NHS England Evidence Review:

Allogenic haematopoietic stem cell transplantation for transfusion dependent thalassaemia in adults

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NHS England Evidence Review

Allogenic haematopoietic stem cell transplantation (HSCT) for transfusion dependent thalassaemia (TDT) in adults

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Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of allogenic haematopoietic stem cell transplantation (HSCT) compared with standard treatment for adults with transfusion dependent thalassaemia (TDT). The review scope also includes the identification of possible subgroups of patients within the included studies who might benefit from treatment with allogenic HSCT more than others.

Standard treatment for TDT involves blood transfusions every 3 to 4 weeks for life. Repeated blood transfusions cause accumulation of iron in the liver, heart and endocrine glands, which can lead to organ damage and, if left untreated, organ failure. Therefore, iron chelation therapy (usually daily by mouth or weekly by injection) is used to prevent and treat iron overload. Standard treatment controls TDT whereas allogenic HSCT can be curative, eliminating the need for blood transfusion and iron chelation therapy. The stem cells in allogeneic transplants come from a matched related or unrelated donor rather than the patient themselves. HSCT can have serious complications, such as graft versus host disease (GVHD) and graft rejection or failure.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of allogenic haematopoietic stem cell transplantation (HSCT) compared with standard treatment (blood transfusions and iron chelation) for adults with transfusion dependent thalassaemia (TDT). The searches for evidence published since December 2011 were conducted on 1 December 2021 and identified 1218 references. The titles and abstracts were screened and 25 full text papers were obtained and assessed for relevance.

No relevant studies identified in the searches included adults only. Four papers were included in the evidence review (Baronciani et al. 2016, Caocci et al. 2017, Li et al. 2019 and Uygun et al. 2012). These studies included both adults and children, but all reported subgroup analyses in adults only. Two studies compared allogenic HSCT with standard treatment (blood transfusions and iron chelation). One of these was a retrospective case control study in Italy (Caocci et al. 2017, 194 adults) and the other was retrospective cross-sectional study in Turkey (Uygun et al. 2012, 21 adults). The other 2 studies were retrospective case series (Baronciani et al. 2016 and Li et al. 2019), with no comparator. The study by Baronciani et al. was undertaken in 127 centres worldwide, which were mainly in Europe (82 adults), and the study by Li et al. was undertaken in 50 centres in China, India and the US (33 adults).

In terms of clinical effectiveness:

Critical outcomes

- Overall survival. One case control study provided very low certainty evidence that overall survival rates were similar in adults with TDT who had HSCT (n=97) or standard treatment (n=97), with about 70% of adults surviving in each group after 23 years (no statistically significant difference). Similarly, 1 case series (n=82) provided very low certainty evidence that that 80% of adults who had HSCT survived after 2 years and the other (n=33) provided very low certainty evidence that 63% survived after 5 years.
- Event free survival. One case control study (n=97) and 2 case series (n=82 and n=33) provided very low certainty evidence that 63% to 76% of adults who had HSCT survived free of thalassaemia for between 2 and 23 years. In the case control study, no data were reported for event free survival in adults who had standard treatment.
- Quality of life. One cross-sectional study used the WHOQoL-BREF questionnaire to assess participants' health and well-being over the previous 2 weeks. On this questionnaire, higher scores indicate better quality of life. The study provided very low certainty evidence that adults with TDT who had HSCT at least 2 years previously (n=9) rated their overall health (80.6 vs 60.4, p=0.034), physical health (79.7 vs 66.6, p=0.041), sleep (86.1 vs 68.8, p=0.023) and 'drug independence for a functional life' (91.7 vs 31.3, p=0.001) statistically significantly better than adults who had standard treatment (n=12). However, there was no significant difference between the groups for other quality of life outcomes, including total score (78.2 vs 72.7, p=0.181).

Important outcomes

- Red blood cell transfusion requirement. No evidence was identified for this outcome.
- Time to donor haematological reconstitution. No evidence was identified for this outcome.
- Donor chimerism. No evidence was identified for this outcome.

- Hospitalisation due to TDT or problems secondary to TDT. No evidence was identified for this outcome.

In terms of safety:

- One case control study (n=97) provided very low certainty evidence that 27% of adults who had HSCT had acute graft versus host disease (GVHD) (any severity) after 100 days, and 12% had severe (grade 3 or 4) acute GVHD. These results were supported by very low certainty evidence from the 2 case series. The rate of acute GVHD was 30% in one case series (n=33) and the rate of severe acute GVHD was 9% in the second case series (total population n=1223; GVHD was not assessed in the adult subgroup in this study, but authors stated that no significant effect of age was seen on acute or chronic GVHD).
- One case control study (n=97) and 1 case series (total population n=1140, no significant effect of age was seen on chronic GVHD) provided very low certainty evidence that between 6% and 15% of adults with TDT who have HSCT will experience chronic GVHD a few months after the transplant.
- One case control study (n=97) provided very low certainty evidence that 4.7% of adults with TDT who have HSCT will experience graft rejection. One case series (n=33) provided very low certainty evidence that 21% of adults with TDT who have HSCT will experience graft failure.

In terms of cost effectiveness:

- No evidence was identified for cost effectiveness.

In terms of subgroups:

- Age. A case series (n=1493, 82 adults) found that rates of overall survival and event free survival at 2 years were significantly worse in adults who had HSCT compared with children (both $p<0.001$), but there was no difference in rates of acute and chronic GVHD based on age. By contrast, the second case series (n=1110, 33 adults) found that acute GVHD and graft failure occurred significantly more often in adults compared with children (all $p<0.05$).
- Type of donor. A case control study (n=97) found that rates of overall survival, event free survival, and acute and chronic GVHD were significantly better in adults with TDT who had matched (identical) sibling HSCT compared with those who had matched unrelated HSCT (all $p<0.05$).
- Conditioning regimen. A case control study (n=97) found no significant differences in overall survival and event free survival in adults who had a busulfan-based conditioning regimen compared with a treosulfan-based regimen.

Limitations

Although the included studies appear appropriately designed, well-reported and of sufficient duration, the evidence for all outcomes is limited and of very low certainly. The studies were all retrospective observational studies, which cannot prove that an intervention (such as HSCT) caused an outcome, only that it is associated with that outcome. Studies without a comparator are particularly prone to bias, limiting their application to clinical practice.

No relevant studies identified in the searches included adults only. The data are difficult to interpret because evidence is based on small subgroup analyses in adults rather than total study populations, and different types of donor, graft, conditioning regimen and GVHD prophylaxis were used within and across the studies. Although some data suggest outcomes of HSCT may be worse in adults compared with children, and matched unrelated HSCT compared with matched sibling HSCT, this is based on evidence from small subgroups of the total population or adult subgroups and is inconclusive.

Only transplant-related adverse events are reported and no information is available about the adverse effects of standard treatment or comparing adverse effects of HSCT with standard treatment.

Conclusion

The case control study found that about 7 out of 10 adults survive after 23 years with both HSCT and standard treatment, and similar results were seen in the 2 case series over shorter timescales. Overall, the 3 studies suggest that 6 or 7 out of 10 adults with TDT who have HSCT survive free of thalassaemia for up to 23 years.

The cross-sectional study found that adults who had HSCT at least 2 years previously rate their overall health, physical health, sleep and ‘drug independence for a functional life’ significantly better than adults who had standard treatment. However, only 21 adults were included in this study and there was little or no difference between HSCT and standard treatment for other quality of life outcomes. The study authors suggest that adults in the HSCT group may have higher quality of life scores in the physical health domain because they no longer have complications caused by iron toxicity or periodic anaemia, which limits the capacity for exercise.

Overall, the case control study and 2 case series found that about 3 out of 10 adults with TDT who have HSCT will experience acute GVHD within 100 days of the transplant, and it will be severe (grade 3 or 4) in 1 out of 10 adults. Also, about 1 out of 10 adults may experience chronic GVHD, and between 5 and 20 out of 100 adults may experience graft rejection or failure.

Regarding subgroups of patients that may benefit from HSCT more than the wider population of interest, limited and inconclusive evidence suggests that outcomes may be affected by age and the type of donor (worse in adults and unmatched HSCT), but not the conditioning regimen (busulfan or treosulfan).

The findings of this evidence review are important for adults with TDT who are receiving standard treatment with blood transfusions and chelation therapy because allogenic HSCT treats the underlying cause of TDT and is potentially curative (assuming there are no complications such as graft rejection or failure), whereas standard treatment controls the disease. Without HSCT, people with TDT need blood transfusions and iron chelation for life, together with regular monitoring for treatment efficacy and screening for complications.

The findings suggest there is no significant difference in overall survival between HSCT and standard treatment, but some aspects of quality of life may be better in people who have a transplant. However, the evidence has many limitations and is of very low certainty. GVHD and graft failure were reported following HSCT in the studies and may be a factor in decision making. No information is available comparing the adverse events of HSCT and standard treatment.

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. In adults with TDT, what is the clinical effectiveness of allogenic HSCT compared with standard care?
2. In adults with TDT, what is the safety of allogenic HSCT compared with standard care?
3. In adults with TDT, what is the cost effectiveness of allogenic HSCT compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from an allogenic haematopoietic stem cell transplant more than the wider population of interest?

See Appendix A for the full PICO document.

Review process

The methodology to undertake this review is specified by NHS England in its '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 1 December 2021.

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 texts of potentially relevant studies 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

Four papers were identified for inclusion (Baronciani et al. 2016, Caocci et al. 2017, Li et al. 2019 and Uygun et al. 2012). Table 1 provides a summary of these included studies and full details are given in Appendix E.

No relevant studies identified in the searches included adults only. The 4 studies included both adults and children, but all reported subgroup analyses in adults only. Two studies compared allogenic HSCT with standard treatment (blood transfusions and iron chelation). One of these was a retrospective case control study (Caocci et al. 2017) and the other was retrospective cross-sectional study (Uygun et al. 2012).

The other 2 studies were retrospective registry analyses (case series, Baronciani et al. 2016 and Li et al. 2019). The registry studies did not compare allogenic HSCT with standard treatment but are included because they provide additional data for a relatively large number of adults with TDT.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Baronciani et al. 2016 Retrospective registry analysis (EBMT registry, 2000 to 2010) 127 centres worldwide (mainly Europe)	1493 people with TDT who had allogenic HSCT (53% male) 133 (9%) people in the study were 18 years or older (median age 22.9 years, range 18 to 45 years). Of these, 82 (62%) had an HLA-identical sibling donor Most transplants were performed using HLA-identical sibling donors (1061/1493, 71%) or another HLA-matched relative (127/1493, 9%) Two thirds of transplants were undertaken in Europe (990/1493, 66%)	**Intervention** HSCT with an HLA-identical sibling donor (82 adults aged 18 years or older) Minimum follow-up was 6 months per case. Median observation time in the study was 2 years **Comparison** None	**Critical outcome** • Overall survival • Event free survival **Safety Outcomes** • GVHD
Caocci et al. 2017 Retrospective case control study (1987 to 2016) Single centre in Italy	258 people who had allogenic HSCT were age-sex matched with 258 people who had standard treatment randomly selected from a wider population (total n=516) 97/258 (38%) people who had HSCT were aged 16 years or older (median age 23 years, range 16 to 45 years; 54% male) Most transplants in the study were performed using sibling donors (173/258, 67%) compared with unrelated donors (85/258, 33%) Transplants were performed using sibling donors in 48 adults and unrelated donors in 37 adults.[1]	**Intervention** HSCT with an HLA-identical sibling or unrelated donor (97 adults aged 16 years or older) Median follow-up was 14 years (range 1 to 23 years) **Comparison** Standard treatment with blood transfusions and iron chelation (97 age-sex matched adults)	**Critical outcome** • Overall survival • Event free survival **Safety Outcomes** • GVHD • Graft rejection
Li et al. 2019 Retrospective registry analysis (data reported to CIBMTR) (2000 to 2016) 50 centres in China, India and the US	1110 people with TDT aged 25 years or younger who had allogenic HSCT (63% male) 33 (3%) were aged 16 to 25 years (median age of subgroup not reported) Most transplants were performed using HLA-matched related donors (677/1110, 61%) or HLA-matched unrelated donors (252/1110, 23%)	**Intervention** HSCT with an HLA- matched or mismatched, related or unrelated donor (33 adults aged 16 to 25 years) Median follow-up of surviving patients was 48 months (range 3 to 193 months). **Comparison** None	**Critical outcome** • Overall survival • Event free survival **Safety Outcomes** • GVHD • Graft failure
Uygun et al. 2012 Retrospective cross-sectional	99 consecutively invited people (45% male) with TDT who had allogenic	**Intervention**	**Critical outcome**

comparative study (1998 to 2008) Single centre in Turkey	HSCT at least 2 years previously (n=49) or standard treatment (n=50) The study included 21 adults (21%) aged over 18 years (median age of subgroup not reported) All transplants in the study were performed using HLA-matched related donors	HSCT with an HLA-matched related donor (9 adults aged over 18 years) Median time between HSCT and the assessment day was 4.4 years (range 2 to 12 years) **Comparison** Standard treatment with blood transfusions and iron chelation (12 adults aged over 18 years) People in this group were under observation for at least 1 year	• Quality of life (the WHOQoL-BREF questionnaire was used for adults)

Abbreviations

CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Society for Blood and Bone Marrow Transplantation; GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; TDT, transfusion dependent thalassaemia: WHOQoL-BREF, a self-administered questionnaire with 26 questions on the person's perceptions of their health and well-being over the previous 2 weeks

1 Note that the figures reported in the paper do not add up to 97

5. Results

In adults with TDT, what is the clinical effectiveness and safety of allogenic HSCT compared with standard care?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Overall survival **Certainty of evidence:** Very low	This outcome is important to patients because it reflects how long people live after transplant, although it does not provide information about patients' health and wellbeing during that time. In total, 3 studies (1 retrospective case control study and 2 retrospective case series) provided evidence relating to overall survival measured at different time points (2 years, 5 years and 23 years). All included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series were uncontrolled registry studies, which included people who had allogenic HSCT. One case series (Baronciani et al. 2016) included 133 adults aged 18 years or older (median age 22.9 years), but survival data are reported only for 82 adults (62%) who had an HLA-identical sibling donor. The other case series (Li et al. 2019) included 33 adults aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT compared with standard treatment*** In the case control study (Caocci et al. 2017), there was no difference in overall survival in adults who had HSCT (n=97) or standard treatment with blood transfusions and iron chelation (n=97). After 23 years, the probability of overall survival was 70.0% in the HSCT group compared with 71.2% in the standard treatment group (no statistically significant difference, p value not reported). **(VERY LOW)** ***Allogenic HSCT (no comparator)*** In the first case series (Baronciani et al. 2016, n=82), 2-year overall survival was 80% in the adult subgroup. **(VERY LOW)** In the second case series (Li et al. 2019, n=33), 5-year overall survival was 63% (95% CI 45% to 82%) in the adult subgroup after adjusting for donor type and conditioning regimen. **(VERY LOW)** **One case control study provided very low certainty evidence that overall survival rates are similar in adults with TDT who have allogenic HSCT or standard treatment, with about 7 out of 10 people surviving at 23 years in each group. Two case series provided very low certainty evidence that 8 out of 10 adults with TDT who have allogenic HSCT survive after 2 years and 6 out of 10 adults survive after 5 years.**
Event free survival **Certainty of evidence:** Very low	This outcome is important to patients because it reflects how long people live after transplant until either death or thalassaemia recurrence. In total, 3 studies (1 retrospective case control study and 2 retrospective case series) provided evidence relating to overall survival measured at different time points (2 years, 5 years and 23 years). All included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series were uncontrolled registry studies, which included people who had allogenic HSCT. One case series (Baronciani et al. 2016) included 133 adults aged 18 years or older (median age 22.9 years), but survival data are reported only for 82 adults (62%) who had an HLA-

	identical sibling donor. The other case series (Li et al. 2019) included 33 adults aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for event free survival in adults who had standard treatment. After 23 years, the probability of event free survival was 67.3% in adults who had HSCT (n=97). **(VERY LOW)** In the first case series (Baronciani et al. 2016, n=82), 2-year event free survival was 76% in the adult subgroup. **(VERY LOW)** In the second case series (Li et al. 2019, n=33), 5-year event free survival was 63% (95% CI 48% to 78%) in the adult subgroup after adjusting for donor type and conditioning regimen. **(VERY LOW)** **One case control study and 2 case series provided very low certainty evidence that 6 or 7 out of 10 adults with TDT who have allogenic HSCT survive free of thalassaemia for up to 23 years.**
Quality of life **Certainty of evidence:** Very low	This outcome is important to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. One retrospective cross-sectional study (Uygun et al. 2012) provided evidence relating to quality of life in people with TDT who had allogenic HSCT at least 2 years previously (n=49) or standard treatment (n=50). The study included 21 adults aged over 18 years (median age of subgroup not reported) and used the WHOQoL-BREF the questionnaire to assess their health and well-being over the previous 2 weeks. On this questionnaire, higher scores indicate better quality of life. ***Allogenic HSCT compared with standard treatment*** In the cross-sectional study (Uygun et al. 2012), few significant differences were found between HSCT (n=9) and standard treatment with blood transfusions and iron chelation (n=12). The mean quality of life score for the physical domain of the questionnaire was significantly higher in the HSCT group compared with the standard treatment group (79.7 vs 66.6, p=0.041), as was perception of overall health was (80.6 vs 60.4, p=0.034). 'Drug independence for a functional life' and sleep satisfaction were significantly better in the HSCT group compared with the standard treatment group (91.7 vs 31.3, p=0.001, and 86.1 vs 68.8, p=0.023, respectively). There was no difference between the groups in the total score (78.2 with HSCT vs 72.7 with standard treatment, p=0.181). **One cross-sectional study provided very low certainty evidence that adults with TDT who had allogenic HSCT at least 2 years previously rate their overall health, physical health, sleep and 'drug independence for a functional life' significantly better than adults who have regular blood transfusions and iron chelation. However, there may be little or no difference between the treatments for other quality of life outcomes.**
Important outcomes	
Red blood cell transfusion requirement **Certainty of evidence:** Not applicable	This outcome is important to patients because the intention of allogenic HSCT is to replace the need for ongoing transfusion therapy which has major implications on the quality of life and psychological health of patients. A requirement for red blood cell transfusion may also be an indicator of graft failure. **No evidence was identified for this outcome.**
Time to donor haematological reconstitution	This outcome is important to patients because of its significance for the recovery and long-term survival after allogenic HSCT. Reconstitution of the donor-derived immune

Certainty of evidence: Not applicable	system is important for control of infectious complications, susceptibility to GVHD and relapse. **No evidence was identified for this outcome.**
Donor chimerism **Certainty of evidence:** Not applicable	This outcome is important to patients because chimerism is an important indication of disease relapse, graft rejection or graft-versus-host disease. **No evidence was identified for this outcome.**
Hospitalisation due to TDT or problems secondary to TDT **Certainty of evidence:** Not applicable	This outcome is important to patients because frequent hospital attendances can have a negative impact on the psychological health of patients. **No evidence was identified for this outcome.**
Safety	
Acute GVHD **Certainty of evidence:** Very low	GVHD is a possible complication of allogenic HSCT that occurs when the donor's stem cells (the graft) react against the recipient's (host's) body. Acute GVHD usually develops within the first 100 days after transplant. GVHD is important to patients because it can sometimes be severe and life threatening. In total, 3 studies (1 retrospective case control study and 2 retrospective case series) provided evidence relating to acute GVHD. All included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series were uncontrolled registry studies, which included people who had allogenic HSCT. One case series (Baronciani et al. 2016) included 133 adults aged 18 years or older (median age 22.9 years) and the other (Li et al. 2019) included 33 adults aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for acute GVHD in adults who had standard treatment (who would not be expected to experience transplant-related adverse events). After 100 days, 26.7% of adults who had HSCT (n=97) had acute GVHD of any severity and 11.6% had severe (grade 3 or 4) acute GVHD. **(VERY LOW)** In the first case series (Baronciani et al. 2016), GVHD was not assessed in the adult subgroup. However, the risk of developing severe (grade 3 or 4) acute GVHD within 100 days of HSCT was 9% in the whole population (n=1223) and the study authors stated that no significant effect of age on acute GVHD was observed. **(VERY LOW)** In the second case series (Li et al. 2019, n=33), 30% of adults had acute GVHD. **(VERY LOW)** **One case control study and 2 case series provided very low certainty evidence that about 3 out of 10 adults with TDT who have allogenic HSCT will experience acute GVHD, and it will be severe in 1 out of 10 adults.**
Chronic GVHD **Certainty of evidence:** Very low	GVHD is a possible complication of allogenic HSCT, which occurs when the donor's stem cells (the graft) react against the recipient's (host's) body. Chronic GVHD can develop a few months after the transplant or be a progression of acute GVHD. GVHD is important to patients because it can sometimes be severe and life threatening. In total, 2 studies (1 retrospective case control study and 1 retrospective case series) provided evidence relating to acute GVHD. Both included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case

	series (Baronciani et al. 2016) was an uncontrolled registry study in people who had allogenic HSCT including 133 adults aged 18 years or older (median age 22.9 years). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for chronic GVHD in adults who had standard treatment (who would not be expected to experience transplant-related adverse events). Of 84 adults who had HSCT and were considered to be at risk, 12.2% had chronic GVHD (median follow up 14 years). **(VERY LOW)** In the case series (Baronciani et al. 2016), GVHD was not assessed in the adult subgroup. However, risk of developing limited chronic or extended chronic GVHD (no definition provided) after 2 years was 15% and 6% respectively in people who survived with a functioning graft for more than 100 days (n=1140) and the study authors stated that no significant effect of age on chronic GVHD was observed. **(VERY LOW)** **One case control study and 1 case series provided very low certainty evidence that about 1 out of 10 adults with TDT who have allogenic HSCT will experience chronic GVHD.**
Graft rejection or failure **Certainty of evidence:** Very low	Graft rejection or failure occurs when the transplanted stem cells fail to function by producing new cells. This may be because they fail to attach to the hosts bone marrow and grow or because the host's immune cells reject the donor stem cells. It is important to patients because it can be severe and life threatening. In total, 2 studies (1 retrospective case control study and 1 retrospective case series) provided evidence relating to graft rejection or failure. Both included children in the total population but presented subgroup analyses in adults. In the case control study (Caocci et al. 2017), 97 adults aged 16 years or older (median age 23 years) who had allogenic HSCT were matched according to age and sex with 97 adults who had standard treatment. The case series ((Li et al. 2019) was an uncontrolled registry study in people who had allogenic HSCT including 33 adults aged 16 to 25 years (median age of subgroup not reported). ***Allogenic HSCT (no comparator)*** In the case control study (Caocci et al. 2017), no data were reported for chronic GVHD in adults who had standard treatment (who would not be expected to experience transplant-related adverse events). Of 84 adults who had HSCT and were considered to be at risk, 4.7% had graft rejection (median follow up 14 years). **(VERY LOW)** In the case series (Li et al. 2019, n=33), 21% of adults had graft failure. **(VERY LOW)** **One case control study provided very low certainty evidence that about 5 out of 100 adults with TDT who have allogenic HSCT will experience graft rejection. One case series provided very low certainty evidence that about 20 out of 100 adults with TDT who have allogenic HSCT will experience graft failure.**

Abbreviations

CI, confidence interval; GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; P, p value; TDT, transfusion dependent thalassaemia

In adults with TDT, what is the cost effectiveness of allogenic HSCT compared with standard care?

Outcome	Evidence statement
Cost effectiveness	**No evidence was identified regarding the cost effectiveness of allogenic HSCT for adults with TDT compared with standard care.**

Abbreviations

HSCT, haematopoietic stem cell transplantation; TDT, transfusion dependent thalassaemia

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

Outcome	Evidence statement
Subgroup: age	One case series (Baronciani et al. 2016) found that 2-year overall survival and event free survival significantly decreased with increasing age in the total study population (n=1493, both p<0.001). The case series by Baronciani et al. found age had no significant effect on the rate of acute or chronic GVHD. However, the second case series (Li et al. 2019) found adults aged 16 to 25 years (n=33) were at significantly higher risk of acute GVHD than children aged under 7 years (p=0.007) and children aged 7 to 15 years (p=0.01). Similarly, adults aged 16 to 25 years were at significantly higher risk of graft rejection than children aged under 7 years (p=0.006) and children aged 7 to 15 years (p=0.04). **Evidence from 1 case series suggests that rates of overall survival and event free survival at 2 years are worse in adults with TDT who have allogenic HSCT compared with children, but there is no difference in rates of acute and chronic GVHD based on age. By contrast, a second case series provides conflicting information on transplant-related complications and suggests acute GVHD and graft failure occur more often in adults compared with children. This evidence is inconclusive.**
Subgroup: type of donor	In a case control study (Caocci et al. 2017, n=97 adults who had HSCT), 23-year overall survival and event free survival were significantly higher in adults who had matched sibling HSCT compared with matched unrelated HSCT (78.0% vs 57.6%, p=0.014 and 76.5% vs 53.5%, p=0.006, respectively). Unrelated HSCT was associated with a higher rate of acute GVHD and chronic GVHD (OR 12.5, 95% CI 2.42 to 64.77, p=0.003 and OR 6.77, 95% CI 1.07 to 42.95, p=0.042, respectively). **Evidence from a case control study suggests that rates of overall survival, event free survival, and acute and chronic GVHD are better in adults with TDT who have matched sibling HSCT compared with those who have matched unrelated HSCT. However, this evidence is based on analyses of small subgroups and is inconclusive.**
Subgroup: conditioning regimen	In a case control study (Caocci et al. 2017, n=97 adults who had HSCT), no significant difference was found in 23-year overall survival or event free survival in adults with a busulfan-based conditioning regimen compared with a treosulfan-based regimen. **Evidence from a case control study suggests that rates of overall survival and event free survival are similar whether adults with TDT and allogenic HSCT have a conditioning regimen based on busulfan or treosulfan. However, this evidence is based on analyses of small subgroups and is inconclusive.**

Abbreviations

CI, confidence interval; GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; OR, odds ratio; P, p value; TDT, transfusion dependent thalassaemia

6. Discussion

The evidence review included 4 retrospective observational studies. Of these, a case control study (Caocci et al. 2017) and a cross-sectional study (Uygun et al. 2012) compared allogenic HSCT with standard treatment (blood transfusions and iron chelation). The other 2 studies were case series (Baronciani et al. 2016 and Li et al. 2019) with no comparator.

The included studies appear appropriately designed and well-reported, and of sufficient duration to assess outcomes of interest. However, retrospective observational studies are subject to bias and confounding, meaning unknown or unmeasured factors may have influenced the findings. Observational studies cannot prove that an intervention (such as HSCT) caused an outcome, only that it is associated with that outcome. Studies without a comparator are particularly prone to bias, limiting their application to clinical practice.

No relevant studies identified in the searches included adults only. All 4 studies identified included both adults and children, but all reported subgroup analyses in adults only. The sample size of some of the subgroups may have been too small to provide reliable data to inform base decision making. For example, the case series by Li et al. included only 33 adults and the cross-sectional study by Uygun et al. included only 21 adults. It is unclear whether these samples are representative of the general population of adults who have had HSCT, or for whom HSCT is likely to be considered in the UK.

The different types of donor, graft, conditioning regimen and GVHD prophylaxis make it difficult to interpret the results of the studies, particularly when considering the adult subgroups only. Also, the dates of the study range from 1987 to 2016 and treatments have improved over this period, which will have affected outcomes over time.

Most HSCTs in people in the studies were performed using HLA-identical sibling donors or another HLA-matched relative, followed by HLA-matched unrelated donors and, occasionally, unmatched donors. Several types of stem cell graft were used across the studies (primarily bone marrow but also peripheral blood and, occasionally, cord blood).

The eligibility criteria for undergoing HSCT may have caused differences between the groups in the case control study (Caocci et al. 2017). The authors reported that 96.5% of people in the standard treatment group lacked a compatible donor, but it is also possible that there were more comorbidities in this group than in the HSCT group. Li et al. reported that most people in their analyses were inadequately chelated and were, therefore, more likely to have hepatomegaly and portal fibrosis with increasing age. These are conditions that could reduce eligibility for HSCT.

The cross-sectional study (Uygun et al. 2012) assessed quality of life scores in 2 different groups of patients rather than assessing the same group before and after HSCT to see whether the treatment improved their quality of life. People in the HSCT group were assessed between 2 and 11 years after transplantation and quality of life scores would be expected to be change over time. The study authors state that selection of patients for HSCT group could be biased because these patients were ‘well-conditioned’ before HSCT.

Various iron chelating treatments were used over time in the studies. Caocci et al. stated that, after deferasirox became available in 2006, its use rapidly increased and it was the most used iron chelator (39%) in the case control study population, followed by deferoxamine (25%), deferiprone (18%) and deferoxamine plus deferiprone (18%). In the studies that reported which myeloablative conditioning regimens were used, these were mainly busulfan-based (over 80%) but treosulfan based regimens were also used. A variety of regimens were used for GVHD prophylaxis within and across the studies.

7. Conclusion

Overall, 4 retrospective observational studies provided evidence for the clinical effectiveness and safety of HSCT for adults with TDT. A case control study (Caocci et al. 2017) and a cross-sectional study (Uygun et al. 2012) compared allogenic HSCT with standard treatment (blood transfusions and iron chelation). The other 2 studies were case series (Baronciani et al. 2016 and Li et al. 2019) with no comparator.

The case control study (Caocci et al. 2017) and 2 case series (Baronciani et al. 2016 and Li et al. 2019) provided very low certainty evidence for the critical outcomes, overall survival and event free survival. The cross-sectional study (Uygun et al. 2012) provided very low certainty evidence for the critical outcome, quality of life. No evidence was identified for the important outcomes, red blood cell transfusion requirement, time to donor haematological reconstitution, donor chimerism or hospitalisation due to TDT or problems secondary to TDT.

The case control study (Caocci et al. 2017) found that the probability of overall survival was similar in the HSCT and standard treatment groups, with about 70% of adults surviving in each group after 23 years (no statistically significant difference). Similarly, 1 case series (Baronciani et al. 2016) found that 80% of adults who had HSCT survived after 2 years and the other (Li et al. 2019) found that 63% survived after 5 years. Overall, the 3 studies found that 63% to 76% of adults who had HSCT survived free of thalassaemia over between 2 and 23 years. All these outcomes are of very low certainty.

The cross-sectional study (Uygun et al. 2012) provided very low certainty evidence that adults with TDT who had HSCT at least 2 years previously rated their overall health ($p=0.034$), physical health ($p=0.041$), sleep ($p=0.023$) and ‘drug independence for a functional life’ ($p=0.001$) statistically significantly better than adults who had standard treatment. However, there was no difference between the groups for other quality of life outcomes, including total score ($p=0.181$).

The case control study (Caocci et al. 2017) and 2 case series (Baronciani et al. 2016 and Li et al. 2019) provided very low certainty evidence for the safety outcomes, acute and chronic GVHD, and graft rejection and failure. The case control study (Caocci et al. 2017) found that 27% of adults who had HSCT had acute GVHD (any severity) after 100 days, 12% had severe (grade 3 or 4) acute GVHD, and 12% had chronic GVHD These results were supported by results from the 2 case series. In the case control study, 5% of adults had graft rejection, and 21% of adults had graft failure in the case series by Li et al.

Regarding subgroups of patients that may benefit from HSCT more than the wider population of interest, limited and inconclusive evidence suggests that outcomes may be affected by age and the type of donor, but not the conditioning regimen (busulfan or treosulfan). One case series (Baronciani et al. 2016) found that rates of overall survival and event free survival at 2 years were significantly worse in adults who had HSCT compared with children (both $p<0.001$), but there was no difference in rates of acute and chronic GVHD based on age. By contrast, the second case series (Li et al. 2019) found that acute GVHD and graft failure occurred significantly more often in adults compared with children (all $p<0.05$). However, this evidence is inconclusive.

The case control study (Caocci et al. 2017) found that rates of overall survival, event free survival, and acute and chronic GVHD were significantly better in adults with TDT who had matched (identical) sibling HSCT compared with those who had matched unrelated HSCT (all $p<0.05$). The case control study also found no significant differences in overall survival and event free survival in adults who had a busulfan-based conditioning regimen compared with a

treosulfan-based regimen. However, this evidence is based on analyses of small subgroups and is inconclusive.

No evidence was identified regarding the cost effectiveness of allogenic HSCT for adults with TDT compared with standard treatment.

The findings of this evidence review are important for adults with TDT who are receiving standard treatment with blood transfusions and chelation therapy because allogenic HSCT treats the underlying cause of TDT and is potentially curative (assuming there are no complications such as graft rejection or failure), whereas standard treatment controls the disease. Without HSCT, people with TDT need blood transfusions (every 3 to 4 weeks) and iron chelation (usually daily by mouth or weekly by injection) for life. They also need regular monitoring for treatment efficacy and screening for complications, so the burden of TDT is high. In England, allogenic HSCT is currently offered to eligible children with TDT.

The findings of the evidence review are important because they suggest that there is no difference in overall survival between HSCT and standard treatment, but some aspects of quality of life may be better in people who have a transplant. In the small cross-sectional study, adults in the HSCT group had better scores in the physical health domain, which the authors suggest might be because they no longer had complications caused by iron toxicity or periodic anaemia, which limits the capacity for exercise. Compared with people who had standard treatment, people who had HSCT also had better quality of life scores for overall health, sleep satisfaction and ‘drug independence for a functional life’. The studies in the evidence review provide some information about the risk of complications of HSCT in adults (GVHD and graft failure), but no information is available comparing the adverse events of HSCT and standard treatment.

Although the included studies appear appropriately designed, well-reported and of sufficient duration, the evidence for all outcomes is limited and of very low certainly. The studies were all retrospective observational studies, which cannot prove that an intervention (such as HSCT) caused an outcome, only that it is associated with that outcome. Studies without a comparator are particularly prone to bias, limiting their application to clinical practice. The data are difficult to interpret because evidence is based on small subgroup analyses in adults rather than total study populations, and different types of donor, graft, conditioning regimen and GVHD prophylaxis were used within and across the studies. Although some data suggest outcomes of HSCT may be worse in adults compared with children and matched unrelated HSCT compared with matched sibling HSCT, this is based on evidence from small subgroups of the total population or adult subgroups and is inconclusive.

Appendix A PICO document

The review questions for this evidence review are:

1. In adults with TDT, what is the clinical effectiveness of allogenic HSCT compared with standard care?
2. In adults with TDT, what is the safety of allogenic HSCT compared with standard care?
3. In adults with TDT, what is the cost effectiveness of allogenic HSCT compared with standard care?
4. From the evidence selected, are there any subgroups of patients that may benefit from an allogenic haematopoietic stem cell transplant more than the wider population of interest?

P –Population and Indication	Adults with TDT. [For information only: TDT is the most severe form of beta-thalassaemia. It is characterised by severe anaemia and requires lifelong blood transfusions to maintain haemoglobin levels. This policy proposition is intended to cover adults. Allo-HSCT is commissioned as current standard of care for children aged up to 18 with TDT.]
I – Intervention	Allogenic Haematopoietic Stem Cell Transplant (Allo-HSCT) [For information only: Allo-HSCT may also be referred to as: transplant, stem cell transplantation, donor transplant, bone marrow transplant. Allo-HSCT will be delivered in accredited transplant units. It is intended as a curative intervention following medical optimisation with regular transfusion and iron chelation therapy. In most cases, donors are Human Leukocyte Antigen (HLA)-matched siblings though an unrelated HLA-matched donor is a suitable alternative if a relative is not available.]
C – Comparator(s)	Current standard treatment which involves regular blood transfusion and iron chelation therapy. [For information only: Regular blood transfusions are delivered through day unit facilities on a monthly basis. After the first year of regular blood transfusions, iron chelation therapy is commenced. Iron chelation therapy is either a daily tablet or S/C infusion over 10 hours 5-7 nights/week. Transfusion and chelation therapy are expected to continue lifelong and requirement for both increases with age. Monitoring of efficacy includes review in clinic, checking for compliance, side effects and blood tests to measure ferritin. MRI imaging is performed to measure iron overload annually (for liver) and 1-2 yearly (for heart).]
O – Outcomes	There are no known standard minimal clinically important differences for any of the Allo-HSCT outcome measures for

	patients with TDT. The clinical effectiveness outcomes may be reported at 6 months, 1 year, 3 years, 5 years and then every 10 years. **Clinical Effectiveness** *Critical to decision-making:* • **Overall survival** This outcome is important to patients because it reflects how long people live after transplant, although it does not provide information about patients' health and wellbeing during that time. • **Event free survival** This outcome is important to patients because it reflects how long people live after transplant until either death or thalassaemia recurrence. • **Quality of life** This outcome is important to patients as it provides a holistic evaluation and indication of an individual's general health and self-perceived well-being and their ability to participate in activities of daily living. Quality of life can inform the patient centred shared decision making and health policy. Quality of life questionnaires include but are not limited to the EQ-5D & SF 36 which can provide information regarding improvement in symptoms. *Important to decision-making:* • **Red blood cell transfusion requirement** This outcome is important to patients because the intention of Allo-HSCT is to replace the need for ongoing transfusion therapy which has major implications on the quality of life and psychological health of patients. A requirement for red blood cell transfusion may also be an indicator of graft failure. • **Time to donor haematological reconstitution** This outcome is important to patients because of its significance for the recovery and long-term survival after Allo-HSCT. Reconstitution of the donor-derived immune system is important for control of infectious complications, susceptibility to GvHD and relapse. • **Donor chimerism** This outcome is important to patients because chimerism is an important indication of disease relapse, graft rejection or graft-versus-host disease. • **Hospitalisation due to TDT or problems secondary to TDT** This outcome is important to patients because frequent hospital attendances can have a negative impact on the psychological health of patients.

	<u>Safety</u> • **Transplant related adverse events (such as graft rejection, acute/chronic graft vs host disease)** Transplant-related mortality is the major problem in adults. **<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	Adults
Date limits	2011-2021
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-publication prints and guidelines
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase and the Cochrane Library were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, commentaries, letters, editorials and case reports were excluded.

Search dates: 1 December 2021

Database search strategies

Database: Medline ALL

Platform: Ovid
Version: 1946 to November 30, 2021
Search date: 1st December 2021
Number of results retrieved: 601
1 thalassemia/ (11024)
2 beta-thalassemia/ (9316)
3 thalassaemi*.tw. (5097)
4 thalassemi*.tw. (18372)
5 ((cooley* or erythroblastic or mediterranean or erythroblastic) adj2 (anaemia* or anemia*)).tw. (567)
6 microcytemia*.tw. (10)
7 microcytaemia*.tw. (1)
8 "hemoglobin f disease*".tw. (0)
9 "haemoglobin f disease".tw. (0)
10 or/1-9 (27172)
11 exp Hematopoietic Stem Cell Transplantation/ (50951)
12 transplant*.tw. (494292)
13 sct.tw. (9512)
14 hsct.tw. (13878)
15 stem cell therapy.tw. (6333)
16 "marrow therapy".tw. (21)
17 or/11-16 (512548)
18 10 and 17 (1678)
19 limit 18 to yr="2011 -Current" (684)
20 limit 19 to (clinical conference or comment or congress or consensus development conference or consensus development conference, nih or editorial or guideline or letter or preprint) (41)
21 19 not 20 (643)
22 exp Animals/ not Humans/ (4923451)
23 21 not 22 (628)
24 limit 23 to english language (601)

Database: Embase

Platform: Ovid
Version: 1996 to 2021 November 30
Search date: 1st December 2021
Number of results retrieved: 817
Search strategy:

1 thalassemia/ or exp beta thalassemia/ or transfusion dependent thalassemia/ (20572)
2 thalassaemi*.tw. (4407)
3 thalassemi*.tw. (21472)
4 ((cooley* or erythroblastic or mediterranean or erythroblastic) adj2 (anaemia* or anemia*)).tw. (142)
5 microcytemia*.tw. (5)
6 microcytaemia*.tw. (1)
7 "hemoglobin f disease*".tw. (0)
8 "haemoglobin f disease".tw. (0)
9 or/1-8 (28974)
10 allogeneic hematopoietic stem cell transplantation/ (27933)
11 transplant*.tw. (652463)
12 sct.tw. (19363)
13 hsct.tw. (33137)
14 stem cell therapy.tw. (8808)
15 "marrow therapy".tw. (23)
16 or/10-15 (669468)
17 9 and 16 (3333)
18 limit 17 to yr="2011 -Current" (2316)
19 18 (2316)
20 limit 19 to english language (2279)
21 limit 20 to conference abstract status (1379)
22 20 not 21 (900)
23 limit 22 to (editorial or letter or note) (61)
24 22 not 23 (839)
25 nonhuman/ not human/ (3669390)
26 24 not 25 (817)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL

Platform: Wiley
Version:
CDSR –Issue 12 of 12, November 2021
CENTRAL – Issue 11 of 12, November 2021
Search date: 1st December 2021
Number of results retrieved: CDSR – 3; CENTRAL – 38.

ID	Search
#1	[mh ^thalassemia]
#2	[mh ^"beta-thalassemia"]
#3	thalassaemi*:ti,ab
#4	thalassemi*:ti,ab
#5	((cooley* OR erythroblastic OR mediterranean OR erythroblastic) NEAR/2 (anaemia* OR anemia*)):ti,ab
#6	microcytemia*:ti,ab
#7	microcytaemia*:ti,ab
#8	(hemoglobin NEXT f NEXT disease*):ti,ab
#9	(haemoglobin NEXT f NEXT disease*):ti,ab
#10	{or #1-#9}
#11	[mh "Hematopoietic Stem Cell Transplantation"]
#12	transplant*:ti,ab
#13	sct:ti,ab
#14	hsct:ti,ab
#15	"stem cell therapy":ti,ab
#16	"marrow therapy":ti,ab
#17	{or #11-#16}
#18	#10 AND #17
#19	(trialsearch OR who or isrctn OR clinicaltrials):so
#20	#18 NOT #19

Date limited using on-screen filters to papers first published from 2011 on.

Reference list checking

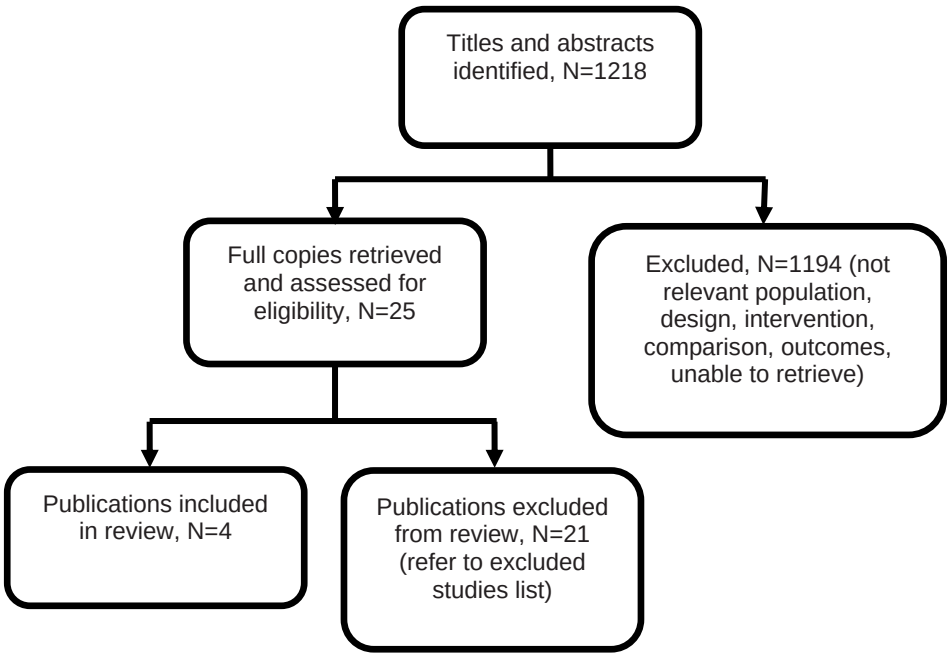
Fifteen references identified as being includable during the initial sift were used as the basis for backwards citation searching using citationchaser. Three of these references are duplicates of the same Cochrane review. One (Ghavamzadeh et al, 2019) couldn't be found in lens.org, the database behind citationchaser.

355 additional references were found by citationchaser and imported into EPPI reviewer.

Appendix C Evidence selection

The literature searches identified 1218 references. These were screened using their titles and abstracts and 25 references were obtained in full text and assessed for relevance. Of these, 4 references are included in the evidence summary. The remaining 21 references were excluded and 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
Gaziev, J et al. (2005). Bone Marrow Transplantation in Adults with Thalassaemia. *New York Academy of Sciences*. 1054, p196-205	Excluded: outside of search date limits
Li, C et al. (2019). Related and unrelated donor transplantation for b-thalassemia major: results of an international survey. *Blood Advances*. 3 (17), p2562-2570	Included
Baronciani, D et al. (2016). Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000–2010. *Nature*. 51 (1), p536-541	Included

Appendix D Excluded studies table

Study reference	Reason for exclusion
Anurathapan, Usanarat, Hongeng, Suradej, Pakakasama, Samart et al. (2020) Hematopoietic Stem Cell Transplantation for Severe Thalassemia Patients from Haploidentical Donors Using a Novel Conditioning Regimen. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation 26(6): 1106-1112	Assesses conditioning regimen not HSCT
Aydogdu, Selime, Toret, Ersin, Aksoy, Basak A et al. (2021) Comparison of Hematopoietic Stem Cell Transplantation Results in Patients with beta-Thalassemia Major from Three Different Graft Types. Hemoglobin 45(1): 25-29	No adult subgroup
Badawy, Sherif M, Beg, Usman, Liem, Robert I et al. (2021) A systematic review of quality of life in sickle cell disease and thalassemia after stem cell transplant or gene therapy. Blood advances 5(2): 570-583	No adult subgroup
Bardon Cancho, Eduardo J, Garcia-Morin, Marina, Belendez, Cristina et al. (2020) Update of the Spanish registry of haemoglobinopathies in children and adults. Medicina clinica 155(3): 95-103	Does not look at outcomes following HSCT
Choudhary, Dharma, Doval, Divya, Sharma, Sanjeev K et al. (2019) Allogenic Hematopoietic Cell Transplantation in Thalassemia Major: A Single-center Retrospective Analysis From India. Journal of pediatric hematology/oncology 41(5): e296-e301	No adult subgroup
Ghavamzadeh, Ardeshir, Kasaeian, Amir, Rostami, Tahereh et al. (2019) Comparable Outcomes of Allogeneic Peripheral Blood versus Bone Marrow Hematopoietic Stem Cell Transplantation in Major Thalassemia: A Multivariate Long-Term Cohort Analysis. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation 25(2): 307-312	Compares types of graft not HSCT vs standard care. Iranian population also included in larger study by Baronciani et al.
Ghavamzadeh, A, Rostami, T, Nikbakht, M et al. (2019) Twenty-six years of experience on allogeneic HSCT in thalassemia major patients: a long-term survey and Cotransplantation of Mesenchymal Stem Cells (MSCs). Bone marrow transplantation 53: 485	Conference abstract
Hsieh, Matthew M, Fitzhugh, Courtney D, Weitzel, R Patrick et al. (2014) Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. JAMA 312(1): 48-56	Assesses conditioning regimen not HSCT
Jagannath, Vanitha A., Fedorowicz, Zbys, Hajeri, Amani Al et al. (2021) The Cochrane Library - Hematopoietic stem cell transplantation for people with ß-thalassaemia major. The Cochrane database of systematic reviews 11(10): 008708-NA	Cochrane review found no relevant studies
Jagannath, Vanitha A, Fedorowicz, Zbys, Al Hajeri, Amani et al. (2011) Hematopoietic stem cell transplantation for people with B-thalassaemia major. Cochrane database of systematic reviews (Online): cd008708	Cochrane review found no relevant studies
Javanbakht, Mehdi, Keshtkaran, Ali, Shabaninejad, Hossien et al. (2015) Comparison of Blood Transfusion Plus Chelation Therapy and Bone Marrow Transplantation in Patients with beta-Thalassemia: Application of SF-36, EQ-5D, and Visual Analogue Scale	Age at transplant not reported

Measures. International journal of health policy and management 4(11): 733-40	
Khalil, Abdalla, Zaidman, Irena, Elhasid, Ronit et al. (2012) Factors influencing outcome and incidence of late complications in children who underwent allogeneic hematopoietic stem cell transplantation for hemoglobinopathy. Pediatric hematology and oncology 29(8): 694-703	No adult subgroup
La Nasa, Giorgio, Caocci, Giovanni, Efficace, Fabio et al. (2013) Long-term health-related quality of life evaluated more than 20 years after hematopoietic stem cell transplantation for thalassemia. Blood 122(13): 2262-70	Comparator is general population not standard treatment. Includes a comparison of HSCT versus standard care but no adult subgroup.
Li, Qiaochuan, Luo, Jianming, Zhang, Zhongming et al. (2019) G-CSF-Mobilized Blood and Bone Marrow Grafts as the Source of Stem Cells for HLA-Identical Sibling Transplantation in Patients with Thalassemia Major. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation 25(10): 2040-2044	No adult subgroup
Raj, Revathi, Swaminathan, Venkateswaran Vellaichamy, Meena, Satishkumar et al. (2021) Donor Characteristics Predict the Success of Allogeneic Hematopoietic Stem Cell Transplantation in Thalassemia Major: A Single-Center Analysis of 250 Patients. Indian Journal of Hematology and Blood Transfusion	No adult subgroup
Rostami, Tahereh, Mohammadifard, Mohammad Amir, Ansari, Shahla et al. (2020) Indicators of male fertility potential in adult patients with beta-thalassemia major: a comparative study between patients undergone allogeneic stem cell transplantation and transfusion-dependent patients. Fertility research and practice 6: 4	No PICO outcomes
Shamshad, Ghassan Umair, Ahmed, Suhaib, Bhatti, Farhat Abbas et al. (2012) Mixed donor chimerism in non-malignant haematological diseases after allogeneic bone marrow transplantation. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP 22(12): 765-8	No adult subgroup
Sharma, A; Jagannath, VA; Puri, L (2021) Hematopoietic stem cell transplantation for people with β-thalassaemia. Cochrane Database of Systematic Reviews	Cochrane review found no relevant studies
Sharma, Akshay; Jagannath, Vanitha A; Puri, Latika (2021) Hematopoietic stem cell transplantation for people with beta-thalassaemia. The Cochrane database of systematic reviews 4: cd008708	Cochrane review found no relevant studies
Weidlich, Diana; Kefalas, Panos; Guest, Julian F (2016) Healthcare costs and outcomes of managing beta-thalassemia major over 50 years in the United Kingdom. Transfusion 56(5): 1038-45	Assesses overall cost of treating thalassaemia
Zhai, Lu, Liu, Yuhua, Huo, Rongrui et al. (2021) Quality of Life in Patients with beta-thalassemia Major: Short-term and Long-term Effects After Haematopoietic Stem Cell Transplantation. Current stem cell research & therapy 16(8): 924-930	Narrative review. No additional relevant evidence identified from cited studies.

Appendix E Evidence table

Study details	Population	Interventions	Study outcomes	Appraisal and funding
Full citation Baronciani D, Angelucci E, Potschger U et al. (2016) Hemopoietic stem cell transplantation in thalassemia: a report from the European Society for Blood and Bone Marrow Transplantation Hemoglobinopathy Registry, 2000-2010. Bone marrow transplantation 51(4): 536-41 **Study location** 127 centres worldwide, two thirds of transplants were undertaken in Europe (990/1493, 66.3%) **Study type** Retrospective registry analysis using the EBMT registry (case series) **Study aim** The study aimed 'to verify the distribution, activity and outcomes of HSCT in the large EBMT multicenter setting' **Study dates** 2000 to 2010	**Inclusion criteria** All patients registered in the ProMISe database of the EBMT hemoglobinopathy registry **Exclusion Criteria** • Transplants performed before 2000 • People with sickle-cell disease or other hemoglobinopathies • People with no follow up data **Total sample size** 1493 people with TDT who had allogenic HSCT (53% male) **No. of participants in each treatment group** There was no comparator in this study **Baseline characteristics** 133 (8.9%) people in the study were 18 years or older (median age 22.9 years, range 18 to 45 years). Of these, 82 (61.6%) had an HLA-identical sibling donor Most transplants were performed using HLA-identical sibling donors (1061/1493, 71.1%) or another HLA-matched relative (127/1493, 8.5%) Stem cells were sourced from bone marrow (1012/1493, 67.8%) or peripheral blood in	**Intervention** HSCT with an HLA-identical sibling donor (82 adults aged 18 years or older) Minimum follow-up was 6 months per case. Median observation time in the study was 2 years **Comparator** None	**Critical outcomes** **Overall survival** Overall survival was calculated from date of first HSCT to death from any cause 2-year overall survival in the adult subgroup was 80% ± 5% Overall survival was found to significantly decrease with increasing age in the total study population (p<0.001) **Event free survival** Event free survival was calculated as the time to death or thalassemia recurrence, whichever was first (thalassaemia free survival). Only first HSCT was considered in people who had more than 1 transplant 2-year event free survival in the adult subgroup was 76% ± 5% Event free survival was found to significantly decrease with increasing age in the total study population (p<0.001) **Safety outcomes** **GVHD** Acute GVHD was graded according to the revised Glucksberg scale[a]. Chronic GVHD was graded as either limited or extended (not defined) The risk of developing severe (grade 3 or 4) acute GVHD within 100 days of HSCT was 9% (108/1223) in the whole population. A lower risk (7%; 70/901) was observed in people with an HLA-matched sibling donor (p=0.001). The 2-year risk of developing limited chronic or extended chronic GVHD (no definition provided)	This study was appraised using the JBI Critical Appraisal Checklist for Case Series 1. Yes 2. Probably yes 3. Probably yes 4. Probably yes 5. Probably yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes Other comments: this is a large, appropriately designed and well-reported case series. However, case series have no comparators and unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating Source of funding: The study was approved and supported by the EBMT Pediatric Disease Working Group

	most patients (303/1493, 20.3%) Most transplants were performed in Italy (39%), Turkey (14%) and the UK (9%) Conditioning regimens and GVHD prophylaxis are not reported		was 15% ±1% and 6% ±1% respectively in 1140 people who survived with a functioning graft for more than 100 days The study authors stated that no significant effect of age on acute or chronic GVHD was observed	
Full citation Caocci G, Orofino, MG, Vacca A et al. (2017) Long-term survival of beta thalassemia major patients treated with hematopoietic stem cell transplantation compared with survival with conventional treatment. American journal of hematology 92(12): 1303-10 **Study location** Single centre in Italy **Study type** Retrospective case control study **Study aim** The study aimed 'To provide physicians and patients with additional information on the advantages and potential risks of HSCT and support them in the decision-making process' **Study dates** 1987 to 2016	**Inclusion criteria** People with TDT who had allogenic HSCT (sibling or unrelated donor) were compared with people with TDT who had standard treatment (regular blood transfusions and iron chelation) **Exclusion Criteria** No exclusions were reported **Total sample size** 516 people with TDT (54.3% male) **No. of participants in each treatment group** 258 people who had allogenic HSCT were age-sex matched with 258 people who had standard treatment randomly selected from a wider population **Baseline characteristics** 97/258 (37.6%) people who had HSCT were aged 16 years or older (median age 23 years, range 16 to 45 years; 53.6% male) Most transplants in the study were performed using sibling donors (173/258, 67.1%) compared with unrelated donors (85/258, 32.9%)	**Intervention** HSCT with an HLA-identical sibling or unrelated donor (97 adults aged 16 years or older) Median follow-up was 14 years (range 1 to 23 years) **Comparator** Standard treatment with blood transfusions (every 2 to 5 weeks in adults) and an iron chelating regimen (97 age-sex matched adults) according to International Guidelines for the Management of TDT	**Critical outcomes** **Overall survival** Overall survival was not defined In the adult subgroup, the 23-year Kaplan–Meier probability of overall survival was 70.0% ± 5% in the transplant group compared with 71.2% ± 5% in the standard treatment group (no statistically significant difference, p value not reported) In this age group, overall survival was significantly higher in sibling HSCT compared with unrelated HSCT (78.0% ± 5.8% vs 57.6% ± 8.9%, p=0.014) No significant difference was found in overall survival in adults with a busulfan-based conditioning regimen compared with a treosulfan-based regimen **Event free survival** Event free survival (thalassaemia free survival) was based on the patients' data recorded at time of death or graft failure. The 23-year Kaplan–Meier probability of event free survival was 67.3% ± 5% in the adult transplant group. No data were reported for the control group In this age group, event free survival was significantly higher in sibling HSCT compared with unrelated HSCT (76.5% ± 5.9% vs 53.5% ± 8.8%, p=0.006) No significant difference was found in event free survival in adults with a busulfan-based	This study was appraised using the CASP Case Control Study Checklist 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Unclear 7. Analysis is appropriate to estimate time-related events and no significant difference was found between groups in the adult sub-population for OS 8. P values, confidence intervals and standard deviations suggest results for the total population are precise. Authors also considered important variables. 9. Yes 10. Yes 11. Unclear Other comments: The study is a retrospective observational study and is, therefore subject to bias and confounding. For example, it is possible that eligibility criteria for undergoing HSCT may have caused differences between the groups. Nevertheless, it appears to be well designed and reported.

	Transplants were performed using sibling donors in 48 adults and unrelated donors in 37 adults.[b] Stem cells were sourced from bone marrow in all but 2 people in the study (256/258, 99.2%) People who had HSCT had a busulfan- (81/97 adults, 83.5%) or treosulfan-based (16/97 adults 16.5%) conditioning regimen. A variety of regimens were used for GVHD prophylaxis		conditioning regimen compared with a treosulfan-based regimen **Safety outcomes** **GVHD** It is unclear how acute and chronic GVHD were assessed In the adult subgroup, cumulative probabilities of 100-day all-grade and grade 3 or 4 (severe) acute GVHD were 26.7% and 11.6%, respectively. The incidence of acute GVHD did not improve across the decades (1987 to 1999: 24.8%; 2000 to 2009: 29.8%; 2010 to 2017: 22.3%). In 84 adults assessed as being at risk, the cumulative incidence of chronic GVHD was 12.2% Unrelated HSCT was associated with a higher rate of acute (OR 12.5, 95% CI 2.42 to 64.77, p=0.003) and chronic GVHD (OR 6.77, 95% CI 1.07 to 42.95, p=0.042) **Graft rejection** In 84 adults assessed at being at risk, the cumulative incidence of graft rejection was 4.7% **Transplant-related mortality** 3 malignant tumours (2 cases of squamous cell carcinoma of the oral cavity and 1 of osteosarcoma) occurred in the adult subgroup. All resulted in death Other reasons for transplant-related mortality are not reported for the adult subgroup alone	Source of funding: The funding source is not reported. However, it is stated that the authors had no competing financial interests
Full citation Li C, Mathews V, Kim S et al. (2019) Related and unrelated donor transplantation for beta-thalassemia major: results of an international survey. Blood advances 3(17): 2562-70 **Study location**	**Inclusion criteria** People registered on the CIBMTR database with TDT aged 25 years or younger who had their first allogenic HSCT between 2000 and 2016 **Exclusion Criteria** • Patients aged over 25 years	**Intervention** HSCT with an HLA-matched or mismatched, related or unrelated donor (33 adults aged 16 to 25 years) Median follow-up of surviving patients was 48 months (range 3 to 193 months). **Comparison**	**Critical outcomes** **Overall survival** Overall survival was defined as death from any cause The 5-year probability of overall survival was 63% (95% CI 45% to 82%) in the adult subgroup after adjusting for donor type and conditioning regimen	This study was appraised using the JBI Critical Appraisal Checklist for Case Series 1. Yes 2. Probably yes 3. Probably yes 4. Probably yes

50 centres in China, India and the US **Study type** Retrospective registry analysis using data reported to CIBMTR (case series) **Study aim** The study aimed 'to address outcomes after transplantation in children and young adults and use of alternative donors relative to HLA-matched related donor transplantation in 3 geographic regions' **Study dates** 2000 to 2016	• Reduced intensity conditioning regimen transplantation **Total sample size** 1110 people with TDT aged 25 years or younger who had allogenic HSCT (62.7% male) **No. of participants in each treatment group** There was no comparator in this study **Baseline characteristics** 33/1110 (3.0%) were aged 16 to 25 years (median age of subgroup not reported) Stem cells were sourced from bone marrow (321/1110, 28.9%) or peripheral blood in most patients (682/1110, 61.4%) Most transplants were performed using HLA-matched related donors (677/1110, 61.0%) or HLA-matched unrelated donors (252/1110, 22.7%) All patients received myeloablative conditioning regimens, mostly including busulfan. A variety of regimens were used for GVHD prophylaxis	None	Of 24 adults who had HLA-matched related donor transplants, 15 survived (63%) All 4 adults (100%) who had HLA-matched unrelated donor transplants survived. Of 4 adults who had HLA-mismatched related donor transplants, 2 survived (50%) 1 adult who had HLA-mismatched unrelated donor transplant died **Event free survival** Event free survival was defined as death from any cause or graft failure The 5-year probability of event free survival was 63% (95% CI 48% to 78%) in the adult subgroup after adjusting for donor type and conditioning regimen Of 24 adults who had HLA-matched related donor transplants, 14 survived event free (58%) **Safety outcomes** **GVHD** GVHD was graded using standard criteria 10/33 adults (30%) had acute GVHD Adults aged 16 to 25 years were at a significantly higher risk of acute GVHD compared with those aged under 7 years (p=0.007) and those aged 7 to 15 years (p=0.01) **Graft failure** 7/33 adults (21%) had graft failure Adults aged 16 to 25 years were at a significantly higher risk of graft failure compared with those aged under 7 years (p=0.006) and those aged 7 to 15 years (p=0.04)	5. Probably yes 6. Yes 7. Yes 8. Yes 9. Yes 10. Yes Other comments: this is a large, appropriately designed and well-reported case series. However, case series have no comparators and unknown or unmeasured factors may have influenced the findings reported. Case series cannot prove cause and effect and should only be considered hypothesis generating Source of funding: The CIBMTR was supported by grants from the National Institutes of Health, National Cancer Institute, National Heart Lung and Blood Institute, the National Institute of Allergy and Infectious Diseases and the Health Services Research Administration, Department of Health and Human Services
Full citation Uygun V, Tayfun F, Akcan M et al. (2012) Quality of life assessment in hematopoietic stem cell transplantation performed on thalassemia major patients. Pediatric	**Inclusion criteria** Consecutively invited people with TDT who had allogenic HSCT at least 2 years previously (at the same centre) or standard treatment (regular	**Intervention** HSCT with an HLA-matched related donor (9 adults aged over 18 years)	**Critical outcome** **Quality of life** The WHOQoL-BREF[c] questionnaire was used for adults, with the assistance of study coordinators in the hospital	This study was appraised using the JBI Critical Appraisal Checklist for Cross Sectional Studies 1. Yes 2. Yes

hematology and oncology 29(5): 461-71 **Study location** Single centre in Turkey **Study type** Retrospective cross-sectional comparative study **Study aim** The aim 'was to study the QoL in transplanted thalassemic patients in a developing country, on whom thalassemia major may have had a more deleterious effect and may have shown that HSCT had a greater effect on their QoL' **Study dates** 1998 to 2008	blood transfusions and iron chelation) **Exclusion Criteria** As all the transplanted patients' Karnofsky and Lansky performance levels were above 80 before and after transplantation, 3 nontransplanted thalassaemic patients with scores of less than 80 and 2 patients taking antipsychotics were excluded from the study **Total sample size** 99 people with TDT (45.5% male) **No. of participants in each treatment group** 49 people who had allogenic HSCT at least 2 years previously were compared with 50 people who had standard treatment **Baseline characteristics** The study included 21 adults (21.2%) aged over 18 years (median age of subgroup not reported) All transplants in the study were performed using HLA-matched related donors. The source of stem cells is not reported No information is reported on which myeloablative conditioning regimens and GVHD prophylaxis were used	Median time between HSCT and the assessment day was 4.4 years (range 2 to 12 years) **Comparison** Standard treatment with blood transfusions (every 2 to 4 weeks) and an iron chelating regimen (12 adults aged over 18 years) People in this group were under observation for at least 1 year	In adults, when mean scores were calculated, a significant difference was seen only in the physical domain, with a higher mean score in the HSCT group (79.7 vs 66.6 in the standard treatment group, p=0.041). The perception of overall health was significantly higher in the HSCT group compared with the standard treatment group (80.6 vs 60.4, p=0.034) There were no significant differences in mean scores for most items on the questionnaire, or for the total score (78.2 with HSCT vs 72.7 with standard treatment, p=0.181). 'Drug independence for a functional life' and sleep satisfaction were significantly better in the HSCT group compared with the standard treatment group (91.7 vs 31.3, p=0.001, and 86.1 vs 68.8, p=0.023, respectively)	3. Yes 4. Yes 5. Unclear 6. Unclear 7. Yes 8. Yes Other comments: The study appears to be well designed and reported but has several limitations. It assessed quality of life scores in 2 different groups of patients rather than assessing the same group before and after HSCT to see whether the treatment improved their quality of life. Patients in the HSCT group were assessed between 2 and 11 years after transplantation and quality of life scores would be expected to be change over time. The study authors state that selection of patients for HSCT group could be biased because these patients were 'well-conditioned' before HSCT Source of funding: The funding source is not reported. However, it is stated that the authors had no conflicts of interest.

Abbreviations

CI, confidence interval; CIBMTR, Center for International Blood and Marrow Transplant Research; EBMT, European Society for Blood and Bone Marrow Transplantation; GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; OR, odds ratio; P, p value; QoL, quality of life; TDT, transfusion dependent thalassaemia

[a] The Glucksberg scale stages each of skin, lower gastrointestinal tract and liver on a scale of 0 (absent) to 4 (severe) points to create a final overall grade of I (mild) to IV (life-threatening)
[b] Note that the figures reported in the paper do not add up to 97
[c] WHOQoL-BREF, a self-administered questionnaire with 26 questions on the person's perceptions of their health and well-being over the previous 2 weeks. An additional question about the environment was added to the questionnaire, and a question on sexual activity was left out. Higher scores indicate better quality of life

Appendix F Quality appraisal checklists

CASP Case Control Study Checklist

1. Did the study address a clearly focused issue?
2. Did the authors use an appropriate method to answer their question?
3. Were the cases recruited in an acceptable way?
4. Were the controls selected in an acceptable way?
5. Was the exposure accurately measured to minimise bias?
6. Aside from the experimental intervention, were the groups treated equally?

   Have the authors taken account of the potential confounding factors in the design and/or in their analysis?
7. How large was the treatment effect?
8. How precise was the estimate of the treatment effect?
9. Do you believe the results?
10. Can the results be applied to the local population?
11. Do the results of this study fit with other available evidence?

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?

JBI Critical Appraisal Checklist for Cross-Sectional Studies

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?

7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

Appendix G GRADE profiles

Table 2: Question: In adults with TDT, what is the clinical effectiveness and safety of allogenic HSCT compared with standard care

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
							Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Allogenic HSCT	Standard care	Result		
Overall survival (1 retrospective case control study)									
23-year probability of overall survival (Kaplan–Meier)									
Retrospective case control study (Caocci et al. 2017)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	70.0% ± 5%	71.2% ± 5%	No statistically significant difference, p value not reported	Critical	Very low
Event free survival (1 retrospective case control study)									
23-year probability of event free survival (Kaplan–Meier)									
Retrospective case control study (Caocci et al. 2017)	Serious limitations[2]	Serious indirectness[1]	Not applicable	Not calculable	67.3% ± 5%	Not reported	No statistical analysis	Critical	Very low
Quality of life (1 retrospective cross-sectional study)									
Mean total scores (WHOQoL-BREF questionnaire, higher scores indicate better quality of life)									
Retrospective cross-sectional comparative study (Uygun et al. 2012)	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	78.2	72.7	No statistically significant difference, p=0.181	Critical	Very low
Mean scores for physical health (WHOQoL-BREF questionnaire, higher scores indicate better quality of life)									
Retrospective cross-sectional comparative study	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	79.7	66.6	Statistically significant difference in favour of HSCT, p=0.041	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
							Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Allogenic HSCT**	**Standard care**	**Result**		
(Uygun et al. 2012)									
Mean scores for perception of overall health (WHOQoL-BREF questionnaire, higher scores indicate better quality of life)									
Retrospective cross-sectional comparative study (Uygun et al. 2012)	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	80.6	60.4	Statistically significant difference in favour of HSCT, p=0.034	Critical	Very low
Mean scores for 'drug independence for a functional life' (WHOQoL-BREF questionnaire, higher scores indicate better quality of life)									
Retrospective cross-sectional comparative study (Uygun et al. 2012)	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	91.7	31.3	Statistically significant difference in favour of HSCT, p=0.001	Critical	Very low
Mean scores for satisfaction with sleep (WHOQoL-BREF questionnaire, higher scores indicate better quality of life)									
Retrospective cross-sectional comparative study (Uygun et al. 2012)	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	86.1	68.8	Statistically significant difference in favour of HSCT, p=0.023	Critical	Very low
Transplant-related adverse events (1 retrospective cross-sectional study)									
100-day cumulative probability of all-grade acute GVHD									
Retrospective case control study (Caocci et al. 2017)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	26.7%	Not applicable	No statistical analysis	Safety	Very low
100-day cumulative probability of grade 3–4 (severe) acute GVHD									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
							Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Allogenic HSCT**	**Standard care**	**Result**		
Retrospective case control study (Caocci et al. 2017)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	11.6%	Not applicable	No statistical analysis	Safety	Very low
Cumulative incidence of chronic GVHD (median follow up 14 years)									
Retrospective case control study (Caocci et al. 2017)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	12.2%	Not applicable	No statistical analysis	Safety	Very low
Cumulative incidence of graft rejection (median follow up 14 years)									
Retrospective case control study (Caocci et al. 2017)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	4.7%	Not applicable	No statistical analysis	Safety	Very low

Abbreviations

GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; P, p value; TDT, transfusion dependent thalassaemia

1 Downgraded. The study includes people of all ages with TDT (n=516), not adults alone (n=194). The results for adults are subgroup analyses and are likely to be less robust than for the total population because of the small number of patients in each group
2 Downgraded. No results are reported for the standard care group for this outcome
3 Downgraded. The study includes people of all ages with TDT (n=99), not adults alone (n=21). The results for adults are subgroup analyses and are likely to be less robust than for the total population because of the small number of patients in each group

Table 3: Question: In adults with TDT, what is the clinical effectiveness and safety of allogenic HSCT (no comparator)

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
							Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**allogenic HSCT**	**None**	**Result**		
Overall survival (2 retrospective case series)									
2-year overall survival									
Retrospective case series (Baronciani et al. 2016)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	80% ± 5%	Not applicable	No comparison	Critical	Very low
5-year overall survival									
Retrospective case series (Li et al. 2019)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	63% (95% CI 45% to 82%)	Not applicable	No comparison	Critical	Very low
Event free survival (2 retrospective case series)									
2-year event free survival									
Retrospective case series (Baronciani et al. 2016)	No serious limitations	Serious indirectness[1]	Not applicable	Not calculable	76% ± 5%	Not applicable	No comparison	Critical	Very low
5-year event free survival									
Retrospective case series (Li et al. 2019)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	63% (95% CI 48% to 78%)	Not applicable	No comparison	Critical	Very low
Transplant-related adverse events (2 retrospective case series)									
Risk of all-grade acute GVHD (median follow up 2 years)									
Retrospective case series (Li et al. 2019)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	30% (10/33)	Not applicable	No comparison	Safety	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
							Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	allogenic HSCT	None	Result		
100-day risk of grade 3–4 (severe) acute GVHD									
Retrospective case series (Baronciani et al. 2016)	No serious limitations	Serious indirectness[3]	Not applicable	Not calculable	9% (108/1223)	Not applicable	No comparison	Safety	Very low
2-year risk of limited chronic GVHD (no definition provided)									
Retrospective case series (Baronciani et al. 2016)	No serious limitations	Serious indirectness[4]	Not applicable	Not calculable	15% ±1%	Not applicable	No comparison	Safety	Very low
2-year risk of extended chronic GVHD (no definition provided)									
Retrospective case series (Baronciani et al. 2016)	No serious limitations	Serious indirectness[4]	Not applicable	Not calculable	6% ±1%	Not applicable	No comparison	Safety	Very low
Risk of graft failure (median follow up 2 years)									
Retrospective case series (Li et al. 2019)	No serious limitations	Serious indirectness[2]	Not applicable	Not calculable	21% (7/33)	Not applicable	No comparison	Safety	Very low

Abbreviations

CI, confidence interval; GVHD, graft versus host disease; HSCT, haematopoietic stem cell transplantation; P, p value; TDT, transfusion dependent thalassaemia

1 Downgraded. The study includes people of all ages with TDT (n=1493), not adults alone (n=133). The results for adults are subgroup analyses and are likely to be less robust than for the total population because of the small number of patients
2 Downgraded. The study includes people of all ages with TDT (n=1110), not adults alone (n=33). The results for adults are subgroup analyses and are likely to be less robust than for the total population because of the small number of patients
3 Downgraded. The result is for people of all ages with TDT (n=1223), not adults alone. It is included because the authors state that no significant effect of age on GVHD was observed; however, applying this result to the adult population is less certain than for the total population
4 Downgraded. The result is for people of all ages with TDT (1140 people who survived with a functioning graft for more than 100 days), not adults alone. It is included because the authors state that no significant effect of age on GVHD was observed; however, applying this result to the adult population is less certain than for the total population

Glossary

Glucksberg scale	The Glucksberg classification for GVHD was first proposed in the 1970s based on a cohort of 60 patients evaluated for acute GVHD after myeloablative conditioning. This classification staged each of skin, lower gastrointestinal tract and liver on a scale of 0 (absent) to 4 (severe) points, to create a final overall grade of I (mild) to IV (life-threatening).
Graft versus host disease (GVHD)	GVHD is a possible complication of allogenic HSCT that occurs when the donor's stem cells (the graft) react against the recipient's (host's) body. Acute GVHD usually develops within the first 100 days after transplant. Chronic GVHD can develop a few months after the transplant or be a progression of acute GVHD. GVHD can sometimes be severe and life threatening.
WHOQOL-BREF	The WHOQOL-BREF is a shorter version of the WHOQOL-100. Both were developed by the World Health Organisation (WHO). The WHOQOL-BREF is a self-administered questionnaire with 26 questions on the person's perceptions of their health and well-being over the previous 2 weeks. Responses to questions are on a 1 to 5 scale where 1 represents "disagree" or "not at all" and 5 represents "completely agree" or "extremely". The WHOQOL-BREF covers 4 domains (physical health, psychological, social relationships and environment). Higher scores indicate better quality of life.

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