EDSS[b] <6: 9/14 (64.3%)
	EDSS ≥6: 5/14 (35.7%)
	
	Loes score[c] ≤10: 10/14 (71.4%)
	Loes score >10: 4/14 (28.6%)
	
	Subgroups by EDSS score before HSCT and presence or absence or early transplant complications
		Intervention
		Allogeneic HSCT
		
		Comparison
		No comparator
		
		12/14 patients received additional serotherapy for GvHD prophylaxis
			Outcomes reported at median (range) follow-up of 65 months (38 to 116) unless otherwise stated
			
			Critical outcomes
			• Stabilisation or improvement in MRI findings of C-ALD
			  • Median Loes score (before HSCT, 6 to 12 months after HSCT and >12 months after HSCT)
			  • Gd enhancement (at >6 months)
			• Survival
			• Cognitive function
			  • Cognitive function status after HSCT
			
			Important outcomes
			• Progression free survival
			  • Median EDSS (before HSCT, <6 months after HSCT and 24 months after HSCT)
			  • Median AACS[d] (before HSCT, <6 months after HSCT and 24 months after HSCT) (for subgroups)
			  • Motor function status at >36 months
			• Activities of daily living
			  • Status after HSCT
			  • Modified Rankin Score[e] (before HSCT, <6 months after HSCT and 24 months after HSCT) (for subgroups)
			• Quality of life
			  • Status after HSCT

Study	Population	Intervention and comparison	Outcomes reported

			• Safety
			  • Mortality from HSCT
			  • Infection
			  • Transplant adverse events
			  • GvHD

Matsukawa et al 2020
 	
Prospective cohort study
 	
Single centre, Japan
	20 males with adolescent/ adult-onset cerebral form/ cerebello-brainstem form of ALD
	
	HSCT: 12
	No HSCT: 8
	
	<u>HSCT</u>
	Median (range) age at HSCT: 31 years (18 to 45)
	
	EDSS <6: 7/12 (58.3%)
	EDSS ≥6: 5/12 (41.7%)
	
	Loes score ≤10: 10/12 (83.3%)
	Loes score >10: 2/12 (16.7%)
	
	<u>No HSCT</u>
	Median (range) age at considering HSCT: 47.5 years (29 to 76)
	
	EDSS <6: 4/8 (50%)
	EDSS ≥6: 2/8 (25%)
	Not available: 2/8 (25%)
	
	Loes score ≤10: 6/8 (75%)
	Loes score >10: 2/8 (25%)
	
	No subgroups reported
		Intervention
		Allogeneic HSCT
		
		Comparison
		No HSCT (standard care)
		
		12/12 HSCT patients received GvHD prophylaxis
			Outcomes reported at last follow-up unless otherwise stated. Median (range) follow-up:
			• HSCT: 28.6 months (4.2 to 125.3)
			• No HSCT: 69.1 months (16.0 to 104.1)
			
			Critical outcomes
			• Stabilisation or improvement in MRI findings of C-ALD
			  • Median Loes score
			  • Gd enhancement before and after HSCT
			  • White matter lesions
			• Survival
			
			Important outcomes
			• Progression free survival
			  • Median EDSS (before HSCT and median follow-up 13.5 months for HSCT; at time HSCT considered and >12 months for no HSCT)
			• Activities of daily living
			  • Median Barthel Index[f] (before HSCT and median follow-up 13.5 months for HSCT; at time HSCT considered and >12 months for no HSCT)
			  • Median ALD-Disability Rating Scale[g] (before HSCT and median follow-up 13.5 months for HSCT; at time HSCT considered and >12 months for no HSCT)
			  • Status after HSCT
			• Safety
			  • Transplant adverse events
			  • GvHD

Study	Population	Intervention and comparison	Outcomes reported

Waldhüter et al 2019
 	
Retrospective case series
 	
Single centre, Germany
	15 adult males with C-ALD[h]
	
	Median (range) age at HSCT: 33 years (26 to 50)
	
	EDSS <6: 9/15 (60%)
	EDSS ≥6: 6/15 (40%)
	
	Loes score ≤10: 11/15 (73.3%)
	Loes score >10: 4/15 (26.7%)
	
	Subgroup analysis by EDSS score and symptoms before HSCT
		Intervention
		Allogeneic HSCT
		
		Comparison
		No comparator
		
		15/15 patients received anti-thymocyte globulin for GvHD prophylaxis
			Outcomes reported at median (range) follow-up (for survivors) of 56 months (20 to 104) unless otherwise stated
			
			Critical outcomes
			• Survival
			• Cognitive function
			  • Median AACS cortical subdomain[i] (before HSCT, 24 months after HSCT and at last follow-up)
			  • Cognitive function status at last follow-up
			
			Important outcomes
			• Progression free survival
			  • Event-free survival
			  • Median EDSS (before HSCT, 24 months after HSCT and at last follow-up)
			  • Change in EDSS
			  • Median AACS (before HSCT, 24 months after HSCT and at last follow-up)
			  • Change in AACS
			  • Motor function at last follow-up
			• Activities of daily living
			  • Status after HSCT
			• Safety
			  • Mortality from HSCT (within 1 year of HSCT)
			  • Infection (within 1 year of HSCT)
			  • Transplant adverse events
			  • GvHD

Abbreviations
AACS: Adult ALD Clinical Score; ALD: Adrenoleukodystrophy; C-ALD: Cerebral ALD; Gd: Gadolinium; EDSS: Expanded Disability Symptom Score; GvHD: Graft-versus-host disease; HSCT: Haematopoietic stem cell transplant; MRI: Magnetic resonance imaging

a 8 of these patients were also included in Waldhüter et al (2019)
b The EDSS is a clinical scoring system. Scores range from 0 to 10 points where 0 = no deficits, 6 = inability to walk without assistance and 10 = death
c Loes MRI severity score is a 34-point scale that assigns a score to a MRI based on the extent of white matter lesions. Higher scores indicate more significant ALD involvement. Loes score minimum of 1 is used to be considered for HSCT and shows evidence of MRI Gd enhancement around a consistent lesion
d The AACS is a composite score of motor (0-6 points), bladder (0-3 points), sensory (0-3 points) and cortical (0-12 points). Composite scores range from 0 points (normal) to 24 (maximum dysfunction)
e The Modified Rankin Score describes disability status in daily activities. It is scored from 0 to 6 with higher scores indicating greater disability. A score of 0 = no symptoms, 1 = no significant disability despite symptoms, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, 6= dead

Study	Population	Intervention and comparison	Outcomes reported
f The Barthel Index consists of 10 items that measure a person's daily functioning including feeding, transfers from bed to wheelchair and to and from a toilet, grooming, walking on a level surface, going up and down stairs, dressing, continence of bowels and bladder. Scores from the 10 items are added to give a total score ranging from 0 (totally dependent) to 100 (completely independent) g The ALD-Disability Rating Scale assesses function level as a composite score. Scores range from 0 to IV representing increasing disability. A score of 0 = no difficulties; I = mild learning or coordination difficulties from ALD not requiring support or intervention; II = moderate learning, sensory and/ or neurologic abnormality requiring support or intervention in a few areas; III = severe learning, sensory and/ or neurologic abnormality requiring support or intervention in many areas; IV = loss of cognitive ability and disorientation, patient requires constant supervision h 8 of these patients were also included in Kühl et al (2017) i The AACS cortical subdomain is one of 4 subdomains of the Adult ALD Clinical Score (AACS). The cortical subdomain is scored from 0 to 12 with higher scores indicating higher dysfunction. A score of >3 points in the cortical domain is defined as moderate cerebral dysfunction			

5. Results

In adult males with X-linked C-ALD, what is the clinical effectiveness and safety of allogeneic HSCT compared with standard of care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Stabilisation or improvement in MRI findings of C-ALD **Certainty of evidence:** Very low	Stabilisation and/ or improvement of MRI findings is critical to patients as all individuals with C-ALD will demonstrate a progression in their disease, including individuals undergoing HSCT. Stabilisation or improvement indicates that cerebral symptoms of ALD are not progressing and may be associated with improvement in clinical features of neuro-disability such as cognition or motor function. Longer term outcomes (>12 months after HSCT) would be of critical importance to patients to demonstrate the MRI findings (as the intervention takes time to stabilise the disease). Given the progressive nature of the disease an individual is not expected to return to their baseline pre-intervention level. In total, two studies (one prospective cohort study and one retrospective case series) provided evidence relating to stabilisation or improvement in MRI findings of C-ALD in adult males with X-linked C-ALD. The prospective cohort study compared HSCT to no HSCT. Outcomes reported included Loes score[11], Gd enhancement and white matter lesions. **For HSCT vs no HSCT** ***Loes score*** **At approximately 1.5 years[12]:** • One prospective cohort study (Matsukawa et al 2020) reported an improvement in median (range) Loes score from 6 (2 to 13) before HSCT (n=12) to 5.25 (1.5 to 13) after HSCT (n=12). Median (range) follow-up was 1.55 years (0.1 to 6.7). The authors stated that “the Loes score increased by one point in [3 patients] with atrophic changes of the brainstem, but otherwise stabilised or even improved”. For patients who did not receive HSCT, the median (range) Loes score worsened from 5.5 (3 to 13.5) at the time HSCT was considered (n=8) to 8 (6 to 13.5) up to 12 months after HSCT was considered (n=3). More than 12 months after HSCT was considered (n=3) this had further worsened to 16 (8 to 34). No statistical comparison between groups or over time was reported. **(VERY LOW)** ***Gd enhancement*** **At up to 80 months follow-up:** • One prospective cohort study (Matsukawa et al 2020) described Gd enhancement before HSCT and at last follow-up. For 2/12 (16.7%) patients, with one and three months follow-up respectively, this was ‘not enhanced’ before and after HSCT. For 8/12 (66.7%) patients this was ‘enhanced’ before HSCT and ‘not enhanced’ after HSCT at between one and 80 months follow-up. For 2/12 (16.7%) patients, with two and three months follow-up respectively, this was ‘enhanced’ before HSCT and ‘obscure’ after HSCT. **(VERY LOW)**

[11] Loes MRI severity score is a 34-point scale that assigns a score to a MRI based on the extent of white matter lesions. Higher scores indicate more significant ALD involvement. Loes score minimum of 1 is used to be considered for HSCT and shows evidence of MRI Gd enhancement around a consistent lesion
[12] Based on the median follow-up of HSCT patients

Outcome	Evidence statement
	White matter lesions **At approximately 2 years[13]:** • One prospective cohort study (Matsukawa et al 2020) described white matter lesion status for HSCT and no HSCT patients. Of the 12 HSCT patients, seven (58.3%) were described as having a reduction in size of white matter lesions after HSCT and five (41.7%) as having stabilisation of enlargement of white matter lesions. The authors stated that white matter lesions stopped enlarging within two months for nine patients and within 12 months for three patients. No new white matter lesions had appeared in any HSCT patients at last follow-up. All eight patients who did not receive HSCT were described as having white matter lesions that continued to enlarge accompanied by marked atrophic changes in the brain. Median (range) follow-up was 28.6 months (4.2 to 125.3) for HSCT patients and 69.1 months (16.0 to 104.1) for no HSCT patients. **(VERY LOW)** **For HSCT (no comparator)** ***Loes score*** **At up to >12 months after HSCT:** • One retrospective case series (Kühl et al 2017) reported a worsening in median (range) Loes score from 6.5 (2 to 14) before HSCT (n=14) to 11.5 (7 to 15.5) between six and 12 months after HSCT (n=7). At >12 months after HSCT (n=9) the median Loes score improved (relative to the six to 12 months score) to 10 (5 to 12). The authors noted that "there was no significant increase in Loes score beyond 12 months post-HSCT in comparison to Loes score before HSCT among the eight survivors (median 8 points (range 2.5 to 12 points) before HSCT; median 10 points (range 5 to 12 points) >12 months post-HSCT)". No statistical comparison was reported. **(VERY LOW)** ***Gd enhancement*** **At >6 months:** • One retrospective case series (Kühl et al 2017) reported that none of the 11 patients examined >6 months after HSCT showed further Gd enhancement of cerebral demyelinating lesions. **(VERY LOW)** ***For HSCT vs no HSCT:*** **One prospective cohort study provided very low certainty evidence that median Loes score improved from before HSCT to a median of 1.55 years after HSCT. For 'no HSCT' patients, the median Loes score worsened over time. No statistical comparison was reported. The same prospective cohort study also provided very low certainty evidence that Gd enhancement was 'not enhanced' or 'obscure' after HSCT for all patients, with follow-up ranging from one to 80 months, and that white matter lesions stabilised or reduced in size for all patients who received HSCT (within 12 months) and continued to enlarge for all 'no HSCT' patients.** ***For HSCT (no comparator):*** **One retrospective case series provided very low certainty evidence that median Loes score worsened during the first year after HSCT but then improved beyond 12 months after HSCT, whilst remaining higher than the before HSCT median score. No statistical comparison was reported. The same retrospective case series also provided very low certainty evidence that no patients examined more than six months after HSCT showed further Gd enhancement of cerebral demyelinating lesions.**

[13] Based on the median follow-up of HSCT patients

Outcome	Evidence statement
Survival **Certainty of evidence:** Very low	Survival is critical to patients as the median overall survival is 3.9 years once adult onset cerebral adrenoleukodystrophy enters the active neuroinflammation phase[14]. Interventions which improve the survival outcome for patients are critical for individuals and families affected by C-ALD for whom there are only supportive treatment options. In total, three studies (one prospective cohort study and two retrospective case series[15]) provided evidence relating to survival in adult males with X-linked C-ALD. The prospective cohort study compared HSCT to no HSCT. **For HSCT vs no HSCT** **At approximately 2 years:** • One prospective cohort study (Matsukawa et al 2020) reported that survival probability[16] (Kaplan-Meier) was *statistically significantly higher* in patients who underwent HSCT vs patients who did not receive HSCT (p=0.0089). 12/12 (100%) HSCT patients were alive at a median (range) follow-up of 28.6 months (4.2 to 125.3) after HSCT. 2/8 (25%) patients who did not receive HSCT were alive at a median (range) follow-up of 69.1 months (16.0 to 104.1) from lesion or symptom onset. **(VERY LOW)** **For HSCT (no comparator)** **At approximately 5 years:** • One retrospective case series (Kühl et al 2017) reported that 8/14 (57.1%) HSCT patients were alive at a median (range) follow-up of 65 months (38 to 116). The estimated mean ± SD survival probability (Kaplan-Meier) was 57.1% ± 13.2. **(VERY LOW)** • One retrospective case series (Waldhüter et al 2019) reported that 11/15 (73%) HSCT patients were alive at a median (range) follow-up of 56 months (20 to 104). The estimated mean ± SD survival probability (Kaplan-Meier) was 73% ± 11. **(VERY LOW)** ***For HSCT vs no HSCT:*** **One prospective cohort study provided very low certainty evidence of statistically significantly higher survival probability in patients who received HSCT compared to 'no HSCT' patients, with median follow-up of 29 months for HSCT patients and 69 months for 'no HSCT' patients.** ***For HSCT (no comparator):*** **Two retrospective case series provided very low certainty evidence of 57% survival at a median follow-up of 65 months and 73% at a median follow-up of 56 months after HSCT respectively.**
Cognitive function **Certainty of evidence:** Very low	Cognitive function is a critical outcome for patients as C-ALD causes a progressive loss of cognitive function, including individuals undergoing HSCT. The ability to have preserved cognition can facilitate active participation in work and family roles and promote independence. Longer term outcomes (>12 months after HSCT) would be important to patients to demonstrate the cognitive function after an intervention (as the intervention takes time to stabilise the disease). In total, two retrospective case series provided evidence relating to cognitive function following HSCT in adult males with X-linked C-ALD. Outcomes reported included AACS cortical subdomain[17] and cognitive function status at follow-up.

[14] De Beer M, Engelen M, van Geel BM. 2014. Frequent occurrence of cerebral demyelination in adrenomyeloneuropathy. Neurology 2014; 83; 2227-31

[15] Eight patients included in the retrospective case series by Waldhüter et al (2019) were also included in the retrospective case series by Kühl et al (2017)

[16] Determined from the earliest time of either the onset of cerebral/ cerebellar/ brainstem MRI lesions or the onset of clinical symptoms attributable to cerebral/ cerebellar/ brainstem lesions

[17] The AACS cortical subdomain is one of 4 subdomains of the Adult ALD Clinical Score (AACS). The cortical subdomain is scored from 0 to 12 with higher scores indicating higher dysfunction. A score of >3 points in the cortical domain is defined as moderate cerebral dysfunction

Outcome	Evidence statement
	For HSCT (no comparator) ***AACS cortical subdomain*** **At up to approximately 5 years:** • One retrospective case series (Waldhüter et al 2019) reported an improvement in median (range) AACS cortical subdomain score from 6 (0 to 9) before HSCT (n=15) to 3 (0 to 9) 24 months after HSCT (n=11) and 3 (0 to 9) at last follow-up (n=9). Last follow-up was at median (range) 59 months (29 to 104). No statistical comparison was reported. **(VERY LOW)** ***Cognitive function status*** **At approximately 5 years:** • One retrospective case series (Kühl et al 2017) reported that cognitive function remained stable in five (62.5%) of eight surviving patients after HSCT. The remaining three (37.5%) surviving patients had moderate cognitive decline)[18]. Median (range) follow-up was 65 months (38 to 116). **(VERY LOW)** • One retrospective case series (Waldhüter et al 2019) reported cognitive function at last follow-up for nine patients with >24 months follow-up. This was improved for two (22.2%) patients, stable[19] for five (55.6%) and had deteriorated for two (22.2%). Median (range) follow-up was 59 months (29 to 104). **(VERY LOW)** ***For HSCT (no comparator):*** **One retrospective case series provided very low certainty evidence of an improvement in median AACS cortical subdomain score from before HSCT up to a median of approximately five years, after HSCT. No statistical comparison was reported. This same case series reported that cognitive function for nine patients with more than 24 months follow-up was improved for 22%, stable for 56% and deteriorated for 22%. A second retrospective case series provided very low certainty evidence that for eight surviving patients, cognitive function remained stable for 63% and had moderately deteriorated for 38% at a median of approximately five years after HSCT. These studies do not provide any evidence about cognitive function for HSCT compared with standard of care.**
Important outcomes	
Progression free survival **Certainty of evidence:** Very low	Progression free survival (the length of time an individual lives without the disease getting worse) is important to patients as it reflects the ability to maintain neurological and motor function with C-ALD, and may reflect the ability to participate in activities of daily living and work and family roles. C-ALD is a progressive condition which leads to ongoing resultant disability and death. It is expected that all individuals with C-ALD will demonstrate a progression in their disease, including individuals undergoing HSCT. HSCT impacts on cerebral neurological function (e.g. cognition, vision, cerebellar signs) but other elements such as adrenomyeloneuropathy (AMN) symptoms can continue to progress. Longer term outcomes (>12 months after HSCT) would be important to patients to demonstrate the progression-free intervals after an intervention (as the intervention takes time to stabilise the disease). In total, three studies (one prospective cohort study and two retrospective case series) provided evidence relating to progression free survival in adult males with X-linked C-ALD. The prospective cohort study compared HSCT to no HSCT.

[18] Stable neurocognition post-HSCT was defined as deterioration in IQ <15 (<1 SD) or no cognitive deterioration as detected by care givers. Severe deterioration in intellectual function was classified as obvious cognitive decline or inability to test for IQ anymore. Moderate deterioration was defined as anything less than severe

[19] The number of patients that had stable cognitive function is described differently in different sections of the paper. The descriptions and numbers presented in the paper's table of results have been extracted

Outcome	Evidence statement
	Outcomes reported included event-free survival, EDSS[20], AACS[21] and motor function status. **For HSCT vs no HSCT** ***EDSS*** **At approximately 1 year:** • One prospective cohort study (Matsukawa et al 2020) reported a worsening in median (range) EDSS score from 3.75 (2.0 to 9.0) before HSCT (n=12) to 6.25 (2.0 to 8.5) after HSCT (n=12). Median (range) follow-up was 13.5 months (1 to 95). The authors stated that "neurological outcomes were stable for 12/12 HSCT patients at median (range) follow-up of 2.4 years (0.3 to 10.4)". For patients who did not receive HSCT, the median (range) EDSS score worsened from 3.5 (2.0 to 9.0) at the time HSCT was considered (n=6) to 10 (6.5 to 10) >12 months after HSCT was considered (n=8). Median (range) follow-up was 55.5 months (13 to 98). No statistical comparison between groups or over time was reported. **(VERY LOW)** **For HSCT (no comparator)** ***Event free survival[22]*** **At approximately 5 years** • One retrospective case series (Waldhüter et al 2019) reported event free survival (Kaplan-Meier) mean ± SD of 36% ± 17 for HSCT patients (n=7). Median (range) follow-up was 56 months (20 to 104). **(VERY LOW)** • Waldhüter et al (2019) also stated that event free survival was 2/8 (25%) for patients transplanted before 2013 and 5/7 (71.4%) after 2013 (p=0.132). ***EDSS*** **At up to 24 months after HSCT:** • One retrospective case series (Kühl et al 2017) reported a worsening in median (range) EDSS score from 4 (1 to 7) before HSCT (n=14) to 7.25 (1 to 9.5) in the six months following HSCT (n=14). At 24 months after HSCT (n=11) the median EDSS score improved (relative to the <6 months score) to 6 (1 to 10). No statistical comparison was reported. **(VERY LOW)** **At up to approximately 5 years:** • One retrospective case series (Waldhüter et al 2019) reported a worsening in median (range) EDSS score from 4 (3 to 6.5) before HSCT (n=15) to 6 (3 to 7) 24 months after HSCT (n=11). The median (range) score was also 6 (2 to 7) at last follow-up at median (range) 59 months (29 to 104) (n=9). No statistical comparison was reported. **(VERY LOW)** • Waldhüter et al (2019) also reported change in EDSS score 24 months after HSCT vs before HSCT for 11 surviving patients. For four (36.4%) patients there was no change, for four (36.4%) the score had worsened by 0.5 points and for three (27.3%) it had worsened by 2 points. **(VERY LOW)**

[20] The Expanded Disability Symptom Score (EDSS) is a clinical scoring system. Scores range from 0 to 10 points where 0 = no deficits, 6 = inability to walk without assistance and 10 = death
[21] The Adult ALD Clinical Score (AACS) is a composite score of motor (0-6 points) bladder (0-3 points), sensory (0-3 points) and cortical (0-12 points). Composite scores range from 0 points (normal) to 24 (maximum dysfunction)
[22] Defined as survival with stable cognition and no deterioration in motor

Outcome	Evidence statement
	AACS **At up to approximately 5 years:** • One retrospective case series (Waldhüter et al 2019) reported a worsening in median (range) AACS score from 10 (1 to 14) before HSCT (n=15) to 12 (1 to 17) 24 months after HSCT (n=11). At last follow-up at median (range) 59 months (29 to 104) (n=9) the median AACS score was again 10 (4 to 19). No statistical comparison was reported. **(VERY LOW)** • Waldhüter et al (2019) also reported change in AACS score 24 months after HSCT vs before HSCT for 11 surviving patients. For one (9.1%) patient this had improved by one point and for four (36.4%) there was no change. For six patients the score had worsened by one point (n=1, 9.1%), two points (n=3, 27.3%), five points (n=1, 9.1%) and six points (n=1, 9.1%) respectively. **(VERY LOW)** ***Motor function status*** **At >36 months:** • One retrospective case series (Kühl et al 2017) described motor function status[23] at last follow-up (>36 months) for eight patients. This was 'improved' for four (50%) patients, 'stable' for two (25%) and 'deteriorated vs early post-HSCT period' for two (25%). **(VERY LOW)** **At up to approximately 5 years:** • One retrospective case series (Waldhüter et al 2019) described motor function status at median (range) follow-up of 59 months (29 to 104) for nine patients. This was 'improved' for two (22.2%) patients, 'stable' for six (66.7%) and 'mildly deteriorated' for one (11.1%). **(VERY LOW)** • Waldhüter et al (2019) also stated that survival with stable cognition and motor function two years post-HSCT was 0/8 (0%) for patients transplanted before 2013 and 5/7 (71.4%) after 2013 (p<0.001). ***For HSCT vs no HSCT:*** **One prospective cohort study provided very low certainty evidence of a worsening in median EDSS score from before HSCT to a median follow-up of 14 months after HSCT but with stabilisation at a median of 2.4 years after HSCT. For 'no HSCT' patients, the median EDSS score worsened over time. No statistical comparison between groups or over time was reported.** ***For HSCT (no comparator):*** **One retrospective case series provided very low certainty evidence that event-free survival was 36% at a median of approximately five years after HSCT.** **One retrospective case series provided very low certainty evidence that median EDSS score initially worsened after HSCT but was improving 24 months after HSCT. A second retrospective case series provided very low certainty evidence that median EDSS score worsened from before HSCT up to a median of approximately five years after HSCT. No statistical comparison was reported in either study. The second retrospective case series also provided very low certainty evidence that 36% of 11 surviving patients experienced no change in EDSS score from before HSCT to 24 months follow-up. For other surviving patients EDSS score worsened by up to 2 points.** **One retrospective case series provided very low certainty evidence that median AACS score worsened from before HSCT to 24 months after HSCT but returned to the before HSCT value at a median of five years after HSCT. No statistical comparison was reported. This same retrospective case series also provided very low certainty evidence that for 11 surviving patients,**

[23] Stable motor function post-HSCT was defined as an increment in EDSS <1 point with preserved/ maintained ambulation (EDSS<7). Severe deterioration in motor function was classified as increment in EDSS ≥2 points or to EDSS ≥7

Outcome	Evidence statement
	AACS score at 24 months after HSCT had improved (for 9%), remained the same (for 36%) or worsened (55%) by between one and six points. **One retrospective case series provided very low certainty evidence that motor function status at more than 36 months follow-up was improved for 50% of eight patients, stable for 25% and had deteriorated for 25%. A second retrospective case series provided very low certainty evidence that motor function status at a median follow-up of approximately five years was improved for 22% of nine patients, stable for 67% and mildly deteriorated for one patient (11%).**
Activities of daily living (ADLs) **Certainty of evidence:** Very low	ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home and recreational settings. They encompass patients' individual needs and facilitate inclusion and participation. C-ALD leads to progressive neuro-cognitive impairment and challenges the ability to complete ADLs without assistance. Longer term outcomes (>12 months after HSCT) would be important to patients as the intervention takes time to stabilise the disease and the intervention of HSCT can impact on ADLs in the short-term post procedure. HSCT impacts on cerebral neurological function (e.g. cognition, vision, cerebellar signs) but other elements such as adrenomyeloneuropathy (AMN) symptoms can continue to progress. In total, three studies (one prospective cohort study and two retrospective case series) provided evidence relating to activities of daily living in adult males with X-linked C-ALD. The prospective cohort study compared HSCT to no HSCT. Outcomes reported included Barthel Index[24], ALD Disability Rating Scale[25] and status at follow-up. **For HSCT vs no HSCT** ***Barthel Index*** **At approximately 1 year:** • One prospective cohort study (Matsukawa et al 2020) reported a worsening in median (range) Barthel Index from 100 (10 to 100) before HSCT (n=12) to 85 (15 to 100) after HSCT (n=12). Median (range) follow-up was 13.5 months (1 to 95). For patients who did not receive HSCT, the median (range) Barthel Index worsened from 70 (0 to 100) at the time HSCT was considered (n=8) to 0 (0 to 50) >12 months after HSCT was considered (n=8). Median (range) follow-up was 55.5 months (13 to 98). No statistical comparison between groups or over time was reported. **(VERY LOW)** ***ALD-Disability Rating Scale*** **At approximately 1 year:** • One prospective cohort study (Matsukawa et al 2020) reported the same median (range) ALD-Disability Rating Scale score of II (I to III) before HSCT (n=12) and after HSCT (n=12). Median (range) follow-up was 13.5 months (1 to 95). For patients who did not receive HSCT, the median (range) ALD-Disability Rating Scale score worsened from II (I to III) at the time HSCT was considered (n=5) to IV (III to IV) >12 months after HSCT

[24] The Barthel Index consists of 10 items that measure a person's daily functioning including feeding, transfers from bed to wheelchair and to and from a toilet, grooming, walking on a level surface, going up and down stairs, dressing, continence of bowels and bladder. Scores from the 10 items are added to give a total score ranging from 0 (totally dependent) to 100 (completely independent)

[25] The ALD-Disability Rating Scale assesses function level as a composite score. Scores range from 0 to IV representing increasing disability. A score of 0 = no difficulties; I = mild learning or coordination difficulties from ALD not requiring support or intervention; II = moderate learning, sensory and/ or neurologic abnormality requiring support or intervention in a few areas; III = severe learning, sensory and/ or neurologic abnormality requiring support or intervention in many areas; IV = loss of cognitive ability and disorientation, patient requires constant supervision

Outcome	Evidence statement
	was considered (n=8). Median (range) follow-up was 55.5 months (13 to 98). No statistical comparison between groups or over time was reported. **(VERY LOW)** ***Status at last follow-up*** **At up to approximately 2 years:** • One prospective cohort study (Matsukawa et al 2020) described 6/12 (50%) of HSCT patients as working or studying after HSCT. 4/12 (33.3%) patients were described as having received HSCT recently and were awaiting follow-up. The remaining two patients (16.7%) were described as remaining at home. Median (range) follow-up was 28.6 months (4.2 to 125.3). The two surviving patients who did not receive HSCT were described as 'wheelchair bound due to disease progression' after a median (range) follow-up of 69.1 months (16.0 to 104.1). **(VERY LOW)** **For HSCT (no comparator)** ***Status at last follow-up*** **At 24 months:** • One retrospective case series (Waldhüter et al 2019) described status 24 months after HSCT for the 11 surviving patients. Three (27.3%) patients were 'employed' (no further detail on ADL) and three (27.3%) were 'retired from work but fully active/ good activity in daily life'. Two (18.2%) patients were 'severely handicapped with restricted activity in daily life', one (9.1%) patient was 'severely handicapped, needs support in activity in daily life', one (9.1%) patient was 'retired from work, needs support in activity in daily life' and one (9.1%) patient was 'retired from work, development of depressive mood disorder' (no further detail on ADL). **(VERY LOW)** **At up to approximately 5 years:** • One retrospective case series (Kühl et al 2017) described ADL status at last follow-up for five patients who had maintained their vocational status prior to HSCT. This was 'continued as students' (n=2), 'unable to resume work' (n=1) and 'died following-HSCT' (n=2). Median (range) follow-up was 65 months (38 to 116). **(VERY LOW)** ***For HSCT vs no HSCT:*** **One prospective cohort study provided very low certainty evidence that from before HSCT to a median follow-up of 14 months after HSCT, the median Barthel Index score worsened and the median ALD-Disability Rating Scale score remained the same-. For 'no HSCT' patients, the median Barthel Index and ALD-Disability Rating Scale scores worsened over time. No statistical comparison between groups or over time was reported for either measure.** **One prospective cohort study described status at last follow-up (median approximately two years) and provided very low certainty evidence that 50% of 12 HSCT patients were working or studying after HSCT. The remaining patients had received HSCT recently (33%) or remained at home (17%). The two surviving patients who did not receive HSCT were 'wheelchair bound due to disease progression'.** ***For HSCT (no comparator):*** **One retrospective case series described status 24 months after HSCT for 11 patients and provided very low certainty evidence that six were employed or retired but fully active. Two patients needed support in ADL and two were restricted in ADL. The remaining patient had developed a 'depressive mood disorder' (no further detail on ADL). A second retrospective case series provided very low certainty evidence that for five patients who maintained their occupational status prior to HSCT, two had continued as students, one was unable to resume work and two had died following HSCT.**

Outcome	Evidence statement
Quality of life **Certainty of evidence:** Very low	Quality of life is an important outcome to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. The intervention of HSCT is a significant undertaking by patients and their families and quality of life is also affected by the progressive nature of C-ALD. Longer term outcomes (>12 months post HSCT) would be important to patients as the intervention can take time to stabilise the disease and can impact on quality of life measures in short-term assessments. HSCT impacts on cerebral neurological function (e.g. cognition, vision, cerebellar signs) but other elements such as adrenomyeloneuropathy (AMN) symptoms can continue to progress and may still impact on quality of life. In total, one retrospective case series provided evidence relating to quality of life in adult males with X-linked C-ALD. **For HSCT (no comparator)** **At >12 months:** • One retrospective case series (Kühl et al 2017) described 4/8 (50%) of surviving patients as having a good quality of life at between 38 and 116 months follow-up. A further one patient (12.5%) was described as having an excellent quality of life at 59 months follow-up. The three remaining patients were respectively described as 'depression improved at 12 months' (with no further detail on quality of life), 'depression improved at 12 months but still low quality of life' and 'depression deteriorated vs early post-HSCT at 72 months follow-up. **(VERY LOW)** ***For HSCT (no comparator):*** **One retrospective case series provided very low certainty evidence that eight surviving patients had a good (50%) or excellent (12.5%) quality of life at between 38 and 116 months follow-up. The three remaining surviving patients were described as having a low quality of life or with depression that had improved or deteriorated respectively, with no further comment on quality of life. This study does not provide any evidence about quality of life for HSCT compared with standard of care.**
Safety	
Adverse events **Certainty of evidence:** Very low	Safety is a key factor to patients as it demonstrates the risks of an invasive procedure. This can include potential complications such as longer-term morbidity and/ or hospitalisation. In total, three studies (one prospective cohort study and two retrospective case series) provided evidence relating to safety following HSCT in adult males with X-linked C-ALD. Outcomes reported included transplant-related mortality, infection, transplant adverse events[26] and GvHD. **For HSCT (no comparator)** ***Transplant-related mortality*** **At median follow-up of approximately 5 years:** • One retrospective case series (Kühl et al 2017) reported transplant-related mortality in 3/14 (21.4%) patients. Median (range) follow-up was 65 months (38 to 116). **(VERY LOW)** **Within 1 year of HSCT:** • One retrospective case series (Waldhüter et al 2019) reported transplant-related mortality in 3/15 (20%) patients within one year of HSCT. **(VERY LOW)** ***Infection*** **At median follow-up of approximately 5 years:**

[26] Assessed using the National Cancer Institute common terminology criteria for adverse events version 3.0

Outcome	Evidence statement
	• One retrospective case series (Kühl et al 2017) reported no significant infection in 5/14 (35.7%) patients. The remaining nine patients experienced severe infection (≥ Grade 3) (3/14, 21.4%), life-threatening infection (4/14, 28.6%) or fatal infection (2/14, 14.3%). Median (range) follow-up was 65 months (38 to 116. **(VERY LOW)** **Within 1 year of HSCT:** • One retrospective case series (Waldhüter et al 2019) reported fatal infection in 4/15 (26.7%) patients within one year of HSCT. **(VERY LOW)** ***Transplant adverse events*** **At approximately 5 years:** • One retrospective case series (Kühl et al 2017) reported significant (≥ Grade 3) non-neurological toxicity in 6/14 (42.9%) patients. These included haemorrhagic cystitis (n=3), multi-organ failure (n=3), pneumonia (n=3), thrombotic microangiopathy (n=1), immune nephrotic failure (n=1), end-stage renal failure (n=1), polyserositis (n=1), sepsis (n=1). Median (range) follow-up was 65 months (38 to 116. **(VERY LOW)** • One retrospective case series (Waldhüter et al 2019) reported significant (>Grade 2) transplant complications in 11/15 (73.3%) patients. These included sepsis (n=8), haemorrhagic cystitis (n=5), pneumonia (n=4), multi-organ failure (n=2), transient hepatopathy (n=1), cytomegalovirus with encephalitis (n=1), relapsing urogenital infections (n=1), secondary graft failure (n=1), post-transplant lymphoproliferative disease triggered by Epstein-Barr virus (n=1). Median (range) follow-up (for survivors) was 56 months (20 to 104. **(VERY LOW)** **At approximately 2 years:** • One prospective cohort study (Matsukawa et al 2020) reported adverse events (grade not stated) in 3/12 (25%) patients after HSCT. These were cryptogenic organising pneumonia (n=1), transplantation-associated thrombotic microangiopathy with declining renal function (n-1) and suspected tacrolimus-induced nephrotoxicity with declining renal function (n=1). Median (range) follow-up was 28.6 months (4.2 to 125.3). **(VERY LOW)** • Matsukawa et al (2020) also reported that no Grade IV infections or other serious complications, including neurological problems, were observed in the 12 patients who received HSCT. ***GvHD*** **At median follow-up of approximately 5 years:** • One retrospective case series (Kühl et al 2017) reported acute GvHD Grade I in 5/14 (35.7%) of patients and acute GvHD ≥ Grade II in 1/14 (7.1%) patients. Median (range) follow-up was 65 months (38 to 116). **(VERY LOW)** • Kühl et al (2017) also reported chronic GvHD in 4/14 (28.6%) patients. Median (range) follow-up was 65 months (38 to 116). **(VERY LOW)** • One retrospective case series (Waldhüter et al 2019) reported acute GvHD Grade I in 4/15 (26.7%) patients and acute GvHD ≥ Grade II in 2/15 (13.3%) patients. Median (range) follow-up for survivors was 56 months (20 to 104). **(VERY LOW)** • Waldhüter et al (2019) also reported chronic GvHD in 3/15 (20%) patients. Median (range) follow-up for survivors was 56 months (20 to 104). **(VERY LOW)** **At median follow-up of approximately 2 years:** • One prospective cohort study (Matsukawa et al 2020) reported acute GvHD Grade I in 4/12 (33.3%) of patients and acute GvHD ≥ Grade II in 1/12 (8.3%) patients. Median (range) follow-up was 28.6 months (4.2 to 125.3). **(VERY LOW)**

Outcome	Evidence statement
	• Matsukawa et al (2020) also reported chronic GvHD in 2/12 (16.7%) patients. Median (range) follow-up was 28.6 months (4.2 to 125.3). **(VERY LOW)** **Two retrospective case series provided very low certainty evidence of transplant-related mortality in approximately 20% of patients.** **One retrospective case series provided very low certainty evidence of fatal infections in 27% of patients within one year of HSCT. A second retrospective case series provided very low certainty evidence of fatal, life-threatening and severe infections in 14%, 29% and 21% of patients respectively. 36% of patients in this study had no significant infections with a median follow-up of 65 months.** **One prospective cohort study provided very low certainty evidence of adverse events in 25% of patients (grade not stated) at approximately two years median follow-up. This study also reported no Grade IV infections or other serious complications. Two retrospective case series provided very low certainty evidence of significant transplant adverse events in 43% and 73% of patients respectively at approximately five years median follow-up.** **One prospective cohort study and two retrospective case series provided very low certainty evidence of acute GvHD Grade I in between 27% and 36% of patients, and acute GvHD ≥ Grade II in between 7% and 13% of patients. These studies also reported chronic GvHD in between 17% and 29% of patients. Median follow-up was approximately two years in the prospective cohort study and approximately five years in both case series.** **These studies do not provide any evidence about safety for HSCT compared with standard of care.**
Abbreviations AACS: Adult ALD Clinical Score; ADL: Activities of daily living; ALD: Adrenoleukodystrophy; AMN: Adrenomyeloneuropathy; C-ALD: Cerebral ALD; EDSS: Expanded Disability Symptom Score; Gd: Gadolinium; GvHD: Graft-versus-host disease; HSCT: Haematopoietic stem cell transplant; MRI: Magnetic resonance imaging; SD: Standard deviation	

In adult males with X-linked C-ALD, what is the cost effectiveness of HSCT compared with standard of care?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified for cost effectiveness.**

From the evidence selected, are there any subgroups of patients that may benefit from HSCT more than the wider population of interest?

Outcome	Evidence statement

Subgroups	Analysis by subgroups was reported for the critical outcomes of stabilisation or improvement in MRI findings of C-ALD, cognitive function and survival and the important outcomes of progression free survival and activities of daily living (ADL).
	
	Stabilisation or improvement in MRI findings of C-ALD
	• One retrospective case series (Kühl et al 2017) reported:
	  • *No statistically significant difference* (p>0.05) in median Loes score between two subgroups of patients based on EDSS score before HSCT and whether they had transplant complications.
	  • *No statistically significant difference* (p>0.05) between median Loes score before and after HSCT for either of the subgroups.
	  • Subgroup median (IQR) Loes scores:

Outcome	Evidence statement

	• For patients with an EDSS score <6 before HSCT and without transplant complications (n=6): 9.3 (6.0 to 11.0) before HSCT and 9.3 (8.0 to 11.0) ~24 months[27] after HSCT.
	• For patients with a EDSS score ≥6 before HSCT or early transplant complications[28]: 5.3 (3.5 to 8.8) before HSCT (n=8) and 11.0 (9.5 to 16) ~24 months after HSCT (n=4).
	
	Survival
	• One retrospective case series (Kühl et al 2017) reported that superior survival (Kaplan-Meier) was *statistically significantly* associated with:
	  • EDSS score <6 before HSCT and without transplant complications vs EDSS score ≥6 or early transplant complications. Estimated survival probability (mean ± SD): 100% (n=6) vs 25.0% ± 15.3 (n=8), p=0.008.
	  • EDSS score before HSCT <6 vs ≥6. Estimated survival probability mean ± SD: 77.8% ± 13.9 (n=9) vs 20.0% ± 17.9 (n=5), p=0.048.
	  • Median (range) follow-up was 65 months (38 to 116).
	• One retrospective case series (Waldhüter et al 2019) reported that higher overall survival (Kaplan-Meier) was *statistically significantly* associated with no or mild cerebral symptoms (n=8) vs moderate or severe cerebral symptoms (n=7) before HSCT (p=0.014)[29].
	• Waldhüter et al (2019) also reported overall survival for subgroups of patients based on their characteristics before HSCT[30]:
	  • EDSS score <6 and without cerebellum or thalamus involvement (n=8): 100%
	  (the presence vs absence of this characteristic was *statistically significant* (p<0.05)).
	  • EDSS score ≥6 (n=6) mean ± SD: 50% ± 20
	  (the presence vs absence of this characteristic was *not statistically significant*).
	  • Median (range) follow-up was 56 months (20 to 104).
	
	Cognitive function
	• One retrospective case series (Waldhüter et al 2019) reported survival with stable cognition[31] (Kaplan-Meier) for subgroups of patients based on their characteristics before HSCT:
	  • EDSS score <6 and without cerebellum or thalamus involvement before HSCT (n=8) mean ± SD: 66% ± 21
	  (the presence vs absence of this characteristic was *statistically significant* (p<0.05)).
	  • EDSS score ≥6 before HSCT (n=6) mean ± SD: 33% ± 19
	  (the presence vs absence of this characteristic was *not statistically significant*).
	  • Moderate or severe cerebral symptoms (n=8) mean ± SD: 25% ± 15 (*statistically significantly lower* vs no or mild symptoms (mean ± SD not reported) (p<0.05)).
	  • Median (range) follow-up was 56 months (20 to 104).
	
	Progression free survival
	• One retrospective case series (Kühl et al 2017) reported that the number (%) of patients who developed neurological symptoms during the six

[27] Timeframe ~24 months as reported in the study. Not further defined
[28] Early transplant complications were at least life-threatening infections during early transplant phase or graft rejection
[29] Moderate or severe cerebral symptoms = AACS cerebral function domain score >3. No or mild symptoms = AACS cerebral function domain score ≤3
[30] Most of the subgroup outcomes in this study were reported for specific characteristics, with the significance testing comparing whether the respective characteristics were present vs absent. No mean ± SD was reported for patients for who the specific characteristic was 'absent'
[31] No deterioration in cortical functions detected by relatives, at work, or by neuropsychological testing (ΔIQ <20)

Outcome	Evidence statement
	months after HSCT was *statistically significantly* lower with limited AMN (EDSS score <6) (1/9, 11%) vs advanced AMN (EDSS score ≥6) before HSCT (4/5, 80%), p=0.045. • Kühl et al (2017) also reported EDSS score after HSCT for subgroups by EDSS score before HSCT and whether they had transplant complications: *In a comparison over time for two different subgroups:* • For patients with an EDSS score <6 before HSCT and without transplant complications (n=6): There was *no statistically significant difference* in median (IQR) EDSS score ≤6 months after HSCT (6.5 (3.0 to 6.5)) or ~24 months after HSCT (5.0 (3.0 to 6.0)) vs before HSCT (3.8 (3.0 to 4.0)), p>0.05. • For patients with an EDSS score ≥6 before HSCT or early transplant complications: Median (IQR) EDSS score was *statistically significantly higher* ≤6 months after HSCT (8.3 (7.5 to 9.5), n=8) and ~24 months after HSCT (9.0 (6.8 to 10.0), n=5) vs before HSCT (6.3 (3.3 to 6.5), n=8), p<0.05. *In a comparison between subgroups:* • EDSS scores at ≤6 months and ~24 months after HSCT were also *statistically significantly higher* for patients with EDSS score ≥6 before HSCT or early transplant complications vs ~24 months after HSCT for patients with EDSS score <6 before HSCT and without transplant complications (p<0.05). • Kühl et al (2017) also reported AACS score after HSCT for subgroups by EDSS score before HSCT and whether they had transplant complications: *In a comparison over time for two different subgroups:* • For patients with EDSS score <6 before HSCT and without transplant complications (n=6): Median (IQR) AACS score was *statistically significantly higher* ≤6 months after HSCT (13.0 (10.0 to 15.0)) vs before HSCT (7.5 (7.0 to 10)), p<0.05. However, there was *no statistically significant difference* ~24 months after HSCT (9.0 (7.0 to 12.0)) vs before HSCT, p>0.05. • For patients with EDSS score ≥6 before HSCT or early transplant complications: Median (IQR) AACS score was *statistically significantly higher* ≤6 months after HSCT (18.0 (16.5 to 22.5), n=8) and ~24 months after HSCT (21.0 (15.8 to 24), n=5) vs before HSCT (11.5 (5.5 to 12.5), n=8), p<0.05. *In a comparison between subgroups:* • AACS scores at ≤6 months and ~24 months after HSCT were also *statistically significantly higher* for patients with EDSS ≥6 before HSCT or early transplant complications vs ~24 months after HSCT for patients with EDSS score <6 before HSCT and without transplant complications (p<0.05) • One retrospective case series (Waldhüter et al 2019) reported event free survival[32] (Kaplan-Meier) for subgroups of patients based on their characteristics before HSCT: • EDSS score <6 and without cerebellum or thalamus involvement before HSCT (n=8) mean ± SD: 50% ± 23 (the presence vs absence of this characteristic was *statistically significant* (p<0.05)) • EDSS score ≥6 before HSCT (n=6) mean ± SD: 33% ± 19 (the presence vs absence of this characteristic was *not statistically significant*) • Moderate or severe cerebral symptoms (n=8) mean ± SD: 25% ± 15 (*statistically significantly lower* vs no or mild symptoms (mean ± SD not reported) (p<0.05)). • Median (range) follow-up was 56 months (20 to 104).

[32] Survival with stable cognition and no deterioration in motor function

Outcome	Evidence statement
	ADL • One retrospective case series (Kühl et al 2017) reported Modified Rankin Score[33] after HSCT for subgroups by EDSS score before HSCT and whether they had transplant complications: *In a comparison over time for two different subgroups:* • For patients with EDSS score <6 before HSCT and without transplant complications (n=6): Median (IQR) Modified Rankin score was *statistically significantly higher* ≤6 months after HSCT (4.0 (3.0 to 5.0)) vs before HSCT (2.0 (1.0 to 3.0)), p<0.05. However, there was *no statistically significant difference* ~24 months after HSCT (3.5 (2.0 to 4.0)) vs before HSCT, p>0.05. • For patients with EDSS score ≥6 before HSCT or early transplant complications: Median (IQR) Modified Rankin score was *statistically significantly higher* ≤6 months after HSCT (5.0 (5.0 to 6.0), n=8) and ~24 months after HSCT (6.0 (4.0 to 6.0), n=5) vs before HSCT (3.5 (1.5 to 4.0), n=8), p<0.05. *In a comparison between subgroups:* • Modified Rankin score ≤6 months after HSCT was also *statistically significantly higher* for patients with EDSS score ≥6 before HSCT or early transplant complications vs ~24 months after HSCT for patients with EDSS score <6 before HSCT and without transplant complications (p<0.05). There was no statistically significant difference between the Modified Rankin score ~24 months after HSCT between the two subgroups **One retrospective case series reported no statistically significant difference in stabilisation or improvement in MRI findings of C-ALD between subgroups of patients, or before and after HSCT for the different subgroups. The subgroups were based on EDSS score before HSCT and whether they had transplant complications.** **One retrospective case series reported that superior survival was statistically significantly associated with an EDSS score of <6 before HSCT and also with an EDSS score of <6 without transplant complications. A second retrospective case series reported that higher overall survival was statistically significantly associated with no or mild cerebral symptoms before HSCT and also with an EDSS score of <6 without cerebellum or thalamus involvement. There was no statistically significant difference in survival based on whether the EDSS score before HSCT was above or below six alone.** **One retrospective case series reported that higher survival with stable cognition was statistically significantly associated with an EDSS score of <6 without cerebellum or thalamus involvement and also with no or mild cerebral symptoms before HSCT. There was no statistically significant difference in survival with stable cognition based on whether the EDSS score before HSCT was above or below six alone.** **One retrospective case series reported a statistically significant association between fewer patients with neurological symptoms in the six months following HSCT and an EDSS of <6 before HSCT. The same retrospective case series reported that EDSS score and AACS score both statistically significantly worsened to ~24 months for patients who had an EDSS score of ≥6 before HSCT or early transplant complications, but that there was no statistically significant change in these scores after ~24 months for patients with an EDSS score <6 before HSCT and without transplant complications. In a comparison between subgroups, better EDSS and AACS scores after**

[33] The Modified Rankin Score describes disability status in daily activities. It is scored from 0 to 6 with higher scores indicating greater disability. A score of 0 = no symptoms, 1 = no significant disability despite symptoms, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, 6= dead

Outcome	Evidence statement
	HSCT were statistically significantly associated with lower EDSS score before HSCT (<6) in combination with the absence of early transplant complications. A second retrospective case series reported that higher event-free survival was statistically significantly associated with an EDSS score of <6 without cerebellum or thalamus involvement and also with no or mild cerebral symptoms before HSCT. There was no statistically significant difference in event free survival based on whether the EDSS score before HSCT was above or below six alone. **One retrospective case series reported that Modified Rankin score was statistically significantly worse at ~24 months, compared to before HSCT, for patients with an EDSS score of ≥6 before HSCT or early transplant complications. However, there was no statistically significant change from before HSCT to ~24 months for patients with an EDSS <6 before HSCT and without transplant complications. There was no statistically significant difference in a comparison between these subgroups at ~24 months after HSCT.**
Abbreviations AACS: Adult ALD Clinical Score; ADL: Activities of daily living; ALD: Adrenoleukodystrophy; AMN: Adrenomyeloneuropathy; C-ALD: Cerebral ALD; EDSS: Expanded Disability Symptom Score; HSCT: Haematopoietic stem cell transplant; IQR: Inter quartile range; MRI: Magnetic resonance imaging	

From the evidence selected, what are the criteria used by the research studies to define those patients with X-linked C-ALD who are eligible to receive HSCT?

Outcome	Evidence statement
Criteria for treatment commencement with HSCT	In Matsukawa et al (2020), the indications for receiving HSCT included cerebral form of ALD or cerebello-brainstem form of ALD with Loes scores up to 13, the presence of progressively enlarging white matter lesions and/ or lesions with gadolinium enhancement on brain MRI. This study excluded patients with severe neuropsychiatric symptoms that made coordinated treatment during HSCT difficult. Kühl et al (2017) stated that patients were offered HSCT on an individually selected compassionate basis in accordance with the practice guidelines of the Working Party on Inborn Errors of the European Group for Blood and Marrow Transplantation[34] Waldhüter et al (2019) stated that patients were offered HSCT on an individually selected compassionate basis. No further detail was provided.
Abbreviations ALD: Adrenoleukodystrophy; HSCT: Haematopoietic stem cell transplant; MRI: Magnetic resonance imaging	

[34] Peters C, Steward CG. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. Bone Marrow Transplant 2003; 31: 229–39

6. Discussion

This evidence review considered the clinical effectiveness and safety of allogeneic HSCT compared to standard care for the treatment of X-linked C-ALD in adult males. The critical outcomes of interest were stabilisation or improvement in MRI findings of C-ALD, survival and cognitive function. Important outcomes were progression free survival, activities of daily living, quality of life and safety. Evidence on cost effectiveness was also sought.

Evidence was available from one prospective cohort study comparing HSCT to no HSCT and two retrospective case series. The prospective cohort study included 20 patients and was conducted at one centre in Japan between 2003 and 2018. The retrospective case series by Kühl et al (2017) included 14 patients and was conducted at four centres; two in Germany (Berlin n=8; Hannover n=1), one in France (n=4) and one in the UK (n=1) between 2003 and 2012. The eight patients treated in Berlin were also included in the retrospective case series by Waldhüter et al (2019) which included 15 patients in total. The dates of this study were not provided, but some analysis was done comparing outcomes for patients who received HSCT after (n=7) or before (n=8) 2013. This suggested better survival with stable cognition and motor function (71% vs 0%) and event free survival (71% vs 25%) in patients treated after 2013, although the difference was not statistically significant for event free survival. Kühl et al (2017), who included patients from four centres, stated that local standard protocols were used in the treatment of patients. It is not clear to what extent the results of these studies might be generalisable to the UK population or to current practice.

All studies included adult males with X-linked cerebral ALD. The indication for offering HSCT to patients was unclear in one of the retrospective case series. The prospective cohort study reported results for patients who received HSCT in comparison to patients who were considered for, but did not receive, HSCT. However, the eight patients who did not receive HSCT consisted of five patients who were described by the study authors as not fulfilling the inclusion criteria and three patients who were described as having declined HSCT. It is not clear why some of these patients did not meet the inclusion criteria although they were also described as having advanced stages of disease. It is not possible to say that the two groups were similar at baseline. Any comparisons reported between these groups should be interpreted with caution.

The duration of follow-up of individual patients within the included studies varied considerably and some outcomes were reported at different timepoints for different patients. The overall median and range of follow-up suggests that all patients in the two retrospective case series were followed-up for at least 20 months. However, the lower end of the follow-up range was 4.2 months in the prospective cohort study for HSCT patients and 16 months for no HSCT patients. Cerebral ALD is a progressive disease and the status of the patients at baseline also varied with regard to measures that were also used to assess outcomes. Due to the progressive nature of the disease, patients may not return to their pre-treatment baseline scores after treatment. In addition, it can take time for HSCT to stabilise the disease and the HSCT itself can negatively impact some outcomes in the short-term, such as activities of daily living and quality of life. Longer term outcomes (>12 months) after HSCT are therefore of particular interest. The duration of the follow-up period was sufficient for the outcomes assessed for some, but not all, patients.

Evidence was identified for all the clinical outcomes of interest for this review. Some of the outcome measures reported in the included studies covered aspects of function relevant to more than one of the outcomes listed in the PICO. The text provided in the PICO was used to determine which category was the best fit for the outcome measures available. The outcomes reported were primarily objective or assessed using standardised assessment

tools. Some outcomes around activities of daily living and quality of life were reported as narrative descriptions. For these, it was not clear how the judgements reported were made or by whom. The use of standardised outcome measures allows some interpretation of the level of function associated with specific scores. However, it was not always clear how clinically significant the changes observed on some scales were. No specific detail about what the minimal clinically important thresholds or differences might be was reported for the outcomes considered.

Both the retrospective case series reported that post-HSCT MRI scans were not available for three patients due to poor clinical status. Given the overlap in the populations of the two studies, it is possible that these were the same three patients. Few statistical comparisons were reported, between groups for the prospective cohort study, or for comparisons over time in any of the studies.

All the outcomes reported were classified as very low certainty evidence. Limitations reducing certainty for the outcomes reported in the prospective cohort study included differences between the groups at baseline, lack of adjustment for potential confounding factors and variable duration of follow-up of patients. Limitations reducing certainty in the outcomes reported in the two retrospective case series included uncertainty about whether the inclusion of participants was complete or consecutive. Lack of statistical analysis was also a limitation across all three studies for some outcomes.

The two retrospective case series reported results for patient subgroups. The reporting of the results for subgroups was complex with one of the case series reporting outcomes for subgroups that combined patient factors such as EDSS score prior to HSCT with transplant factors such as the presence or absence of early transplant complications. Some outcome measures, relating to progression free survival and activities of daily living, were only reported by patient subgroup.

No evidence on cost effectiveness was identified.

7. Conclusion

This evidence review includes one prospective cohort study and two retrospective case series. The prospective cohort study compared HSCT to no HSCT. The populations of all three studies were adult males with X-linked C-ALD. Some patients (n=8) were included in the populations of both the retrospective case series.

The prospective cohort study provided data contrasting HSCT to no HSCT and reported more positive results with HSCT for the critical outcomes of stabilisation or improvement in MRI findings of C-ALD and survival. The cohort study also reported results for the important outcomes of progression free survival and activities of daily living, with some evidence that HSCT may stabilise disease compared to no HSCT, but with a shorter follow-up time for HSCT patients. Comparisons between these groups should be interpreted with caution as the patients in the two groups were not similar at baseline in terms of meeting the study's inclusion criteria to receive HSCT. Non-comparative data were available for all the outcomes of interest. Due to the progressive nature of the disease, it is expected that patients may not return to their pre-treatment baseline scores after treatment. The outcomes reported generally provided evidence that HSCT can stabilise disease over time after an initial decline in the period after HSCT as might be expected in this context. Longer term outcomes (>12 months) after HSCT were of particular interest. The duration of the follow-up period was sufficient for the outcomes assessed for some, but not all, patients. The results also suggest variability in the outcomes achieved by individual patients, for example, in outcomes around function and quality of life.

Safety outcomes were reported for patients who received HSCT. These suggested that severe adverse events can be associated with HSCT with this affecting around a quarter of patients in the studies, although this proportion was higher in one study. Conversely some patients did not experience any severe adverse events.

Limitations reducing certainty in the evidence identified included differences between the cohort groups at baseline, lack of adjustment for potential confounding factors and variable duration of follow-up of patients. For the case series, limitations included uncertainty about whether the inclusion of participants was complete or consecutive. Lack of statistical analysis was also a limitation across all three studies for some outcomes.

There was some evidence that patients with an EDSS score of less than six before HSCT may benefit more from HSCT than the wider population of interest. However, this was usually when in combination with another characteristic such as the absence of cerebellum or thalamus involvement or the absence of transplant complications. There was also evidence that patients with no or mild cerebral symptoms before HSCT had better outcomes than patients with moderate or severe cerebral symptoms.

No evidence on cost effectiveness was identified.

The studies identified for this review therefore provide very low certainty evidence suggesting positive results associated with allogeneic HSCT for adult males with X-linked C-ALD. There was some evidence that patients with no or mild cerebral symptoms prior to HSCT or an EDSS score <6 in combination with other factors may benefit more than the wider population of interest.

Appendix A PICO Document

The review questions for this evidence review are:

1. In adult males with X-linked C-ALD, what is the clinical effectiveness of allogeneic HSCT compared with standard of care?

2. In adult males with X-linked C-ALD, what is the safety of allogeneic HSCT compared with standard of care?

3. In adult males with X-linked C-ALD, what is the cost effectiveness of allogeneic HSCT compared with standard of care?

4. From the evidence selected, are there any subgroups of patients that may benefit from HSCT more than the wider population of interest?

5. From the evidence selected, what are the criteria used by the research studies to define those patients with X-linked C-ALD who are eligible to receive HSCT?

P-Population and Indication	Adult males (≥ 18 years) X-linked cerebral adrenoleukodystrophy (C-ALD) Subgroups of interest: • Individuals with a low Expanded Disability Symptom Score (EDSS) (e.g. < 6 compared with EDSS ≥ 6) • Individuals with a low Loes score (e.g. ≤10 compared to Loes score > 10) • Individuals with no or mild cerebral symptoms compared with moderate or severe cerebral symptoms. [**X-linked Cerebral Adrenoleukodystrophy** (C-ALD), also known as Adult CALD (ACALD) would be diagnosed with elevated concentrations of very long chain fatty acids (VLCFA) and ABCD1 gene mutations. Cerebral ALD includes cerebral, cerebellum and brain stem lesions on MRI (this might be described as white matter lesions or lesions with gadolinium enhancement on brain MRI). It involves a variation of clinical presentation including motor and cognitive deficits] [**Expanded Disability Symptom Score (EDSS)** is a clinical scoring system. Scored from 0-10 points; 0= no deficits 6= inability to walk without assistance; 10= death]. [**Loes MRI severity score** is a 34-point scale that assigns a score to an MRI based on the extent of white matter lesions (higher scores indicate more significant ALD involvement). Loes score of minimum of 1 is used to be considered for HSCT and shows evidence of MRI gadolinium enhancement around a consistent lesion)] [**Adult ALD Clinical Score (AACS)** is a composite score of motor (0-6 points) bladder and sensory (0-3 points) and cortical dysfunction (0-12 points). Normal = 0 points, with 24= maximum dysfunction, with > 3 points in the cortical domain is defined as moderate cerebral dysfunction]
I-Intervention	Allogeneic Haematopoietic Stem Cell Transplant (HSCT) [Is the transplant of multipotent hematopoietic stem cells, usually derived from the bone marrow or peripheral blood of a donor. It would involve 5 distinct stages; conditioning, transplant, neutropenic, engraftment and

	post-engraftment stage. Any conditioning and transplant regimen is appropriate for inclusion within this PICO]
C-Comparator	Standard care No comparator • [Standard care for adults with C-ALD is currently supportive care for the physical and neurological symptoms as they develop, which may include palliative input as symptoms progress]
O-Outcomes	**Clinical Effectiveness** *Critical to decision-making:* • **Stabilisation or improvement in MRI findings of C-ALD** Stabilisation and/ or improvement of MRI findings is critical to patients as all individuals with C-ALD will demonstrate a progression in their disease, including individuals undergoing HSCT. Stabilisation or improvement indicates that cerebral symptoms of ALD are not progressing and may be associated with improvement in clinical features of neuro-disability such as cognition or motor function. Longer term outcomes (>12 months after HSCT) would be of critical importance to patients to demonstrate the MRI findings (as the intervention takes time to stabilise the disease). Given the progressive nature of the disease an individual is not expected to return to their baseline pre-intervention level. This could include but is not limited to: • Improvement in the Loes MRI score (*defined above*) • Gadolinium-enhanced brain lesions disappearing or becoming more obscure on MRI • White matter lesions becoming stable, smaller or not visible on MRI • No new lesions emerging • **Survival** Survival is critical to patients as the median overall survival is 3.9 years once adult onset cerebral adrenoleukodystrophy enters the active neuroinflammation phase.[35] Interventions which improve the survival outcome for patients are critical for individuals and families affected by C-ALD for whom there are only supportive treatment options. This could include, but is not limited to: • Kaplan-Meier survival analysis • Mortality or survival rate • **Cognitive function** Cognitive function is a critical outcome for patients as C-ALD causes a progressive loss of cognitive function, including individuals undergoing HSCT. The ability to have preserved cognition can facilitate active participation in work and family roles and promote independence. Longer term outcomes (>12 months after HSCT) would be important to patients to demonstrate the cognitive function after an intervention (as the intervention takes time to stabilise the disease). This could include, but is not limited to: • Timed task completion • Composite measures of cognitive function assessed using a tool (*as AACS score defined above*)

[35] De Beer M, Engelen M, van Geel BM. 2014. Frequent occurrence of cerebral demyelination in adrenomyeloneuropathy. Neurology 2014; 83; 2227-31

- Subjective/ self-reported assessment (e.g. by the individual, carer or MDT. This could include self-reported questionnaires/ survey methods, or reported dependency on others

[Definitions of stable neurocognition post-HSCT commonly used are a deterioration in IQ < 15 (< 1 standard deviation (SD) or no cognitive decline as detected by caregivers]

Important to decision-making:

- **Progression free survival**

Progression free survival (the length of time an individual lives without the disease getting worse) is important to patients as it reflects the ability to maintain neurological and motor function with C-ALD, and may reflect the ability to participate in activities of daily living and work and family roles.

C-ALD is a progressive condition which leads to ongoing resultant disability and death. It is expected that all individuals with C-ALD will demonstrate a progression in their disease, including individuals undergoing HSCT. HSCT impacts on cerebral neurological function (e.g. cognition, vision, cerebellar signs) but other elements such as adrenomyeloneuropathy (AMN) symptoms can continue to progress. Longer term outcomes (>12 months after HSCT) would be important to patients to demonstrate the progression-free intervals after an intervention (as the intervention takes time to stabilise the disease).

This could include subjective (self-reported or carer reported) assessment or formal tool assessment including:

- Progression-free survival of cognitive function
- Progression-free survival of motor function
- Progression-free survival of composite clinical scores of function (commonly used scales in C-ALD are described below)

[Neurologic Function Scale (NFS) is a 25-point ALD-specific tool that assesses the severity of neurologic dysfunction by assigning scores to 15 different disabilities (lower scores indicate fewer symptoms). Adult ALD Clinical Score (AACS) and Expanded Disability Symptom Score (EDSS) are described above.]

- **Activities of daily living (ADLs)**

ADLs are important outcomes to patients as they facilitate enablement and independence, allowing individuals to function in education, work, home and recreational settings. They encompass patients individual needs and facilitate inclusion and participation. C-ALD leads to progressive neuro-cognitive impairment and challenges the ability to complete ADLs without assistance.

Longer term outcomes (>12 months after HSCT) would be important to patients as the intervention takes time to stabilise the disease and the intervention of HSCT can impact on ADLs in the short-term post procedure. HSCT impacts on cerebral neurological function (e.g. cognition, vision, cerebellar signs) but other elements such as adrenomyeloneuropathy (AMN) symptoms can continue to progress.

This could include, but is not limited to:

- Timed task completion (e.g. timed repeatable test such as dressing, meal preparation or patient specific ADL goal)
- ADLs assessment using a tool (e.g. Barthel Index (BI) or Independence in Activities of Daily Living (ADL)
- Subjective/ self-reported assessment (e.g. by the individual, carer or MDT. This could include self-reported questionnaires such as participation in work and other activities).

	• **<u>Quality of life</u>** Quality of life is an important outcome to patients as it provides an indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. The intervention of HSCT is a significant undertaking by patients and their families and quality of life is also affected by the progressive nature of C-ALD. Longer term outcomes (>12 months post HSCT) would be important to patients as the intervention can take time to stabilise the disease and can impact on quality of life measures in short-term assessments. HSCT impacts on cerebral neurological function (e.g. cognition, vision, cerebellar signs) but other elements such as adrenomyeloneuropathy (AMN) symptoms can continue to progress and may still impact on quality of life. • Assessed through a validated questionnaire (e.g. EuroQOL EQ-5D, Hospital Anxiety and Depression Score (HADs) or other disease specific questionnaire. • Subjective/ self-reported/ carer reported experiences. • **<u>Safety</u>** Safety is a key factor to patients as it demonstrates the risks of an invasive procedure. This can include potential complications such as longer-term morbidity and/ or hospitalisation. This could include (but not limited to): • Mortality from HSCT intervention • Infection • Transplant adverse events (National Cancer Institute common terminology for adverse events (CTCAE V3.0) • Graft v's host disease (GvHD) • Hospitalisation due to HSCT complications • **<u>Cost effectiveness</u>**
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher-level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2012-2022
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines.
Study design	Case reports, resource utilisation studies.

Appendix B Search strategy

Medline, Embase, the Cochrane Library and the TRIP database were searched limiting the search to papers published in the English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, case reports, trial registrations and resource utilisation studies were excluded.

Search dates: 1 January 2012 to 17 May 2022

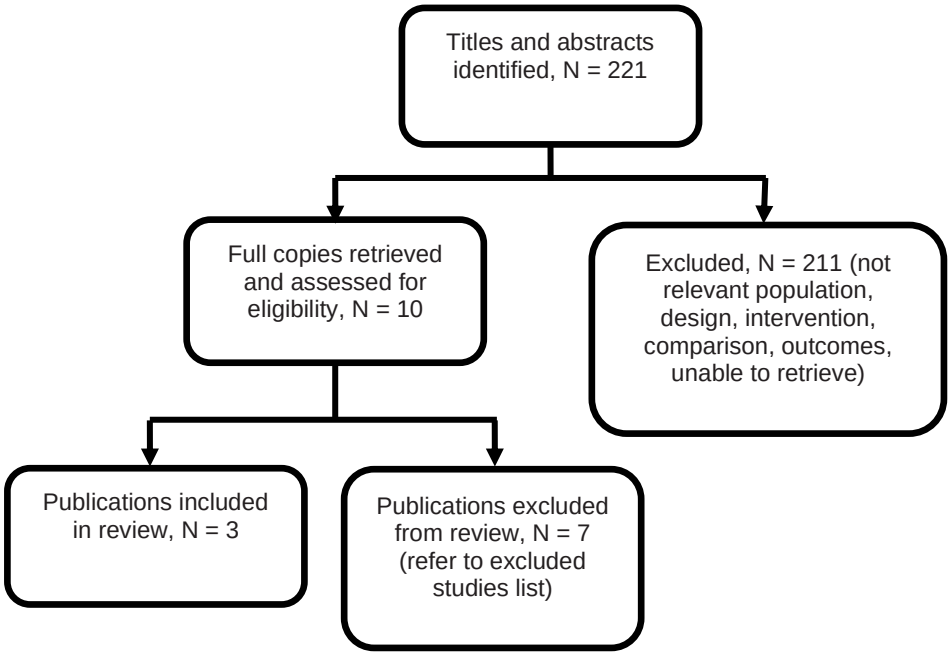
Medline search strategy:

1	Adrenoleukodystrophy/
2	(adrenoleukodystroph* or adreno-leukodystroph*).ti,ab,kf.
3	(xald or x-ald or cald or c-ald).ti,ab,kf.
4	1 or 2 or 3
5	Hematopoietic Stem Cell Transplantation/
6	(h?ematopoietic adj3 (stem transplant* or cell transplant* or bone marrow transplant*)).ti,ab,kf.
7	(allogenic adj5 transplant*).ti,ab,kf.
8	(allograft* or (allogeneic adj5 transplant*)).ti,ab,kf.
9	hsct.ti,ab,kf.
10	5 or 6 or 7 or 8 or 9
11	4 and 10
12	exp animals/ not humans.sh.
13	11 not 12
14	limit 13 to (english language and yr="2012 -Current")

Appendix C Evidence selection

The literature search identified 221 potential references. These were screened using their titles and abstracts and 10 references potentially relating to the use of allogeneic HSCT for X-linked C-ALD in adult males were obtained in full text and assessed for relevance. Of these, three references are included in this evidence review. The seven references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Waldhüter N, Köhler W, Hemmati PG, Jehn C, Peceny R, Vuong GL, Arnold R, Kühl JS. Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy. J. Inherited Metabolic Disease. 2019; 42: 313-324.	Included in the review
Matsukawa T, Yamamoto T, Honda A, Toya T, Ishiura H, Mitsui J, Tanaka M, Hao A, Shinohara A, Ogura M, Kataoka K, Seo S, Kumano K, Hosoi M, Narukawa K, Yasunaga M, Maki H, Ichikawa M, Nannya Y, Imai Y, Takahashi T, Takahashi Y, Nagasako Y, Yasaka K, Mano KK, Matsukawa MK, Miyagawa T, Hamada M, Sakuishi K, Hayashi, Iwata A, Terao Y, Shimizu J, Goto J, Mori H, Kunimatsu A, Aoki S, Hayashi S, Nakamura F, Arai S, Momma K, Ogata K, Yoshida T, Abe O, Inazawa J, Toda T, Kurokawa M, Tsuji S. Clinical efficacy of haematopoietic stem cell transplantation for adult adrenoleukodystrophy. Brain Commun. 2020;14;2(1).	Included in the review
Kühl JS, Suarez F, Gillett GT, Hemmati PG, Snowden JA, Stadler M, Vuong GL, Aubourg P, Köhler W, Arnold R. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. Brain. 2017;140(4):953-966.	Included in the review

Appendix D Excluded studies table

Study reference	Reason for exclusion
Fernandes JF, Bonfim C, Kerbauy FR, Rodrigues M, Esteves I, Silva NH, et al. Haploidentical bone marrow transplantation with post transplant cyclophosphamide for patients with X-linked adrenoleukodystrophy: a suitable choice in an urgent situation. Bone marrow transplantation. 2018;53(4):392-9.	N=9, 1 of which was an adult at HSCT. Have studies with larger number of adult patients for these outcomes
Kato K, Maemura R, Wakamatsu M, Yamamori A, Hamada M, Kataoka S, et al. Allogeneic stem cell transplantation with reduced intensity conditioning for patients with adrenoleukodystrophy. Molecular genetics and metabolism reports. 2019;18:1-6.	Population all children
Mitchell R, Nivison-Smith I, Anazodo A, Tiedemann K, Shaw PJ, Teague L, et al. Outcomes of haematopoietic stem cell transplantation for inherited metabolic disorders: a report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. Pediatric transplantation. 2013;17(6):582-8.	Population all children
Musolino PL, Lund TC, Pan J, Escolar ML, Paker AM, Duncan CN, et al. Hematopoietic stem cell transplantation in the leukodystrophies: A systematic review of the literature. Neuropediatrics. 2014;45(3):169-74.	Included studies covered different leukodystrophies and both children and some adults. No separate reporting of results for adults with C-ALD
Orchard PJ, Nascene DR, Miller WP, Gupta A, Kenney-Jung D, Lund TC. Successful donor engraftment and repair of the blood-brain barrier in cerebral adrenoleukodystrophy. Blood. 2019;133(12):1378-81.	Age range (4.4 to 47.1) suggests at least one adult in the population but number/ proportion unknown. No separate reporting of results for adults with C-ALD
Saute JAM, Souza CFMd, Poswar FdO, Donis KC, Campos LG, Deyl AVS, et al. Neurological outcomes after hematopoietic stem cell transplantation for cerebral X-linked adrenoleukodystrophy, late onset metachromatic leukodystrophy and Hurler syndrome. Arquivos de neuro-psiquiatria. 2016;74(12):953-66.	N=7 (for C-ALD), 2 of which were adults. Have studies with larger number of adult patients for these outcomes
Wadhwa A, Chen Y, Holmqvist A, Wu J, Ness E, Parman M, et al. Late Mortality after Allogeneic Blood or Marrow Transplantation for Inborn Errors of Metabolism: A Report from the Blood or Marrow Transplant Survivor Study-2 (BMTSS-2). Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2019;25(2):328-34.	Age range (4.0 to 23.3) suggests at least one adult in the population but number/ proportion unknown. No separate reporting of results for adults with C-ALD

Appendix E Evidence Table

For abbreviations see list after table

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Kühl JS, Suarez F, Gillett GT, Hemmati PG, Snowden JA, Stadler M, Vuong GL, Aubourg P, Köhler W, Arnold R. Long-term outcomes of allogeneic haematopoietic stem cell transplantation for adult cerebral X-linked adrenoleukodystrophy. Brain. 2017;140(4):953-966. **Study location** 4 centres in Germany, France and the UK **Study type** Retrospective case series **Study aim** To retrospectively analyse the feasibility,	Adult males with C-ALD **Inclusion criteria** The authors stated that patients were offered HSCT on an individually selected compassionate basis in accordance with the practice guidelines of the Working Party on Inborn Errors of the European Group for Blood and Marrow Transplantation[36] **Exclusion criteria** None stated **Total sample size** n=14 **Baseline characteristics** Age:	**Intervention** Allogeneic HSCT *Donor source:* • ≥9/10-HLA-matched unrelated donor: 9/14 (64.3%) • Genotypical HLA-identical sibling: 3/14 (21.4%) • Unrelated cord blood transplantation: 2/14 (14.3%) *Stem cell source:* • Bone marrow: 12/14 (85.7%) • Stem cells: 2/14 (14.3%) *Conditioning regimen:* • Myeloablative with busulfan and	Median (range) follow-up: 65 months (38 to 116) No statistical comparison over time reported unless otherwise stated **Critical outcomes** **Stabilisation or improvement in MRI findings of C-ALD** *Loes score*[37] Median (range) Loes score: • Before HSCT (n=14): 6.5 (2 to 14) • Between 6 months and up to 12 months following HSCT (n=7): 11.5 (7 to 15.5) • >12 months after HSCT (n=9): 10 (5 to 12) The authors stated that “there was no significant increase in Loes score beyond 12 months post-HSCT in comparison to Loes score before HSCT among the eight survivors (median 8 points (range 2.5 to 12 points) before HSCT; median 10 points (range 5 to 12 points) >12 months post-HSCT)”	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments**: This was a retrospective case series. It was not clear if all potentially eligible patients were included in the study. The study was conducted at 2 centres in Germany (Berlin n=8; Hannover n=1)), 1 centre in France (n=4) and 1

[36] Peters C, Steward CG. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. Bone Marrow Transplant 2003; 31: 229–39

[37] Loes MRI severity score is a 34-point scale that assigns a score to an MRI based on the extent of white matter lesions. Higher scores indicate more significant ALD involvement. Loes score of minimum of 1 is used to be considered for HSCT and shows evidence of MRI Gd enhancement around a consistent lesion

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
toxicity and long-term neurological outcomes for adult males treated with HSCT for C-ALD **Study dates** 2003 to 2012	• Median (range) age at diagnosis of C-ALD: 33 years (21 to 48) • Median (range) age at HSCT: 34 years (21 to 48) EDSS <6: 9/14 (64.3%) EDSS ≥6: 5/14 (35.7%) Loes score ≤10: 10/14 (71.4%) Loes score >10: 4/14 (28.6%)	cyclophosphamide: 12/14 (85.7%) • Reduced-intensity conditioning: 2/14 (14.3%) **Comparison** No comparator 12/14 patients received additional serotherapy for GvHD prophylaxis The authors stated that GvHD prophylaxis and supportive care measures were delivered according to standard of care protocols at the individual centres	*Subgroup comparison of Loes score by EDSS score before HSCT* Median (IQR) Loes score for patients with EDSS score <6 before HSCT and without transplant complications (n=6): • Before HSCT: 9.3 (6.0 to 11.0) • ~24 months[38] after HSCT: 9.3 (8.0 to 11.0) Median (IQR) Loes for patients with EDSS score ≥6 before HSCT or early transplant complications[39]: • Before HSCT (n=8): 5.3 (3.5 to 8.8) • ~24 months after HSCT (n=4): 11.0 (9.5 to 16.0) No statistically significant differences reported between groups or before and after HSCT (p>0.05) *Gd enhancement* The authors stated that none of the 11 patients examined beyond 6 months after HSCT showed further Gd enhancement of cerebral demyelinating lesions **Survival** 8/14 (57.1%) were alive at median (range) follow-up of 65 months (38 to 116) Estimated mean ± SD survival probability (Kaplan-Meier): 57.1% ± 13.2	UK centre (n=1). The 8 patients treated in Berlin were also included in Waldhüter et al 2019. Post-HSCT MRI scans were not available for 3 patients due to poor clinical status or early death. AACS, EDSS and modified-Rankin scale were assessed pre-HSCT, for the worst status during 6 months post-HSCT and approximately 24 months post-HSCT (minimum ≥12 months). AACS and Rankin scores were reported by subgroups of patients. Neuropsychometric assessment was performed pre-HSCT and whenever possible at various timepoints post-HSCT. IQ measures were generated by appropriate tools according to the preference of each centre. The outcomes reported were objective or mostly assessed using standardised

[38] Timeframe ~24 months as reported in the paper. Not further defined
[39] Early transplant complications were at least life-threatening infections during early transplant phase or graft rejection

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			3 patients died from transplant-related mortality and 3 patients died from disease progression *Subgroups* Superior survival was significantly associated with: • EDSS score before HSCT <6 vs ≥6. Estimated survival probability (Kaplan-Meier) (mean ± SD): 77.8% ± 13.9 (n=9) vs 20.0% ± 17.9 (n=5), p=0.048 • EDSS score <6 before HSCT and without transplant complications vs EDSS score ≥6 or early transplant complications. Estimated survival probability (Kaplan-Meier) (mean ± SD): 100% (n=6) vs 25.0% ± 15.3 (n=8), p=0.008 **Cognitive function** Change in cognitive function after HSCT (for survivors)[40]: • Remained stable: 5/8 (62.5%) • Moderate cognitive decline: 3/8 (37.5%) **Important outcomes** **Progression free survival** *EDSS[41]* Median (range) EDSS:	assessment tools. The reporting of quality of life was descriptive and it is not clear how the judgements were made or by whom. The study was conducted in 4 European centres over a 9 year period. One patient was treated at a UK centre. Local standard protocols were used in the treatment of patients. Any impact on the results is not clear. **Source of funding:** The authors acknowledged support from the Myelin Project Germany, StopALD, USA and ALD Charity Switzerland. No statement was made regarding any conflicts of interest.

[40] Stable neurocognition post-HSCT was defined as deterioration in IQ <15 (<1 SD) or no cognitive deterioration as detected by care givers. Severe deterioration in intellectual function was classified as obvious cognitive decline or inability to test for IQ anymore. Moderate deterioration was defined as anything less than severe.

[41] The Expanded Disability Symptom Score (EDSS) is a clinical scoring system. Scores range from 0 to 10 points where 0 = no deficits, 6 = inability to walk without assistance and 10 = death

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Before HSCT (n=14): 4 (1 to 7) • In the 6 months following HSCT (n=14): 7.25 (1 to 9.5) • 24 months after HSCT (n=11): 6 (1 to 10) *EDSS subgroups* The number (%) of patients who developed neurological symptoms during the 6 months after HSCT was statistically significantly associated with: • Limited AMN (EDSS score <6 before HSCT) (1/9, 11%) vs advanced AMN (EDSS score ≥6 before HSCT) (4/5, 80%), p=0.045 In a comparison of EDSS over time by EDSS score before HSCT: Median (IQR) for patients with EDSS score <6 before HSCT and without transplant complications (n=6): • Before HSCT: 3.8 (3.0 to 4.0) • ≤6 months after HSCT: 6.5 (3.0 to 6.5) • ~24 months after HSCT: 5.0 (3.0 to 6.0) No statistically significant difference between EDSS scores: • at ≤6 months after HSCT vs before HSCT • ~24 months after HSCT vs before HSCT p>0.05 Median (IQR) for patients with EDSS score ≥6 before HSCT or early transplant complications: • Before HSCT (n=8): 6.3 (3.3 to 6.5) • ≤6 months after HSCT (n=8): 8.3 (7.5 to 9.5) • ~24 months after HSCT (n=5): 9.0 (6.8 to 10.0)	

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			EDSS scores statistically significantly higher at: • ≤6 months after HSCT vs before HSCT • ~24 months after HSCT vs before HSCT p<0.05 EDSS scores at ≤6 months and ~24 months after HSCT were also statistically significantly higher for patients with EDSS score ≥6 before HSCT or early transplant complications vs ~24 months after HSCT for patients with EDSS score <6 before HSCT and without transplant complications (p<0.05). *AACS[42] reported as subgroups for EDSS score* before HSCT Median (IQR) AACS for patients with EDSS score <6 before HSCT and without transplant complications (n=6): • Before HSCT: 7.5 (7.0 to 10) • ≤6 months after HSCT: 13.0 (10.0 to 15.0) • ~24 months after HSCT: 9.0 (7.0 to 12.0) AACS score at ≤6 months after HSCT was statistically significantly higher vs before HSCT (p<0.05). There was no statistically significant difference between scores at ~24 months vs before HSCT Median (IQR) AACS for patients with EDSS score ≥6 before HSCT or early transplant complications: • Before HSCT (n=8): 11.5 (5.5 to 12.5)	

[42] The Adult ALD Clinical Score (AACS) is a composite score of motor (0-6 points) bladder (0-3 points), sensory (0-3 points) and cortical (0-12 points). Composite scores range from 0 points (normal) to 24 (maximum dysfunction)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• ≤6 months after HSCT (n=8): 18.0 (16.5 to 22.5) • ~24 months after HSCT (n=5): 21.0 (15.8 to 24) AACS scores statistically significantly higher at: • ≤6 months after HSCT vs before HSCT • ~24 months after HSCT vs before HSCT p<0.05 AACS scores at ≤6 months and ~24 months after HSCT were also statistically significantly higher for patients with EDSS ≥6 before HSCT or early transplant complications vs ~24 months after HSCT for patients with EDSS score <6 before HSCT and without transplant complications (p<0.05) *Motor function status* The authors described motor function at last follow-up (>36 months) for 8 patients[43]: • Improved: 4/8 (50%) • Stable: 2/8 (25%) • Deteriorated compared to early post-HSCT period: 2/8 (25%) **Activities of daily living** The authors reported outcomes for 5 patients who had maintained their vocational status prior to HSCT: • Continued as students: 2 patients • Unable to resume work: 1 patient	

[43] Stable motor function post-HSCT was defined as an increment in EDSS <1 point with preserved / maintained ambulation (EDSS<7). Severe deterioration in motor function was classified as increment in EDSS ≥2 points or to EDSS ≥7

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Died following HSCT: 2 patients *Modified Rankin Score[44] reported by EDSS baseline score subgroups* Median (IQR) Modified Rankin score for patients with EDSS score <6 before HSCT and without transplant complications (n=6): • Before HSCT: 2.0 (1.0 to 3.0) • ≤6 months after HSCT: 4.0 (3.0 to 5.0) • ~24 months after HSCT: 3.5 (2.0 to 4.0) Modified Rankin score at ≤6 months after HSCT was statistically significantly higher than scores before HSCT (p<0.05). There was no statistically significant difference between scores at ~24 months and baseline Median (IQR) Modified Rankin score for patients with EDSS score ≥6 before HSCT or early transplant complications: • Before HSCT (n=8): 3.5 (1.5 to 4.0) • ≤6 months after HSCT (n=8): 5.0 (5.0 to 6.0) • ~24 months after HSCT (n=5): 6.0 (4.0 to 6.0) Modified Rankin scores at ≤6 months and ~24 months after HSCT significantly higher vs before HSCT (p<0.05) Modified Rankin score ≤6 months after HSCT statistically significantly higher for patients with EDSS score ≥6 before HSCT or early transplant	

[44] The Modified Rankin Score describes disability status in daily activities. It is scored from 0 to 6 with higher scores indicating greater disability. A score of 0 = no symptoms, 1 = no significant disability despite symptoms, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, 6= dead

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			complications vs ~24 months after HSCT for patients with EDSS score <6 before HSCT and without transplant complications (p<0.05). There was no statistically significant difference between the Modified Rankin score ~24 months after HSCT between the two subgroups **Quality of life (QoL)** The authors made statements relating to QoL for 8 surviving patients: • Good QoL (between 38 and 116 months follow-up): 4/8 (50%) • Excellent QoL (at 59 months follow-up): 1/8 (12.5%) • 'Depression improved at 12 months' (no further detail on QoL): 1/8 (12.5%) • 'Depression improved at 12 months but still low QoL' (follow-up 45 months): 1/8 (12.5%) • 'Depression deteriorated compared to early post-HSCT' at 72 months follow-up: 1/8 (12.5%) **Safety** *Mortality from HSCT:* • Transplant-related mortality: 3/14 (21.4%) *Infection:* • No significant infection: 5/14 (35.7%) • Severe infection (≥ Grade 3[45]): 3/14 (21.4%) • Life-threatening infection: 4/14 (28.6%)	

[45] National Cancer Institute common terminology criteria for adverse events version 3.0

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Fatal infection: 2/14 (14.3%) *Transplant adverse events:* • Significant (≥ Grade 3) non-neurological toxicity: 6/14 (42.9%) These included haemorrhagic cystitis (n=3), multi-organ failure (n=3), pneumonia (n=3), thrombotic microangiopathy (n=1), immune nephrotic failure (n=1), end-stage renal failure (n=1), polyserositis (n=1), sepsis (n=1) *GvHD:* • Acute GvHD Grade I: 5/14 (35.7%) • Acute GvHD Grade ≥ II: 1/14 (7.1%) • Chronic GvHD: 4/14 (28.6%)	
Matsukawa T, Yamamoto T, Honda A, Toya T, Ishiura H, Mitsui J, Tanaka M, Hao A, Shinohara A, Ogura M, Kataoka K, Seo S, Kumano K, Hosoi M, Narukawa K, Yasunaga M, Maki H, Ichikawa M, Nannya Y, Imai Y, Takahashi T, Takahashi Y, Nagasako Y, Yasaka K, Mano KK, Matsukawa MK, Miyagawa T, Hamada M, Sakuishi K, Hayashi, Iwata A, Terao Y, Shimizu J, Goto J, Mori H, Kunimatsu A, Aoki S,	Males with adolescent/ adult-onset cerebral form/ cerebello-brainstem form of ALD **Inclusion criteria** Indications for HSCT included cerebral form of ALD or cerebello-brainstem form of ALD with Loes scores up to 13, the presence of progressively enlarging white matter lesions and/ or lesions with gadolinium enhancement on brain MRI **Exclusion criteria**	**Intervention** Allogeneic HSCT *Donor source:* • 8/8-allele-matched unrelated donor: 7/12 (58.3%) • One-antigen (DRB1) mismatched unrelated donor: 3/12 (25%) • 8/8-allele-matched related donor: 2/12 (16.7%) *Stem cell source:* Bone marrow: 12/12 (100%) *Conditioning regimen*	Median (range) follow-up: • After HSCT: 28.6 months (4.2 to 125.3) 8/12 (66.7%) HSCT patients followed-up for >12 months • No HSCT: 69.1 months (16.0 to 104.1) No statistical comparison reported between groups or over time unless otherwise stated **Critical outcomes** **Stabilisation or improvement in MRI findings of C-ALD** *Loes score* Median (range) Loes score <u>HSCT</u> • Before HSCT (n=12): 6 (2 to 13) • After HSCT (n=12): 5.25 (1.5 to 13)	This study was appraised using the JBI checklist for cohort studies: 1. No 2. Yes 3. Yes 4. Yes 5. No 6. Unclear 7. Yes 8. Unclear 9. Yes 10. N/A 11. Yes **Other comments** This prospective study followed-up a cohort of 45 patients at one centre over time and presented outcomes

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Hayashi S, Nakamura F, Arai S, Momma K, Ogata K, Yoshida T, Abe O, Inazawa J, Toda T, Kurokawa M, Tsuji S. Clinical efficacy of haematopoietic stem cell transplantation for adult adrenoleukodystrophy. Brain Commun. 2020;14;2(1). **Study location** Single centre, Japan **Study type** Prospective cohort study **Study aim** To evaluate the clinical efficacy and safety of HSCT for adult-onset cerebral form of ALD **Study dates** 2003 to 2018	Patients with severe neuropsychiatric symptoms that made coordinated treatment during HSCT difficult were not enrolled **Total sample size** n=20 HSCT: n=12 No HSCT: n=8 **Baseline characteristics** *HSCT* Age: • Median (range) age at onset of cerebral/ cerebellar brainstem lesions: 30 years (16 to 43) • Median (range) age at HSCT: 31 years (18 to 45) Phenotype: • AMN-Cer: 6 (50%) • CB: 3 (25%) • AMN-CB: 1 (8.3%) • Adolescent-onset C-ALD: 1 (8.3%) • Adult-onset C-ALD: 1 (8.3%)	All described as non-myeloablative regimens: • Fludarabine, melphalan, rabbit antithymocyte globulin and total body irradiation with brain shielding: 7/12 (58.3%) • Fludarabine, melphalan and total body irradiation with brain shielding: 2/12 (16.7%) • Busulfan, cyclophosphamide and total body irradiation with brain shielding: 2/12 (16.7%) • Busulfan, cyclophosphamide and total lymphoid irradiation: 1/12 (8.3%) 12/12 patients received GvHD prophylaxis, either with tacrolimus and methotrexate (n=11) or cyclosporine and methotrexate (n=1)	Median (range) follow-up 1.55 years (0.1 to 6.7) The authors stated that “the Loes score increased by one point in [3 patients] with atrophic changes of the brainstem, but otherwise stabilised or even improved” <u>No HSCT</u> • At time HSCT considered (n=8): 5.5 (3 to 13.5) • ≤12 months after HSCT considered (n=3): 8 (6 to 13.5) Median (range) follow-up of 0.5 years (0.1 to 0.9) • >12 months after HSCT considered (n=3): 16 (8 to 34) Median (range) follow-up of 4.8 years (2.5 to 8.1) *Gd enhancement* <u>HSCT</u> Gd enhancement description on brain MRI: • ‘Not enhanced’ before and after HSCT: 2/12 (16.7%) Follow-up 1 and 3 months respectively • ‘Enhanced’ before HSCT and ‘not enhanced’ after HSCT: 8/12 (66.7%) Follow-up between 1 and 80 months • ‘Enhanced’ before HSCT and ‘obscure’ after HSCT: 2/12 (16.7%) Follow-up 2 and 3 months respectively *White matter lesions* <u>HSCT</u>	for patients who did, and did not, receive HSCT. 25 patients were considered for HSCT and 12 received HSCT. For the remaining 13 patients: • 5 were in advanced stages and did not fulfil the inclusion condition • 3 declined HSCT • 3 had minute white matter lesions without any neurological symptoms and were under careful observation • 2 were preparing for HSCT The comparator group was formed of 8 patients who did not have HSCT. This consisted of the 5 patients in advanced stages and the 3 patients who declined HSCT. 5 of these patients were described as not meeting the inclusion condition. The reason(s) for not meeting the inclusion condition were not clear, although they are described as having more advanced disease. It is therefore not possible to say that the 2 groups were similar

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	EDSS <6: 7/12 (58.3%) EDSS ≥6: 5/12 (41.7%) Loes score ≤10: 10/12 (83.3%) Loes score >10: 2/12 (16.7%) *No HSCT* Age: • Median (range) age at onset of cerebral/ cerebellar brainstem lesions: 42 years (29 to 76) • Median (range) age at considering HSCT: 47.5 years (29 to 76) Phenotype: • AMN-Cer: 6 (75%) • CB: 1 (12.5%) • Adult-onset C-ALD: 1 (12.5%) EDSS <6: 4/8 (50%) EDSS ≥6: 2/8 (25%) Not available: 2/8 (25%) Loes score ≤10: 6/8 (75%)	**Comparison** Some outcomes were reported for 8 patients who did not receive HSCT	• Reduction in size of white matter lesions: 7/12 (58.3%) • Stabilisation of enlargement of white matter lesions: 5/12 (41.7%) The authors stated that white matter lesions stopped enlarging within 2 months for 9 patients and within 12 months for 3 patients. No new white matter lesions had appeared in any HSCT patients at last follow-up <u>No HSCT</u> The authors stated that for all patients who did not receive HSCT, white matter lesions continued to enlarge accompanied by marked atrophic changes in the brain **Survival** • HSCT: 12/12 (100%) Median (range) follow-up after HSCT 28.6 months (4.2 to 125.3) • No HSCT: 2/8 (25%) Median (range) follow-up from lesion or symptom onset 69.1 months (16.0 to 104.1) Median (range) follow-up from lesion or symptom onset not reported for HSCT patients Survival probability[46] (Kaplan-Meier) statistically significantly higher in patients who underwent HSCT (p=0.0089)	at baseline and any comparisons between the groups should be treated with caution. The authors considered potentially confounding factors and presented detailed information on disease stage and follow-up. However, no adjustment for any potential confounding factors was made. C-ALD is a progressive disease and the status of the patients at baseline varied with regards to the measures used to assess outcomes. The outcomes reported were objective or assessed using standardised assessment tools. Loes score on brain MRI was evaluated by the radiologist and neurologist independently with the ultimate decision made by mutual agreement. Follow-up was complete and detailed information was provided about when

[46] Determined from the earliest time of either the onset of cerebral/ cerebellar/ brainstem MRI lesions or the onset of clinical symptoms attributable to cerebral/ cerebellar/ brainstem lesions

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Loes score >10: 2/8 (25%) EDSS and Loes scores reported at the time that HSCT was being considered		**Important outcomes** **Progression free survival** *EDSS* Median (range) EDSS: HSCT • Before HSCT (n=12): 3.75 (2.0 to 9.0) • After HSCT (n=12): 6.25 (2.0 to 8.5) Median (range) follow-up 13.5 months (1 to 95) No HSCT • At time HSCT considered (n=6): 3.5 (2.0 to 9.0) • >12 months after HSCT considered (n=8): 10 (6.5 to 10) Median (range) follow-up 55.5 months (13 to 98) The authors stated that neurological outcomes were stable for 12/12 HSCT patients at median (range) follow-up of 2.4 years (0.3 to 10.4) **Activities of daily living** *Barthel Index*[47] Median (range) Barthel Index: HSCT • Before HSCT (n=12): 100 (10 to 100)	assessments were completed for each patient for the different outcomes assessed. However, the duration of follow-up varied considerably between patients in both groups and individual outcome measures were assessed for different patients at different timepoints. The duration of the follow-up period was sufficient for the outcomes assessed for some, but not all, patients. Statistical comparison of the groups was only reported for survival. Otherwise no statistical analysis was conducted between groups or between baseline and follow-up assessments. In the discussion the authors stated that a good condition in activities of daily living was a prerequisite for HSCT. However, this was not clearly stated earlier in the paper.

[47] The Barthel Index consists of 10 items that measure a person's daily functioning including feeding, transfers from bed to wheelchair and to and from a toilet, grooming, walking on a level surface, going up and down stairs, dressing, continence of bowels and bladder. Scores from the 10 items are added to give a total score ranging from 0 (totally dependent) to 100 (completely independent)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			After HSCT (n=12): 85 (15 to 100) Median (range) follow-up 13.5 months (1 to 95) <u>No HSCT</u> • At time HSCT considered (n=8): 70 (0 to 100) • >12 months after HSCT considered (n=8): 0 (0 to 50) Median (range) follow-up of 55.5 months (13 to 98) *ALD-Disability Rating Scale*[48] Median (range) ALD-Disability Rating Scale: <u>HSCT</u> • Before HSCT (n=12): II (I to III) After HSCT (n=12): II (I to III) Median (range) follow-up 13.5 months (1 to 95) <u>No HSCT</u> • At time HSCT considered (n=5): II (I to III) • >12 months after HSCT considered (n=8): IV (III to IV) Median (range) follow-up of 55.5 months (13 to 98)	The study was conducted in 1 centre in Japan over a 15 year period. The generalisability of the results to the NHS in England is unclear. **Source of funding:** The study was supported in part by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan, the Ministry of Health, Labour and Welfare and from the Japan Agency for Medical Research and development. Five of the authors declared competing interests.

[48] The ALD-Disability Rating Scale assesses function level as a composite score. Scores range from 0 to IV representing increasing disability. A score of 0 = no difficulties; I = mild learning or coordination difficulties from ALD not requiring support or intervention; II = moderate learning, sensory and/ or neurologic abnormality requiring support or intervention in a few areas; III = severe learning, sensory and/ or neurologic abnormality requiring support or intervention in many areas; IV = loss of cognitive ability and disorientation, patient requires constant supervision

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			ADL status at last follow-up <u>HSCT</u> 6/12 (50%) HSCT patients were described as working or studying after HSCT: • Returned to previous working place: n=3 • Started to work at another place or started to work from home: n=2 • Returned to university: n=1 4 of the remaining patients had received HSCT recently and were awaiting follow-up 2 patients were described as remaining at home <u>No HSCT</u> The authors stated that the 2 surviving patients who did not receive HSCT became wheelchair bound due to disease progression **Safety** *Transplant adverse events:* • Adverse events (grade not stated): 3/12 (25%) These were cryptogenic organising pneumonia (n=1), transplantation-associated thrombotic microangiopathy with declining renal function (n-1) and suspected tacrolimus-induced nephrotoxicity with declining renal function (n=1) The authors stated that no Grade IV[49] infections or other serious complications, including neurological problems, were observed in patients after HSCT	

[49] National Cancer Institute common terminology criteria for adverse events version 3.0

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			GvHD: • Acute GvHD Grade I: 4/12 (33.3%) • Acute GvHD Grade ≥ II: 1/12 (8.3%) • Chronic GvHD: 2/12 (16.7%)	
Waldhüter N, Köhler W, Hemmati PG, Jehn C, Peceny R, Vuong GL, Arnold R, Kühl JS. Allogeneic hematopoietic stem cell transplantation with myeloablative conditioning for adult cerebral X-linked adrenoleukodystrophy. J. Inherited Metabolic Disease. 2019;42**:**313-324. **Study location** Single centre, Germany **Study type** Retrospective case series **Study aim** To analyse data from adult C-ALD patients to characterise potential indicators for stable neurological and	Adult males with C-ALD **Inclusion criteria** The authors stated that patients were offered HSCT on an individually selected compassionate basis. No further detail reported **Exclusion criteria** None stated **Total sample size** n=15 **Baseline characteristics** • Median (range) age at HSCT: 33 years (26 to 50) EDSS <6: 9/15 (60%) EDSS ≥6: 6/15 (40%) Loes score ≤10: 11/15 (73.3%) Loes score >10: 4/15 (26.7%)	**Intervention** Allogeneic HSCT ***Donor source:*** • ≥9/10-HLA-matched unrelated donor: 12/15 (80%) • ≥9/10-HLA-matched related donor: 3/15 (20%) *Stem cell source:* • Bone marrow: 11/15 (73.3%) • Stem cells: 4/15 (26.7%) ***Conditioning regimen*** • Myeloablative with busulfan and cyclophosphamide: 15/15 (100%) **Comparison** No comparator	Median (range) follow-up (for survivors) of 56 months (20 to 104) No statistical comparison over time reported unless otherwise stated **Critical outcomes** **Survival** 11/15 (73%) were alive at median (range) follow-up of 56 months (20 to 104) Estimated mean ± SD survival probability (Kaplan-Meier): 73% ± 11 The authors stated that 3 patients died primarily by infection and 1 patient died from disease progression triggered by infection *Subgroups* Higher overall survival statistically significantly associated with no or mild cerebral symptoms (n=8) vs moderate or severe cerebral symptoms (n=7) before HSCT (p=0.014)[50]	This study was appraised using the JBI checklist for case series 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. No 10. Yes **Other comments**: This was a retrospective case series. Limited details were provided about the criteria for selecting patients for HSCT. It was not clear if all potentially eligible patients were included in the study. The study was conducted at 1 centre in Germany (Berlin). Some outcomes were reported for patients treated

[50] Moderate or severe cerebral symptoms = AACS cerebral function domain score >3. No or mild symptoms = AACS cerebral function domain score ≤3

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
neurocognitive outcomes **Study dates** Not stated	Subgroup analysis by EDSS score and symptoms before HSCT	15/15 patients received anti-thymocyte globulin for GvHD prophylaxis. The authors stated that "additional GvHD prophylaxis depended on varying standards"	Overall survival (Kaplan-Meier)[51]: • EDSS score <6 and without cerebellum or thalamus involvement before HSCT (n=8): 100% (the presence vs absence of this characteristic was statistically significant (p<0.05)) • EDSS score ≥6 before HSCT (n=6) mean ± SD: 50% ± 20 (the presence vs absence of this characteristic was not statistically significant) **Cognitive function** *AACS cortical subdomain*[52] Median (range) AACS cortical subdomain: • Before HSCT (n=15): 6 (0 to 9) • 24 months after HSCT (n=11): 3 (0 to 9) • At last follow-up (n=9): 3 (0 to 9) Median (range) follow-up 59 months (29 to 104) The authors described cognitive function at last follow-up (median (range) 59 months (29 to 104)) for 9 patients with >24 months follow-up: • Improved: 2/9 (22.2%) • Stable[53]: 5/9 (55.6%) • Deteriorated: 2/9 (22.2%)	before and after 2013, but the period of time over which patients were treated was not reported. Eight of the 15 patients were also included in Kühl et al 2017. These 8 patients were treated before 2013. Post-HSCT MRI scans were not available for 3 patients due to poor clinical status. The outcomes reported were objective or mostly assessed using standardised assessment tools. The reporting of activities of daily living was descriptive and it is not clear how the judgements were made or by whom. **Source of funding:** No statement on funding was reported. Five of the authors declared conflicts of interests.

[51] Most of the subgroup outcomes in this study were reported for specific characteristics, with the significance testing comparing whether the respective characteristics were present vs absent. No mean ± SD was reported for patients for who the specific characteristic was 'absent'
[52] The AACS cortical subdomain is one of 4 subdomains of the Adult ALD Clinical Score (AACS). The cortical subdomain is scored from 0 to 12 with higher scores indicating higher dysfunction. A score of >3 points in the cortical domain is defined as moderate cerebral dysfunction
[53] The number of patients that had stable cognitive function is described differently in different sections of the paper. The descriptions and numbers presented in the paper's table of results have been extracted

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Subgroups Survival with stable cognition[54] (Kaplan-Meier): • EDSS score <6 and without cerebellum or thalamus involvement before HSCT (n=8) mean ± SD: 66% ± 21 (the presence vs absence of this characteristic was statistically significant (p<0.05)) • EDSS score ≥6 before HSCT (n=6) mean ± SD: 33% ± 19 (the presence vs absence of this characteristic was not statistically significant) • Moderate or severe cerebral symptoms (n=8): 25% ± 15 (statistically significantly lower vs no or mild symptoms (mean ± SD not reported) (p<0.05)) **Important outcomes** **Progression free survival** *Event free survival[55]* Estimated event free survival (Kaplan-Meier) mean ± SD: 36% ± 17 (n=7) Event free survival was 2/8 (25%) for patients transplanted before 2013 and 5/7 (71.4%) after 2013 (p=0.132) *Subgroups* Event free survival (Kaplan-Meier):	

[54] No deterioration in cortical functions detected by relatives, at work, or by neuropsychological testing (ΔIQ <20)
[55] Survival with stable cognition and no deterioration in motor function

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• EDSS score <6 and without cerebellum or thalamus involvement before HSCT (n=8) mean ± SD: 50% ± 23 (the presence vs absence of this characteristic was statistically significant (p<0.05)) • EDSS score ≥6 before HSCT (n=6) mean ± SD: 33% ± 19 (the presence vs absence of this characteristic was not statistically significant) • Moderate or severe cerebral symptoms (n=8): 25% ± 15 (statistically significantly lower vs no or mild symptoms (mean ± SD not reported) (p<0.05)) *EDSS* Median (range) EDSS: • Before HSCT (n=15): 4 (3 to 6.5) • 24 months after HSCT (n=11): 6 (3 to 7) • At last follow-up (n=9): 6 (2 to 7) Median (range) follow-up 59 months (29 to 104) EDSS score 24 months after HSCT compared to baseline before HSCT for survivors: • No change: 4/11 (36.4%) • Worsened by 0.5 points: 4/11 (36.4%) • Worsened by 2 points: 3/11 (27.3%) *AACS*[56] Median (range) composite AACS: • Before HSCT (n=15): 10 (1 to 14) • 24 months after HSCT (n=11): 12 (1 to 17)	

[56] The Adult ALD Clinical Score (AACS) is a composite score of motor (0-6 points) bladder (0-3 points), sensory (0-3 points) and cortical (0-12 points). Composite scores range from 0 points (normal) to 24 (maximum dysfunction)

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• At last follow-up (n=9): 10 (4 to 19) Median (range) follow-up 59 months (29 to 104) AACS score 24 months after HSCT compared to baseline before HSCT for survivors: • Improved by 1 point: 1/11 (9.1%) • No change: 4/11 (36.4%) • Worsened by 1 point: 1/11 (9.1%) • Worsened by 2 points: 3/11 (27.3%) • Worsened by 5 points: 1/11 (9.1%) • Worsened by 6 points: 1/11 (9.1%) The authors described motor function at last follow-up (median (range) 59 months (29 to 104)) for 9 patients: • Improved: 2/9 (22.2%) • Stable[57]: 6/9 (66.7%) • Mildly deteriorated: 1/9 (11.1%) Survival with stable cognition and motor function 2 years post-HSCT was 0/8 (0%) for patients transplanted before 2013 and 5/7 (71.4%) after 2013 (p<0.001) **Activities of daily living (ADL)** The authors described the patient's status 24 months after HSCT for the 11 survivors: • Employed (no further detail on ADL): 3/11 (27.3%)	

[57] The number of patients that had stable motor function is described differently in different sections of the paper. The descriptions and numbers presented in the paper's table of results have been extracted

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			• Retired from work but fully active/ good activity in daily life: 3/11 (27.3%) • 'Severely handicapped with restricted activity in daily life: 2/11 (18.2%) • 'Severely handicapped, needs support in activity in daily life': 1/11 (9.1%) • 'Retired from work, needs support in activity in daily life': 1/11 (9.1%) • 'Retired from work, development of depressive mood disorder' (no further detail on ADL): 1/11 (9.1%) **Safety** *Mortality from HSCT* • Transplant-related mortality[58] within the first year after HSCT: 3/15 (20%) *Infection* • Fatal infection within the first year of HSCT: 4/15 (26.7%) The authors stated that 3 patients died primarily by infection and 1 patient died from disease progression triggered by infection *Transplant adverse events* • Significant (> Grade 2[59]) transplant complications: 11/15 (73.3%) These included sepsis (n=8), haemorrhagic cystitis (n=5), pneumonia (n=4), multi-organ failure (n=2),	

[58] The study authors described 3 of the 4 patient deaths as transport-related mortality. The other death was described as due to 'progression'
[59] National Cancer Institute common terminology criteria for adverse events version 3.0

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			transient hepatopathy (n=1), cytomegalovirus with encephalitis (n=1), relapsing urogenital infections (n=1), secondary graft failure (n=1), post-transplant lymphoproliferative disease triggered by Epstein-Barr virus (n=1) *GvHD:* • Acute GvHD Grade I: 4/15 (26.7%) • Acute GvHD Grade ≥ II: 2/15 (13.3%) • Chronic GvHD: 3/15 (20%)	

Abbreviations
AACS: Adult ALD Clinical Score; ADL: Activities of daily living; ALD: Adrenoleukodystrophy; AMN: Adrenomyeloneuropathy; AMN-CB: AMN with later development of cerebello-brainstem form of ALD; AMN:-Cer: AMN with later development of cerebral form of ALD; C-ALD: Cerebral ALD; CB: cerebello-brainstem form of ALD; EDSS: Expanded Disability Symptom Score; Gd: Gadolinium; GvHD: Graft-versus-host disease; HLA: Human leukocyte antigen; HSCT: Haematopoietic stem cell transplant; IQ: Intelligence quotient; IQR: Inter-quartile range; MMSE: Mini-mental state examination; MRI: Magnetic resonance imaging; QoL: Quality of life; SD: Standard deviation

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for Cohort Studies

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

JBI Critical Appraisal Checklist for Case Series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for the identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?
10. Was statistical analysis appropriate?

Appendix G GRADE profiles

In adult males with X-linked C-ALD, what is the clinical effectiveness and safety of allogeneic HSCT compared with standard of care?

For abbreviations and footnotes see end of tables.

Table 2. Allogeneic HSCT compared to no HSCT

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	HSCT	No HSCT	Result		
Stabilisation or improvement in MRI findings of C-ALD (1 cohort study)									
Loes score median (range) before and at median (range) follow-up of 1.55 years (0.1 to 6.7) for HSCT and at time HSCT considered, and ≤12 months, and >12 months later, for no HSCT (benefit indicated by lower score)									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	HSCT • Before: 6 (2 to 13) • After: 5.25 (1.5 to 13) No HSCT • At time HSCT considered (n=8): 5.5 (3 to 13.5) • ≤12 months after HSCT considered (n=3): 8 (6 to 13.5) Median (range) follow-up 0.5 years (0.1 to 0.9) • >12 months after HSCT considered (n=3): 16 (8 to 34) Median (range) follow-up 4.8 years (2.5 to 8.1) No statistical comparison between groups or over time	Critical	Very low

Gd-enhancement description on brain MRI (number, %) at up to 80 months follow-up									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	12	Not reported	Gd enhancement description on brain MRI: • 'Not enhanced' before and after HSCT: 2/12 (16.7%) Follow-up 1 and 3 months • 'Enhanced' before HSCT and 'not enhanced' after HSCT: 8/12 (66.7%) Follow-up between 1 and 80 months • 'Enhanced' before HSCT and 'obscure' after HSCT: 2/12 (16.7%) Follow-up 2 and 3 months	Critical	Very low
White matter lesions (number, %) at median (range) follow-up of 28.6 months (4.2 to 125.3) for HSCT and 69.1 months (16.0 to 104.1) for no HSCT									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	<u>HSCT</u> • Reduction in size: 7/12 (58.3%) • Stabilisation of enlargement: 5/12 (41.7%) Lesions stopped enlarging within 2 months for 9 patients and within 12 months for 3 patients. No new white matter lesions had appeared in any HSCT patients at last follow-up <u>No HSCT</u> For all patients, white matter lesions continued to enlarge accompanied by marked atrophic changes in the brain	Critical	Very low
Survival (1 cohort study)									
Survival (number, %) at median (range) follow-up of 28.6 months (4.2 to 125.3) for HSCT and 69.1 months (16.0 to 104.1) for no HSCT									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[3]	No serious indirectness	Not applicable	Not calculable	12/12 (100%)	2/8 (25%)	Survival probability (Kaplan-Meier) statistically significantly higher in patients who underwent HSCT (p=0.0089)	Critical	Very low

Progression free survival (1 cohort study)									
EDSS score median (range) before and at median (range) follow-up of 13.5 months (1 to 95) for HSCT and at time HSCT considered and >12 months later for no HSCT (median (range) follow-up 55.5 months (13 to 98)) (benefit indicated by lower score)									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	HSCT • Before: 3.75 (2.0 to 9.0) • After: 6.25 (2.0 to 8.5) No HSCT • At time HSCT considered (n=6): 3.5 (2.0 to 9.0) • >12 months after HSCT considered (n=8): 10 (6.5 to 10) No statistical comparison between groups or over time	Important	Very low
Activities of daily living (ADL) (1 cohort study)									
Barthel Index median (range) before and at median (range) follow-up of 13.5 months (1 to 95) for HSCT and at time HSCT considered and >12 months later for no HSCT (median (range) follow-up 55.5 months (13 to 98)) (benefit indicated by higher score)									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	HSCT • Before: 100 (10 to 100) • After: 85 (15 to 100) No HSCT • At time HSCT considered: 70 (0 to 100) • >12 months after HSCT considered: 0 (0 to 50) No statistical comparison between groups or over time	Important	Very low
ALD-Disability Rating Scale median (range) before and at median (range) follow-up of 13.5 months (1 to 95) for HSCT and at time HSCT considered and >12 months later for no HSCT (median (range) follow-up 55.5 months (13 to 98)) (benefit indicated by lower score)									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	8	HSCT • Before: II (I to III) • After: II (I to III) No HSCT • At time HSCT considered (n=5): II (I to III)	Important	Very low

							• >12 months after HSCT considered (n=8): IV (III to IV) No statistical comparison between groups or over time		
ADL status at last follow-up (median (range)) 28.6 months (4.2 to 125.3) for HSCT and 69.1 months (16.0 to 104.1) for no HSCT									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[1]	No serious indirectness	Not applicable	Not calculable	12	2	<u>HSCT</u> • Working or studying after HSCT: 6/12 (50%) • Awaiting follow-up: 4/12 (33.3%) • Remaining at home: 2/12 (16.7%) <u>No HSCT</u> The 2 surviving patients became wheelchair bound due to disease progression	Important	Very low
Safety (1 cohort study)									
Transplant adverse events (number, %) at median (range) follow-up 28.6 months (4.2 to 125.3)									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	3/12 (25%)	None	Cryptogenic organising pneumonia (n=1), transplantation-associated thrombotic microangiopathy with declining renal function (n-1), suspected tacrolimus-induced nephrotoxicity with declining renal function (n=1). Grade not reported No Grade IV infections or other serious complications, including neurological problems	Important	Very low
Acute GvHD (number, %). Median (range) follow-up 28.6 months (4.2 to 125.3)									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	5/12 (41.7%)	None	• Grade I: 4/12 (33.3%) • Grade ≥ II: 1/12 (8.3%)	Important	Very low

Chronic GvHD (number, %). Median (range) follow-up 28.6 months (4.2 to 125.3)									
1 prospective cohort study Matsukawa et al 2020	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	2/12 (16.7%)	None	Chronic GvHD: 16.7%	Important	Very low

Abbreviations

ADL: Activities of daily living; ALD: Adrenoleukodystrophy; C-ALD: Cerebral ALD; EDSS: Expanded Disability Symptom Score; Gd: Gadolinium; GvHD: Graft-versus-host disease; HSCT: Haematopoietic stem cell transplant; MRI: Magnetic resonance imaging

1. Risk of bias. Very serious limitations due to differences between the groups at baseline, lack of adjustment for potential confounding factors, variable duration of follow-up of patients and lack of statistical analysis
2. Indirectness: Serious indirectness due to lack of a comparator group
3. Risk of bias. Very serious limitations due to differences between the groups at baseline, lack of adjustment for potential confounding factors and variable duration of follow-up of patients

Table 3. Allogeneic HSCT (no comparator)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	HSCT	No comparator	Result		
Stabilisation or improvement in MRI findings of C-ALD (1 case series)									
Loes score median (range) before HSCT and 6 to 12 months, and >12 months, after HSCT (benefit indicated by lower score)									
1 retrospective case series Kühl et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14 (baseline), 9 (>12 months)	None	• Before HSCT (n=14): 6.5 (2 to 14) • 6 to 12 months after HSCT (n=7): 11.5 (7 to 15.5) • >12 months after HSCT (n=9): 10 (5 to 12) No statistical test reported	Critical	Very low
Gd enhancement >6 months after HSCT									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	11	None	The authors stated that none of the 11 patients examined >6 months after HSCT showed further Gd enhancement of cerebral demyelinating lesions	Critical	Very low
Survival (2 case series)									
Survival at median (range) follow-up of 65 months (38 to 116)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8/14 (57.1%)	None	Estimated mean ± SD survival probability (Kaplan-Meier): 57.1% ± 13.2	Critical	Very low
Survival at median (range) follow-up of 56 months (20 to 104)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	11/15 (73%)	None	Estimated mean ± SD survival probability (Kaplan-Meier): 73% ± 11	Critical	Very low

Cognitive function (2 case series)									
AACS cortical subdomain median (range) before HSCT and 24 months, and >29 months, after HSCT (benefit indicated by lower score)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15 (baseline), 11 (24 months)	None	• Before HSCT (n=15): 6 (0 to 9) • 24 months after HSCT (n=11): 3 (0 to 9) • Last follow-up after HSCT (n=9): 3 (0 to 9) Median (range) follow-up 59 months (29 to 104) No statistical test reported	Critical	Very low
Cognitive function status of survivors after HSCT. Median (range) follow-up 65 months (38 to 116)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	None	• Remained stable: 5/8 (62.5%) • Moderate cognitive decline: 3/8 (37.5%)	Critical	Very low
Cognitive function status of patients with >24 months follow-up after HSCT. Median (range) follow-up 59 months (29 to 104)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	9	None	• Improved: 2/9 (22.2%) • Stable: 5/9 (55.6%) • Deteriorated: 2/9 (22.2%)	Critical	Very low
Progression free survival (2 case series)									
Estimated event free survival. Median (range) follow-up 56 months (20 to 104)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	7	None	Mean ± SD: 36% ± 17 (Kaplan-Meier)	Important	Very low
EDSS score median (range) before HSCT and up to 6 months, and 24 months, after HSCT (benefit indicated by lower score)									
1 retrospective case series Kühl et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14 (baseline), 11 (24 months)	None	• Before HSCT (n=14): 4 (1 to 7) • Up to 6 months after HSCT (n=14): 7.25 (1 to 9.5) • 24 months after HSCT (n=11): 6 (1 to 10) No statistical test reported	Important	Very low

EDSS score median (range) before HSCT and 24 months, and >29 months, after HSCT (benefit indicated by lower score)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15 (baseline), 11 (24 months)	None	• Before HSCT (n=15): 4 (3 to 6.5) • 24 months after HSCT (n=11): 6 (3 to 7) • At last follow-up (n=9): 6 (2 to 7) Median (range) follow-up 59 months (29 to 104) No statistical test reported	Important	Very low
Change in EDSS score from baseline to 24 months after HSCT for survivors									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	11	None	• No change: 4/11 (36.4%) • Worsened by 0.5 points: 4/11 (36.4%) • Worsened by 2 points: 3/11 (27.3%)	Important	Very low
AACS score median (range) before HSCT and 24 months, and >29 months, after HSCT (benefit indicated by lower score)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15 (baseline), 11 (24 months)	None	• Before HSCT (n=15): 10 (1 to 14) • 24 months after HSCT (n=11): 12 (1 to 17) • At last follow-up (n=9): 10 (4 to 19) Median (range) follow-up 59 months (29 to 104) No statistical test reported	Important	Very low
Change in AACS score from baseline to 24 months after HSCT for survivors									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	11	None	• Improved by 1 point: 1/11 (9.1%) • No change: 4/11 (36.4%) • Worsened by 1 point: 1/11 (9.1%) • Worsened by 2 points: 3/11 (27.3%) • Worsened by 5 points: 1/11 (9.1%) • Worsened by 6 points: 1/11 (9.1%)	Important	Very low

Motor function status at last follow-up (>36 months)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	None	• Improved: 4/8 (50%) • Stable: 2/8 (25%) • Deteriorated compared to early post-HSCT period: 2/8 (25%)	Important	Very low
Motor function status at last follow-up. Median (range) follow-up 59 months (29 to 104)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	9	None	• Improved: 2/9 (22.2%) • Stable[A]: 6/9 (66.7%) • Mildly deteriorated: 1/9 (11.1%)	Important	Very low
Activities of daily living (ADL) (2 case series)									
ADL status after HSCT for patients who had maintained their vocational status prior to HSCT. Median (range) follow-up 65 months (38 to 116)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	5	None	• Continued as students: 2 patients • Unable to resume work: 1 patient • Died following HSCT: 2 patients	Important	Very low
ADL status 24 months after HSCT for surviving patients									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	11	None	• Employed (no further detail on ADL): 3/11 (27.3%) • Retired from work but fully active/ good activity in daily life: 3/11 (27.3%) • 'Severely handicapped with restricted activity in daily life: 2/11 (18.2%) • 'Severely handicapped, needs support in activity in daily life': 1/11 (9.1%) • 'Retired from work, needs support in activity in daily life': 1/11 (9.1%) • 'Retired from work, development of depressive mood disorder' (no further detail on ADL): 1/11 (9.1%)	Important	Very low

Quality of life (QoL) (1 case series)									
QoL status after HSCT for surviving patients. Follow-up >12 months									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	8	None	• Good QoL (between 38 and 116 months follow-up): 4/8 (50%) • Excellent QoL (at 59 months follow-up): 1/8 (12.5%) • 'Depression improved at 12 months' (no further detail on QoL): 1/8 (12.5%) • 'Depression improved at 12 months but still low QoL' (follow-up 45 months): 1/8 (12.5%) • 'Depression deteriorated compared to early post-HSCT at 72 months follow-up': 1/8 (12.5%)	Important	Very low
Safety (2 case series)									
Transplant-related mortality. Median (range) follow-up 65 months (38 to 116)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	3/14 (21.4%)	None	Transplant-related mortality: 21.4%	Important	Very low
Transplant-related mortality within 1 year of HSCT									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	3/15 20%	None	Transplant-related mortality: 20%	Important	Very low
Infection. Median (range) follow-up 65 months (38 to 116)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	14	None	• No significant infection: 5/14 (35.7%) • Severe infection (≥ Grade 3): 3/14 (21.4%) • Life-threatening infection: 4/14 (28.6%) • Fatal infection: 2/14 (14.3%)	Important	Very low

Fatal infection within 1 year of HSCT									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	4/15 (26.7%)	None	Fatal infection: 26.7%	Important	Very low
Significant (≥ Grade 3) non-neurological toxicity. Median (range) follow-up 65 months (38 to 116)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	6/14 (42.9%)	None	These included haemorrhagic cystitis (n=3), multi-organ failure (n=3), pneumonia (n=3), thrombotic microangiopathy (n=1), immune nephrotic failure (n=1), end-stage renal failure (n=1), polyserositis (n=1), sepsis (n=1)	Important	Very low
Significant (> Grade 2) transplant complications. Median (range) follow-up (survivors) 56 months (20 to 104)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	11/15 (73.3%)	None	These included sepsis (n=8), haemorrhagic cystitis (n=5), pneumonia (n=4), multi-organ failure (n=2), transient hepatopathy (n=1), cytomegalovirus with encephalitis (n=1), relapsing urogenital infections (n=1), secondary graft failure (n=1), post-transplant lymphoproliferative disease triggered by Epstein-Barr virus (n=1)	Important	Very low
Acute GvHD (number, %). Median (range) follow-up 65 months (38 to 116)									
1 retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	14	None	• Grade I: 5/14 (35.7%) • Grade ≥ II: 1/14 (7.1%)	Important	Very low
Acute GvHD (number, %). Median (range) follow-up (survivors) 56 months (20 to 104)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	15	None	• Grade I: 4/15 (26.7%) • Grade ≥ II: 2/15 (13.3%)	Important	Very low

Chronic GvHD (number, %). Median (range) follow-up 65 months (38 to 116)									
Retrospective case series Kühl et al 2017	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	4/14 (28.6%)	None	Chronic GvHD: 28.6%	Important	Very low
Chronic GvHD (number, %). Median (range) follow-up (survivors) 56 months (20 to 104)									
1 retrospective case series Waldhüter et al 2019	Serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	3/15 (20%)	None	Chronic GvHD: 20%	Important	Very low

Abbreviations

AACS: Adult ALD Clinical Score; ADL: Activities of daily living; C-ALD: Cerebral ALD; EDSS: Expanded Disability Symptom Score; Gd: Gadolinium; GvHD: Graft-versus-host disease; HSCT: Haematopoietic stem cell transplant; MRI: Magnetic resonance imaging; QoL: Quality of life; SD: Standard deviation

1. Risk of bias. Serious limitations due to uncertainty about whether the inclusion of participants was complete or consecutive and lack of statistical analysis
2. Indirectness: Serious indirectness due to lack of a comparator group
3. Risk of bias. Serious limitations due to uncertainty about whether the inclusion of participants was complete or consecutive

A. The number of patients that had stable motor function is described differently in different sections of the paper. The descriptions and numbers presented in the paper's table of results have been extracted

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Baseline	The set of measurements at the beginning of a study (after any initial 'run-in' period with no intervention), with which subsequent results are compared.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Case series	Reports of several patients with a given condition, usually covering the course of the condition and the response to treatment. There is no comparison (control) group of patients.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Comparative cohort study	An observational study with two or more groups (cohorts) of people with similar characteristics. One group has a treatment, is exposed to a risk factor or has a particular symptom and the other group does not.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Minimal clinically important difference	The smallest change in a treatment outcome that people with the condition would identify as important (either beneficial or harmful), and that would lead a person or their clinician to consider a change in treatment.
Objective measure	A measurement that follows a standardised procedure which is less open to subjective interpretation by potentially biased observers and people in the study.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
Prospective study	A research study in which the health or other characteristic of patients is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
P-value (p)	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Standard deviation (SD)	A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.

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