CLINICAL PRIORITIES ADVISORY GROUP
6th September 2023

Agenda Item No	2.2
National Programme	Women and Children's Programme of Care
Clinical Reference Group	Metabolic
URN	2203

Title
Allogeneic Haematopoietic Stem Cell Transplant for patients with X-linked cerebral adrenoleukodystrophy (Adults)

Actions Requested	1. Support the adoption of the policy
	2. Recommend its approval as an IYSD

Proposition

For routine commissioning

X-linked adrenoleukodystrophy (X-ALD) is a genetic (inherited) disease that affects the nervous system (brain, spinal cord and nerves throughout the body) and the adrenal glands (small glands located on top of each kidney). X-ALD is caused by mutations (changes) in the ABCD1 gene, which leads to very long chain fatty acids (VLCFA) building up in the body. This can lead to several effects including acute brain inflammation and demyelination (loss of the protective nerve coating), and progressive damage to the brain, spinal cord, nerves and the adrenal glands.
The most severe forms of X-ALD are seen in males. This is because the ABCD1 gene is on the "X" chromosome, which is why the condition is called "X-linked". Men only have one copy of ABCD1 as they have an "XY" chromosome pattern and will be clinically affected if it is faulty. Women who have the "XX" chromosome pattern can have a working copy of ABCD1, as well as a faulty copy. This means women with X-ALD present at a later age with limited features of the disease which progress at a slower rate compared to males. Women are not known to be affected by C-ALD.
It is important to detect and treat C-ALD as early as possible to alleviate progression. Early-stage cerebral changes can be stabilised with allo-HSCT. The aim of treatment would be to reverse the cerebral changes (if possible) but also to halt or slow down the progression of cerebral disease. Allo-HSCT is currently commissioned for male paediatric patients with C-ALD.

Clinical Panel recommendation
The Clinical Panel recommended that the policy proposition progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposition has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes confirms the proposition is supported by an: Impact Assessment; Engagement Report; Equality and Health Inequalities Impact Assessment; Clinical Policy Proposition. The relevant National Programme of Care has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Statement
2.	Engagement Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality and Health Inequalities Impact Assessment

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.

Outcome	Evidence statement
	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[1], Gd enhancement and white matter lesions. **For HSCT vs no HSCT** ***Loes score*** **At approximately 1.5 years[2]:** • 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)**

[1] 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

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

Outcome	Evidence statement
	White matter lesions **At approximately 2 years[3]:** • 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)**

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

Outcome	Evidence statement
	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.**
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[4]. 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[5]) 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[6] (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

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

[5] 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)

[6] 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

Outcome	Evidence statement
	(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[7] and cognitive function status at follow-up.

[7] 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)[8]. 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[9] 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**

[8] 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.

[9] 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
	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. Outcomes reported included event-free survival, EDSS[10], AACS[11] 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

[10] 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

[11] 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)

Outcome	Evidence statement
	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***[12] **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)** ***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

[12] Defined as survival with stable cognition and no deterioration in motor

Outcome	Evidence statement
	(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[13] 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.**

[13] 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
	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, 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

Outcome	Evidence statement
	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[14], ALD Disability Rating Scale[15] 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 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)**

[14] 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).

[15] 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
	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-**

Outcome	Evidence statement
	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.**
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

Outcome	Evidence statement
	'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[16] 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:** • One retrospective case series (Kühl et al 2017) reported no significant infection in 5/14 (35.7%) patients. The

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

Outcome	Evidence statement
	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.

Outcome	Evidence statement
	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)** • 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**

Outcome	Evidence statement
	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

Patient Impact Summary

The condition has the following impacts on the patient's everyday life:

- **mobility:** Patients have moderate/severe problems in walking about OR are unable to walk about
- **ability to provide self-care: Patients** have moderate/severe problems in washing or dressing OR are unable to wash or dress
- **undertaking usual activities:** Patients have moderate/severe problems in doing their usual activities OR are unable to do their daily activities
- **experience of pain/discomfort:** Patients have moderate/severe/extreme pain or discomfort
- **experience of anxiety/depression:** Patients are extremely anxious or depressed

Further details of impact upon patients:

Cerebral adrenoleukodystrophy (C-ALD) leads to rapid, progressive neurological damage (due to an inflammatory leukodystrophy, loss of the white matter within the brain) which affects learning, behaviour, vision and physical functioning. Without early treatment, C-ALD leads to permanent disability and death, with the median life expectancy in adults after onset is about 4 years. Patients will experience a progressive neuro-cognitive (brain and functioning) disability which affects their ability to complete work and family roles, including activities of daily living (ADLs).

Further details of impact upon carers:

Those that need to care for patients with C-ALD, often family members and spouses/partners, witness the progressive changes in an individual with the condition including decline in speech, movement and memory and/or issues with behaviour change. This can mean carers and family members will need to assist an individual more to complete activities of daily living. These significant changes to a patient's abilities to care for themselves and participate in daily life has a profound effect on those that care for them, often both psychologically and physically. Carers will often have to change or even curtail careers, move to more suitable accommodation and reduce social and sometimes financial activities to manage their caring duties. The psycho-social effect on the children of fathers affected by C-ALD is equally significant and should not be underestimated. Often children will experience notable decline in schoolwork and social activities, as well as dealing with the emotional challenges having a terminally ill parent can bring. There is currently no treatment option for adult males with C-ALD.

Considerations from review by Rare Disease Advisory Group
The Rare Disease Advisory Group confirmed support for this policy proposition in February 2023

Pharmaceutical considerations
Not applicable.

Considerations from review by National Programme of Care
The proposal received the full support of the Women and Children's Programme of Care Board on 22nd March 2023.