Allogeneic Haematopoietic Stem Cell Transplant in the Management of Haematological Malignancy Relapsed After Initial Allogeneic Transplant

QUESTIONS TO BE ADDRESSED:

1. Is allogeneic haematopoietic stem cell transplant (allo-HSCT) clinically effective in the treatment of adult patients with haematological malignancy who have relapsed following an initial allogeneic transplant?

2. Is allo-HSCT cost effective in the treatment of adult patients with haematological malignancy who have relapsed following an initial allogeneic transplant?

3. Is there any evidence to indicate the comparative effectiveness of allo-HSCT compared to other management strategies in adult patients who have relapsed following an initial allogeneic transplant?

4. Is it possible to specify selection criteria which would enable the identification of those patients relapsing after an initial allo-HSCT who are most likely to have a favourable outcome from a second allo-HSCT?

SUMMARY:

This report updates a previous one issued by Solutions for Public Health in August 2012. That review had a broader scope, including treatment for relapse after a previous allo- or auto-HSCT. By contrast, this review is limited to second allo-HSCTs.

Background

- Haematopoietic stem cell transplant offers potential cure, or long term survival, in a range of haematological malignancies.
- Relapse rates following initial transplant vary depending on the underlying disease, disease stage at transplant and type of transplant.
- Relapse rates following allogeneic transplant (allo-HSCT) for acute leukaemia in first remission are around 30% at five years.
- Patients relapsing after an initial transplant have poor prognosis and present a significant management challenge.
- A further allo-HSCT following relapse after a first allo-HSCT is one option. Others include chemotherapy/supportive care, withdrawal of immunosuppressive treatment to enable a graft-versus-leukaemia effect, donor lymphocyte infusion or treatment with cytokines.
- The second allo-HSCT may be given after high dose myelo-ablative treatment or after a reduced intensity regime. The latter allows treatment to be offered to patients who would not tolerate a myelo-ablative regime and may generate a clinically useful graft-versus-leukaemia effect.
- In 2013, the latest year for which published data are available, there were 90 non-first transplant allo-HSCTs (6% of total allo-transplants) in Great Britain and Ireland. It is not known how many of these were for relapsed disease, or how many followed a first allo-HSCT rather than an initial autologous transplant.

- NICE published guidance on haematological malignancy, including the role of high dose therapy and stem cell transplant, in 2003. This made no recommendation regarding allo-HSCT as a second transplant for relapsed disease.
- The British Society for Bone Marrow Transplantation (BSBMT) guidance recommends the use of a first allograft after an autograft and subsequent relapse as a standard of care in Hodgkin lymphoma, mantle-cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma and peripheral T-cell lymphoma. The BSBMT does not specify any circumstances in which a second allo-HSCT following relapse after a first allo-HSCT is indicated.

Clinical Effectiveness

- Published evidence is limited to retrospective case series, with two recent controlled studies.
- These are from single centres, and report patients treated over periods in excess of 20 years over which time approaches to treatment may have changed.
- The studies are very heterogeneous with regard to underlying disease, disease stage, previous treatment, outcomes reported and statistical analysis of results.
- Non-relapse mortality was reported in four studies as between 18 to 63% at times varying between 100 days and 5 years.[1]
- Overall survival at five years was reported as 25% to 28%.
- Regression analysis suggested that time to relapse from first transplant (longer versus shorter) may be associated with longer survival from second transplant. In one of the four studies, age at time of second transplant (younger versus older) and stage of disease at second transplant (early versus advanced) may be associated with longer survival.
- We found some recently published papers:
    - A systematic review by Oliansky included a controlled study in acute lymphoblastic leukaemia in which the overall five-year survival after a second allo-HSCT was 16% to 23%, depending on whether the donor was related to the recipient. These results were better than those reported after chemotherapy, though the comparison may be confounded.
    - A controlled study by Sauer et al in acute myeloid leukaemia and myelodysplastic syndrome reported median overall survival of 130 days, from the date when relapse was diagnosed. There was no significant difference in one-year survival rates between people treated with supportive care, palliative or intensive chemotherapy, a second allo-HSCT or other treatments. The only factor influencing overall survival was time to relapse after first allo-HSCT.
    - An uncontrolled study by Christopeit et al in acute leukaemia reported complete remission in 74% of the 179 participants, though half of these participants later relapsed.
    - A second uncontrolled study by Benjanyan et al reported 12-month survival of 49% after a second allo-HSCT for relapsed acute myeloid leukaemia.
    - A third uncontrolled study by Andreola et al reported that 10% of patients with relapsed acute leukaemia treated with a second allo-HSCT were alive after median follow-up of 11.3 years. Two-year survival was 21% and five-year survival was 14%. Survival was better in those in remission at second transplant, those with an

[1] Definitions used for end-points in studies of transplant outcome are not always consistent across studies. EBMT point out that 'non-relapse mortality' has been defined as both 'deaths which could not be attributed to disease relapse or progression' and 'deaths without previous relapse or progression'. See: http://portal.ebmt.org/sites/clint2/clint/Documents/Statistical%20Endpoints_CLINT%20Project_final%20version.pdf (accessed 28 August 2012)

interval from first transplant to relapse of more than ten months and those who received total body irradiation.

Cost Effectiveness

- We found one cost study published since our first review. The authors identified 245 people with a previous allo- or auto-HSCT who had a second allo-HSCT at a hospital in the United States.
- The median costs for a second allo-HSCT were US$151,000 (£98,800), range $62,000 to $405,000 (£40,600 to £265,100). This was higher than the median cost of $109,000 (£71,300) recorded for allo-HSCT after a previous auto-HSCT. Median length of stay was 23 days, range 0 to 76 days.
- Multivariate analysis for the allo-allo group showed that costs were higher in patients with graft failure as a cause of the second transplant, a mismatched donor, acute graft-versus-host disease, pulmonary complications or infection costs were not associated with age, diagnosis, disease status or conditioning regime.

Safety

- Allo-HSCT carries a high risk of procedure related mortality and morbidity, particularly from graft-versus-host disease and infection. The studies included in this review reported rates of acute graft-versus-host disease varying between 20 and 65%; and rates of chronic disease between 17 and 76%. Transplant-related or non-relapse mortality was reported at rates between 18 and 63% at time points between 100 days and five years.

1 Context

1.1 Introduction

Haematopoietic stem cell transplant (HSCT) is used in the management of haematological malignancy to replace diseased bone marrow after the latter has been destroyed by chemotherapy. This is often referred to as stem cell rescue (or transplantation) after high dose therapy. The cells used for an HSCT may be from the patient's own bone marrow. This is termed an autologous (or auto-) HSCT. When donor cells are used, the procedure is an allogeneic (allo-) HSCT. The donor and recipient of an allo-HSCT need to be suitably matched for white blood cell antigens. Closer matches are generally possible when a sibling donor is available. Alternatively, a suitably matched unrelated donor may be used. Stem cells are derived from bone marrow, peripheral blood and umbilical cord.[1]

High dose therapy destroys the patient's diseased bone marrow and is therefore described as myelo-ablative. Treatment involves chemotherapy and/or radiotherapy. Recently, lower dose regimes which do not fully destroy the bone marrow have been introduced. These are known as reduced intensity conditioning (RIC) or non-myelo-ablative (NMA) regimes.[2] They may enable older, less fit patients, who would not tolerate high dose therapy, to have a transplant. By sparing some of the patient's own bone marrow, when used with an allo-HSCT, RIC may enable a graft-versus-leukaemia effect which may improve outcome.

Allo-HSCT is established in younger patients with leukaemias not responding to chemotherapy alone. Over recent years, allo-HSCT has also been used in younger

[2] Non-myeloablative conditioning before allo-HSCT is referred to as 'mini-allo' in the 2003 NICE 'improving outcomes' guidance.[1] This terminology does not seem to be widely used.

patients with myeloma and some lymphomas. The introduction of RIC regimes has extended the use of allo-HSCT to patients in whom it would not previously have been considered.[1]

Although allo-HSCT may be potentially curative in a range of haematological malignancies, disease relapse after a first transplant remains a significant problem and is the major cause of post-transplant (that is, non-transplant related) mortality.[2]

The prognosis for patients with any haematological malignancy relapsing after an initial HSCT is poor and the best therapeutic option at this point in the care pathway is uncertain. For patients relapsing after a first allo-HSCT, treatment options include further chemotherapy; withdrawal of immunosuppressive treatment (given to reduce graft-versus-host disease) in order to enable a graft-versus-leukaemia response; infusion of donor lymphocytes; treatment with cytokines; or a second allo-HSCT.[3]

This report reviews the evidence for allo-HSCT as a second transplant in patients with any haematological malignancy who have relapsed after an initial allo-HSCT. It does not include review of the evidence for a second auto-HSCT in patients relapsing after an initial autologous transplant, or the evidence for allo-HSCT in patients relapsing after an initial auto-HSCT, or the evidence for alternative treatment strategies at this point in the patient pathway (that is, at the point of relapse following an initial transplant). It updates the review issued by Solutions for Public Health in August 2012: we repeated the literature search and added more recent publications, but otherwise made only minor changes to the text.

1.2 Existing national policies and guidance

The National Institute for Health and Clinical Excellence (NICE) published guidance in 2003 supporting the availability of auto- and allo-HSCT for the treatment of specified haematological malignancies. This guidance made no recommendations regarding the use of second transplants in patients who relapsed following an initial transplant.[1] The guidance has not been updated.

The British Society for Bone Marrow Transplantation (BSBMT) guidance recommends the use of a first allograft after an autograft and subsequent relapse as a standard of care in Hodgkin lymphoma, mantle-cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma and peripheral T-cell lymphoma. The BSBMT does not specify any circumstances in which a second allo-HSCT following relapse after a first allo-HSCT is indicated.[4]

2 Epidemiology

HSCT offers a potential long-term curative option for a range of haematological malignancies but is associated with high treatment related mortality.[1] Repeat transplant may be considered for primary graft failure/failure of engraftment as well as for treatment of relapse of the underlying disease. Relapse is the major cause of mortality in patients who have had an initially successful transplant.[2,3]

Post-transplant relapse rates vary by underlying condition and by clinical state at first transplantation (for example, whether the transplant was done in first or second remission; whether or not complete remission had been achieved at the time of transplantation, etc.). The five -year incidence of relapse in low- and intermediate-risk leukaemias undergoing first allo-HSCT in one US centre was reported as 32%.[7] For acute lymphoblastic

leukaemia, a five -year relapse rate of 29% (+/- 9%) has been reported for patients transplanted whilst in first remission; and a rate of 52% (+/-8%) for patients transplanted in second remission.[8]

The BSBMT maintains a register of HSCTs undertaken in the UK and Republic of Ireland. In 2013, the latest year for which published data are available, there were 3840 stem cell transplants. Of these, 1615 (42%) were allo-HSCTs and 2218 (58%) were auto-HSCTs. The majority of allografts (1525/1615, 94%) were first transplants. There were 90 non-first transplant allo-HSCTs (6% of total allo transplants). In 2010, the majority of these used peripheral blood as the source of stem cells (79/90, 88%); this information is no longer routinely published. The BSBMT registry does not publish the indications for these non-first transplant allo-HSCTs, so these will include not only second transplants for relapsed haematological malignancy but other indications as well. It is also not possible to identify how many of these non-first all-HSCTs followed an initial auto-HSCT rather than being a second allo transplant. The figures include all activity throughout Great Britain and Ireland, with no breakdown by country or age of recipient.[5]

We received more detailed data from NHS England:

“Specifically, in relation to the BSBMT registry based data, over a 10 calendar year period (2000-2009, inclusive), 184 patients underwent a second AlloSCT for relapse disease, primarily for acute myeloid leukaemia (AML 51%, CML 14%, lymphoma 7%, myeloma 2% & MDS 25%). Across the period the proportion of patients receiving a second AlloSCT with a PFS1 >12 months was 67% with year-on-year trends (Figure 1A). Furthermore, when status at transplant is considered, only 36% of patients are in CR though a further 12% have chemo-sensitive disease.”(Personal communication from Dr Sally Nelson, quoting Professor Gordon Cook)

The available data are insufficient to determine either the extent to which allo-HSCT is being used as a second transplant procedure for relapsed haematological malignancy after a first allo transplant in the NHS in England and Wales or whether there is any trend for year-on-year increase (or decrease) in the numbers of procedures for this indication.

3 The intervention

The procedure is similar to that for a first allo-HSCT. The patient is admitted to hospital for treatment with a conditioning regime (myelo-ablative or RIC) and the donor stem cells are then given via transfusion into a central venous line. The patient remains in hospital for weeks or months following transplantation during which time they are monitored for immunosuppression, infection, signs of engraftment and graft-versus-host disease.[10]

As noted in section 1 above, the prognosis for relapsed disease following initial transplantation is poor. There are a number of options for treatment at this point in the care pathway, including chemotherapy, supportive care, donor lymphocyte infusion, withdrawal of immunosuppressive therapy, cytokines or second transplant.

4 Findings

We included all the papers from the 2012 review. This identified no systematic reviews or randomised controlled trials. It included two review papers analysing outcomes from allo-HSCT as a second transplant procedure in patients with haematological malignancy; and

three additional case series published subsequent to the reviews, each of which contained at least 50 patients. All the studies included in these reviews, and those published subsequently, were retrospective case series. It also included one follow-up study of patients treated with allo-HSCT for acute leukaemias, since within this cohort was a group who relapsed after transplant, some of whom went on to second allo-HSCT. Although the reviews did not describe their methodology, and cannot therefore be confirmed as systematic reviews, we did not find any relevant studies published within the relevant search dates that had been missed by the reviews.

In August 2015, we carried out a second database search including MedLine, Embase, Cochrane and TRIP. Full details of the search strategy and inclusion criteria are given in section 7, below. We excluded uncontrolled studies with fewer than 150 participants, because they would have added little additional information. We included one systematic review [11] which included a controlled study [12], one controlled study published since the systematic review [13] one uncontrolled study [14] and one cost study [15].

The included reviews and primary studies are summarised in Tables 1, 2 and 3, with the new studies in italics. We summarise the new studies' results separately below.

4.1 Evidence of effectiveness

Table 1. Second Allogeneic Transplant for Haematological Malignancy, Evidence Summary Table (*new studies in italics*)

Study	Patients	Intervention(s)	Outcomes	Comments
Reviews				
Arfons, 2009 [16] Review of allo-HSCT as a second transplant procedure in patients with myeloid malignancy **(search strategy and inclusion criteria not described)**	9 studies (total 221 patients) with myeloid malignancy and **Graft failure after allo-HSCT** or umbilical cord blood transplantation Number of patients per study ranged from 4-82 Adults and children (age range 2 months to 75 years)	Second allo-HSCT Myelo-ablative conditioning (various regimens)	**Engraftment**: reported in 8 studies, 62-100% (Largest study, n=82, 62%) **Acute GvHD**: reported in 8 studies, 2/11 to 6/9 (largest study, n=82, 41±7% **Chronic GvHD**: Reported in 8 studies, 1/11 to 3/4 (largest study, n=82, 17±5%) **TRM or NRM**: 18 to 63% (largest study, n=82, 53±6%) **Relapse rate**: 1/11 to 53±9% (time of occurrence varied) **PFS/OS**: Different measures used in each study. Largest study, n=82, reported 3 year EFS 26±5% and OS 30±5%	All studies appear to be retrospective case series Authors conclude that small study sizes, heterogeneity between and within studies etc preclude clear recommendations re second allo-transplantation. Authors note lack of any prospective studies addressing second transplantation after graft failure or relapse. Available data indicates that for patients in relapse, best candidates for second allo-HSCT are younger, have late-relapsed disease and are in remission at time of consideration for second transplant. Large, multi-centre trials are needed to confirm these findings.
Arfons (continued)	8 studies (712 patients) with myeloid malignancy and **Relapse after allo-HSCT** Number of patients per study ranged from 6-279 Adults and children (age range 1.5 to 69 years)	Allo-HSCT Myelo-ablative conditioning , various regimens (7 studies) Combination of myelo-ablative and non-myelo-ablative regimens (1 study)	**Engraftment**: reported in 6 studies, 83%-98% **Acute GvHD**: reporting varied between studies. Largest study, n=279, 29% at 100 days **Chronic GvHD**: reporting varied between studies. Largest study, n=279, 41% at 5 years. **TRM or NRM**: reporting varied between studies, Bosi, n=170, 46% at 5 years;	

			Eapen, n=279, 30% at 5 years. **Relapse rate**: reporting varied between studies, Bosi: 59% at 5 years; Eapen, 42% at 5 years. **PFS/OS**: reporting varied between studies, Bosi: 5 year DFS: 25%, OS: 26%; Eapen: 5 year DFS 28%, OS 28%.	
Freytes, 2009 [17] **Review of second allo-HSCT in patients with lymphoma** **(search strategy and inclusion criteria not described)**	11 studies (197 patients) with lymphoma relapsing after **auto**-HSCT Number of patients per study: 2 to 114 Age reported in 8 studies (range 15 to 65 years)	Allo-HSCT **Myeloablative conditioning** (various regimens)	**TRM**: Length of follow up and reporting varied between studies Largest study: n=114, 21% at 1 year, 25% at 5 years Other outcomes varied between studies **DFS/OS**: largest study, n=114, at 5 years: OS 24%, DFS 5%	All studies appear to be retrospective case series. Authors suggest responsive disease and prolonged time interval between transplants as selection criteria Authors conclude from available data that <5% of patients can be considered cured of lymphoma by myelo-ablative allo-HSCT Long term studies needed to confirm cure rates from RIC allo-HSCT Studies needed to address optimal patient selection
	15 studies (569 patients) with lymphoma relapsing after **auto**-HSCT Number of patients per study: 2 to 247 Adults and children (range 9 to 70 years)	Allo-HSCT **Reduced intensity conditioning** (various regimens)	**TRM**: Length of follow up and reporting varied between studies. Largest study: n=247, 10% at 30 days, 31% at 100 days Other outcomes varied between studies **PFS/OS** Largest study, n=247, at 5 years: **OS** 28%, **PFS** 19%	
Oliansky, 2012 [11] ***Review of treatment of acute lymphoblastic leukaemia (ALL)***	*302 participants with ALL in first relapse. 182 had chemotherapy, 65 MUD allo-SCT, 42 MSD allo-SCT ad 13 auto-SCT*	*Matched related allo-HSCT, matched unrelated allo-HSCT, auto-HSCT, chemotherapy.*	***5-year OS:** Matched related allo-HSCT 23% (95% confidence interval 10% to 36%), matched unrelated allo-HSCT 16% (7% to 26%), auto-HSCT 15% (0% to 35%, chemotherapy 4% (1% to 7%).* *Any SCT versus chemotherapy: P < 0.001*	*Unclear degree of confounding. Grade 2++ by systematic review authors ("high-quality systematic reviews of case-control or cohort studies; or high quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal")*

Primary Studies (n>50 patients, *n>150 patients*)				
Hosing, 2005 [18] **Retrospective case series** **Single-centre, USA**	72 patients (median age 42 years, range 14 to 75) undergoing second allo-HSCT for acute myelogenous leukaemia Patients treated between 1989 and 2003 97% had adverse or intermediate cytogenetics at time of initial diagnosis 87% received 2nd allo for disease relapse or progression 13% received 2nd allo for failure to engraft after 1st transplant At time of 2nd transplant, 50% were in untreated relapse, only 3% were in complete remission	2nd allo-HSCT Various conditioning regimens: 51% myelo-ablative; 47% reduced intensity 79% same donor as 1st transplant	Engraftment: 87.3% (n=62) Median time to engraftment: 12 days (range 6 to 50) Acute GvHD: 35% (25 out of 71 evaluable patients) Chronic GvHD: 31% (16 out of 51 evaluable patients) Complete remission: 74% (n=52) (CR defined on bone marrow aspiration at day 30) TRM: 36%, 24 patients died within 100 days of second transplant Death during follow-up: 60 patients, of whom 32 (53%) died of disease relapse/progression OS: at median follow-up of 25 months, median survival was 6 months; OS in patients achieving CR was 18% Univariate analysis to identify predictors of response and survival: Only factor statistically significantly associated with survival was time to relapse after first transplant: patients with relapse or progression more than 1 year after first transplant had better outcome than those relapsed/progressed < one year after first transplant: HR 2.4, 95% CI 0.99 to 5.7, p=0.04.	Patients heterogeneous, particularly in terms of transplant regimens used Retrospective analysis Authors note that 40% of patients with lower leukaemia burden at time of second transplant survived at least 2 years. However, in univariate analysis >5% BM blasts at time of 2nd transplant was not a statistically significant predictor of survival (HR1.7, CI 0.9 to 3.1, P=0.08). Patients treated over 14 year period during which approaches to conditioning changed and new chemotherapeutic agents came into use Time points for measuring outcomes not clearly defined

Hill, 2010 [19] **Retrospective series** **Single-centre, USA**	98 consecutive patients (age range 18 to 63) treated between 1987 and 2008 48 (49%) had previous **auto-HSCT** 50 (51%) had previous **allo-HSCT** Diagnoses included acute leukaemias, chronic leukaemias, lymphoma, myeloma, myeloproliferative disease and aplastic anaemia 14 (23.7%) in complete remission at time of 2nd allo 45 (76.3%) were <CR at 2nd allo	Allo-HSCT Myelo-ablative conditioning 60% (n=59) Non-myelo-ablative conditioning 40% (n=39)	Patients undergoing NMA conditioning were older than patients undergoing myelo-ablative conditioning (P=<0.001) **Median survival**: 3.2 months – myelo-ablative 14.7 months – NMA (P=<0.001) **NRM (cumulative):** 36 (61%) – myelo-ablative 16 (41%) – NMA (P=0.16) ie difference not statistically significant **Relapse:** 15 (25.4%) – myelo-ablative 18 (46.2%) – NMA (P=0.12) ie difference not statistically significant Prognostic variables (univariate analysis): **Myelo-ablative vs NMA**: NRM: HR 2.24 (1.73 to 6.63, P=0.008) Mortality: HR 2.3 (1.42 to 3.74, P<0.001) Relapse: HR 0.75 (0.42 to 1.65, P=0.6) ie difference not statistically significant **Time between transplants <3months vs >3months**: NRM: HR 4.1 (2.22 to 7.60, P=<0.001) ie difference statistically significant Mortality: HR 2.97 (1.69 to 5.22, P=<0.001) ie difference statistically significant **Disease status at 2nd transplant: <CR vs CR** Relapse: HR 3.22 (1.12 to 9.27, P=0.031) ie difference statistically significant NRM: HR 1.18 (0.62 to 2.25, P=0.62) ie	Reason for 2nd transplant (eg relapsed, refractory or progressive disease; failure of engraftment, etc) not reported Patient heterogeneity in respect of condition, prior treatment, conditioning regimen etc Patients treated over nearly 20 year period during which approaches to conditioning changed and new chemotherapeutic agents came into use Authors note that high NRM following myelo-ablative conditioning seen in this study is similar to that found by others Authors conclude that greater risk of relapse following NMA (although this was not, in fact, statistically significant) is offset by the lower risk of NRM compared to myelo-ablative conditioning Authors conclude that their data support use of NMA conditioning for 2nd allo-HSCT and identify duration between transplants and disease status as predictors of relapse, NRM and death.

			difference not statistically significant Mortality: HR 1.22 (0.72 to 2.08, P=0.46) ie difference not statistically significant	
Rezvani, 2012 [20] **Retrospective case series** **Single-centre, UK**	124 consecutive patients (age range not given – ages categorised as: <20 years: n=4 20-40: n=62 >40: n=63 Treated between 1985 and 2010 64 (51.6%) had previous **auto-HSCT** 60 (48.4%) had previous **allo-HSCT** Diagnoses included acute leukaemias, chronic leukaemias, myelo-dysplastic syndrome, non-Hodgkins lymphoma and 'other'	Allo-HSCT Myelo-ablative conditioning: 72 (58.1%) Reduced intensity conditioning: 52 (41.9%)	Median survival: 9.6 months NRM at 1 year: 45% (95% CI 37 to 55%) – 41.9% RIC vs 58.1% MA OS at 5 years: 25.4% (18 to 34%) Cox regression analysis used to correlate pre-2nd allo patient characteristics with NRM (1 year) and OS (5 year): Statistically significant positive correlation with **NRM** found for following risk factors: **Disease stage**: advanced: 54.1% (95% CI 43 to 68%) vs early: 10% (2 to 64%), P=0.008 **Age**: <20: 50% (5-100% 20-40: 35.8% (26 to 50%) >40: 54.6% (43 to 69%), P=0.007 **Interval between 1st and 2nd HSCT**: <20 months: 59.8% (48 to 74%) >20 months: 30.3% (21 to 44%), P=0.001 Diagnosis, 1st HSCT auto vs allo, duration of disease, donor match HLA-match sib vs other, patient/donor sex, conditioning RIC vs MA, cells infused and GvHD prophylaxis were not statistically significantly correlated with NRM (P>0.05) Statistically significant positive correlation with **OS** found for following risk factors: **Disease stage**: Early: 57.1% (28 to 82%) vs	Indications for second transplant not described Patients treated over a 25 year period during which approaches to conditioning changed and new chemotherapeutic agents came into use Patients appear highly heterogeneous in terms of condition, previous treatments and disease status at 2nd transplant

			Advanced: 12.4% (6 to 25%), P=0.019 **Age:** <20: 25% (5 to 67%) 20-40:36.7% (26 to 49%) >40: 12.4 (6 to 25%), P=0.016 **Interval between 1st and 2nd HSCT**: <20 months:14.7% (7 to 27%) >20 months: 34.7% (26 to 45%), P=0.005 Diagnosis, 1st HSCT auto vs allo, duration of disease, donor match HLA-match sib vs other, patient/donor sex, conditioning RIC vs MA, cells infused and GvHD prophylaxis were not statistically significantly correlated with OS (P>0.05) **1 year NRM stratified by EBMT risk score** (a composite score combining risk factors): Low risk (score 0-3): 28% (15 to 53% Intermediate risk (score 4): 33.2% (21 to 52%)) High risk (score >4): 58.8% (47 to 73), P=0.0003 **5 year OS stratified by EBMT risk score**: Low risk (score 0-3): 51.7% (33 to 70%) Intermediate risk (score 4): 29.3% (17 to 46%) High risk (score >4): 10.4% (2 to 42%), P=0.0003	
Sauer, 2015 [13]	*108 patients with AML or MDS with previous allo-*	*Best supportive care 11 (10%*	***Adjusted overall one-year survival:*** *Best supportive care 0%*	*Analysis adjusted for predictive variables including age, disease*

Controlled study ***Single centre, Germany***	*HSCT, a CR and subsequent relapse*	*Palliative chemotherapy 27 (25%)* *Intensive chemotherapy 16 (15%)* *Intensive chemotherapy plus stem cell boost 16 (15%)* *Second allo-HSCT 19 (18%)* *Chemotherapy followed by DLI 3 (3%)* *Tapering of immunosuppression followed by DLI 1 (1%)*	*Palliative chemotherapy 3.6%* *Intensive chemotherapy 34%* *Intensive chemotherapy plus stem cell boost 29%* *Second allo-HSCT 26%* *Chemotherapy followed by DLI 0%* *Tapering of immunosuppression followed by DLI 100%* *These survival rates did not differ significantly.* *Factors influencing overall survival: time to relapse after first allo-HSCT. No other factor was significant.*	*status before first transplantation and genetic risk profile.* *Lack of significant differences may be due to lack of power. Sauer et al do not report a power calculation.*
Christopeit, 2013 [14] ***Cohort study*** ***Several centres in Germany***	*179 patients with AML (132, 74%), ALL (46, 26%), unclassifiable leukaemia (1, <1%). All had a relapse after previous HSCT.* *Median age at second HSCT 39 years, range 16 to 68 years.*	*Second matched allo-HSCT.*	***Complete remission:*** *132/179 (74%).* ***Relapse after initial remission:*** *65/132 (49%).* ***2-year overall survival:*** *25%, standard error 4%.* ***Factors associated with overall survival after second HSCT:*** *remission duration after HSCT1 hazard ratio (HR) = 2.37, 95% CI = 1.61 to 3.46, P < 0.001.* *stage at HSCT2: HR = 0.53, 95% CI = 0.34 to 0.83, P = 0.006.* *Outcome of HSCT2 was better after related HSCT1 than after unrelated HSCT1: 2-year OS 37% +/- 6% v 16% +/- 4%, respectively, HR = 0.68, 95% CI = 0.47 to 0.98, P = 0.042.*	
Benjanyan, 2015	*1788 patients with AML*	*Second allo-HSCT +/-*	*Survival for 12 months or more after*	*No other results were reported for*

[21] ***Cohort study*** ***More than 500 centres, worldwide***	*who relapsed after previous allo-HSCT, of whom 369 were treated with a second allo-HSCT.* *For all 1788 patients, median age was 32 years and 613 (34%) were 18 years or younger. Their median time from relapse to second allo-HSCT was 3 months.*	*DLI =/- chemotherapy.* *MA conditioning 181 (49%), RIC/NMA conditioning 110 (30%), missing 25 (9%).*	*relapse: 182 (49%)*	*the patients who had a second allo-HSCT.*
Andreola, 2015 [22] ***Cohort study*** ***120 European centres***	*286 patients with acute leukaemia (AML 166 (58%), ALL 120 (42%)) who relapsed after previous allo-HSCT and who were treated with a second HSCT.* *Median age at 2nd HSCT 30 years.*	*Second allo-HSCT +/- chemotherapy*	*Median follow-up 11.3 years.* ***Survival:*** *30 patients (10%), of whom 21 (7%) had no evidence of disease.* ***Overall survival:*** *2 years 21%, 5 years 14%, 10 years 10%.* ***Leukaemia-free survival (LFS):*** *2 years 15%, 5 years 12%, 10 years 7%.* ***Prognostic factors on multivariate analysis for overall survival****: complete remission at second transplant, hazard ratio (HR) 0.59, 95% CI 0.43 to 0.81; interval from first transplant to relapse of > 10 months, HR 0.54, 95% CI 0.40 to 0.74; total body irradiation, HR 0.49, 95% CI 0.33 to 0.74. These three factors were also significantly associated with LFS and cumulative incidence of relapse.*	

GvHD – graft versus host disease; TRM – transplant-related mortality; MDS – myelodysplastic syndrome; CR – complete response; DLI – donor lymphocyte infusion NRM – non-relapse mortality; PFS – progression-free survival; OS – overall survival; DFS – disease-free survival; CR – complete remission; NMA- non-myeloablative conditioning; HR – hazard ratio; RIC – reduced intensity condition; EBMT – European Bone Marrow Transplant. The EBTM risk score is shown at Section 10.

We found one study (Arellano et al, 2007) which followed a cohort of 310 patients with acute leukaemia (229 with AML, 81 with ALL) receiving allogeneic-HSCT from HLA-matched donors between 1982 and 2005. Mean follow-up post-transplant was 5 years (range 0.5 to 22 years). Of the cohort of 310 patients, 100 relapsed after transplant (32%). These included 28 of 81 patients with ALL (35%); and 72 of 229 (31%) of patients with AML. The authors present the outcomes of different treatment strategies for the relapsed patients. The outcomes are summarised in Table 2.

We have included this study even though the number of patients receiving a second allo-HSCT was very small (13 patients) because it provides some comparison with outcomes from alternative interventions. However, the methodological problems inherent in the study design (both bias and confounding) do not enable any firm conclusions to be drawn.

Table 2. Outcomes from treatment for relapsed acute leukaemia after initial allo-HSCT

Study	Outcome	Initial salvage therapy following relapse (100 patients)				Comments
Arellano, 2007 Retrospective cohort study Single-centre, USA		**Chemo/supportive care** (n=69)	**Second transplant** (n=13)	**DLI ± chemotherapy** (n=11)	**Cytokines (GM-CSF/IFN-a)** (n=7)	Non-randomised, retrospective observational study. Patients treated over a period of 23 years. No data presented to indicate whether baseline characteristics in the four treatment groups were similar and no discussion of how treatment modalities were decided for each patient – so selection bias for different treatments cannot be excluded Conditioning regimen(s) for patients undergoing 2nd allo-HSCT not
	Complete remission:	5 (8%)	8 (62%)	5 (45%)	5 (71%)	
	GvHD post relapse:	5 (8%)	7 (54%)	4 (36%)	5 (71%)	
	Post-relapse survival (days) – median (range):	51 (0 to 1556)	303 (40 to 3695)	84 (15 to 882)	442 (149 to 1272)	
	Patients alive (days after relapse for each patient):	3 (1556, 963, 832)	1 (3695)	0	3 (400, 1247, 1272)	

						described Authors conclude that their study confirms poor outcomes in acute leukaemia relapsed after allo-HSCT and 'underlines the need for prospective studies aimed at inducing durable GvL effects'.

DLI: donor lymphocyte infusion

The authors used uni- and multi-variate analysis to identify factors associated with death following post-transplantation relapse. This analysis is shown in Table 3.

Table 3. Factors associated with death after post-transplantation relapse (from Arellano et al, 2007)

Factor	P-value		Odds Ratio (95% CI)	Comments
	Univariate	Multivariate		
Time to relapse >136 days	<0.001	<0.001	0.35 (0.22 to 0.57)	Authors suggest immune-based therapy (to induce a GvL effect) may be 'promising' (reviewer note: this is based on very small numbers, inherent bias from the study design and the 95% CI upper limit is close to 1 – ie no statistically significant difference between groups)
Immune-based salvage therapy	<0.001	0.025	0.63 (0.38 to 0.98)	
Peripheral blood as stem cell source	<0.001	<0.001	0.38 (0.24 to 0.61)	
Favourable cytogenetic risk group	0.040	NS	-	

All the included studies were case series based on retrospective review of patient notes. There is potential for both bias and confounding in this type of study design. It is not clear how full ascertainment of patients was or how complete follow-up after second transplant was. All the studies included patients who had been treated over periods in excess of 20 years, during which time treatment regimens and selection criteria are likely to have changed. The reason for second transplant is not always made clear, with some studies including patients who had failure to engraft/primary graft failure as well as those with disease relapse. Selection criteria are not clearly described and it is not clear how patients offered allo-HSCT as a second transplant procedure would compare with the overall cohort of patients relapsed after initial HSCT. It is also unclear whether selection criteria varied between centres (studies) or within centres over time. Two primary studies

included patients with a wide variety of diagnoses, whereas the remaining studies focussed on particular haematological malignancies. Prior treatments (including whether first transplant was an auto- or allo-HSCT) and disease state at time of second transplant varied widely between patients. The outcomes reported by the various studies varied, some reported outcomes (survival, mortality etc) at a fixed time point (usually 5-years) whilst others used actuarial measures (Kaplan-Meier curves etc).

Across all studies, rates of engraftment of the second allo-HSCT varied between 62 and 100% in those studies in which this outcome was reported. Overall survival (OS) varied between studies with one study (Hosing, 2005) reporting an OS of 18% in acute myelogenous leukaemia patients transplanted in complete remission at median follow up of 25 months. Other studies reported 3-year survivals of 30% (Arfons 2009, patients with myeloid malignancy relapsed after allo-HSCT), and 27% for related donor and 44% for unrelated donor (Arfons, patients with myeloid malignancy relapsed after auto-HSCT). Five-year survival rates of 25.4% to 28% were reported across those studies using this outcome.

In studies in which outcomes after myelo-ablative and non-myelo-ablative conditioning regimes were reported separately, myelo-ablative conditioning was found to be associated with greater risk of non-relapse mortality than non-myelo-ablative conditioning in two studies (Hill, 2010; Rezvani, 2012).

Three studies (Hosing, 2005; Hill, 2010; and Rezvani, 2012) used univariate analysis to identify statistically significant predictors of response and survival. In all three studies, longer time to relapse after first transplant was found to be associated with better survival from second transplant. In addition, Rezvani, 2012, also found statistically significant correlations between disease stage (early vs advanced) at second transplant and overall survival; and age (less than 40 vs over 40) and overall survival.

The study by Arellano, 2007, presents outcomes from different treatments given to patients who had relapsed following an initial allo-HSCT for acute leukaemia. It is not possible to draw any conclusions regarding the comparative effectiveness of the different treatments since the clinical criteria by which patients were selected for the different treatments are not stated and there may have been significant differences in the baseline characteristics of the different treatment groups. For example, it is likely that patients who had chemotherapy/supportive care may have had more advanced disease and/or been more unwell than patients given other treatments. As this study included patients who had had initial transplant over a period of 23 years, we cannot be sure that the criteria for determining which treatment would be offered did not change as a result of changing clinical practice. We cannot also be sure whether or not all the treatment options were available throughout the period or whether some are more recent innovations.

The studies reviewed here reflect the scope of the first review, which included studies of participants who relapsed after an auto-HSCT. There was no separate reporting by type pf first transplant. We have not removed these studies from the second edition of the review, but the studies' heterogeneity should be taken into account by readers.

4.1.1 New studies

The systematic review [11] found one study [12] comparing survival rates after transplantation and chemotherapy. The overall five-year survival rate was 16% to 23%, depending on whether the donor was related to the recipient. Survival rates were higher after transplantation but it is unclear the extent to which confounding might explain this.

Sauer et al reported no differences in adjusted one-year survival rates between patients with relapsed AML and MDS treated with best supportive care, chemotherapy and a second allo-HSCT.[13] Lack of significant differences may be due to lack of power – Sauer et al do not report a power calculation. The only factor which significantly predicted response to salvage treatment or survival was time to relapse after the first allo-HSCT.

Christopeit et al published a study of second HSCT in people with relapsed acute leukaemia.[14] They reported a complete remission in 74% of the 179 participants, though half of these participants later relapsed. Two-year overall survival was 25%. Longer survival was associated with longer duration of remission after first allo-HSCT, with lower stage at second HSCT and with a related fist HSCT.

Benjanyan et al reported one-year survival in 49% of those treated with a second allo-HSCT for relapsed AML.[21]

Andreola et al reported that 10% of patients with relapsed acute leukaemia treated with a second allo-HSCT were alive after median follow-up of 11.3 years.[22] Two-year survival was 21% and five-year survival was 14%. Survival was better in those in remission at second transplant, with an interval from first transplant to relapse of more than ten months and those who received total body irradiation.

4.2 Trials in progress

We searched clinicaltrials.gov for studies of second allo-HSCTs following a previous allo-HSCT and subsequent relapse. We found no such studies, but the website only allows text searching. It was therefore difficult to specify the search terms with precision and some studies may have been inadvertently overlooked.

4.3 Evidence of cost-effectiveness

We found one cost study published since our first review.[15] The authors, Khera et al, identified 245 people with a previous allo- or auto-HSCT who had a second allo-HSCT. All the second transplants and 66% of the first transplants were at a single hospital in Phoenix, USA.

Only the 55 patients with a previous allograft were eligible for inclusion in this report. Of these, 36 (65%) of second transplants were for relapse, with nearly all the others (14 (25%)) being for graft failure. Results for the patients without relapse were not separately reported, so strictly the paper by Khera et al fell outside the criteria for inclusion in this review. However, because of the lack of other cost studies, we include this one.

Inpatient and outpatient cost data were ascertained from the hospital's administrative database, from seven days before the transplant until one hundred days after transplant. Costs were denominated in 2010 United States dollars, with a method of cost allocation described as "traditional" rather than activity-based. Costs of donor identification and graft procurement, patient time and productivity losses, transport and accommodation were excluded; more critically, the authors did not include professional charges and the costs of prescription medications.

The median costs for a second allo-HSCT were $151,000 (£98,800), range $62,000 to $405,000 (£40,600 to £265,100). This was higher than the median $109,000 (£71,300) recorded for allo-HSCT after a previous auto-HSCT. Median length of stay was 23 days, range 0 to 76 days.

Multivariate analysis for the allo-allo group showed that costs were higher in patients with graft failure as a cause of the second transplant, a mismatched donor, acute graft-versus-host disease, pulmonary complications or infection Costs were not associated with age, diagnosis, disease status or conditioning regime.

This study has a number of limitations:

- It was conducted in the United States, which limits its generalisability to the NHS.
- Several important costs were excluded from the analysis.
- The method of allocation of costs, especially overheads, may not have been wholly accurate.
- The study did not relate costs to outcomes, so that the cost effectiveness of the procedure cannot be estimated.

4.4 Safety

The high rates of morbidity and mortality from allo-HSCT are well known, mainly from graft-versus-host disease and infection. Early complications include mucositis, hepatic veno-occlusive disease (painful hepatomegaly, jaundice and fluid retention), transplant-related lung injury, infections secondary to mucositis or immunosuppression and acute graft-versus-host disease (aGvHD). Delayed complications include chronic graft-versus-host disease (cGvHD) which may cause significant morbidity and be difficult to manage, and infertility. The frequency of secondary malignancy is increased after HSCT.[2]

The studies included in this review reported rates of aGvHD varying between 20 and 65%; and rates of cGvHD between 17 and 76%. Transplant-related or non-relapse mortality was reported at rates between 18 and 63% at time points between 100 days and 5 years.

4.5 Summary of section 4

Evidence on the clinical effectiveness of allo-HSCT as a second transplant procedure in patients who have relapsed following an initial allo transplant for haematological malignancy is limited to retrospective case series only and two controlled studies. These are from single centres and report on patients treated over periods in excess of 20 years, over which time clinical practice and treatment options may have changed. This means that, in addition to the problems of bias and confounding that are inherent in retrospective case series, there is also very wide heterogeneity both between and within studies. Many of the studies included patients who had had an initial auto-HSCT as well as patients whose first transplant was allo. The auto-allo group are outside the scope of this review. However, the analysis of these studies indicated that auto vs allo as first transplant was not correlated with outcome.

The available data indicate that, across a range of haematological malignancies, allo-HSCT undertaken as a second transplant for relapse after a first allo-HSCT is associated with a non-relapse mortality of between 18% and 63% at points varying between 100 days and five years after transplantation (depending on the way in which this outcome was reported in the different studies). Overall survival was reported as varying between 23% and 28% at 5-years in those studies reporting this outcome.

One study in the first version of this review also reported outcomes from other interventions at this point in the care pathway (chemotherapy/supportive care, donor lymphocyte infusion, cytokines) as well as from second allo-HSCT. As this study was neither randomised nor controlled, and we cannot know whether the patients were comparable at baseline, we cannot conclude anything about the comparative effectiveness of the different interventions.

One more recent controlled study reported better results in relapsed ALL after HSCT than after chemotherapy; another reported no significant differences between supportive care, chemotherapy and HSCT in AML and MDS.

Univariate regression analysis in studies cited in the first version of this review suggests that time between first transplant and relapse (longer vs shorter), stage of disease (early vs advanced) and age of patient (younger vs older) may predict better overall survival from allo-HSCT as a second transplant procedure in relapsed haematological disease. More recent studies report better outcomes are associated with longer duration of remission after first allo-HSCT, with lower stage at second HSCT and with a related first HSCT donor.

5 Discussion and conclusions

1. Is allogeneic haematopoietic stem cell transplant clinically effective in the treatment of adult patients with haematological malignancy who have relapsed following an initial allogeneic transplant?

   Published evidence of clinical effectiveness is limited to retrospective case series and two controlled studies. These are mostly single centre and report outcomes on patients treated over periods of more than twenty years, during which time approaches to treatment and options available may have varied. Risks of bias and confounding are inherent in the study design. The patients reported in these studies are heterogeneous with respect to disease, disease stage, previous treatment, conditioning regimes as well as demographic factors (age, gender, etc). The outcomes reported from these studies indicate a 5-year overall survival from allo-HSCT as a second transplant of 16% to 28%. Non-relapse mortality was reported as 18 to 63% over periods varying from 100 days to 5 years.

2. Is allogeneic haematopoietic stem cell transplant cost effective in the treatment of adult patients with haematological malignancy who have relapsed following an initial allogeneic transplant?

   We found a study indicating the cost of second HSCTs at a hospital in the United States, but it did not report the cost effectiveness of the procedure.

3. Is there any evidence to indicate the comparative effectiveness of allo-HSCT compared to other management strategies in adult patients who have relapsed following an initial allogeneic transplant?

   We found one study of the comparative effectiveness of allo-HSCT compared to other management strategies in patients who have relapsed following an initial transplant for haematological malignancy. It reported no significant difference in one-year survival rates between people with acute myeloid leukaemia and myelodysplastic syndrome treated with supportive care, palliative or intensive chemotherapy, a second allo-HSCT or other treatments. The only factor influencing overall survival was time to relapse after first allo-HSCT.

4. Is it possible to specify selection criteria which would enable the identification of those patients relapsing after an initial transplant who are most likely to have a favourable outcome from an allo-HSCT?

   Univariate regression analysis in four studies suggested that longer time interval between first transplant and relapse (>1 year vs <1 year) is associated with better

survival. One study also suggested that younger age (<40 years vs >40 years) at time of 2nd transplant and disease stage at second transplant (early versus advanced) may also be associated with better survival. Another study reported that longer survival was associated with longer duration of remission after first allo-HSCT, with lower stage at second HSCT and with a related first HSCT. A further study reported better outcomes in patients in remission at second transplant, with an interval from first transplant to relapse of more than ten months and those who received total body irradiation.

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7 Search Strategy

Population, Intervention, Comparator and Outcomes (PICO)

Search strategy *Indicate all terms used in the search*	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	*Adults with haematological malignancy relapsed after initial allogeneic HSCT*
I – Intervention Which intervention, treatment or approach should be used?	*Allogeneic stem cell transplantation*
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Usual care
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	*Critical to decision-making:* *Overall survival* *Progression-free survival* *Cost-effectiveness* *Important to decision-making:* *Safety and complications Quality of life*
Assumptions / limits applied to search *Inclusion and exclusion criteria e.g. study design, date limits, patients, intervention, language, setting, country etc.* *Systematic review, meta-analysis, primary clinical study (any type)* *Economic study (any type).* *Since 16 July 2012 (date of last search)* *English only*	

Search date: 5th August 2015
Databases searched: Medline, Embase, Cochrane, TRIP and NICE Evidence Search
Limited to studies published in English and 2012 onwards

1 exp myelodysplastic syndrome/
2 exp myeloproliferative disorder/
3 hematologic malignancy/
4 exp leukemia/
5 exp lymphoma/
6 ((hematologic* or haematologic*) adj5 (malignan* or cancer* neoplasm*)).ti,ab.
7 (leukaemia or leukemia or lymphoma*).ti,ab.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 hematopoietic stem cell transplantation/
10 autolog*.ti,ab.
11 9 and 10
12 allogeneic hematopoietic stem cell transplantation/ or autologous hematopoietic stem cell transplantation/
13 autologous stem cell transplantation/
14 ((autolog* or allogenic) adj3 stem cell transplant*).ti,ab.
15 11 or 12 or 13 or 14
16 (transplant* adj6 (repeat* or second or double or retreat* or re-treat)).ti,ab.
17 (repeat* or second or double or retreat* or re-treat or relapse*).ti.
18 16 or 17
19 8 and 15 and 18
20 limit 19 to (english language and yr="2012 -Current")
21 conference*.pt.
22 20 not 21

Following consultation a minor typographical error in the search terms was identified and a further search undertaken.

Search date: 9th October 2015
Databases searched: Medline, Embase, Cochrane, TRIP and NICE Evidence Search
Limited to studies published in English and 2012 onwards

1 exp myelodysplastic syndrome/
2 exp myeloproliferative disorder/
3 hematologic malignancy/
4 exp leukemia/
5 exp lymphoma/
6 ((hematologic* or haematologic*) adj5 (malignan* or cancer* neoplasm*)).ti,ab.
7 (leukaemia or leukemia or lymphoma*).ti,ab.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 hematopoietic stem cell transplantation/
10 autolog*.ti,ab.
11 9 and 10

12 allogeneic hematopoietic stem cell transplantation/ or autologous hematopoietic stem cell transplantation/
13 autologous stem cell transplantation/
14 ((autolog* or allogeneic) adj3 stem cell transplant*).ti,ab.
15 (allohct or allo-hct).ti,ab.
16 11 or 12 or 13 or 14 or 15
17 ((transplant* or allohct or allo-hct) adj6 (repeat* or second or double or retreat* or re-treat)).ti,ab.
18 (repeat* or second or double or retreat* or re-treat or relaps*).ti.
19 17 or 18
20 8 and 16 and 19
21 limit 20 to (english language and yr="2012 -Current")
22 conference*.pt.
23 21 not 22

8 EBTM Risk Score

This is an aggregate risk score with the following components:

Risk factor	Score
Age	
<20	0
20-40	1
>40	2
Disease stage	
Early	0
Intermediate	1
Advanced	2
Duration of disease	
Pre-second HSCT	
<12 months	0
>12 months	1
Donor match	
HLA-id.sib	0
Other	1
Patient/donor gender	
M/F	1
Other	0

From: Rezvani, 2012 [20]