Health Technology Assessment 2010; Vol. 14: No. 54

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December 2010
10.3310/hta14540

Health Technology Assessment
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Declared competing interests of authors: none

Published December 2010
DOI: 10.3310/hta14540

This report should be referenced as follows:

Ashfaq K, Yahaya I, Hyde C, Andronis L, Barton P, Bayliss S, *et al*. Clinical effectiveness and cost-effectiveness of stem cell transplantation in the management of acute leukaemia: a systematic review. *Health Technol Assess* 2010;**14**(54).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 08/07/01. The contractual start date was in November 2008. The draft report began editorial review in September 2009 and was accepted for publication in March 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

Abstract

Clinical effectiveness and cost-effectiveness of stem cell transplantation in the management of acute leukaemia: a systematic review

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Background: Acute leukaemia is a group of rapidly progressing cancers of bone marrow and blood classified as either acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL). Haemopoietic stem cell transplantation (SCT) has developed as an adjunct to or replacement for conventional chemotherapy with the aim of improving survival and quality of life.
Objectives: A systematic overview of the best available evidence on the clinical effectiveness and cost-effectiveness of SCT in the treatment of acute leukaemia.
Data sources: Clinical effectiveness: electronic databases, including MEDLINE, EMBASE and the Cochrane Library, were searched from inception to December 2008 to identify published systematic reviews and meta-analyses. Cochrane CENTRAL, MEDLINE, EMBASE and Science Citation Index (SCI) were searched from 1997 to March 2009 to identify primary studies. Cost-effectiveness: MEDLINE, EMBASE, Database of Abstracts of Reviews of Effects (DARE) and NHS Economic Evaluation Database (NHS EED) were searched from inception to January 2009.
Study selection: Potentially relevant papers were retrieved and independently checked against predefined criteria by two reviewers (one in the case of the cost-effectiveness review).
Study appraisal: Included reviews and meta-analyses were critically appraised and data extracted and narratively presented. Included randomised controlled trials (RCTs) and donor versus no donor (DvND) studies were mapped to the evidence covered in existing systematic reviews and meta-analyses according to a framework of 12 decision problems (DPs): DP1 related to SCT in adults with AML in first complete remission (CR1); DP2 to adults with AML in second or subsequent remission or with refractory disease (CR2+); DP3 to children with AML in CR1; DP4 to children with AML in CR2+; DP5 to adults with ALL in CR1; DP6 to adults with ALL in CR2+; DP7 to children with ALL in CR1; DP8 to children with ALL in CR2+; DP9 to comparison of different sources of stem cells in transplantation; DP10 to different conditioning regimens; DP11 to the use of purging in autologous SCT; and DP12 to the use of T-cell depletion in allogeneic SCT.
Results: Fifteen systematic reviews/meta-analyses met the inclusion criteria for the review of clinical effectiveness, thirteen of which were published from 2004 onwards. Taking into account the timing of their publications, most reviews appeared to have omitted an appreciable proportion of potentially available evidence. The best available evidence for effectiveness of allogeneic SCT using stem cells from matched sibling donors came from DvND studies: there was sufficient evidence to support the use of allogeneic SCT in DP1 (except in good-risk patients), DP3 (role of risk stratification unclear) and DP5 (role of risk stratification unclear). There was conflicting evidence in DP7 and a paucity of evidence from DvND studies for all decision problems concerning patient groups in CR2+. The best available evidence for effectiveness of autologous SCT came from RCTs: overall, evidence suggested that autologous SCT was either similar to or less effective than chemotherapy. There was a paucity of evidence from published

reviews of RCTs for DPs 9–12. Nineteen studies met the inclusion criteria in the cost-effectiveness review, most reporting only cost information and only one incorporating an economic model. Although there is a wealth of information on costs and some information on cost-effectiveness of allogeneic SCT in adults with AML (DPs 1 and 2), there is very limited evidence on relative costs and cost-effectiveness for other DPs.
Limitations: Time and resources did not permit critical appraisal of the primary studies on which the reviews/meta-analyses reviewed were based; there were substantial differences in methodologies, and consequently quantitative synthesis of data was neither planned in the protocol nor carried out; some of the studies were quite old and might not reflect current practice; and a number of the studies might not be applicable to the UK.
Conclusions: Bearing in mind the limitations, existing evidence suggests that sibling donor allogeneic SCT may be more effective than chemotherapy in adult AML (except in good-risk patients) in CR1, childhood AML in CR1 and adult ALL in CR1, and that autologous SCT is equal to or less effective than chemotherapy. No firm conclusions could be drawn regarding the cost-effectiveness of SCT in the UK NHS owing to the limitations given above. Future research should include the impact of the treatments on patients' quality of life as well as information on health service use and costs associated with SCT from the perspective of the UK NHS.

Contents

Glossary and list of abbreviations

Glossary

Allogeneic stem cell transplantation (SCT) Transplantation in which the stem cells being transplanted are obtained from a donor (i.e. not the patient him- or herself). In this report, allogeneic SCT refers to transplantation using stem cells from a human leucocyte antigen (HLA)-matched sibling of the patient (the most common and possibly the most suitable donor) unless otherwise specified.

Donor versus no donor (DvND) [comparison/study] This is a specific type of analysis in which outcomes of all patients with an HLA-matched sibling donor in a defined cohort are compared with the outcomes of all those without an HLA-matched sibling in the cohort, irrespective of the actual treatments they receive. It has been suggested that such comparison is effectively a random evaluation, as whether or not a sibling is a HLA-matched donor depends on the random assortment of genes at fertilisation. See Chapter 2, Explanation of comparisons presented in DPs 1–8, for further detail.

Minimal residual disease Leukaemia cells surviving cytotoxic chemotherapy that are undetectable by conventional light microscopy surveys.

Philadelphia chromosome (Ph) A specific chromosomal abnormality that is associated with various types of leukaemia. In acute lymphoblastic leukaemia, patients with Philadelphia chromosome are associated with poor prognosis.

List of abbreviations

ALL	acute lymphoblastic leukaemia (or acute lymphocytic leukaemia)
AML	acute myeloid leukaemia
APL	acute promyelocytic leukaemia
ASBMT	American Society for Blood and Marrow Transplantation
BMT	bone marrow transplantation
BSBMT	British Society of Blood and Marrow Transplantation
CBF	core binding factor
CBSCT	cord blood stem cell transplantation
CCG	Children's Cancer Group
CCT	clinical controlled trial
CEAC	cost-effectiveness acceptability curve
CR	complete remission (numbered)
DFS	disease-free survival
DP	decision problem (numbered)
DvND	donor versus no donor (see glossary)
EFS	event-free survival
G-CSF	granulocyte colony-stimulating factor
GvHD	graft-versus-host disease
HLA	human leucocyte antigen
HR	hazard ratio
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IL-2	interleukin-2
IPD	individual patient data
ITT	intention to treat
LYS	life-year saved
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
OR	odds ratio
OS	overall survival
PBSCT	peripheral blood stem cell transplantation
PFS	progression-free survival
Ph	Philadelphia chromosome
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RFS	recurrence-free survival
RIC	reduced intensity conditioning
RT-PCR	reverse transcription-polymerase chain reaction
RR	relative risk (risk ratio)
SCT	stem cell transplantation
TBI	total body irradiation
TRM	treatment-related mortality
WBC	white blood cell

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Acute leukaemia is a group of rapidly progressing cancers of bone marrow and blood. It is broadly classified as either acute myeloid leukaemia (AML) or acute lymphoblastic leukaemia (ALL). Acute leukaemia can occur at any age. The incidence of AML rises sharply in middle age and is highest among older people, whereas ALL occurs mainly in children and younger adults.

Conventional chemotherapy has varied degrees of success in treating acute leukaemia, and long-term survival for many patient groups remains poor. Different forms of haemopoietic stem cell transplantation (SCT) have been used in addition to or in place of chemotherapy at various stages of the treatment pathway in the hope of improving survival and/or quality of life. Much research has been done on the effectiveness of SCT (and, to a lesser extent, its cost-effectiveness), including systematic reviews and meta-analyses. These have used different methodologies, dealt with different types of SCT and/or different types of leukaemia and/or different age groups, and many may not be sufficiently up to date. Consequently, it is difficult to easily identify which aspects of the effectiveness of SCT are supported by both a good quality and a good quantity of evidence and which areas require priority for further research.

Objectives

This report aims to provide a systematic overview of the best available evidence on the clinical effectiveness and cost-effectiveness of SCT in the treatment of acute leukaemia. The specific objectives were: (1) to systematically identify and review published systematic reviews, meta-analyses and economic literature in this field; (2) to systematically identify new evidence from randomised controlled trials (RCTs) and donor versus no donor (DvND) studies that has not been included in previous reviews and meta-analyses; and (3) to map information from the above two sources and generate an inventory of best available evidence to help inform the commissioning of future research.

Methods

A systematic review of published systematic reviews and meta-analyses was carried out. Electronic databases including MEDLINE, EMBASE and the Cochrane Library [Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and NIHR Health Technology Assessment (HTA) databases] were searched from inception to December 2008. Retrieved records were screened for relevance. Potentially relevant papers were retrieved and independently checked against predefined criteria for inclusion by two reviewers. Included reviews and meta-analyses were critically appraised and data were extracted and narratively presented.

A separate search of RCTs and DvND studies was performed. Cochrane CENTRAL (Central Register of Controlled Trials), MEDLINE, EMBASE and SCI (Science Citation Index) were searched from 1997 to March 2009. Retrieved records were screened and relevant papers were selected following the same procedure described above. Included RCTs and DvND studies were mapped to the evidence covered in existing systematic reviews and meta-analyses according to a framework of 12 decision problems (DPs): DP1 related to SCT in adults with AML in first complete remission (CR1); DP2 related to adults with AML in second or subsequent remission or with refractory disease (CR2+); DP3 related to children with AML in CR1; DP4 related to children with AML in CR2+; DP5 related to adults with ALL in CR1; DP6 related to adults with ALL in CR2+; DP7 related to children with ALL in CR1; DP8 related to children with ALL in CR2+; DP9 related to comparison of different sources of stem cells in transplantation in any acute leukaemia or age group; DP10 related to different conditioning regimens; DP11 related to the use of purging in autologous stem cell transplantation (autologous SCT); and DP12 related to the use of T-cell depletion in allogeneic stem cell transplantation (allogeneic SCT). Evidence from new RCTs and DvND studies not covered in existing reviews and meta-analyses was briefly described alongside evidence from existing reviews in each decision problem. In addition, research registers were searched for ongoing trials

and relevant studies were mapped to individual decision problems.

For the cost-effectiveness review, MEDLINE, EMBASE, DARE and NHS Economic Evaluation Database (EED) (via the Cochrane Library) were searched from inception to January 2009. Retrieved records were screened and relevant economic literature, including full economic evaluations and cost studies, was selected and reviewed by one reviewer. Results were tabulated and described narratively.

Results

Volume and quality of available systematic reviews and meta-analyses

Fifteen systematic reviews and/or meta-analyses published between 1998 and 2008 met the inclusion criteria. These included five systematic reviews (without quantitative synthesis of evidence), six meta-analyses (with or without systematic searches of literature), three individual patient data meta-analyses and one HTA report. Thirteen of the included reviews/meta-analyses were published from 2004 onwards. Nine studies searched MEDLINE only and three did not describe any search of literature. Ten reviews/meta-analyses focused on evidence from RCTs and/or DvND studies, whereas the other five included broader evidence from cohort studies and/or case series. DP1 (adults with AML in CR1) was covered in seven reviews/meta-analyses, whereas relatively few reviews/meta-analyses covered children and adult patients in second complete remission and beyond (CR2+). Taking into account the timing of their publications, most reviews appeared to have omitted an appreciable proportion of potentially available evidence when the lists of included studies in existing reviews addressing the same decision problem were cross-checked against each other.

Clinical effectiveness of allogeneic SCT

The best available evidence concerning the effectiveness of allogeneic SCT using stem cells from matched sibling donors came from DvND studies. Among DPs 1–8, there was sufficient evidence from DvND studies to support the use of allogeneic SCT in DP1 (adult AML in CR1 – except in good-risk patients), DP3 (childhood AML in CR1 – role of risk stratification unclear) and DP5 (adult ALL in CR1 – role of risk stratification unclear). There was some conflicting evidence in DP7 (high-risk childhood ALL in CR1) and a paucity of evidence from DvND studies for all the decision problems concerning various patient groups in CR2+. Evidence concerning allogeneic SCT using stem cells from matched unrelated donors was lacking.

Clinical effectiveness of autologous SCT

The best available evidence came from RCTs. Sufficient evidence from RCTs was available for DP1 (adult AML in CR1), DP3 (childhood AML in CR1) and DP5 (adult ALL in CR1). Overall, the evidence suggested that autologous SCT was either of similar effectiveness to or less effective than chemotherapy. Evidence from RCTs for the other decision problems was either lacking or very limited and did not favour autologous SCT over chemotherapy.

Other comparisons

There was a paucity of evidence from RCTs comparing different sources of stem cells (DP9), different conditioning regimens (DP10), purging versus no purging (DP11), and T-cell depletion versus no depletion (DP12) in existing reviews. However, there was emerging evidence from RCTs for DP9 and DP10.

Areas warranting further synthesis of evidence

Our searches of RCTs and DvND studies found a sufficient volume of new evidence to warrant conducting new reviews in DP4 (childhood AML in CR2+, new DvND studies), DP5 (adult ALL in CR1, new DvND studies and RCTs), DP7 (childhood ALL in CR1, new DvND studies), DP8 (childhood ALL in CR2, new DvND studies), DP9 [new RCTs comparing bone marrow transplantation (BMT) with peripheral blood stem cell transplantation (PBSCT)] and DP10 [ongoing RCTs comparing reduced intensity conditioning (RIC) with myeloablative conditioning regimens]. Other decision problems were either covered in sufficiently up-to-date systematic reviews or lacking sufficient new evidence.

Review of cost-effectiveness

Nineteen studies met the inclusion criteria. Most of them reported cost information only. Data on cost-effectiveness were presented in eight studies, only one of which incorporated an economic model. There is a paucity of evidence on most of the considered decision problems. While there exists a wealth of information regarding the costs and some information on cost-effectiveness of allogeneic SCT in adults with AML (DPs 1 and 2), there is very limited evidence on relative costs and cost-effectiveness of different techniques of SCT against further chemotherapy for other decision problems (DPs 3–8).

There is little evidence on the costs and cost-effectiveness of transplantations using different sources of stem cells (DP9) and different conditioning regimens (DP10), with the exception of some indications on costs of BMT being greater than that for PBSCT, and similarly high costs for myeloablative and non-myeloablative regimens in AML. There is no published study comparing the costs and cost-effectiveness of purging versus no purging (DP11) and of T-cell depletion versus no depletion (DP12).

Conclusions

This report provides an overview of the best available evidence on the use of SCT in the treatment of acute leukaemia. Our review demonstrated substantial differences in methodologies and coverage of evidence between existing systematic reviews/meta-analyses addressing the same decision problems. Areas in which new evidence has accumulated or is emerging have been identified. Existing evidence from DvND studies suggests that sibling donor allogeneic SCT may be more effective compared with chemotherapy in adult AML (except in good-risk patients) in CR1, childhood AML in CR1 and adult ALL in CR1, although whether the effectiveness of allogeneic SCT varies between commonly defined risk groups remains uncertain in the last two patient populations. Overall, evidence from RCTs suggested that autologous SCT is of similar effectiveness to or less effective than chemotherapy. Further RCTs and/or DvND studies are needed to evaluate the effectiveness of allogeneic and autologous SCT for adult and childhood AML and ALL in CR2+, to compare bone marrow versus cord blood transplantation and T-cell-depleted versus T-cell-replete allogeneic SCT, and to make comparisons between different myeloablative conditioning regimens.

An appreciable volume of cost studies and limited cost-effectiveness studies exists, but no firm conclusions regarding the cost-effectiveness of SCT in the UK NHS can be drawn from it owing to the methods and applicability (partly related to the age and country of origin of these studies) and significant uncertainty in the effectiveness estimates used. There is a paucity of information regarding the impact of the treatments on patients' quality of life as well as information on health service use and costs associated with SCT from the perspective of the NHS. Future research should collect reliable information on these, and then incorporate robust evidence from more recent RCTs/DvND studies to carry out economic evaluations in clearly specified patient populations. The aforementioned areas in which sufficient clinical evidence supports the use of SCT should be considered as the priority.

Chapter 1
Background

Leukaemia

Leukaemia is a type of cancer of bone marrow and blood. It is characterised by abnormal proliferation of blood cells or their precursors [most commonly those of white blood cells (WBCs)]. Leukaemia accounts for approximately 2.5% of all cancers (incidence cases) in the UK.[1] More than 7000 people are diagnosed with leukaemia each year in the UK, with an age-standardised incidence rate of 9.4 per 100,000 people per year. Leukaemia causes more than 4300 deaths each year and is the 10th most common cause of death from cancer in the UK.[1] About four in five deaths from leukaemias are in people over 60 years of age.

Leukaemia is classified as either chronic or acute depending on how quickly the disease develops and worsens. Chronic leukaemia develops relatively slowly and the abnormal blood cells can still function early in the disease. It mainly affects adults. Acute leukaemia worsens quickly and the number of abnormal cells that do not function increases rapidly. It occurs in both adults and children. This report focuses on acute leukaemia.

Leukaemia is also classified according to the type of blood cells and their precursors that are involved. There are two types of acute leukaemia: acute myeloid leukaemia (AML) and acute lymphocytic leukaemia (ALL). AML is characterised by an increase in the number of (abnormal) myeloid blasts, the precursors of red blood cells, platelets and granulocytes (a type of WBC). It is the most common acute leukaemia affecting adults, and its incidence increases with age. AML accounts for nearly one-third of all new cases of leukaemia. There were 2263 new cases of AML and 2104 deaths from AML in the UK in 2006.[2]

Acute lymphocytic leukaemia is characterised by an increase in the number of (abnormal) lymphoid blasts, the precursors of various WBCs including B lymphocytes, T lymphocytes and natural killer cells. ALL accounts for about 10% of all new cases of leukaemia, and it is the most common type of cancer in children. ALL accounts for approximately 80% of leukaemias in children and 25% of all childhood cancer. There were 691 new cases of ALL and 255 deaths from ALL in the UK in 2006.[2]

Haemopoietic stem cell transplantation (SCT)

Stem cells are cells that give rise to a lineage of cells. Haemopoietic stem cells are the type of stem cells from which blood cells are derived. These stem cells form in bone marrow, develop into immature blood cells called blasts and further differentiate into various types of blood cells there. Mature blood cells then move into peripheral blood.

Types of SCT

Allogeneic SCT and autologous SCT

Haemopoietic SCT is a procedure in which an individual's haemopoietic and immune system is completely or partially destroyed by chemotherapy and/or radiotherapy and then is replaced with either haemopoietic stem cells donated by another individual (allogeneic stem cell transplantation, allogeneic SCT) or a previously collected (harvested) portion of the individual's own haemopoietic stem cells (autologous SCT, autologous SCT). The donor of the stem cells in the case of allogeneic SCT can be either a sibling of the recipient or an unrelated person, but the compatibility between the donor's and the recipient's tissues needs to be checked through human leucocyte antigen (HLA) typing. The chance of a sibling being HLA matched with a patient is approximately 25%, whereas the chance of identifying a matched unrelated donor for a patient without a matched sibling has grown to over 50% (for some ethnic groups) with increasing numbers of volunteer donors on international registries.[3] It is also possible for a patient to obtain stem cells from an identical twin (syngeneic SCT). This type of SCT will not be considered in this review owing to the rarity of this option.

The advantages of autologous SCT are not relying on the availability of a donor and no problems related to the compatibility between the recipient and the transplanted stem cells (which come from the recipient him- or herself). The major drawback, however, is the possibility of reintroducing stem cells contaminated with tumour cells. In addition, autologous SCT does not confer a 'graft-versus-leukaemia' (or 'graft-versus-tumour') effect. The graft-versus-leukaemia effect refers to a phenomenon in which the successfully transplanted blood and immune system (the 'graft') in allogeneic SCT has the ability to recognise and eradicate leukaemia cells that remain in the recipient's body. By contrast, allogeneic SCT is limited by the availability of a suitable donor. Even if the HLA typing indicates a good match between the donor and the recipient, incompatibility between the transplanted blood and immune system and the recipient (the 'host') can still be a problem. Graft-versus-host disease (GvHD) is a disease caused by donor-driven immune cells, which react against recipient's tissues. It can be mild or severe, and can occur soon after SCT (acute GvHD, occurring within 100 days) as well as at a later stage (chronic GvHD). On the other hand, the aforementioned graft-versus-leukaemia effect is considered a major advantage of allogeneic over autologous SCT.

Standard SCT versus mini-SCT

For patients who are to undergo SCT, a procedure called 'conditioning' is carried out prior to the SCT. Conditioning involves high doses of chemotherapy, sometimes in combination with total body irradiation. The aim is to kill any remaining leukaemia cells (as well as suppress the patient's immune system in order to prevent rejection of the 'foreign' stem cells to be transplanted in the case of allogeneic SCT). Although conventional standard conditioning (usually called 'myeloablative' – destroying bone marrow activity) is effective for this aim, it is associated with high treatment toxicity. This toxicity offsets the overall benefit of SCT and also limits the use of SCT in elderly patients or patients with comorbidity who are unlikely to tolerate the treatment-related toxicity. In the last decade, SCT that adopts non-myeloablative or reduced intensity conditioning regimens ('mini-SCT') has therefore been developed. It has been pointed out, however, that there is still a lack of a consistent definition for 'non-myeloablative' or 'reduced intensity conditioning (RIC)' regimens with respect to drug classes, doses and durations, and those that have been used comprise a continuum that overlaps with standard myeloablative regimens.[4] SCTs with RIC regimens have the potential to extend the use of SCTs to a much wider population, including older adults.

Sources of stem cells

Stem cells to be transplanted can be collected from bone marrow, peripheral blood or umbilical cord blood. Bone marrow transplantation (BMT) is the longest established procedure, and involves the aspiration of 500–1200 ml of bone marrow from the iliac crest (the pelvic bone) from the donor (allogeneic SCT) or the patient (autologous SCT), usually under general anaesthesia. Possible complications with bone marrow harvesting include infection, bleeding and problems related to the anaesthetic.

Only a small number of haematopoietic stem cells circulate in peripheral blood, and the number is too small to be useful for transplantation. Peripheral blood stem cell transplantation (PBSCT) has become possible and more widely adopted following the discovery that the number of stem cells in peripheral blood can be increased by the administration of growth factors such as granulocyte colony-stimulating factor (G-CSF). This is also known as 'mobilisation' of stem cells. The administration of G-CSF usually starts 4–6 days before the collection of stem cells by apheresis, a procedure that last a few hours and involves pumping blood through a machine that collects stem cells and returns the remaining blood to the donor or patient. Compared with BMT, PBSCT does not require general anaesthesia during stem cell collection and allows the collection of a larger amount of stem cells. Complications with the collection of peripheral blood stem cells mainly relate to the side effects of G-CSF. PBSCT is associated with faster engraftment (the transplanted stem cells being accepted by the recipient and beginning to produce blood cells) and higher graft-versus-leukaemia effect compared with BMT, but may also be associated with a higher risk of GvHD.

Umbilical cord blood collected at the time of delivery contains a higher concentration of stem cells with superior proliferative capacity compared with stem cells from bone marrow and peripheral blood from adults. Owing to the relatively small volume, however, cord blood stem cell transplantation (CBSCT) is an option mainly for children. The collection of stem cells from cord blood involves minimal risk for both mother and baby. Cord blood is frozen and stored after

necessary processing and testing. It is therefore more readily available for use compared with bone marrow or peripheral blood stem cells. It has also been suggested that CBSCT may require less stringent HLA matching and may be associated with a lower incidence of or less severe GvHD because of to the naive status of cord blood cells.

Additional techniques used in SCT

In order to reduce the risk of reintroducing leukaemia cells into the patient in autologous SCT, a process known as 'purging' has been developed either to remove leukaemia cells by chemical or immunological methods or positively select desirable stem cells using monoclonal antibodies. These processes may damage normal stem cells and thus affect the success of engraftment.

The finding that T cells from the donor play an important role in GvHD has led to attempts to reduce the risk of GvHD by removing T cells from the donor stem cells (T-cell depletion). This technique, however, may eliminate the graft-versus-leukaemia effect and may be associated with increased engraftment failure.[5]

Treatment pathway

Treatment of acute leukaemia is divided into several phases. The first phase of treatment after a patient is diagnosed with acute leukaemia is induction therapy. The aim is to rapidly kill most of the tumour cells and get the patient into a state of complete remission, which is defined as < 5% blasts in the bone marrow, normal peripheral blood counts and no other symptoms or signs of the disease.[3] Once complete remission has been achieved, a phase of consolidation/intensification follows to eradicate remaining leukaemia cells as much as possible and to prevent the return of the disease. SCT may be considered during first complete remission if the patient is judged to be at high risk of relapse. Following consolidation, patients with ALL are usually given central nervous system (CNS) prophylaxis involving cranial irradiation and intrathecal chemotherapy and further maintenance chemotherapy. Autologous SCT is sometimes used as further consolidation following long-term chemotherapy. CNS prophylaxis and maintenance chemotherapy are usually not needed for patients with AML.

If relapse occurs, reinduction therapy can be given and SCT may be considered during subsequent complete remission. For patients who fail to achieve complete remission following first or subsequent induction therapy, further salvage chemotherapy may be given and allogeneic SCT may also be considered.

Additional supportive treatments that deal with infections, haemorrhage and other symptoms that are associated with either the disease itself or the aforementioned treatments may also be needed throughout disease management.

Chemotherapy

Chemotherapy is used at various stages of the treatment of acute leukaemia. As described in the previous section (Treatment pathway), chemotherapy is divided into different phases including induction, consolidation (intensification) and maintenance. Induction and consolidation therapies are intensive treatment that usually require hospitalisation for several weeks or months. For ALL, the maintenance therapy following consolidation can be given on an outpatient basis, but it is a lengthy procedure usually lasting about 2 years.

When chemotherapy is described as the comparator for SCT in this report, it refers to the consolidation chemotherapy (and subsequent maintenance chemotherapy, where applicable). The effectiveness of chemotherapy differs between types of leukaemia, age groups and stages of disease, as well as other characteristics of the patient and disease. Overall, chemotherapy is highly effective for ALL in children in first complete remission but has limited success in bringing about long-term remission for ALL in adults and for AML. Chemotherapy can cause significant treatment-related morbidity, hence potentially impact on patients' quality of life. Although the risk of treatment-related mortality is usually lower compared with SCT, chemotherapy is still also associated with appreciable treatment-related mortality particularly in adults.

Current service provision

The registry of all transplants performed in the UK each year is maintained by the British Society of Blood and Marrow Transplantation (BSBMT), and the most recent statistics shows that overall the rate of allogeneic SCT is increasing for both AML and ALL while autologous SCT is decreasing (see *Figures 1* and *2*). The use of peripheral blood stem cells in allogeneic SCT is increasing for both

ALL and AML, whereas the use of bone marrow is decreasing. Both bone marrow and peripheral blood autografts are decreasing, with no recorded bone marrow autografts for ALL in 2006 and 2007 and only one patient with AML receiving autologous BMT in 2007.

According to the BSBMT registry, 268 patients with AML received a peripheral blood allograft transplant in 2007, an 11% increment compared with the previous year. Fifty-one patients received a bone marrow allograft transplant in 2007 compared with 50 in 2006 and 61 in 2005. Cord blood transplantation started in 2006 with six patients and increased to 14 in the following year. For ALL, in 2007 there was a 23% increase from the previous year in the number of patients who received peripheral blood allografts (91), while the number of bone marrow allografts dropped slightly from 60 in 2006 to 57 in 2007.

Decision problems

Stem cell transplantation is widely used in the treatment of both adult and childhood leukaemia. Despite its widespread use, considerable uncertainty remains with regard to its relative effectiveness compared with chemotherapy at various stages of the disease, and with regard to the relative effectiveness of various types and methods of SCT compared with each other. In addition, SCT is an intervention associated with significant cost. The costs charged in UK NHS transplant centres vary depending on region and are approximately £30,000 to £60,000 for a sibling or unrelated donor transplant (Professor Charles Craddock, University Hospital Birmingham NHS Foundation Trust, 22 January 2010, personal communication). An NHS tariff is to be introduced in the near future. Notwithstanding the high costs, there appears to be very limited information

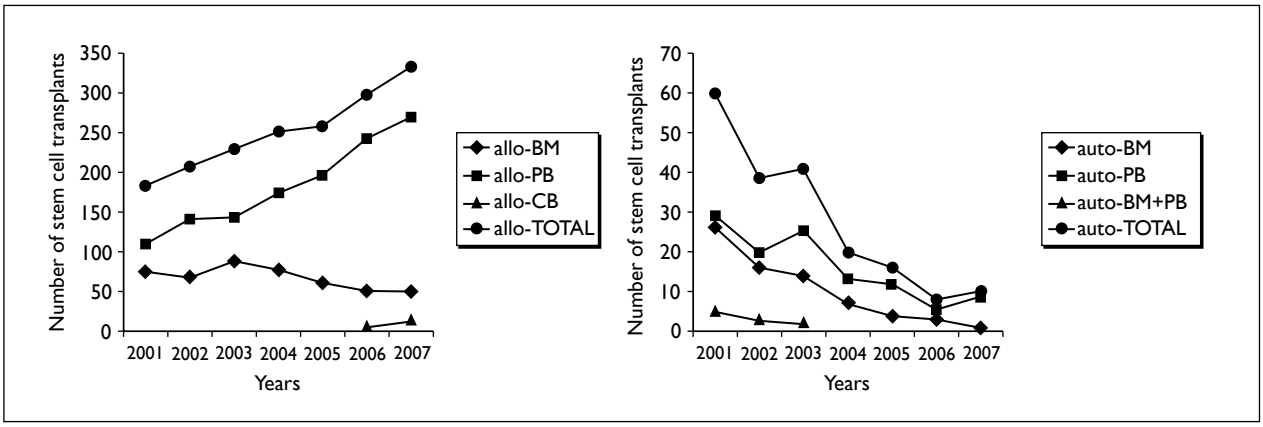

FIGURE 1 *Trends in allogeneic and autologous stem cell transplantation for acute myeloid leukaemia in the UK (2001–7). Note: the numbers shown are for first transplants only. Source of raw data: British Society of Blood and Marrow Transplantation website (www.bsbmt.org/pages/16-About_the_Registry). BM, bone marrow; CB, cord blood; PB, peripheral blood.*

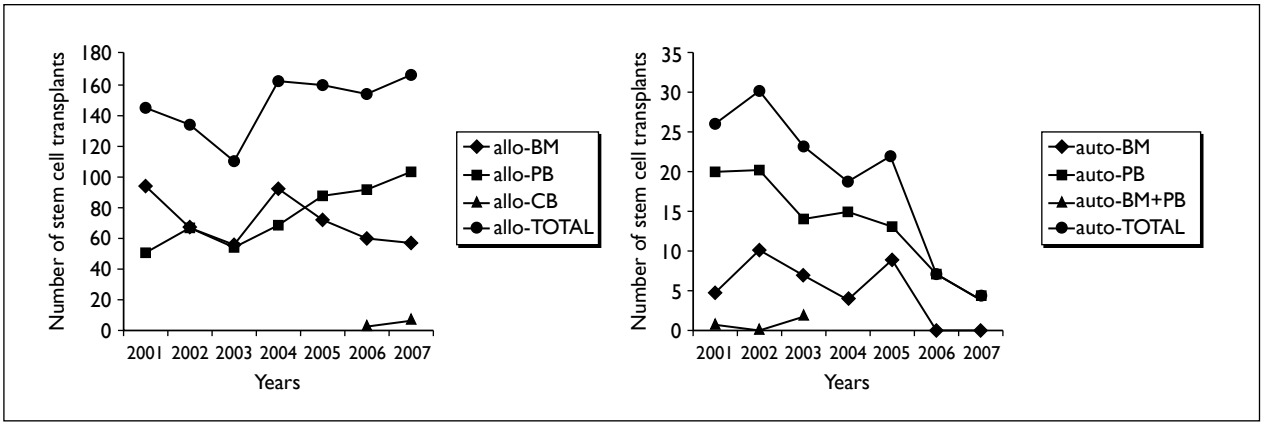

FIGURE 2 *Trends in allogeneic and autologous stem cell transplantation for acute lymphocytic leukaemia in the UK (2001–7). Note: the numbers shown are for first transplants only. Source of raw data: British Society of Blood and Marrow Transplantation website (www.bsbmt.org/pages/16-About_the_Registry). BM, bone marrow; CB, cord blood; PB, peripheral blood.*

regarding the cost-effectiveness of SCT compared with alternative treatment options. Whether the use of SCT, overall or in specific subgroups of patients, represents efficient use of resources within the NHS is therefore currently unknown. The purpose of this report is to summarise the best available evidence on the use of SCT in the management of acute leukaemia. It is hoped that the report will help inform decisions regarding the provision of services and commissioning of research relevant to the use of SCT in these conditions.

Definition of the intervention and indications

Intervention

The technology assessed was haemopoietic SCT (referred to as SCT in the remainder of the report). Methods of performing SCT have been evolving over the past few decades. Consequently, SCT is in fact a collective term that refers to a variety of different procedures and techniques rather than a uniform and standardised procedure. For this review, the following forms of SCT were considered:

1. autologous SCT; allogeneic SCT from HLA-matched sibling; allogeneic SCT from unrelated donor
2. SCT that uses any of the following as the source of stem cells: bone marrow; peripheral blood; umbilical cord blood
3. SCT that adopts different conditioning regimens, including standard myeloablative conditioning regimens and non-ablative (RIC) regimens (mini-SCT)
4. autologous SCT with purging; autologous SCT without purging
5. T-cell depleted allogeneic SCT; T-cell replete allogeneic SCT.

Indications

The indications considered were AML and ALL.

Place of the intervention in the treatment pathway

Patients who are diagnosed with acute leukaemia are usually given an induction treatment which aims to bring about complete remission of the disease. Once complete remission has been achieved, a phase of consolidation/intensification therapy is followed to prevent the relapse of the disease. Further maintenance therapy may also be needed. The effectiveness of these chemotherapies (and sometimes radiotherapy) in inducing remission and preventing relapse varies between types of leukaemia (AML vs ALL), age, and other prognostic factors. For example, complete remission following induction therapy has been achieved in over 90% of children with ALL[3] but only in $< 65\%$ of older adults (≥ 56 years) with AML.[6] SCT provides alternative treatment options that have the potential to reduce the risk of relapse or even cure the disease when chemotherapy alone fails to eradicate the disease and/or when the patient's prognosis remains poor owing to a high risk of relapse. Nevertheless, SCT is not always successful and does not always prevent relapses, and the procedures (in particular allogeneic SCT) involve significant risk of treatment-related mortality and morbidity. Whether SCT would be considered as an alternative/additional treatment to chemotherapy and/or no further therapy in the management of acute leukaemia therefore depends very much on balancing the potential benefit that SCT may confer (taking into account the potential harm that SCT may cause) against the potential risk of relapse or poor prognosis if SCT is not carried out.

SCT is usually considered during the first complete remission following induction therapy, or during subsequent remissions after disease relapse has occurred. Allogeneic SCT may also be considered for patients who are unable to achieve complete remission with chemotherapy (see *Figure 3*). Once SCT is judged to be potentially beneficial, further issues need to be considered to inform the choice of the type of SCT. For patients who have an HLA-matched sibling donor, allogeneic SCT is usually preferred over autologous SCT as the former is thought to have the advantage of a graft-versus-leukaemia effect whereas the latter has the possibility of reintroducing leukaemic cells to patients. For patients without an HLA-matched sibling donor, allogeneic SCT from an HLA-matched unrelated donor may also be considered. Autologous SCT may be considered for patients with no suitable donor, for patients who may not be able to tolerate the intensive conditioning regimen required for allogeneic SCT, such as older patients and patients with comorbidity, and for patients in whom the higher risk of mortality associated with allogeneic SCT is considered unacceptable.

For patients who do not have a matched donor, possible treatment options when remission has been achieved include autologous SCT, further chemotherapy or no further therapy. For patients who fail to achieve remission, possible

treatment options include allogeneic SCT, further chemotherapy or no further therapy.

The use of SCT in the treatment pathway for acute leukaemia is partly reflected in the conduct of controlled clinical trials, the structure of which has been summarised by Johnson *et al*.,[7] as shown in *Figure 4*. Not all possible comparisons have been tested in the trials owing to practical difficulties and ethical issues.

Because any intention to perform allogeneic SCT is restricted by the availability of a matched donor, randomisation to receive either allogeneic SCT or alternative treatment (e.g. autologous SCT or chemotherapy) is possible only among patients with a matched sibling or unrelated donor. Even within this patient population, recruitment to randomised trials comparing allogeneic SCT with chemotherapy is difficult, either because of the significant treatment-related mortality and serious side effects associated with allogeneic SCT, which are considered unacceptable to patients and clinicians, or, conversely, because of their belief that allogeneic SCT (particularly when a matched sibling is available) is the treatment of choice and hence unwillingness to accept the possibility of not having SCT.

Despite the practical difficulties in carrying out a randomised study comparing allogeneic SCT with alternative treatments, it has been pointed out that whether or not a sibling is an HLA-matched donor depends on the random assortment of genes at fertilisation, and thus a comparison of patients with a sibling donor with those without a donor is effectively a randomised evaluation.[8] This 'donor versus no donor' comparison has therefore been used to evaluate the effectiveness of allogeneic SCT from sibling donor compared with alternative treatment options. The 'intention to treat' (ITT) (i.e. to carry out allogeneic SCT from a sibling donor) here is solely dictated by the availability of a matched sibling donor. The term 'donor versus no donor (DvND) studies' will be used in this report to describe this type of study.

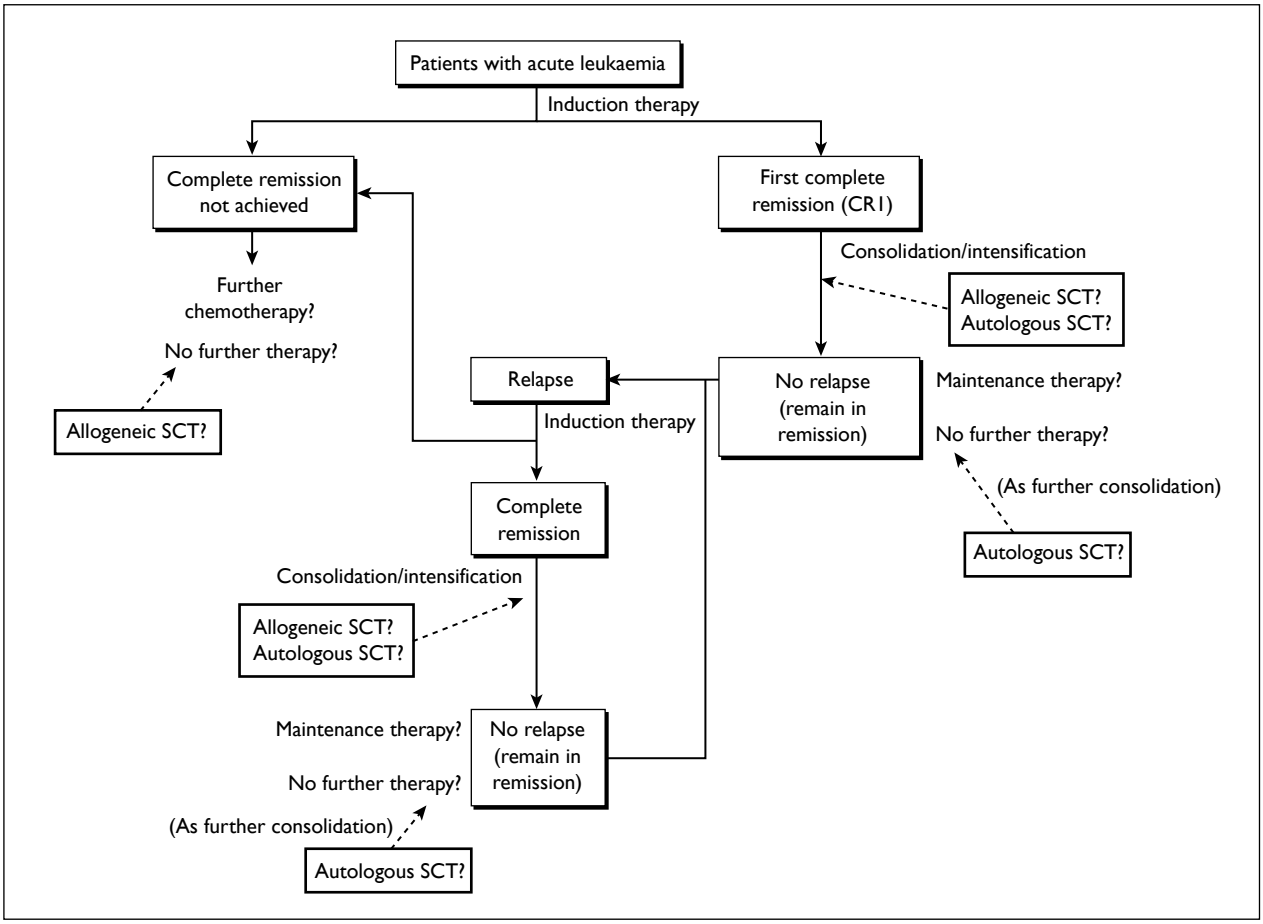

FIGURE 3 *Potential use of stem cell transplantation in the treatment pathway for the management of acute leukaemia.*

Relevant comparators

Potentially relevant comparisons for this review included different forms and techniques of SCT compared with each other, with further chemotherapy or with no further therapy. Possible treatment options were identified on the basis of the characteristics of the specific patient group in question (e.g. adults with AML with high risk of relapse) and its place in the treatment pathway (e.g. in first complete remission). Therefore, appropriate comparators were determined for AML and ALL for a given age/risk group and disease stage. Not all the potential comparators were considered relevant for each patient group/disease stage.

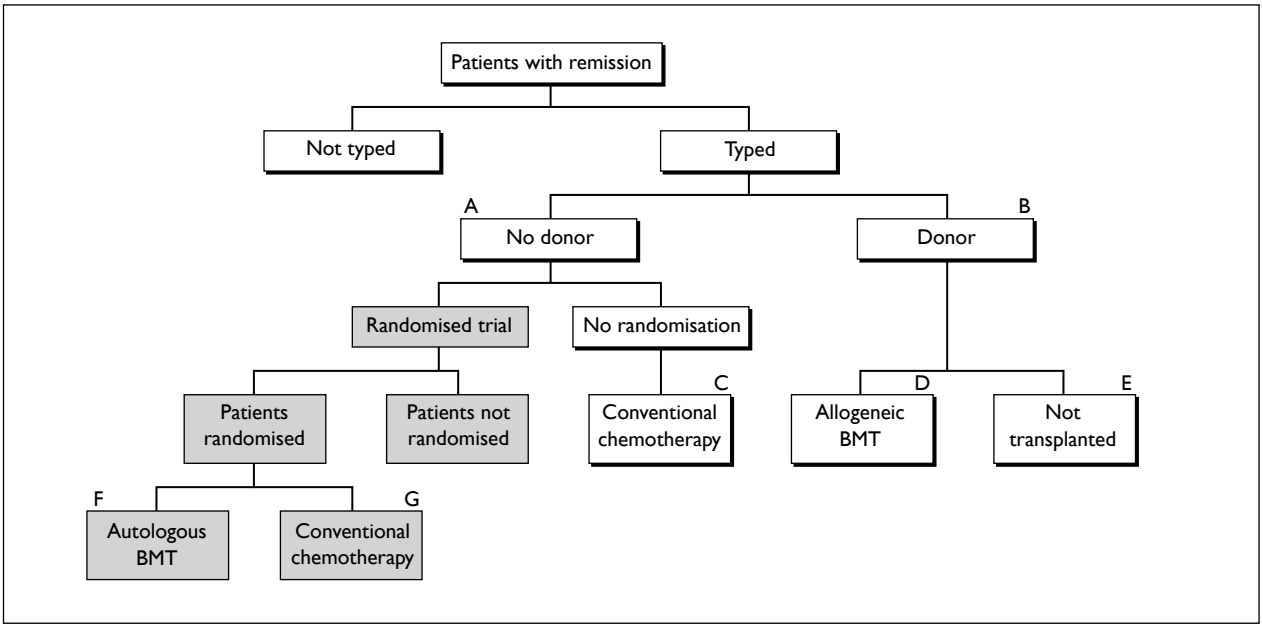

FIGURE 4 *Typical simplified schema for trials comparing sibling allogeneic or autologous transplantation with conventional chemotherapy in acute leukaemia. Adapted from Johnson* et al.[7]

Because the treatment of acute leukaemia is generally standardised across centres, the approach used to conduct most controlled trials is similar. Following induction treatment, patients in remission are given additional therapy to consolidate their response

Patients with a compatible sibling donor (B) undergo high-dose therapy with allogeneic BMT. All other patients receive conventional therapy.

In some trials those patients without a compatible donor are then randomised to receive either conventional consolidation chemotherapy (G) or high-dose therapy and an autologous BMT (F) (shaded areas in schema).

As with all clinical trials, not all patients will follow the protocol design owing to health status, preference or eligibility. When considering the validity of a trial it is important to determine whether these patients have been included appropriately in any analysis (i.e. an intention-to-treat analysis).

Grey boxes denote schema if randomisation between conventional chemotherapy and autologous BMT is part of the trial.

Randomised controlled trials (RCTs)
RCTs comparing autologous transplantation with conventional chemotherapy compare the outcome for patients who reach box F with the outcome for those who reach box G.

Donor versus no donor studies (DvNDs)
DvNDs investigating the potential benefit of sibling allogeneic transplantation compare the outcome of patients in box B (regardless of whether they actually receive a transplant) with those in box A.

Cohort studies
It is often unclear from a report of a trial (especially an abstract) whether a study is a DvND study or whether it is comparing patients who received a transplant (box D) with all the patients who did not receive a transplant (box E), did not have a donor (box A) or did not even get tissue typed.

The comparison of patients who receive conventional chemotherapy in a truly randomised part of a trial with patients who have a matched donor allocated allogeneic transplantation (box G vs box D) is considered to be a cohort study as the groups are unlikely to contain comparable patients.

Specific decision problems

The following specific decision problems were identified on the basis of the scope stated in the commissioning brief of this National Institute for Health Research (NIHR) Health Technology Assessment (HTA) report, taking into account the treatment pathway described above and additional advice from our clinical and methodological experts. As the aim of the review was to provide a critical assessment and summary of best available evidence, these decision problems (DPs) were listed in view of their clinical and economic relevance and not according to whether good-quality evidence related to these decision problems existed.

Management of AML

DP1

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy, in the management of AML in adults of various risk groups in first complete remission?

DP2

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy, in the management of AML in adults of various risk groups in second complete remission or subsequent remission, and in adults with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

DP3

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy in the management of AML in children of various risk groups in first complete remission?

DP4

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy in the management of AML in children of various risk groups in second complete remission or subsequent remission, and in children with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

Management of ALL

DP5

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy, in the management of ALL in adults of various risk groups in first complete remission?

DP6

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy in the management of ALL in adults of various risk groups in second complete remission or subsequent remission, and in adults with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

DP7

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy, in the management of ALL in children of various risk groups in first complete remission?

DP8

What is the clinical effectiveness and cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy, in the management of ALL in children of various risk groups in second complete remission or subsequent remission, and in children with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

Choice of techniques

DP9

What is the clinical effectiveness and cost-effectiveness of BMT versus PBSCT versus CBSCT in the management of acute leukaemia, for a given type of leukaemia (AML/ALL), population (age/risk) and disease stage?

DP10

What is the clinical effectiveness and cost-effectiveness of various conditioning regimens, including standard myeloablative regimens and RIC regimens (mini-SCT), for a given type of SCT (autologous/allogeneic), leukaemia (AML/ALL), population (age/risk) and disease stage?

DP11

What is the clinical effectiveness and cost-effectiveness of autologous SCT with purging, compared with autologous SCT without purging, for a given type of leukaemia (AML/ALL), population (age/risk) and disease stage?

DP12

What is the clinical effectiveness and cost-effectiveness of T-cell depleted allogeneic SCT, compared with T-cell replete allogeneic SCT, for a given type of leukaemia (AML/ALL), population (age/risk) and disease stage?

Chapter 2
Methods

Methods for synthesis of evidence of clinical effectiveness

Search strategy

Full search strategies are detailed in Appendix 1. A scoping search was undertaken to identify existing reviews and other background material. Searches for systematic reviews were carried out using the Aggressive Research Intelligence Facility (ARIF) search protocol and included searches of MEDLINE (Ovid) 1950 to April week 3, 2008, EMBASE (Ovid) 1980 to week 16, 2008, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) as at 24 April 2008 and the Cochrane Library (Wiley) 2008 Issue 3 [Cochrane Database of Systematic Reviews (CDSR), Database of Abstacts of Reviews of Effects (DARE) and HTA databases]. Searches of the same databases, together with the Cochrane Library (Wiley) 2008 Issue 3 [Cochrane Central Register of Controlled Trials (CENTRAL) and NHS Economic Evaluation Database (EED) databases], were undertaken to estimate the volume and nature of primary studies for the topic.

Searches for systematic reviews

Updated searches for systematic reviews were run in December 2008 on MEDLINE (Ovid) 1950 to December week 4, 2008, EMBASE (Ovid) 1980 to week 52, 2008, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) as at 30 December 2008 and the Cochrane Library (Wiley) 2008 Issue 4 (CDSR, DARE and HTA databases).

Effectiveness searches

A comprehensive search to identify primary studies was undertaken using the following:

- bibliographic databases: Cochrane Library Wiley (CENTRAL) 2009 Issue 1, MEDLINE (Ovid) 1950 to March week 3, 2009, MEDLINE In-Process & Other Non-Indexed Citations (Ovid) as at 30 March 2009, EMBASE (Ovid) 1980 to week 13, 2009 and the Science Citation Index (Web of Science) as at 31 March 2009
- research registers of ongoing trials, including the UK NIHR Clinical Research Network Clinical Research Portfolio, Current Controlled Trials metaRegister, ISRCTN (International Standard Randomised Controlled Trial Number) database and ClinicalTrials.gov up to May 2009
- citation lists of relevant studies
- searches of relevant internet sites (American Society of Hematology, European Group for Blood and Marrow Transplantation)
- contact with experts in the field.

The searches were limited by date to the period 1997–2009, given that comprehensive searches of the literature to 1997 covering the same subject area were performed by Johnson *et al*. in the previous HTA report.[7] No language limits were applied.

Study selection criteria

Study selection for review of systematic reviews and meta-analyses

The titles and abstracts of records retrieved from the searches of electronic databases for systematic reviews and meta-analyses, as well as any other potentially relevant articles that were identified through additional searches, were examined for inclusion by two reviewers independently using the criteria listed below.

Inclusion criteria

Study design Systematic reviews and meta-analyses. For the purpose of this project, a systematic review was loosely defined as any review article (including HTA reports) that explicitly stated that a systematic search of the literature had been carried out. A meta-analysis was defined as any article in which data from two or more studies had been quantitatively combined using validated methods. The data used could be either at study level or at individual patient level (IPD meta-analysis). A systematic review need not contain a meta-analysis to be included; similarly, a meta-analysis need not be a systematic review to be included.

Type of publication Full-length articles published in English.

Population Patients with AML or ALL of any age and at any stage of the disease. Studies with mixed

populations (e.g. haematological malignancies) were included if outcomes for patients with AML and ALL were reported separately from other conditions, or if AML and ALL consisted of more than 70% of the included population/studies.

Interventions SCT of any form (see Chapter 1, Types of SCT).

Comparators Chemotherapy, different forms of SCT, no further therapy.

Outcomes At least one of the following: survival; disease free survival (including procedure-related mortality and relapses); treatment toxicity and complications (including infection, GvHD, infertility, cataracts); quality of life (measured using any validated instrument); postoperative complications; or other adverse effects related to donors.

A study needed to meet all of the above inclusion criteria to be selected.

Exclusion criteria

Study design Review articles (including commentaries, editorials, letters) without stating that a systematic search of the literature had been carried out; primary studies [potential randomised controlled trials (RCTs) and DvND studies that were identified during the selection of systematic reviews were subject to the same selection and mapping procedure described below].

Type of publication Reviews/meta-analyses that were published only as conference abstracts were excluded if attempts to obtain full reports were unsuccessful. Reviews and meta-analyses published in languages other than English were excluded owing to time and resource constraints. However, the lists of included primary studies in these reviews/meta-analyses (if they otherwise met the inclusion criteria) were checked for additional relevant RCTs or DvND studies.

Population Reviews/meta-analyses in which AML/ALL accounted for < 70% of included patients/studies and outcomes for patients with AML/ALL were not reported separately were excluded.

Interventions and comparators Studies that compared different induction therapies before SCT and/or that compared different management options after SCT were excluded.

Outcomes Reviews/meta-analyses that did not report any of the outcomes listed under inclusion criteria were excluded.

Studies that met any of the above exclusion criteria were excluded. Discrepancies in study selection between reviewers were resolved by discussion and were referred to project team meetings to reach a consensus if necessary.

Identification of completed and ongoing primary studies (RCTs and DvND studies) for listing

The titles and abstracts of records retrieved from the searches of electronic databases for primary studies, as well as any other potentially relevant articles that were identified through additional searches, were screened by one reviewer to exclude records that were clearly irrelevant. Full text articles of the remaining records were examined for listing by another reviewer using the selection criteria listed below. The criteria were slightly different from those for the review of reviews described above as the main purpose was to identify all relevant RCTs and DvND studies that could be included in future reviews rather than to select RCTs and DvND studies for a detailed review, which is beyond the scope of this report.

Selection criteria

Study design RCTs and DvND studies were listed. Other controlled studies without randomisation and uncontrolled studies were excluded.

Type of publication No restriction was applied. Studies which were published only as conference abstracts and ongoing studies that were not yet published were indicated as such. Multiple publications of an RCT or CCT (clinical controlled trial) were listed under a single study identifier.

Population The population of interest was patients with AML or ALL of any age and at any stage of the disease. Studies with mixed populations (e.g. haematological malignancies) were included if outcomes for patients with AML and ALL were reported separately from other conditions, or if AML and ALL comprised > 70% of included patients.

Interventions SCT of any forms (see Chapter 1, Types of SCT).

Comparators Chemotherapy; different forms of SCT; no further therapy.

Outcomes The selection of primary studies for listing and comment was not restricted by the outcomes reported.

Mapping and listing of RCTs and DvND studies

Where sufficient data were available within a decision problem, a table listing/comparing RCTs and DvND studies included in existing systematic reviews/meta-analyses was complied for each relevant comparison (allogeneic SCT vs other treatment options; autologous SCT vs chemotherapy or no further therapy). RCTs and DvND studies identified from searches of primary studies (as described above) were then mapped to this table. All RCTs and DvND studies (or new data) that have not been included in existing reviews were added to the table. Brief comments were provided for these new trials/data but detailed critical appraisal of these studies was not carried out owing to time constraints.

Data extraction and quality assessment strategy

Data from included systematic reviews and meta-analyses were extracted by one reviewer on to a data extraction form (spreadsheet) adopted from a proforma that had been designed for critical appraisal of systematic reviews. The data extraction was checked by another reviewer to ensure accuracy.

Methods of synthesis and structure of the report

A narrative overview of published systematic reviews and meta-analyses is provided in Chapter 3. Findings from these studies, as well as new evidence from primary studies and information on relevant ongoing trials, is presented in Chapter 4 according to the structure of the decision problems outlined in Chapter 1. Data have been tabulated and summarised in a narrative manner for each decision problem. The strength and weakness of evidence from existing systematic reviews/meta-analyses, and new evidence not covered by these studies and its potential impact, are discussed. An inventory identifying areas of priority for future primary research and evidence synthesis is provided in Chapter 7. No de novo quantitative synthesis of data was planned or carried out.

Explanation of comparisons presented in DPs 1–8

Types of comparisons

As described in Chapter 1, not all treatment options were considered relevant for a specific patient group/disease stage. When complete remission is achieved, the first decision involving SCT is whether the patient should be transplanted at all. Ideally evidence to inform such a decision should come from RCTs. In practice, randomisation is often not feasible and a clinical decision is usually made on the basis of the type (AML or ALL) and stage (CR1 or CR2) of the disease, the patient's age and comorbidity, prognostic factors (responsiveness to initial chemotherapy, cytogenetics, leukaemia morphology) and the patient's and clinician's preference.

As allogeneic SCT from matched sibling donors is usually considered the best option among various types of SCT (e.g. compared with autologous SCT or allogeneic SCT from an unrelated donor), the availability of a matched sibling donor can be a crucial factor determining whether SCT is to be carried out. Other types of SCT are usually considered when a matched sibling donor is not available or when the patient is considered too weak to be subject to the procedure of allogeneic SCT. Where sufficient evidence is available, comparisons presented within DPs 1–8 will reflect the logical sequence of potential clinical decisions. Comparisons involving allogeneic SCT from matched sibling donors will be described first. Given the difficulties in conducting RCTs in this patient population, evidence for comparing allogeneic SCT from matched sibling donors with other treatment options mainly comes from DvND comparisons. These will be expanded further in the next section.

When the possibility of allogeneic SCT from a matched related donor is ruled out, autologous SCT may be considered against other treatment options such as chemotherapy or no further therapy. Best evidence for these comparisons comes from RCTs (which are usually feasible) and will be described following the DvND comparisons.

Attempts have also been made in previous reviews to compare the effectiveness of allogeneic SCT versus autologous SCT. For patients who are fit

enough and have a matched sibling donor, such comparisons do not reflect the actual clinical decisions needing to be made (allogeneic SCT is the preferred option in most cases). Comparison between allogeneic SCT from an unrelated donor and autologous SCT is more clinically relevant but studies with such a focus are rare. There are further problems associated with the evidence comparing allogeneic SCT with autologous SCT in some of the existing reviews and primary studies (see the next section). This comparison (where evidence was described in existing reviews) is therefore only described in Appendix 2.

DvND comparisons

In the absence of randomised comparisons, DvND comparison has been used as an alternative option for evaluating the effectiveness of transplantation versus no transplantation. On the basis of genetic randomisation and under a protocol of all patients being typed and those with a matched sibling donor being submitted to allogeneic SCT, the DvND comparisons provide potentially unbiased estimates of the effectiveness of allogeneic SCT from a matched sibling donor versus other treatment options. Results from DvND comparison may be seen as an indication of whether SCT has any role in the specific place in the treatment pathway (i.e. if allogeneic SCT does not appear to be more effective than other treatment options, other types of SCT are unlikely to be doing any better). Potential biases and limitations associated with DvND comparisons are described in Chapter 6 (Discussion) and these should be borne in mind when interpreting the results.

For a study with a protocol to allocate all patients without a matched sibling donor exclusively to autologous SCT or chemotherapy, the DvND comparison may provide unbiased estimates for allogeneic SCT versus autologous SCT and allogeneic SCT versus chemotherapy, respectively. Nevertheless such a protocol is rarely used and, where adopted, may have poor compliance (hence the statistical power for the intended comparison is diminished).

An extension to DvND comparison is possible when all patients without a matched sibling donor are randomly allocated to either autologous SCT or chemotherapy. In such cases, unbiased estimates for allogeneic versus autologous SCT and allogeneic SCT versus chemotherapy may be obtained by comparing the donor group with each of the randomly allocated 'no-donor' subgroups. Although this design has been adopted in a few studies, what tends to happen in other studies is that patients without a matched sibling donor receive either chemotherapy or autologous SCT or other treatment options on the basis of various factors relating to their prognosis. The allocation of the 'no-donor' group to these treatment options is therefore not random. Attempts to compare the effectiveness of allogeneic SCT with autologous SCT or chemotherapy by comparing the donor group with a subgroup of patients receiving autologous SCT or chemotherapy in the no-donor group in these studies are likely to be confounded by the risk factors that determine what patients receive in the no-donor group. These comparisons therefore do not follow the principle of genetic randomisation and the results are much more susceptible to bias. Some of the existing systematic reviews included studies based on such comparisons. Unless otherwise specified, we have attempted to exclude such evidence (mainly allogeneic versus autologous SCT) from the main text of the report. In decision problems where there is complete absence of evidence from RCTs or DvND studies, other evidence may be briefly mentioned but the non-random nature of the evidence is highlighted.

Methods for synthesising evidence of cost-effectiveness

Search strategies

The following sources were searched to identify information on cost-effectiveness:

- MEDLINE, EMBASE, DARE and NHS EED via the Cochrane Library
- internet sites of national economic units.

There were no date or language restrictions. The reference lists of included systematic reviews were also checked. Full details of the search and databases searched are provided in Appendix 1. The end date for the searches was January 2009.

Study selection criteria

The titles and abstracts of records retrieved from the searches for cost-effectiveness, as well as any other potentially relevant articles that were identified through additional searches, were examined for inclusion by a single reviewer (CH). It was originally hoped that two reviewers would be available to screen, but this was not possible owing

to resource constraints. One reviewer was thought to be acceptable, given the experienced nature of the reviewer. The criteria used are listed as follows.

Selection criteria

Study design Full economic evaluations (cost–consequence, cost–benefit, cost-effectiveness, cost–utility studies) were included. In our review protocol, studies that looked at costs alone without considering consequences/outcomes were to be excluded. However, because of the paucity of true economic evaluations, all costing studies (not just those conducted in the UK from an NHS perspective) were also reviewed.

Type of publication Full-length articles published in English were included. Studies that were published as conference abstracts were excluded if attempts to obtain full reports were unsuccessful. Studies that potentially met the inclusion criteria but were published in languages other than English were excluded. A record of these studies was kept for future reference.

Population Patients with AML and/or ALL of any age and at any stage of the disease were included. Studies that included patients with other conditions were excluded unless AML and/or ALL had been evaluated separately.

Interventions SCT of any forms (see Chapter 1, Decision problems).

Comparators Chemotherapy; different forms of SCT; no further therapy.

Outcomes Study selection was not based on outcomes reported. However, as stated above, a study had to be either a full economic evaluation (i.e. reporting *both* costs and consequences of the intervention and comparator, or incremental outcomes derived from these) or have reported cost information in order to be included.

A study needed to meet all the above inclusion criteria to be selected. As the review was undertaken by a single reviewer (CH), no procedures for disagreement between reviewers were required. Advice on health economics was sought from another author (PB) whenever needed.

Data extraction and quality assessment strategy

Data from the included economic evaluations were extracted and critically appraised according to a published checklist by Philips *et al*.[9] The key items of information to be assessed included:

- details of the study characteristics, such as form of economic analysis, comparators, perspective, time horizon and modelling used
- details of the effectiveness and cost parameters, such as effectiveness data, health state valuations, resource use data, unit cost data, price year, discounting assumptions and productivity costs
- details of the results and sensitivity analysis.

Details and data of costs studies, which we did not originally intend to review, were extracted using a similar framework to that used in an NIHR HTA programme review by Johnson *et al*.[7] on SCT. No detailed critical appraisal was carried out, although major challenges to validity were recorded as notes.

The data extraction and quality assessment was checked by another reviewer (LA) to ensure accuracy. Disagreement between reviewers was resolved by discussion with involvement of a third reviewer when necessary.

Methods of analysis/synthesis

Results of the review of cost-effectiveness literature were tabulated and summarised in a narrative manner for each decision problem. Again the framework employed by the HTA review by Johnson *et al*.[7] on SCT was employed where still appropriate. The strengths and weaknesses of existing economic evaluations were discussed and potential evidence gaps that might impede a reliable economic evaluation or that might be associated with major uncertainty were identified.

Chapter 3

Overview of published systematic reviews and meta-analyses

Quantity and quality of identified systematic reviews and meta-analyses

The process of study selection is summarised in *Figure 5*. Seventy-eight potentially relevant studies were identified on initial screening of 402 titles and abstracts. Of these, 15 studies met all inclusion criteria. In addition to these studies, two protocols of ongoing Cochrane reviews that directly addressed some of the decision problems in this report were also identified.[10,11]

A number of studies of mixed populations fell short of the inclusion criteria as they either did not report separate outcomes for acute leukaemia, or acute leukaemia comprised < 70% of the study population. These studies will be discussed in the context of their respective decision problems. One relevant study could not be included as the full text was only available in German.[12]

An overview of the 15 included studies is presented in *Table 1*. The included studies comprise five systematic reviews (without quantitative synthesis of evidence),[13–17] six meta-analyses (with or without systematic searches of the literature),[18–23] three IPD meta-analyses[24–26] and one HTA report.[7] They were published between 1998 and 2008, with the majority (13/15) being published from 2004 onwards. The studies varied substantially in terms of the breadth of the subject area covered and types of literature searched/included.

Ten of the included studies focused on one decision problem specified in this report; seven of them concerned the use of SCT for adults with AML in CR1 (DP1). The remaining five studies[7,13,14,16,17] covered more than one decision problem specified for this report. Four of them were evidence-based reviews sponsored by the American Society for Blood and Marrow Transplantation (ASBMT).[13,14,16,17] These reviews included studies of various design, including uncontrolled studies/case series. The HTA report by Johnson *et al.*[7] focused on RCTs and DvND studies, but, when such evidence was lacking, cohort studies were also sought.

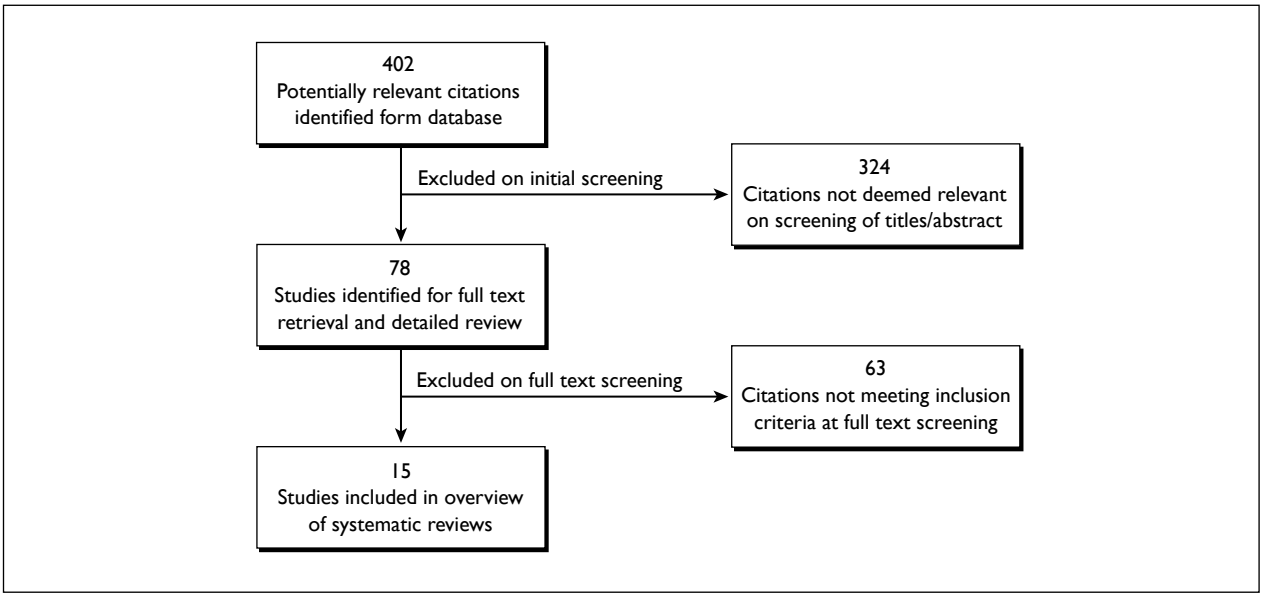

FIGURE 5 *Flow chart of study selection.*

The sources and period searched varied between the 15 studies. Comprehensive searches of electronic databases were carried out in only three studies.[7,20,23] Nine studies searched MEDLINE only, whereas no literature search was described in the remaining three studies,[22,24,25] all of which combined individual patient- or trial-level data from trials conducted by a specific research group or collaboration. The studies also varied in the time period searched. Some studies searched literature dating back to the 1960s,[20,21] whereas others searched only literature published from 1990 onwards[16,17] or even later.[26] The updatedness of the searches was obviously limited by the time when each of the studies was conducted.

Quality assessment of the studies included in these reviews/meta-analyses was clearly described in eight of the fifteen studies. Although not explicitly stated, some degree of quality assessment may have been incorporated into the other reviews/meta-analyses by the use of more stringent inclusion criteria (e.g. only including RCTs or DvND studies) and/or by inclusion of trials that followed prospectively defined treatment protocols, usually carried out by the same research group who conducted the systematic reviews/meta-analyses.

Brief summary of included systematic reviews and meta-analyses

A brief overview of each of the 15 studies is given below, starting with the earliest publication. Key aspects of the German HTA report,[12] derived from the abstract in English, are presented after the overview of included studies. Results described here are based on the review authors' interpretation of findings and conclusions. Pertinent issues identified during our critical appraisal of these reviews that have potential impact on the internal validity or generalisability of their findings will be discussed under individual decision problems in Chapter 4.

Johnson 1998

This HTA report[7] evaluated the effectiveness and cost-effectiveness of SCT compared with conventional chemotherapy for the treatment of a number of haematological and other solid malignancies. It appears to be the first systematic review to assess the efficacy of SCT in acute leukaemia. Studies were identified by electronic search in CancerLit, EMBASE, MEDLINE and NHS EED, by hand searching of conference proceedings of major societies, and by searching within the UK cancer registries/databases.

Randomised controlled trials, DvND studies and cohort studies comparing SCT with chemotherapy were included in the review; the authors did not include case series. For each disease entity, a decision, based on the number of trials, patients and events, but without knowledge of the results, was made as to which level of evidence should be considered. Thus, if sufficient evidence was available from the RCTs, no other studies were reviewed. Similarly, if sufficient evidence was available from the RCTs plus DvND studies, no further studies were reviewed. Otherwise, all categories of study were included but quantitative analyses were performed only for RCTs and DvND studies. No data synthesis was carried out for cohort studies and no conclusions were drawn from them. End points considered were survival and progression-free survival (PFS); odds ratios (ORs) were calculated for each end point.

The analysis of identified DvND studies revealed a survival advantage for allogeneic transplantation over chemotherapy among adults with AML in CR1. For RCTs comparing autologous transplantation with chemotherapy, there was no good evidence of a survival difference between the two treatment approaches but there was some suggestion that autologous SCT might improve PFS. For adult AML in CR2, no RCTs or DvND studies were identified that compared transplantation with chemotherapy; two retrospective cohort studies comparing the two treatment approaches were found but no conclusion was drawn from them.

In the case of children with AML, the results of identified trials that compared allogeneic transplantation with chemotherapy once again suggested a benefit in favour of allogeneic transplantation, for both survival and PFS. However, unlike the case of adults with AML in CR1, all RCTs that compared autologous transplantation with chemotherapy in children in CR1 tended to favour conventional therapy.

The authors also concluded that it was not possible to determine whether transplantation – allogeneic or autologous – offered any benefit over conventional chemotherapy in the consolidation of CR1 in adult ALL, mainly because the trials identified at the time were generally relatively small and inconsistently reported.

DOI: 10.3310/hta14540

TABLE 1 *Overview of included studies*

Study reference	Decision problem	Types of studies included	Period searched	Databases searched	Other sources	Studies quality assessed?	Study type
Johnson 1998[7]	1, 2, 3, 5, 7, 8	RCTs, DvND studies, prospective cohort studies, retrospective cohort studies	Up to and including 1 June 1997	MEDLINE, EMBASE, CancerLit, NHS EED and the PDQ database	UKCCCR, Center Watch Clinical Trials listings; hand-searching of conference proceedings	Levels of evidence considered; no mention of quality assessment	HTA report
Bleakley 2002[23]	3	DvND studies and RCTs	1985–2000	Cochrane Controlled Trials Register, MEDLINE, EMBASE, CancerLit	CancerNet and the UKCCCR Register; hand searching of specialist journals and conference proceedings; citations of identified trials and relevant reviews; contact with researchers for unpublished studies	Yes	Meta-analysis
Levi 2004[21]	1	RCTs	January 1966 to March 2003	MEDLINE	None mentioned	Yes	Meta-analysis
Nathan 2004[20]	1	DvND studies and RCTs	1966–2002	MEDLINE/PREMEDLINE, EMBASE, Cochrane Controlled Trials Registry, CancerLit	Manual searching of reference lists of articles and pertinent reviews	Yes	Meta-analysis
Schlenk 2004[25]	1	DvND studies and RCTs	Not mentioned	None mentioned	None mentioned	Not mentioned	IPD meta-analysis
Hahn 2005[13]	7, 8, 10, 11	Systematic reviews and meta-analyses, RCTs, case–control/ cohort studies, case series/reports > 10 patients	January 1980 to January 2005	MEDLINE	No other sources mentioned	Yes	Systematic review
Yanada 2005[18]	1	DvND studies	January 1995 to December 2003	MEDLINE	No other sources mentioned	Not mentioned	Meta-analysis
Hahn 2006[14]	5, 6, 9	Systematic reviews and meta-analyses, RCTs, case–control/ cohort studies, case series and reports > 10 patients	January 1980 to January 2005	MEDLINE	No other sources mentioned	Yes	Systematic review
Visani 2006[15]	1	DvND studies, RCTs and meta-analyses	1985 to January 2005	MEDLINE	Reference list of identified studies	Not clear	Systematic review

continued

TABLE 1 *Overview of included studies (continued)*

Study reference	Decision problem	Types of studies included	Period searched	Databases searched	Other sources	Studies quality assessed?	Study type
Yanada 2006[19]	5	DvND studies	Period prior to October 2005	MEDLINE	No other sources mentioned	Not mentioned	Meta-analysis
Cornelissen 2007[22]	1	DvND studies	Not mentioned	None mentioned	None mentioned	Not mentioned	Meta-analysis
Olinasky 2007[16]	3, 4, 9	Systematic reviews and meta-analyses, RCTs, case–control/ cohort studies, case series/reports ≥25 patients	1990 to 1 March 2006	MEDLINE	No other sources mentioned	Yes	Systematic review
Orsi 2007[26]	5	RCTs and DvND studies	January 2000 to March 2007	MEDLINE	IDIS (Iowa Drug Information System) CDs; articles surveyed for additional and earlier citations	Yes	IPD meta-analysis
Schaich 2007[24]	1	DvND studies and RCTs	Not mentioned	None mentioned	None mentioned	Not mentioned	IPD meta-analysis
Oliansky 2008[17]	1, 2, 9, 10, 11, 12	Systematic reviews and meta-analyses, RCTs, case–control/ cohort studies, case series/reports ≥50 patients	1990 to 30 April 2007	MEDLINE	No other sources mentioned	Yes	Systematic review

PDQ, Physician Data Query; UKCCCR, United Kingdom Coordinating Committee on Cancer Research.

For children with ALL in first complete remission, one CCT and two cohort studies of allogeneic SCT versus conventional chemotherapy were identified but these did not yield any data on which to draw conclusions. In CR2, despite SCT being perceived as the treatment of choice in the one relevant CCT comparing allogeneic SCT with conventional chemotherapy, there was again insufficient data on which to draw any conclusion.

Bleakley 2002

The systematic review and meta-analysis by Bleakley *et al.*[23] on BMT for children with AML in CR1 included DvND studies comparing the outcome of patients with and without a histocompatible family donor, as well as RCTs comparing autologous BMT with other treatments. For both types of study, only trials enrolling patients from 1985 were included, as BMT was not widely recommended before then.

Relevant studies were identified by electronic searching of several databases (including the Cochrane Controlled Trials Register, MEDLINE, EMBASE, CancerLit) and registers of current cancer trials, hand searching of specialist journals and conference proceedings, descendent searching of identified trials and relevant reviews, as well as contact with researchers. Full texts of trials were assessed for methodological quality using a simple quality assessment system. Outcome measures were relapse, overall survival (OS), disease-free survival (DFS) and treatment-related mortality (TRM).

Relative risk (RR) and absolute risk difference were calculated for each outcome measure and results were pooled where appropriate. The authors' conclusion was that allogeneic transplantation from a histocompatible family donor improved outcomes among children with AML in CR1. They were, however, unable to comment on the value of autologous BMT compared with chemotherapy. This was because of the presence of substantial heterogeneity between the included RCTs, which made it inappropriate to present summary scores.

Levi 2004

Levi *et al.*[21] carried out a meta-analysis comparing autologous BMT transplantation and intensive chemotherapy in adults with AML in CR1. A computerised search of MEDLINE was conducted from January 1966 to March 2003 for RCTs of autologous BMT in this group of patients. Identified studies were appraised and scored using the standard developed by Chalmers *et al.*[27] Risk of dying (death rate) and the risk of relapse or death (event rate) were calculated for each arm; rate ratios of death and events rates for each study were then calculated and aggregated.

The overall estimates of rate ratio indicated that autologous BMT had no advantage over chemotherapy or no further treatment concerning death rate but was superior to chemotherapy with regards to event rate. The authors therefore concluded that autologous BMT improved event-free survival (EFS) but not OS, when compared with chemotherapy or no further treatment in patients with AML in CR1.

Nathan 2004

This meta-analysis[20] was quite similar to the study conducted by Levi *et al.*[21] Two types of trial designs were included: prospective cohort studies that offered allogeneic BMT to all eligible patients in CR1 with an available donor and randomly assigned all remaining patients to either autologous BMT or chemotherapy/no further treatment; RCTs that compared autologous BMT with chemotherapy or no further treatment in all patients in CR1.

Studies were identified by an electronic search of databases (MEDLINE/PREMEDLINE, EMBASE, the Cochrane Controlled Trials Registry and CancerLit) and by manual searching of the reference lists of articles and relevant reviews that were retrieved in full. Publications finally included were assessed for validity with the use of an eight-item checklist. Primary outcomes were OS and DFS and secondary outcomes were TRM and survival of relapsed patients.

A point estimate of the ratio of survival probabilities comparing the autologous BMT group with the chemotherapy group derived from the Kaplan–Meier estimates of survival (as reported in the studies) served as the effect size statistic. As in the meta-analysis by Levi *et al.*,[21] the aggregated results of this study revealed that the OS between the two treatment strategies was similar, and that compared with patients who received chemotherapy or no further therapy, patients who received autologous BMT had a better DFS. This led the authors to conclude that the results did not support the routine use of autologous BMT in adults with AML in CR1.

Schlenk 2004

Schlenk *et al.*[25] performed an IPD meta-analysis on adults with core binding factor (CBF) AML [defined by the presence of t(8;21) or inv(16)] treated between 1993 and 2002 in prospective German AML treatment trials. Their aim was to evaluate prognostic factors for recurrence-free survival (RFS) and OS and to assess the impact of different post-remission therapies in this group of patients.

Survival analysis showed similar OS and RFS for the two groups and ITT analysis for post-remission therapy revealed no difference in RFS and OS between intensive chemotherapy and autologous SCT in the t(8;21) group and between chemotherapy, autologous SCT and allogeneic SCT in the inv(16) group.

In the t(8;21) group, significant prognostic variables for longer RFS and OS were lower WBC and higher platelet counts; loss of the Y chromosome in male patients was prognostic for shorter OS. In the inv(16) group, trisomy 22 was a significant prognostic variable for longer RFS. For patients who experienced relapse, CR2 was significantly lower in patients with t(8;21), resulting in a significantly inferior survival duration after relapse compared with patients with inv(16).

Hahn 2005

The study by Hahn *et al.*[13] on the role of cytotoxic chemotherapy with SCT in the therapy of ALL in children is the third publication to result from the initiative of the ASBMT to sponsor evidence-based reviews of the scientific and medical literature for the use of blood and marrow SCT in the therapy of selected diseases.

Literature searching was carried out within MEDLINE, spanning the period 1 January 1980 to 3 January 2005, and evidence was gathered from all published articles related to SCT for ALL in children. Meeting abstracts and data from non-peer-reviewed journals were excluded, as were case reports (≤ 10 patients), reviews, consensus reports, practice guidelines or laboratory studies with no clinical correlates. All included studies were graded based on the quality of their design and the strength of their evidence as per the system devised by Harbour and Miller.[28]

There was no statistical pooling of results; details were conveyed in text format and in summary tables. Among its recommendations, the review stated that when compared with chemotherapy among children with ALL in CR1, benefit was demonstrable only for matched related allogeneic SCT in very high-risk [Philadelphia chromosome-positive (Ph+ve) only] cases, and that SCT was not recommended for standard or other high-risk (e.g. induction failure, hypodiploidy, etc.) patients in CR1, except in the context of clinical trials.

In the case of patients in CR2, there was a cautious recommendation of matched related allogeneic transplantation over chemotherapy, because part of the evidence came from one prospective trial that did not demonstrate a benefit for transplantation when analysed by the presence versus absence of a related donor in an ITT analysis; no recommendations were made with regard to unrelated allogeneic transplantation versus chemotherapy on the grounds of insufficient evidence.

The review also concluded that regimens including total body irradiation (TBI) had better outcomes than regimens without TBI. No recommendations were made between autologous and allogeneic SCT as the comparison between these two had not been adequately studied at the time.

Yanada 2005

The purpose of this meta-analysis[18] was twofold: to identify the overall efficacy of allogeneic SCT for patients with AML in CR1 and to assess the efficacy for patients stratified into favourable, intermediate and poor cytogenetic risk groups. Literature searching was conducted in MEDLINE for DvND studies published between 1995 and 2003 that, among others, used an ITT analysis and assessed outcomes in terms of OS. The authors used only articles published after 1995 in consideration of the changes in procedures for allogeneic SCT.

Five studies were eventually used for the meta-analysis. Hazard ratios (HRs) were used to assess the survival advantage of allogeneic SCT compared with non-allogeneic SCT, and cytogenetic risk categories were examined using meta-regression analysis. Results showed that there was a statistically significant advantage from allogeneic SCT in terms of OS in this group of patients.

In addition, meta-regression analysis indicated that the benefit of allogeneic SCT was further increased for the poor cytogenetic risk group, mildly increased (but not significant) for the intermediate-risk group and lost for the favourable

cytogenetic risk group. The authors' conclusion was that this suggested that the efficacy of allogeneic SCT for patients with AML in CR1 depended on cytogenetic risk.

Hahn 2006

This is the fourth review[14] to result from the ASBMT initiative mentioned above, and it investigated the roles of cytotoxic therapy and haematopoietic SCT in the treatment of ALL in adults. Literature searching, selection and grading criteria were the same as for the review of SCT in ALL in children. And, just as in the previous reviews, there was no statistical pooling of results; details were conveyed in text format and in summary tables.

The study revealed that in adults with ALL in CR1, SCT yielded outcomes similar to chemotherapy and was thus not recommended as first choice therapy in standard-risk patients. For high-risk patients, there were no direct comparisons, but some data suggested an advantage for SCT. In CR2, SCT was recommended over chemotherapy, as a sizable fraction of patients achieved extended leukaemia-free survival compared with chemotherapy alone; however, there are no direct comparative data.

In the comparison between the transplantation techniques, there was a preponderance of evidence favouring allogeneic over autologous SCT, and in the comparison of conditioning regimens, the authors concluded that there were not enough data to make a recommendation of the superiority of any one regimen. However, there appeared to be a benefit for TBI-containing regimens compared with non-TBI-containing regimens.

Visani 2006

The aim of this systematic review[15] was to define, according to the rules of evidence-based medicine, the role of allogeneic SCT compared with autologous SCT and intensive chemotherapy after achievement of CR1 in adults with AML. The authors searched MEDLINE for reports of cohort studies, RCTs and meta-analyses from 1985 through to January 2005 and also scrutinised the references of the identified articles. To be included, studies had to satisfy strict methodological criteria and had to consider global mortality (OS) and/or DFS as primary outcomes. Aggregation of results was not deemed necessary by the authors because of the inclusion of a reliable recent meta-analysis. Details of each included study were presented in structured tables and in written text.

In their analysis with regard to the comparison between autologous SCT and intensive chemotherapy/no further therapy, the authors opined that there were still contradictory opinions about the role of autologous transplantation in patients with AML in complete remission, as a possible advantage of autologous SCT over intensive chemotherapy was not clearly supported by data from the clinical trials. There was no evidence that autologous SCT was superior in terms of OS to chemotherapy; a differentiated approach in patients with high-, standard- or low-risk AML could also not be suggested because of insufficient data.

The second end point of this review was to establish whether allogeneic SCT was superior to other therapeutic options in improving DFS and/or OS in adults with AML. As no studies effectively compared allogeneic SCT and intensive chemotherapy, the authors mainly focused their analysis on a DvND comparison between allogeneic and autologous SCT. No overall benefit of allografting on survival was demonstrated by any trial. The review concluded by suggesting that, in view of the inconclusive evidence and the emergence of genetic subgroups, there is a need for randomised trials directly focusing on the single entities. Hence, the cure for AML could eventually become the cure for each specific AML subset with its peculiar biological, molecular and prognostic features.

Yanada 2006

This meta-analysis[19] was carried out to provide precise estimates of the clinical efficacy of allogeneic SCT as post-remission therapy for adult patients with ALL, in the presence of inconsistent results being reported by a number of studies. Literature searching was conducted in MEDLINE to include original articles of DvND studies based on an ITT analysis which assessed outcomes in terms of OS.

Quantitative data synthesis involved the calculation of HRs and the estimation of summary HRs. Results demonstrated that patients in the donor groups had significantly better survival than patients in the no-donor groups, but the overall result revealed significant heterogeneity, which was attributable to the high-risk group on subgroup analysis. Furthermore, when only high-risk patients

were included in the analysis, the superiority of the survival advantage was even greater.

In addition, meta-regression analysis was employed to further explore the source of heterogeneity in survival analyses and it revealed that compliance with allogeneic SCT had a significant and positive correlation with survival, i.e. the greater the proportion of patients who actually received allogeneic SCT, the better the survival of the donor group. No beneficial effects of autologous SCT were observed.

The authors concluded that the findings demonstrated that allogeneic SCT improved the outcome of adult patients with high-risk ALL and, as such, allogeneic SCT should be considered for such patients if a suitable donor was available.

Cornelissen 2007

Cornelissen *et al.*[22] presented the results of the HOVON-SAKK collaborative study group, which evaluated outcomes for patients with AML in CR1 that were entered in three consecutive studies according to a DvND comparison. In addition, as reports of three previous major trials failed to demonstrate a significant benefit in terms of OS and also showed disconcordant results in terms of DFS, the authors aggregated their results and those of the three previous studies in a meta-analysis so as to enhance statistical power.

Disease-free survival and OS were analysed by donor availability and broken down for cytogenetic risk category as well as age category. The findings from all four studies were highly consistent and the confidence intervals of the HR estimates for the separate studies all contained the pooled estimate. Pooled results revealed both an enhanced DFS and a statistically significant OS benefit in all AML patients in CR1. However, subgroup analysis revealed that this benefit was not observed in patients with favourable cytogenetics, with benefit being restricted to patients without favourable cytogenetics. The analysis also indicated that in patients younger than 40 years of age, the advantage in the donor group was present but less pronounced for DFS, but absent for OS.

Oliansky 2007

This systematic review,[16] assessing the role of cytotoxic chemotherapy with SCT in the treatment of AML in children, was the fifth of the evidence-based review series arising from the ASBMT initiative. Literature searching for published reports was carried out within MEDLINE, spanning the period 1990–2006. Selection and grading criteria were the same as for the review of SCT; study details were conveyed in text format and in summary tables.

The authors concluded that for children with AML in CR1, autologous SCT and chemotherapy had equivalent survival outcomes, whereas allogeneic SCT was superior to chemotherapy in terms of both OS and leukaemia-free survival. There was also a consensus recommendation for matched related donor allogeneic SCT over chemotherapy in CR2, although there was a lack of evidence comparing these two therapeutic options.

With regard to transplantation techniques, the conclusion was that matched related donor allogeneic SCT had superior survival outcomes compared with autologous SCT in CR1. For CR2, the recommendation was to use allogeneic over autologous SCT. However, this was based on consensus rather than on evidence from trials, as this comparison yielded no evidence that one had better outcomes than the other. In addition, the comparison of allogeneic SCT myeloablative conditioning regimens demonstrated no advantage of one regimen over another with respect to survival data or late effects.

Orsi 2007

Orsi *et al.*[26] conducted a survival meta-analysis from individual patient information, to compare allogeneic transplantation versus chemotherapy/autologous transplantation using an ITT approach, in patients with ALL in CR1. CCTs, wherein allocation to allogeneic transplantation was based on donor availability, to be included in the study were identified by electronic searching of MEDLINE and the Iowa Drug Information System (IDIS) compact disks and subjected to stringent inclusion criteria. Study quality was rated as excellent, good, sufficient or poor, based on subjective assessment.

Event-free survival was chosen as the outcome index for the review as it was the more frequently reported outcome. Data of individual survivals were derived either from the original data provided by the trial's authors or from the information contained in the original survival graphs and the event-free individual survival data were reconstructed on the basis of this. The meta-analytic EFS curves were then generated for the

two treatments; the mean survival gain per patient was estimated and a simplified cost-effectiveness assessment was also carried out.

Results showed a statistically significant EFS difference in the experimental group versus the controls, with a mean survival gain of 1 year per patient. The authors concluded that allogeneic transplantation inpatients with ALL in CR1 improves EFS compared with chemotherapy or autologous transplantation.

Schaich 2007

This IPD meta-analysis[24] was carried out on adult patients with AML and trisomy 8 (+8) (as a sole or an additional aberration) that were part of the same German trials as those in the study by Schlenk *et al.*[25] Trisomy 8 is among the commonest genetic aberrations seen in AML, but the prognostic significance of this and the best consolidation strategy for patients with this numerical aberration remain unclear. The aim of the meta-analysis was, therefore, to compare different consolidation strategies and to reveal new prognostic factors for survival.

Survival analysis showed no significant difference between patients with +8 as a sole aberration and those with +8 and one additional cytogenetic aberration. Results also showed no significant difference on OS among high-dose cytarabine, allogeneic SCT or autologous SCT. A positive impact of allogeneic SCT on RFS compared with other post-remission strategies was however demonstrated.

In addition, multivariate analysis including clinical, laboratory, cytogenetic and therapeutic variables identified age, extramedullary disease and the percentage of +8 positive metaphases at diagnosis as independent prognostic factors for OS. A hierarchical model was built by combining these three variables, whereby patients with +8 could be classified into low-, intermediate- and high-risk groups.

The authors therefore concluded that patients with AML with +8 do not form a homogeneous group and that allogeneic SCT may be the superior post-remission strategy for improving RFS.

Oliansky 2008

This was the sixth review[17] to result from the ASBMT's initiative and it evaluated the role of haematopoietic SCT in the therapy of adult patients with AML. Articles were identified by a MEDLINE search for literature published between 1990 and 2007. Selection and grading criteria were the same as for the previous reviews; study details were conveyed in text format and in summary tables.

Based on the survival data present within the studies, it was the authors' conclusion that there was no significant advantage of autologous SCT over chemotherapy in CR1. For allogeneic SCT versus chemotherapy in CR1, a survival advantage was demonstrable for patients < 55 years old with high-risk cytogenetics but not for patients with intermediate or low risk.

Among other conclusions, it was stated that allogeneic SCT be preferred over autologous SCT if a matched related donor was available and that PBSCT was recommended over BMT. However, there was no evidence of a survival advantage in the following instances: unpurged versus purged SCT; T-cell replete versus T-cell depleted; comparison of two or more high-dose therapy conditioning regimens; and comparison of two or more myeloablative conditioning regimens.

IQWiG 2007

Among others, the aim of this German review,[12] entitled *Stem cell transplantation in adults with acute lymphocytic (ALL) or acute myeloid leukaemia (AML)*, full text not available in English, was to investigate in detail four aspects of SCT: allogeneic SCT with unrelated donors in ALL/AML; autologous SCT in ALL; non-myeloablative allogeneic SCT in ALL/AML; and SCT with in vitro manipulation of the graft in ALL/AML.

All study types that included a control group were considered, including retrospective studies. Case series were included for the group of patients with refractory disease who could not achieve remission with standard therapy. The end points selected were outcomes that enabled an assessment of patient-relevant therapy goals such as OS, DFS, therapy-related complications and health-related quality of life.

Literature searching was performed in MEDLINE, EMBASE and Cochrane CENTRAL in August 2005 and updated in December 2006. Several other sources were screened to identify further published studies. These included institutions that published evidence reports or were specifically

involved in stem cell therapy or research, corresponding study groups, reference lists of relevant publications and reviews and congress proceedings.

No robust evidence showing a clear advantage for the interventions was available for any research question. Interestingly, indications of a superiority of SCT over chemotherapy could only be inferred for non-myeloablative therapy with a related donor in patients with AML. Likewise, the authors posited that the use of allogeneic SCT with dose-reduced conditioning might show an advantage in patients with refractory ALL or AML.

No evidence of an additional benefit was shown in patients with ALL or AML or their subgroups for the following subtypes or modifications of SCT: allogeneic SCT with myeloablative conditioning (compared with non-myeloablative conditioning) as well as in vitro manipulation of the graft in allogeneic or autologous SCT (compared with transplantation without manipulation of the graft). Likewise, no additional benefit of non-myeloablative therapy or autologous SCT (both vs chemotherapy) could be inferred from the data.

In patients with ALL, AML and their subgroups, no evidence of a benefit of allogeneic SCT with an unrelated donor versus chemotherapy could be inferred from direct comparative studies. However, the review states that evaluation of the available literature pointed to the possibility of a benefit as well harm in this regard.

Chapter 4
Clinical effectiveness evidence

This chapter is divided into 12 sections corresponding to the 12 decision problems outlined in Chapter 1. In each of the sections, our purpose is to summarise the best available evidence base. Our focus is on evidence from DvND studies and RCTs; if such evidence is lacking, whatever level of evidence is available in existing systematic reviews and identified primary studies is used to inform whether further evidence synthesis or primary research should be the priority.

To this end, the results of the systematic reviews are first reported and reflected on, considering limitations arising from the way the reviews were done and the limitations of the primary studies reviewed. The section then considers additional information not included in existing reviews: first published RCTs/DvND studies, then ongoing trials. The section concludes with discussions and recommendations for further research.

Potentially relevant comparisons for DPs 1–8 in this review included different forms of SCT compared with each other and further chemotherapy or no further therapy. Where possible, evidence presented in each of these decision problems is broadly categorised into two subsections: (1) evidence from DvND studies that compared matched sibling donor allogeneic SCT with other treatment options; and (2) evidence from RCTs of autologous SCT versus chemotherapy/no further treatment. In addition, evidence from studies comparing allogeneic SCT with autologous SCT was included in several reviews. As mentioned in Chapter 2 (see Explanation of comparisons presented in DPs 1–8), this comparison rarely reflects a real clinical decision (i.e. autologous SCT is usually considered if allogeneic SCT is not available/not suitable for the patient), and studies (and reviews) making such comparisons frequently draw their conclusions from analyses that are neither randomised comparison nor genuine 'DvND' comparison. Evidence for this comparison from existing reviews is therefore included in Appendix 2 of this report for information only.

Where there is a paucity of evidence for a particular decision problem (mainly those related to patients in second or subsequent remission or with refractory diseases), the available evidence is briefly described and the decision problem is not further divided into subsections.

Figure 6 provides a list of studies included in existing reviews for each of the 12 decision problems. In this figure, all the included studies in the reviews covering each of the subsections under each decision problem have been listed, irrespective of whether they are DvND studies/RCTs or not.

DP1: AML in adults in CR1

Trials comparing allogeneic SCT with other therapeutic treatment strategies

Evidence from existing reviews

This comparison was addressed by seven existing reviews. The earliest review was published in 1998 and the latest in 2008. The reviews covered a varied combination of studies but none appears to be sufficiently comprehensive (*Table 2*). Two IPD meta-analyses (Schlenk *et al.*[25] and Schaich *et al.*[24]) included the same set of eight German trials which were not covered in any other reviews. The reasons for the exclusion of these trials from the other reviews are not clear, and it is difficult to verify whether all the trials allowed DvND comparisons.

Like all reviews commissioned by the ASBMT, the review by Oliansky *et al.*[17] included all levels of evidence: RCTs, DvND studies, cohort studies, case–control studies and case series. The distinction between DvND studies and other types of studies in these reviews is not always clear.

Among the seven reviews that compared allogeneic SCT with other treatment options for adult patients with AML in CR1, meta-analysis was carried out in five of the reviews but not in Visani *et al.*[15] and Oliansky *et al.*[17] With the exception of the two IPD meta-analyses that exclusively included

DP 1: Adults with AML in CR1

Allo vs Other	Auto vs Chemo
Johnson 1998[7]	Johnson 1998[7]
Powles 1980[29]	Reiffers 1989[40]
Applebaum 1988[30]	Zittoun 1995[41]
Champlin 1985[31]	Reiffers 1993[42]
Hewlett 1995[32]	Harousseau 1996[43]
Conde 1988[32]	Hubner 1996[44]
Schiller 1992[34]	Burnett 1994[39]
Labar 1991[35]	Levi 2004[21]
Cassileth 1990[36]	Cassileth 1998[58]
Archimbaud 1994[37]	Burnett 1998[59]
Dinsmore 1987[38]	Zittoun 1995[41]
Burnett 1994[39]	Harousseau 1997[57]
Reiffers 1989[40]	Reiffers 1996[51]
Zittoun 1995[41]	Reiffers 1989[40]
Reiffers 1993[42]	Nathan 2004[20]
Harousseau 1996[43]	Reiffers 1996[51]
Hubner 1996[44]	Cassileth 1998[58]
Schlenk 2004[25]	Zittoun 1995[41]
Heil 2004[45]	Harousseau 1997[57]
AML 1/99[26]	Burnett 1998[59]
Schaich 2001[46]	Schienk 2004[25]
Schlenk 2003[47]	Heil 2004[45]
Schlenk 2004[48]	AML 1/99[26]
Buchner 2003[49]	Schaich 2001[46]
Buchner 2002[50]	Schlenk 2003[47]
AML 96 #33[26]	Schlenk 2004[48]
Yanada 2005[18]	Buchner 2003[49]
Reiffers 1996[51]	Buchner 2002[50]
Keating1998[52]	AML 96 #33[26]
Slovak 2000[53]	Visani 2006[15]
Burnett 2002[54]	Zittoun 1995[41]
Suciu 2003[55]	Harousseau 1997[57]
Visani 2006[15]	Cassileth 1998[58]
Reiffers 1996[51]	Burnett 1998[59]
Ferrant 1991[56]	Tsimberidou 2003[60]
Zittoun 1995[41]	Breems 2005[66]
Reiffers 1996[51]	Nathan 2004[20]
Harousseau 1997[57]	Oliansky 2008[17]
Cassileth 1998[58]	Levi 2004[21]
Burnett 1998[59]	Nathan 2004[20]
Tsimberidou 2003[60]	Zittoun 1995[41]
Suciu 2003[55]	Reiffers 1996[51]
Cornelissen 2007[22]	Harousseau 1997[57]
Burnett 2002[54]	Miggiano 1996[67]
Suciu 2003[55]	Burnett 1998[59]
Jourdan 2005[61]	Breems 2005[66]
Schaich 2007[24]	Rohatiner 2000[68]
Schlenk 2003[47]	Cassileth 1998[58]
Schlenk 2004[48]	Bassan 1998[69]
Heil 2004[45]	
AML 1/99[25]	
Buchner 2003[49]	
Buchner 2002[50]	
Schaich 2001[46]	
AML 96 #33[25]	
Oliansky 2008[17]	
Yanada 2005[18]	
Cornelissen 2007[22]	
Harousseau 1997[57]	
Reiffers 1996[51]	
Burnett 2002[54]	
Gale 1996[62]	
Zittoun 1995[41]	
Cassileth 1998[58]	
Cassileth 1992[63]	
Schiller 1992[34]	
Wilemze 1991[64]	
Archimbaud 1994[37]	
Mohty 2005[65]	

DP 2: Adults with AML in ≥ CR2

Allo vs Other	Auto vs Chemo
Johnson 1998[7]	
Gale 1996[70]	
Gale 1991[71]	
Oliansky 2008[17]	
Gale 1996[70]	

DP 3: Children with AML in CR1

Allo vs Other	Auto vs Chemo
Johnson 1998[7]	Johnson 1998[7]
Nesbit 1994[72]	Amadori 1993[76]
Dahl 1990[73]	Ravindranath 1996[77]
Wells 1994[74]	Woods 1996[80]
Michel 1996[75]	Stevens 1995
Amadori 1993[76]	Bleakley 2002[23]
Ravindranath 1996[77]	Amadori 1993[76]
Woods 1996[78]	Woods 1996a[78]
Bleakley 2002[23]	Woods 1996b[79]
Amadori 1993[76]	Stevens 1998[80]
Wells 1994[74]	Burnett 1998[59]
Woods 1996a[78]	Ravindranath 1996[77]
Woods 1996b[79]	Oliansky 2007[16]
Stevens 1998[80]	Alonzo 2005[82]
Shaw 1994[81]	Woods 2001[83]
Michel 1996[75]	Ravindranath 1996[77]
Oliansky 2007[16]	Stevens 1998[80]
Alonzo 2005[82]	Amadori 1993[76]
Woods 2001[83]	Pession 2005 [84]
Ravindranath 1996[77]	
Stevens 1998[80]	
Amadori 1993[76]	
Pession 2005[84]	
Wells 1994[74]	
Nesbit 1994[72]	
Perel 2005[85]	
Lie 2003[86]	
Entz-Werle 2005[87]	
Liang 2006[88]	
Dahl 1990[73]	
Lange 2004[89]	

DP 4: Children with AML in ≥ CR2

Allo vs Other	Auto vs Chemo
Oliansky 2007[16]	
Wells 2003[90]	

FIGURE 6 *List of studies included in existing reviews.*

DP 5: Adults with ALL in CR1

Allo vs Other	Auto vs Chemo
Johnson 1998[7]	Johnson 1998[7]
Proctor 1988[91]	Fiere 1990[103]
Forman, Blume 1991[92]	Sebban 1994[96]
Fiere 1987[93]	Fiere 1994[97]
Mrsic 1993[94]	Bernasconi 1992[105]
Mrsic 1992[95]	Proctor 1988[91]
Sebban 1994[96]	Nemet 1995[119]
Fiere 1994[97]	Proctor 1994[107]
Zander 1988[98]	Diez Martin 1994[106]
Zhang 1995[99]	Hahn 2006[14]
Messerer 1994[100]	Fiere 1993[120]
Messerer 1991[101]	Thomas 2004[109]
Tamura 1992[102]	
Fiere 1990[103]	
Richards 1996[104]	
Bernasconi 1992[105]	
Diez Martin 1994[106]	
Proctor 1994[107]	
Yoshida 1984[108]	
Hahn 2006[14]	
Thomas 1004[109]	
Sebban 1994[96]	
Zhang 1995[99]	
Horowitz 1991[110]	
Messerer1994[100]	
Oh 1998[111]	
Messerer 1991[101]	
Takeuchi 2002[112]	
Gupta 2004[113]	
Ueda 1998[114]	
Tamura 1992[102]	
Yanada 2006[18]	
Sebban 1994[96]	
Takeuchi 2002[112]	
Dombret 2002[115]	
Hunault 2004[116]	
Labar 2004[117]	
Ribera 2004[118]	
Orsi 2007[26]	
Hunault 2004[116]	
Labar 2004[117]	
Ribera 2004[118]	
Thomas 2004[109]	

DP 6: Adults with ALL in ≥ CR2

Allo vs Other	Auto vs Chemo

DP 7: Children with ALL in CR1

Allo vs Other	Auto vs Chemo
Johnson 1998[7]	Johnson 1998[7]
Chessells 1992[121]	Schaison 1993[122]
Schaison 1993[122]	Hahn 2005[13]
Saarinen 1996[123]	Arico 2000[125]
Hahn 2005[13]	
Wheeter 2000[124]	
Chessells 1992[121]	
Arico 2000[125]	
Uderzo 1997[126]	
Saarinen-Pihkala 1996[123]	
Sharathkumar 2004[127]	

DP 8: Children with ALL in ≥CR2

Allo vs Other	Auto vs Chemo
Johnson 1998[7]	Johnson 1998[7]
Johnson 1981[128]	Uderzo 1995[133]
Boulad 1994[129]	Borgmann 1995[149]
Chessells 1986[130]	Hahn 2005[13]
Harris 1987[131]	Wheeler 1998[141]
Torres 1999[224]	Borgmann 1995[144]
Uderzo 1995[133]	Borgmann 1995[149]
Ringden 1989[134]	Messina 1998[146]
Hoogerburgge 1995[135]	Feig 1997[148]
Barrett 1994[136]	
Frassoni 1985[137]	
Bacigalupo 1986[138]	
Dopfer 1991[139]	
Wheeler 1996[140]	
Hahn 2005[13]	
Barrett 1994[136]	
Wheeler 1998[141]	
Uderzo 1995[133]	
Harrison 2000[142]	
Schroeder 1999[143]	
Borgman 1995[144]	
Borgman 2003[145]	
Hoogerbrugge 1995[135]	
Messina 1998[146]	
Boulad 1999[147]	
Feig 1997[148]	
Torres 1989[132]	
Johnson 1981[128]	
Bacigalupo 1986[138]	

FIGURE 6 *List of studies included in existing reviews* (continued).

German trials, there seems to be a reasonable level of overlap between the rest of the reviews with regard to trials included. The most recent review (Oliansky *et al.*[17]) also missed a number of trials by the BGMT (Bordeaux–Grenoble–Marseille–Toulouse), EORTC/GIMEMA (European Organisation for Research and Treatment of Cancer/Gruppo Italiano Malattie EMatologiche dell'Adulto) and SWOG (Southwest Oncology Group) research groups that were included in previous reviews. In addition, because they limited their search to a publication date of 1990 or later, the Oliansky 2008 review[17] did not contain publications prior to 1990 (which comprised the bulk of the evidence in the HTA report by Johnson *et al.*[7]).

On the whole, results from across the seven reviews suggest that, although allogeneic SCT is more beneficial than alternative treatments in the management of adult AML in CR1, the true benefit depends on cytogenetic risk, as survival advantage for allogeneic SCT is observed in high- and intermediate-risk cytogenetics but not in good-risk cytogenetics. A risk-adapted approach to the management of this group of patients is therefore suggested. Further details from each review are provided below.

Johnson 1998[7]

The authors identified 11 DvND studies conducted between 1977 and 1994 which, among them, included > 900 patients, receiving either allogeneic

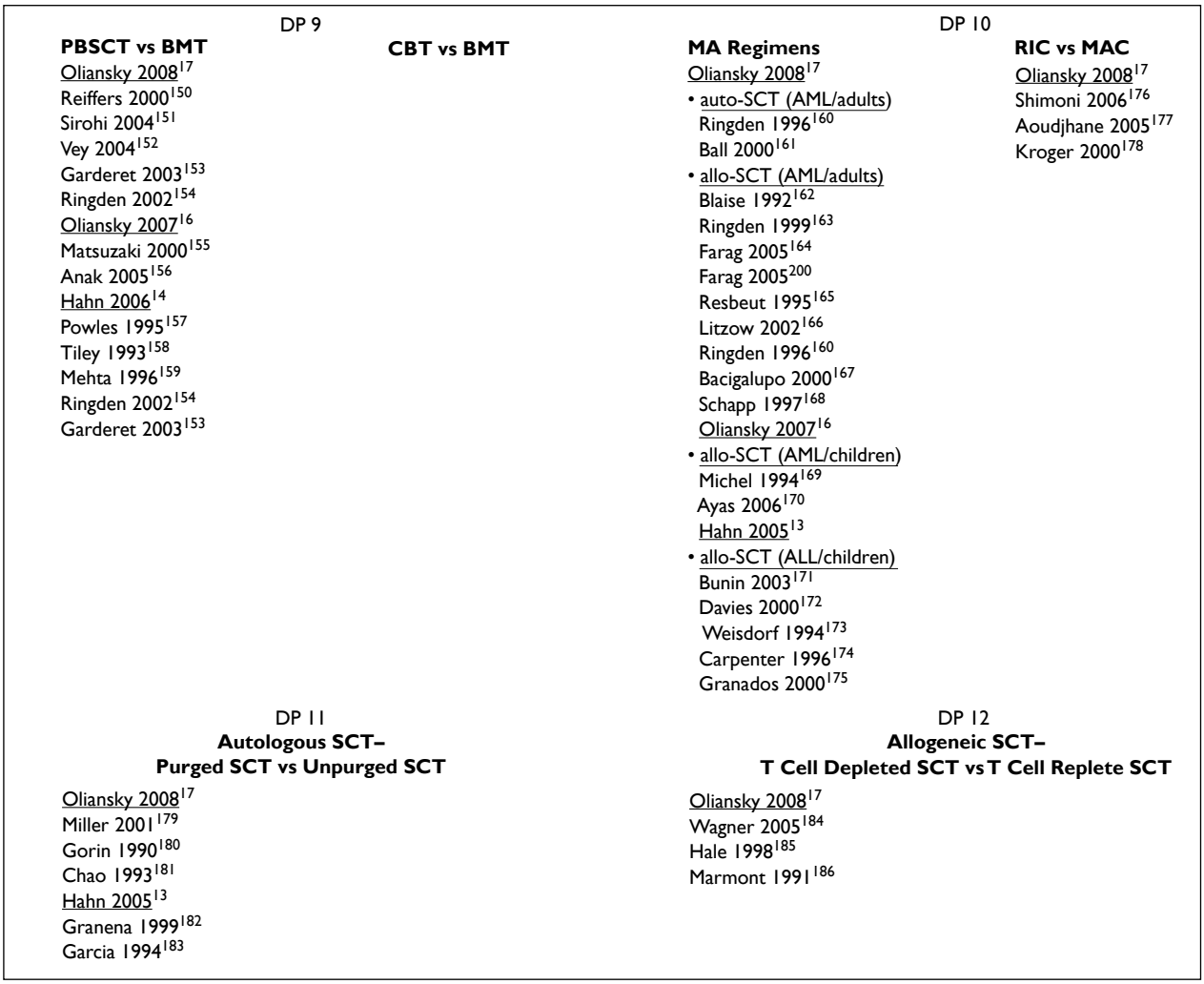

FIGURE 6 *List of studies included in existing reviews* (continued).

transplantation or other therapeutic options in the consolidation of first remission. Ten trials compared the outcome for patients with a donor with the outcome for patients without a donor who were allocated conventional chemotherapy, while one trial (Burnett *et al.*[39]) randomised patients without a donor to autologous transplantation or 'no further therapy'.

The pooled OR across the studies for OS at 2 years was 0.87 (95% CI 0.56 to 1.35). And although the combined results at 4 years appeared to suggest a survival benefit of transplantation (OR 0.31, 95% CI 0.21 to 0.45), this result was largely driven by the extreme results of the study by Labar *et al.*;[35] as it was published as an abstract, it was difficult for the authors of this report to discern whether it was a CCT or a cohort study. Without the results of that study, there was no clear evidence of a survival difference between the two treatment approaches (OR 0.82, 95% CI 0.50 to 1.32).

With regards to PFS, the combined ORs at 2 and 4 years for this metric were given as 0.49 (95% CI 0.31 to 0.66) and 0.47 (95% CI 0.29 to 0.77) respectively, suggesting that SCT might offer an advantage over conventional chemotherapy.

Schlenk 2004[25]

This was an IPD meta-analysis performed on 392 adults with CBF AML, which is defined by the presence of t(8;21) or inv(16). These patients were treated in eight prospective German AML treatment trials between 1993 and 2002.

Among other results, ITT analysis revealed that there was no difference in RFS and OS between allogeneic SCT ($n = 23$), autologous SCT ($n = 74$) and chemotherapy ($n = 73$) in the inv(16) group ($p = 0.22$). The comparison between allogeneic SCT and other treatment options was not performed in the t(8:21) group as only two patients were assigned to allogeneic SCT.

TABLE 2a *DvND studies of allogeneic SCT versus other treatment options among adults with AML in CR1: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Schlenk 2004[25]	Yanada 2005[18]	Visani 2006[15]	Cornelissen 2007[22]	Schaich 2007[24]	Oliansky 2008[17]
ALP 3 and 4	Schiller 1992[34]	×						×
AMLCG 92	Buchner 2003[49]		×				×	
AMLCG 99/2000	Buchner 2002[50]		×				×	
AMLSG Ulm AML HD93	Schlenk 2003[47]		×				×	
AMLSG Ulm AML HD98-A	Schlenk 2004[48]		×				×	
BGMT 84/87/91/95	Jourdan 2005[61]					×		
BGMT 84	Reiffers 1989[40]				×			
BGMT 87	Reiffers 1996[51]			×	×			×
DSIL Dresden AML 96	Schaich 2001[46]		×				×	
ECOG	Cassileth 1990,[36] 1992[63]	×						×
ECOG/SWOG/ CALGB	Cassileth 1998[58]				×			×
EORTC/ GIMEMA	Zittoun 1995[41]				×			×
EORTC/ GIMEMA AML-10	Suciu 2003[55]			×	×	×		
EORTC/ GIMEMA AML-8A	Keating 1998[52]			×				
GOELAM	Harousseau 1996,[43] 1997[57]	×			×			×
Hellenic CG AML-8	Tsimberidou 2003[60]				×			
HOVON/SAKK AML 4/29/42	Cornelissen 2007[22]					×		×
LYLAM 85	Archimbaud 1994[37]	×						×
MRC AML 10	Burnett 1994,[39] 1998,[59] 2002[54]	×		×	×	×		×
OSHO (#33) AML 96	Schlenk 2004,[25] Schaich 2007[24]		×				×	
SHG AML 1/99	Schlenk 2004,[25] Schaich 2007[24]		×				×	
SHG AML 2/95	Heil 2004[45]		×				×	
SWOG 8125	Hewlett 1995[32]	×						
SWOG/ECOG E3489/S9034	Slovak 2000[53]			×				
–	Appelbaum 1988[30]	×						
–	Champlin 1985[31]	×						
–	Conde 1988[33]	×						
–	Dinsmore 1987[38]	×						
–	Ferrant 1991[56]				×			
–	Labar 1991[35]	×						
–	Powles 1980[29]	×						

TABLE 2b *DvND studies of allogeneic SCT versus other treatment options among adults with AML in CR1: trials not included in existing reviews*

Trial ID	Source and details
AML 10, LAM 90	Thomas 2000[187] (full paper), *n* = 144
CETLAM AML 94	Brunet 2004[188] (full paper), *n* = 200
EORTC/GIMEMA AML 12	Willemze 2005[189] (abstract), *n* = 355
GOELAMS AML 2001	Lioure 2006[190,191] (abstract), *n* = 550
JALSG AML 97	Sakamaki 2008[192] (abstract), *n* = 397
–	[a]Ganser 2005[193] (abstract), *n* = 484

a This is the most recent report of the trial; others are Ganser 2004[198] (abstract) and Heil 2004[199] (abstract).

TABLE 2c *DvND studies of allogeneic SCT versus other treatment options among adults with AML in CR1: ongoing or recently completed trials*

Trial ID	Details
MRC AML 15[194]	Completed; trial started 1 March 2002, ended 1 June 2008; *n* = 3000
MRC AML 12[195]	Ongoing but no longer recruiting; trial started January 1994; *n* = 2000
TRALG 1/02[196]	Recruiting; trial started December 2003; expected completion date September 2015; *n* = 352

Yanada 2005[18]

Data from five trials adopting DvND comparisons and covering a total of 3100 subjects (1151 patients received allogeneic SCT and 1949 received alternative treatments) were included in this meta-analysis. The results showed that there was a statistically significant advantage with allogeneic SCT in terms of OS with a summary HR of 1.17 (95% CI 1.06 to 1.30, $p = 0.003$) for the fixed effects model and 1.15 (95% CI 1.01 to 1.32, $p = 0.037$) for the random effects model.

Additional analysis using meta-regression showed a significant coefficient of +0.24 (i.e. the HR for OS using a random effects model would be 1.39; $p = 0.120$) for the poor-cytogenetic-risk group and –0.25 for the favourable-cytogenetic-risk group ($p = 0.108$; statistical significance was defined by the authors as $p < 0.15$ because of the substantially lower statistical power in this method), indicating that the benefit of allogeneic haematopoietic SCT was further increased for the former and lost for the latter. The coefficient for the intermediate-cytogenetic-risk group was +0.09 and was not significant ($p = 0.561$). The authors' conclusion was that the findings suggested that the efficacy of allogeneic haematopoietic SCT for patients with AML in CR1 depended on cytogenetic risk.

Visani 2006[15]

The aspect of this review comparing allogeneic SCT with other options included nine DvND studies that compared allogeneic SCT with autologous SCT on the basis of genetic randomisation. None of the studies was able to demonstrate any difference for OS between allogeneic SCT and autologous SCT; five of the studies could not show any statistical differences for DFS, while in four studies allogeneic SCT obtained a significant benefit concerning DFS and relapse risk. However no quantitative synthesis of evidence was carried out. The authors concluded that there is no overall benefit of allogeneic SCT in terms of survival, compared with autologous SCT.

Cornelissen 2007[22]

The authors presented DvND data from three consecutive studies of the HOVON-SAKK (Dutch–Belgian Hemato-oncology Cooperative Group and the Swiss Group for Clinical Cancer Research) collaborative study group and combined the results with those of MRC (Medical Research Council), BGMT and EORTC trials in a meta-analysis. This offered the opportunity for an analysis with an accumulated number of more than 4000 patients with AML in CR1. DFS and OS were analysed by donor availability and broken down for cytogenetic risk and age category.

Results showed significant survival advantage among the group with a sibling donor for both DFS (pooled HR 0.79, 95% CI 0.72 to 0.88, $p < 0.001$) and OS (pooled HR 0.87, 95% CI 0.79 to 0.97, $p = 0.01$). This benefit was however not observed in the subgroup of patients with favourable cytogenetics (the results of testing for interaction was not described in the paper; however, the difference in HR for this subgroup compared with all other groups combined is likely to be statistically significant on inspection of the forest plot presented in the paper), with further analysis demonstrating a statistically significant OS benefit of 16% (HR 0.84, 95% CI 0.74 to 0.95) for all patients without a favourable cytogenetic profile

Schaich 2007[24]
This IPD meta-analysis was performed on 131 adult patients with AML and trisomy 8 who were treated in the same German trials as those in the Schlenk study.[25] Among others, results showed that there was no difference in 3-year OS rates between high-dose cytarabine (37%, 95% CI 23% to 52%), autologous SCT (34%, 95% CI 3% to 65%) and allogeneic SCT (45%, 95% CI 22% to 68%).

In addition, the TRM rate within the first 3 years was higher among patients who underwent allogeneic SCT than those who did not (27% vs 4%, $p = 0.001$), but the former had a much lower probability of relapse (27% vs 69%, $p = 0.002$). This lower probability of relapse transformed into a better 3-year RFS for patients who were treated with allogeneic SCT (57%, 95% CI 32% to 83%) than for patients who received autologous SCT (25%, 95% CI 0% to 55%) or high-dose cytarabine (42%, 95% CI 26% to 58%), suggesting that allogeneic SCT may be the superior post-remission strategy for improving RFS in patients with AML and trisomy 8.

Oliansky 2008[17]
Like other ASBMT reviews, this one included studies of various design, including non-RCT/CCT. Evidence was taken from 12 studies of adult populations of AML in CR1 that included patients ≥ 15 years of age. The studies consisted of nine DvND studies, one meta-analysis (Yanada *et al.*[18]) and two retrospective studies (Gale *et al.*[62] and Willemze *et al.*[64]). Of the DvND studies, the smallest trial was LYLAM 85 with 58 patients, while the MRC AML 10 trial, which recruited 1287 patients across 163 centres, was the largest.

A statistically significant difference in DFS/EFS in favour of allogeneic SCT was seen in five trials (Cornelissen *et al.*,[22] Reiffers *et al.*,[51] Burnett *et al.*,[54] Zittoun *et al.*[41] and Cassileth *et al.*[63]) and two trials (Cassileth *et al.* 1998[58] and Cassileth *et al.* 1992[63]) found a significant difference in OS. However no quantitative synthesis of evidence was provided.

The overall finding was that a survival advantage for allogeneic SCT versus chemotherapy was present for patients under 55 years of age with high-risk cytogenetics but not for patients of the same age group with a low-risk cytogenetic profile. In addition, there was lack of evidence on the routine use of allogeneic SCT for patients with intermediate-risk cytogenetics, even though this could be considered a reasonable strategy.

Evidence from primary studies not included in existing reviews
Our search identified six trials not included in previous reviews: two were full text publications (Thomas *et al.*[187] and Brunet *et al.*[188]) and the remainder were conference abstracts.

Thomas *et al.*[187] analysed the outcome of 144 young patients (< 41 years) with AML in CR1, based on the presence or absence of an HLA-identical familial donor and ITT. The study included patients that were treated according to three different successive protocols (LYLAM 85, LAM 90, AML-10) in a French institution between 1985 and 1998 and is in fact an update of a previous report on the LYLAM 85 trial carried out by the same institution (Archimbaud *et al.*[37]). Karyotypes at diagnosis were defined as low, intermediate or high risk.

The median follow-up duration was 21.2 months. Relapse rate was lower in the donor group (31% vs 56%, $p = 0.02$) but there was no difference in the 5-year probabilities of OS between patients with and without donors (32% vs 34%, $p =$ not significant) or DFS (37.1% vs 25.4%, $p = 0.53$). There were also no significant differences between the donor and no-donor groups when survival was compared with adjustment for karyotypes. The authors concluded that the availability of a matched sibling donor did not confer any prognostic advantage in terms of outcome for young adults with AML in CR1.

Brunet *et al.*[188] investigated the results of stratifying treatment on the basis of the patients' age, cytogenetics and availability of an HLA-identical sibling among 200 patients with AML in a prospective Spanish multicentre trial. Once in remission, patients with favourable cytogenetics

were scheduled to receive high-dose cytarabine and the remainder were scheduled for allogeneic SCT (if ≤50 years old and with an HLA-identical sibling) or autologous SCT (if > 50 years old or lacking a donor).

In patients with favourable cytogenetics (who were assigned high-dose chemotherapy), the 4-year OS and leukaemia-free survival were 62% ± 9% and 41% ± 10%, respectively, with results being better in patients with t(8;21). Leukaemia-free survival at 4 years in patients ≤50 years old allocated to allogeneic SCT was 41% ± 9% versus 48% ± 8% after allogeneic SCT ($p = 0.22$). Patients over 50 years old assigned to autologous SCT had a 4-year leukaemia-free survival of 17% ± 9%. Adverse cytogenetics and WBC count ≥ 20×10^9/l at diagnosis were associated with a lower probability of survival and leukaemia-free survival. The authors' conclusion was that high-dose chemotherapy seems a good option for patients with low risk, especially t(8;21), and that the results of autologous SCT were poor in patients over 50 years of age, even as autologous and allogeneic SCT had similar leukaemia-free survival in patients ≤50 years. The authors therefore recommended that cytogenetics and other prognostic markers (such as WBC count at diagnosis) should be considered in the design of future risk-adapted trials.

The conference abstract by Willemze *et al.*[189] was the first report on the AML-12 phase III multicentre trial of the EORTC Leukemia Group and GIMEMA which started in 1999. An allogeneic or autologous SCT was planned for all patients who achieved complete remission, according to donor availability and age. Of the 361 patients still in complete remission after consolidation, 156 had no donor, 136 had a donor and 69 were too old to be HLA-typed. In these three groups, the 2-year DFS rates [standard error (SE)] were 51.8% (4.4%), 66.5% (4.3%) and 52.3% (6.7%), respectively.

Among 337 patients with information on cytogenetics, 41 (31%) had good-risk, 167 (53%) normal, 70 (22%) other and 39 (12%) poor-risk cytogenetics. The 2-year EFS rates (SE) were 74.2% (5.7%), 43% (4.1%), 36.3% (6.2%) and 17.4% (7.1%), respectively. Based on these results, the authors concluded, among other things, that patients with a donor have a better outcome, and that those with good-/poor-risk cytogenetics have an excellent/poor outcome, respectively.

Lioure *et al.*[190] presented the first results of the prospective phase III AML 2001 trial of the GOELAMS group, which recruited 832 patients with AML between 2001 and 2005. After achieving complete remission, research to identify an HLA-identical sibling was performed for all patients. 33% had a donor and could proceed to a T-replete allogeneic SCT: either conventional if aged ≤50 years or a non-myeloablative regimen if aged 51–60 years, after intensive consolidation. A small group of patients with a donor but low-risk prognostic features didn't receive first line allogeneic SCT but intensive consolidation; allogeneic SCT was considered at relapse. Patients without a donor proceeded to intensive consolidation then autologous SCT. Actual results thus concerned 532 patients with 15 months follow-up.

Results revealed that conventional allogeneic SCT resulted in better 2-year DFS than in the autologous SCT arms (71% vs 52%, $p = 0.007$), although the 2-year OS advantage was not significant (77% vs 68%, $p = 0.06$) owing to a higher rate of TRM (36% vs 14%). The advantage for non-myeloablative SCT over autologous SCT was not significant for DFS ($p = 0.24$) and OS for all patients, as well as when considering only patients over 50 years of age: EFS (62% vs 50%, $p = 0.27$) and OS (68% vs 65%). Among other things, the authors arrived at the conclusion that conventional allogeneic SCT remains the best consolidation treatment for patients ≤50 years of age with AML in CR1 and that non-myeloablative SCT after intensive consolidation seems promising for older patients and may extend the use of alternative sources of allogeneic SCT.

The final analysis of the AML 97 trial of the Japanese Adult Leukemia Study Group (JALSG AML 97) were presented by Sakamaki *et al.*[192] at the annual meeting of the American Society of Haematology in 2008. The study aimed to investigate the efficacy of allogeneic SCT as a post-remission treatment in patients with intermediate-/poor-risk AML in CR1. Patients who achieved complete remission were categorised into risk groups; intermediate- or poor-risk patients with living siblings were tissue typed. Allogeneic SCT was assigned to patients with a matching donor, and those without a donor were assigned to receive chemotherapy. DFS, TRM, OS and relapse incidence rates were compared between the two groups on an ITT basis.

Of the 503 patients aged 15–50 years registered between 1997 and 2001, 397 achieved complete remission, of which 75 and 95 were assigned to donor and no-donor groups, respectively. The actual risk of relapse at 8 years was significantly lower in the donor group (54% vs 78%, $p = 0.009$) and TRM did not differ significantly (16% vs 17%, $p = 0.948$). The lower relapse rate in the donor group resulted in a significantly better DFS (38% vs 18%, $p = 0.017$), while the significant superiority of DFS in the donor group translated into a higher, but not significantly so, OS rate (45% vs 28%, $p = 0.089$).

Additionally, the OS of patients younger than 35 years of age was comparable between the two groups; however, the OS in the donor group patients over 36 years was significantly better than that in the no-donor group (47% vs 23%, $p = 0.032$). The authors concluded that allogeneic SCT reduced the risk of relapse and contributed to the survival advantage of patients 36–50 years old with AML and intermediate or poor risk.

Ganser *et al.*[193] presented the results of a German trial involving 484 patients aged ≤60 years with AML who were treated with risk-adapted therapy. Patients with t(8;21), inv(16) or normal karyotype and a good response to induction were considered standard risk, all others as high risk. As late consolidation, standard-risk patients with normal karyotype and an HLA-matched sibling received matched related donor transplantation. The remaining standard-risk patients were randomised between high-dose chemotherapy and autologous PBSCT. Ninety per cent of standard-risk patients ($n = 250$) achieved complete remission compared with 58% of those at high risk ($n = 234$). In patients with normal karyotype, OS at 67 months for the standard-risk patients receiving matched related donor transplantation ($n = 37$) was 61% with no significant difference between high-dose chemotherapy or autologous PBSCT.

Ongoing/recently completed trials

The MRC AML 15 trial, which started in 2002 and closed in 2008, accrued 3000 participants with AML under 60 years old.[194] The MRC AML 12 trial started in 1994, has enrolled 2000 patients with AML and is still ongoing but no longer recruiting participants.[195] TRALG 01/02 is expected to enrol 352 intermediate- or poor-risk patients with AML, aged 51–70 years and in CR1, in a DvND trial of reduced intensity conditioning compared with standard treatment (chemotherapy). It was recruiting participants in May 2008 and is due to complete in 2015.[196]

Overall findings and discussion

At least three of the reviews (Johnson *et al.*,[7] Yanada *et al.*[18] and Cornelissen *et al.*[22]) showed that, on the whole, allogeneic SCT was more beneficial than alternative treatments in the management of adults with AML in CR1. However, the more recent reviews seem to suggest a risk-adapted approach to the management of this group of patients. Thus, all of the reviews (with the exception of the HTA report by Johnson *et al.*,[7] which was compiled prior to the development of risk stratification according to cytogenetics) demonstrated that the true benefit of allogeneic SCT depends on cytogenetic risk and age – a survival advantage for allogeneic SCT is observed in patients with high- and intermediate-risk cytogenetics but not in those with good-risk cytogenetics.

The general consensus therefore seems to be that, for patients with good-risk cytogenetics, there is no advantage from allogeneic SCT compared with chemotherapy, in terms of survival, in the consolidation of first remission in AML. The results of the six primary studies also buttress this point.

Conclusion

We identified seven reviews that assessed the benefit of SCT in the management of adults with AML in CR1 on the basis of a DvND comparison, one of which was as recent as 2008. Six primary studies, not included in existing reviews, were also retrieved. The consistent message across almost all of these reviews and primary studies is that currently the best approach to the management of adult AML in CR1 appears to be one that is risk adapted and priority based. This view may however change in view of the results of two major UK MRC trials which are due to be published in the near future.

During the course of our overview, a recent meta-analysis on the role of allogeneic SCT in AML in CR1 was published in JAMA.[197] All the trials included in that review have been covered in our overview and the conclusion of the review is very much in line with our own conclusion: compared with non-allogeneic SCT therapies, allogeneic SCT has significant RFS and OS benefit for intermediate- and poor-risk AML but not for good-risk AML in CR1. In view of this, there may not be much scope for a systematic review or even

additional DvND studies. A collaborative IPD meta-analysis would however be very valuable, especially if the findings of the MRC AML 12 and AML 15 trials can be incorporated into it.

Trials comparing autologous SCT with other post-remission treatment strategies

Evidence from existing reviews

This comparison was addressed by six existing reviews (*Table 3*), the most recent of which is the review by Oliansky *et al.*[17] Just as in the DvND subsection, there is no overlap between the eight German trials included in the IPD meta-analysis by Schlenk *et al.*[25] and the remainder of the trials. With the exception of these trials, the only other trials from existing reviews not included in the Oliansky review[17] are BGMT 84 and Hellenic AML-8, with the absence of the BGMT 84 trial easily attributable to a date of publication prior to 1990.

All of the existing reviews invariably concluded that, in patients with AML in CR1, autologous SCT did not improve OS when compared with chemotherapy/no further therapy, although a few studies did reveal some benefit for allogeneic SCT in terms of EFS. The overall evidence bespeaks no significant advantage of autologous SCT over chemotherapy, thus precluding its routine use in adults with AML in CR1. Further details from each review are given below.

Johnson 1998[7]

The authors included six RCTs of autologous SCT versus chemotherapy in this review. However, results of only five of these were used in data synthesis, as the study by Hubner *et al.*[44] reported results of both randomised and non-randomised

TABLE 3a *RCTs of autologous SCT versus chemotherapy or no further therapy among adults with AML in CR1: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Levi 2004[21]	Nathan 2004[21]	Schlenk 2004[25]	Visani 2006[15]	Oliansky 2008[17]
AMLCG 92	Buchner 2003[49]				×		
AMLCG 99/2000	Buchner 2002[50]				×		
AMLSG Ulm AML HD93	Schlenk 2003[47]				×		
AMLSG Ulm AML HD98-A	Schlenk 2004[48]				×		
BGMT 84	Reiffers 1989[40]	×	×	×			
BGMT 87	Reiffers 1993,[42] 1996[51]	×	×	×			×
DSIL Dresden AML 96	Schaich 2001[46]				×		
ECOG/SWOG/ CALGB	Cassileth 1998[58]		×	×		×	×
EORTC/GIMEMA	Zittoun 1995[41]	×	×	×		×	×
GOELAM	Harousseau 1996,[43] 1997[57]	×	×	×		×	×
Hellenic CG AML-8	Tsimberidou 2003[60]					×	
HOVON/SAKK AML 4	Breems 2005[66]					×	×
MRC AML 10	Burnett 1994,[39] 1998,[59] 2002[54]	×	×	×		×	×
OSHO (#33) AML 96	Schlenk 2004,[25] Schaich 2007[24]				×		
SHG	Hubner 1996[44]	×					
SHG AML 1/99	Schlenk 2004,[25] Schaich 2007[24]				×		
SHG AML 2/95	Heil 2004[45]				×		

TABLE 3b *RCTs of autologous SCT versus chemotherapy or no further therapy among adults with AML in CR1: trials not included in existing reviews*

Trial ID	Source and details
CALGB 8461	[a]Farag 2005[200] (full paper), *n* = 350
–	[b]Ganser 2005[193] (abstract), *n* = 484

a It is unclear from the full publication if this was a randomised trial or not.
b This is the most recent report of the trial; others are Ganser 2004[198] (abstract), Heil 2004[199] (abstract).

TABLE 3c *RCTs of autologous SCT versus chemotherapy or no further therapy among adults with AML in CR1: ongoing or recently completed trials*

Trial ID	Details
AML 01/99[201]	Ongoing but no longer recruiting; trial started January 1999; *n* = 200

patients. Four trials compared autologous SCT with conventional chemotherapy, while the fifth compared autologous SCT with 'no further therapy' and included some children.

Across the five trials, a total of 928 individuals (including children) were randomised between 1984 and 1994. If only adults are considered, this number totals 553 patients across four trials. There was no good evidence of a survival difference in any of these trials or in the combined results (pooled OR calculated for the 4 years = 0.89, 95% CI 0.64 to 1.29).

Combined ORs for RFS at 2 and 4 years were 0.57 (95% CI 0.36 to 0.93) and 0.61 (95% CI 0.41 to 0.90) respectively, which suggests an absolute survival advantage of approximately 14% (95% CI 2% to 23%) at 2 years and 12% (95% CI 35 to 22%) at 4 years, both favouring autologous SCT over chemotherapy.

Levi 2004[21]
The authors of this study conducted a meta-analysis comparing autologous BMT and intensive chemotherapy in adults with AML in CR1. Combined results of 1044 patients from six included RCTs indicated that autologous BMT had no advantage over chemotherapy concerning death rate (overall RR 0.95, 95% CI 0.81 to 1.11) and was superior to chemotherapy concerning event rate (overall RR 0.82, 95% CI 0.71 to 0.94). The authors concluded that autologous BMT did not improve survival but it did improve EFS when compared with chemotherapy or no further treatment in patients with AML in CR1.

Nathan 2004[20]

This meta-analysis, like the one by Levi *et al.*,[21] was conducted to compare the efficacy of autologous BMT with that of non-myeloablative chemotherapy alone (or no further therapy). A total of 1044 in six eligible studies were randomly assigned to receive autologous BMT or non-myeloablative chemotherapy (five studies) or autologous BMT or no further treatment (one study). A fixed effects model was used to calculate the ratio of probabilities for DFS and OS at 48 months or at the nearest recorded assessment point for each study and for all studies combined.

Results showed that, compared with patients who received chemotherapy or no further treatment, patients who received autologous BMT had a better DFS (ratio of DFS probabilities = 1.24, 95% CI 1.06 to 1.44, $p = 0.006$) but a similar OS (ratio of OS probabilities = 1.01, 95% CI 0.89 to 1.15, $p = 0.86$). The authors concluded that their results do not support the routine use of autologous BMT in adults with AML in CR1.

Schlenk 2004[25]
This IPD meta-analysis of 392 adults with CBF AML was described earlier. Among other results, ITT analysis revealed that there was no difference in RFS and OS between chemotherapy, autologous transplantation and allogeneic transplantation in the inv(16) group ($p = 0.22$).

Visani 2006[15]
Six studies in this review addressed the comparison between autologous SCT and intensive chemotherapy/no further therapy. Across the

studies, 3112 patients entered remission and 792 were found to have a matched sibling and were intended to have an allograft. Of the other cases that could have been randomised to autologous SCT or chemotherapy/no further therapy, only 1066 (34% of the available patients) were actually randomised.

None of the studies could demonstrate any difference for OS between autologous SCT and intensive chemotherapy; four could not show any statistical differences for DFS, while in two studies patients submitted to autologous SCT obtained a significant benefit in DFS after a mean follow-up of 4 years, particularly in the favourable-risk cytogenetic group. Thus, autologous SCT seems to reduce the risk of relapse when compared with intensive chemotherapy, but there is no evidence that it is superior to chemotherapy in terms of OS.

Oliansky 2008[17]

The comparison between autologous SCT with chemotherapy in the consolidation of CR1 in adults with AML was addressed in this review by 11 studies, six of which found a significant difference in DFS/RFS/leukaemia-free survival and two a significant difference in OS. Of the included studies, six were RCTs, two were meta-analyses (Levi *et al.*[21] and Nathan *et al.*[20]) and the remaining were of the following study designs – one non-randomised study (Bassan *et al.*[69]), one sequential cohort study (Rohatiner *et al.*[68]) and one retrospective study (Miggiano *et al.*[67]).

Across the six RCTs, a total of 1239 patents were randomised to autologous SCT or chemotherapy. Based on the survival data presented in the studies, there was no significant advantage of autologous SCT over chemotherapy.

Evidence from primary studies not included in existing reviews

Our search identified two studies not included in previous reviews: one full paper (Farag *et al.*[164]) and one meeting abstract (Ganser *et al.*[193]). Farag *et al.*[164] presented a report on 490 patients enrolled into CALGB 8461, a prospective cytogenetics companion study to adult AML treatment protocols, the purpose of which, among others, was to evaluate the outcome of post-remission therapy in adults under 60 years with AML with normal cytogenetics. In total, 370 patients achieving complete remission received intensification therapy as follows: group 1 – one cycle of high-dose cytarabine; group II – three cycles of high-dose cytarabine; group III – four cycles of high-dose cytarabine; group IV – one cycle of high-dose cytarabine and autologous SCT. It is not clear from the paper whether allocation to each of these groups was randomised or not.

Outcomes by ITT analysis of post-remission intensification therapy were given for 280 patients. Results revealed that groups I and II were associated with the lowest 5-year DFS (28% for each of groups I and II compared with 41% and 45% for groups III and IV respectively, $p = 0.02$) and, although there was no significant difference in the proportion of deaths in remission between the four groups ($p = 0.69$), relapses were more frequent in patients in groups I and II. The 5-year cumulative incidence of relapse was highest for groups I (62%) and II (67%), compared with 54% and 44% for patients in groups III and IV respectively ($p = 0.049$).

Among other results, multivariate analysis revealed that four cycles of chemotherapy (group III) resulted in similar DFS to that of patients assigned to group IV ($p = 0.21$). The authors concluded that the post-remission strategies of either four cycles of chemotherapy or one cycle of chemotherapy plus autologous SCT are associated with improved DFS and reduced relapse compared with therapies that include fewer cycles of chemotherapy or no transplantation.

The trial reported by Ganser *et al.*[193] was described in the previous subsection with the results of the DvND comparison presented. Of the standard-risk patients who were randomised between high-dose chemotherapy and autologous PBSCT, OS at 63 months was 59% and 62% respectively ($p = 0.91$, ITT). Median duration of neutropenia was 20 days for high-dose cytosine arabinoside and 8 days for autologous PBSCT ($p < 0.05$). This corresponded to a significantly higher rate of septicaemia (20% vs 10%) and pneumonia (13% vs 3%) after high-dose cytosine arabinoside. The duration of thrombocytopenia was 22 days after high-dose cytosine arabinoside and 11 days after autologous PBSCT ($p < 0.01$). Fourteen patients died in both the high-dose cytosine arabinoside group (four in complete remission and 10 from relapse) and the transplantation group (one in complete remission and 13 from relapse). The authors posited that in standard-risk patients without an HLA-identical sibling donor, autologous PBSCT instead of high-dose cytosine arabinoside is recommended for late consolidation owing to the reduced treatment-related toxicity.

Ongoing/recently completed trials

One trial (AML 01/99) enrolling 200 standard-risk patients with AML, aged 16–60 years, is ongoing at the moment.[201] It is however no longer recruiting participants.

Overall findings and discussion

At least four of the six reviews suggested a reduction in the risk of relapse for autologous SCT when compared with intensive chemotherapy. However, none of the reviews found any evidence of the superiority of autologous SCT to chemotherapy in terms of OS. The findings of the primary studies are in keeping with the general conclusion across the reviews.

Conclusion

Given that the findings from across the reviews and from identified primary studies are essentially consistent and that there is hardly any likelihood for the current view to change in the near future (on account of the number of ongoing trials/recently completed trials), further research – primary or secondary – on this issue may not be of additional value.

DP2: AML in adults in CR2+ or with refractory disease

Evidence from existing reviews

Two existing systematic reviews (Johnson *et al.*[7] and Oliansky *et al.*[17]) covered this decision problem but neither of them identified any CCT or RCT of adults with AML in CR2. The 1998 HTA report by Johnson *et al.*[7] found two retrospective cohort studies comparing allogeneic transplantation with chemotherapy for the consolidation of second remission in AML (Gale *et al.* 1991[70] and Gale *et al.* 1996[70]), although the authors suspected that it was likely that some patients were included in both studies. However, in keeping with the decision made by the authors of the HTA report with regard to cohort studies, no conclusions were drawn from these studies.

The sole study retrieved by Oliansky *et al.*[17] was the 1996 one by Gale *et al.*,[70] which presented a retrospective analysis of 501 adult patients (≤50 years of age) with AML in CR2. Patients were treated with either chemotherapy ($n = 244$) or HLA-matched sibling donor allogeneic SCT ($n = 257$) at over 80 centres between 1980 and 1989. The two groups were similar with respect to sex and WBC count at diagnosis but transplanted patients were younger (median age 26 years vs 35 years), had briefer first remissions, and more had FAB M2 subtype than their chemotherapy counterparts.

The 3-year probabilities of TRM were 56% for transplant and 7% for chemotherapy and, although the probability for a 3-year leukaemia-free survival was higher in the transplant group compared with the chemotherapy group (26%, 95% CI 20% to 32% vs 17%, 95% CI 12% to 23%), this difference was not statistically significant. Outcomes adjusted for time to treatment, age, and duration of CR1 were also presented.

Evidence from primary studies not included in existing reviews

Our search for primary studies yielded one full paper and a meeting abstract. The paper by Thomas *et al.*[202] assessed the safety and efficacy of SCT, mainly autologous SCT, as consolidation therapy in patients with acute promyelocytic leukaemia (APL: AML FAB subtype M3) who relapsed and achieved CR2. Fifty adult patients with a first relapsed APL, of whom 39 had been previously treated with all-*trans*-retinoic acid, entered a multicentre trial of oral all-*trans*-retinoic acid until complete remission was achieved, followed by timed sequential chemotherapy. Forty-five patients were in complete remission after induction therapy and five patients died from infection during aplasia following chemotherapy. Of those who achieved complete remission, 11 had a familial HLA-identical donor and were allografted; the other 34 patients were scheduled for autologous PBSCT (ITT group) but transplantation was actually carried out in only 22 patients. Nine of the patients who did not undergo transplantation received maintenance chemotherapy.

The 3-year DFS rates of the ITT group and the group that received only chemotherapy were 63% and 51% respectively, while the 3-year DFS rate of actually autografted patients was 77% compared with 11% for patients who underwent allogeneic transplantation. Among the 17 autografted patients that remained in CR2, nine had already reached a longer CR2 than CR1. In addition, results of detection of PML/retinoic acid receptor-alpha by reverse transcription-polymerase chain reaction (RT-PCR) after autologous transplantation showed negative findings in eight of the nine patients tested. The authors concluded that, while allogeneic SCT may be too toxic for patients with relapsed APL, the clinical/molecular outcomes of autografted patients were encouraging.

The abstract by Vignetti *et al.*[203] presented the findings of 243 patients with AML in relapse enrolled into a GIMEMA-AIEOP (Associazione Italiana Ematologia Oncologia Pediatrica) prospective study that investigated BMT and immunotherapy with interleukin-2 (IL-2) in this group of patients. Of the 101 patients in complete remission after consolidation, 41 were transplanted (10 received allogeneic and 31 autologous BMT), 32 were randomised to receive or not receive IL-2 and 28 were ineligible either for transplant or for randomisation (and did not receive any other treatment until relapse and/or death). The criteria for transplantation or randomisation were not stated in the protocol.

Probabilities of DFS, projected at 3.5 years were 33% and 37% for autologous and allogeneic transplant respectively, 19% for the randomised group and 34% for the group of patients not eligible to receive any other treatment after consolidation. No definitive conclusions were reached but the authors pointed out that DFS was similar in the transplanted group (either allogeneic or autologous) and in the group of patients in complete remission not eligible for post-remission therapy.

Ongoing trials

No ongoing trial among this group of patients was identified.

Overall findings and discussion

No studies from higher up the evidence hierarchy were identified in the two systematic reviews covering this decision problem: the only evidence came from two retrospective cohort studies, one of which appeared in both reviews. Thus, while Johnson *et al.*[7] did not draw any conclusion from these studies (in keeping with their concerns about less robust studies), the recommendation by Oliansky *et al.*[17] that patients in CR2 receive an allogeneic SCT if a donor is available, otherwise autologous SCT, was based on expert opinion and clinical practice.

The results of the study by Thomas *et al.*[202] tend to favour autologous SCT over allogeneic SCT and chemotherapy but the study recruited only a small number of patients who make up a specific subtype of relapsed AML. The GIMEMA-AIEOP study reported by Vignetti *et al.*[203] found a higher probability of DFS at 3.5 years for allogeneic SCT compared with autologous SCT (p-values not stated) and seems to be in keeping with the recommendation of Oliansky *et al.*[17]

Conclusion

Even though the review by Oliansky *et al.*[17] was fairly recent (2008), it identified only one retrospective study. Our search of primary studies identified a full text and a meeting abstract on the use of stem cells in relapsed AML, with the full paper describing the use of stem cells in the treatment of relapsed APL. Furthermore, no ongoing trials were identified. This may indicate a genuine lack of evidence for this decision problem. More primary research is therefore needed.

DP3: AML in children in CR1

Trials comparing allogeneic SCT with other therapeutic options

Evidence from systematic reviews and meta-analyses

This comparison was addressed by three existing systematic reviews (*Table 4*). The latest review by Oliansky *et al.*[17] (2008) covered all but one study included in the two earlier reviews. Meta-analyses were carried out in these two reviews but not in Oliansky *et al.* 2007.[16]

Overall the three reviews consistently concluded that allogeneic SCT from matched sibling donor is associated with better OS, PFS and lower relapse rate compared with other treatment options. The differences are statistically significant in some of the individual DvND studies and in pooled estimates from meta-analyses. Further details from each review are provided below.

Johnson 1998[7]

The authors identified five DvND studies conducted between 1979 and 1994 that, among them, included more than 1000 patients, receiving either allogeneic transplantation or conventional therapy in the consolidation of CR1. Four of the studies compared allogeneic BMT with conventional chemotherapy while the fifth (Stevens *et al.*[204]) compared patients undergoing allogeneic transplantation with patients receiving autologous transplantation or 'no further therapy'.

The combined OR suggests that survival was in favour of allogeneic BMT at 4 and 5 years (OR 0.69, 95% CI 0.50 to 0.96). Similarly, PFS was higher in the allogeneic BMT group at 2 years and

TABLE 4a *DvND studies of allogeneic stem cell transplant versus other treatment options among children with AML in CR1: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Bleakley 2002[23]	Oliansky 2007[16]
AIEOP LAM 87	Amadori 1993[76]		×	×
AML 80	Dahl 1990[73]	×		×
CCG 213, 251, 2861, 2891, 2941	Alonzo 2005[82]			×
CCG 213	Wells 1994[74]	×	×	×
CCG 251	Nesbit 1994[72]	×		×
CCG 2891	Woods 1996a,[78] 1996b,[79] 2001[83]		×	×
CCG 2941	Lange 2004[89]			×
EORTC 58921	Entz-Werle 2005[87]			×
MRC AML 10	Stevens 1995,[204] 1998[80]	×	×	×
LAME 89/91	Michel 1996,[75] Perel 2005[85]	×	×	×
POG 8821	Ravindranath 1996[77]			×
RAHC/ANZCCSG AML 1	Shaw 1994[81]		×	

TABLE 4b *DvND studies of allogeneic stem cell transplant versus other treatment options among children with AML in CR1: trials not included in existing reviews*

Trial ID	Source and details
DCOG AML 82, 87 & 92/94	Kardos 2005[205] (full paper), *n* = 209
MRC AML 10 & AML 12	Gibson 2005[206] (full paper), *n* = 758
AML-BFM 93	Creutzig 2000[207] (abstract), *n* = 243
POG 9421	Stine 2004[208] (abstract), *n* = 501

TABLE 4c *DvND studies of allogeneic stem cell transplant versus other treatment options among children with AML in CR1: ongoing trials*

Trial ID	Details
NOPHO AML 2004[209]	Recruiting; started January 2004; expected completion date January 2014; *n* = 250

4 years with corresponding combined OR of 0.63, 95% CI 0.48 to 0.84 and 0.54, 95% CI 0.42 to 0.75 respectively.

Bleakley 2002[23]

This review included six prospective cohort studies that compared the outcome of children with AML with and without a matched sibling donor (Amadori *et al.*,[76] Wells *et al.*,[74] Woods *et al.*,[78,79] Stevens *et al.*,[80] Shaw *et al.*[81] and Michel *et al.*[75]). Three of the trials applied an age-limit of 15 years (Amadori *et al.*,[76] Stevens *et al.*[80] and Shaw *et al.*[81]); two trials included patients under 21 years old (Wells *et al.*[74] and Woods *et al.*[78,79]) and one study included patients under 20 years of age (Amadori *et al.*[76]). The proportion of patients with a matched sibling donor who received a transplant ranged from 72% to 100% and was > 90% in four of the six trials.

Pooled results from five studies that reported proportion of relapse showed that the risk of relapse was significantly lower in the donor group than in the no-donor group (RR 0.59, 95% CI 0.48 to 0.72). Similarly, the DFS was better in the donor group than in the no-donor group (RR 0.71, 95% CI 0.58 to 0.86) while the risk of death (OS) was reduced in the donor group with the effect being statistically significant in two studies (Woods *et al.*[78,79]). No statistically significant treatment effect was found between the trials with regard to TRM.

Oliansky 2007[16]

Fourteen studies in this review addressed the comparison between allogeneic BMT and chemotherapy in children with AML in CR1. The evidence was taken from studies of children with AML in CR1, all of which included patients under 21 years of age and consisted of 12 RCTs, one study of cumulative outcomes of five trials (Alonzo *et al.*[82]) and a retrospective study (Pession *et al.*[84]). Most of the studies were multicentre trials in the USA or Europe, ranging from seven centres in the AML 80 trial (Dahl *et al.*[73]) to as many as 236 centres in the Children's Cancer Group (CCG) study CCG 2891 trial (Woods *et al.*[83]). The number of patients recruited in the studies ranged from a minimum of 57 patients in CCG 2941 (Lange *et al.*[89]) to a maximum of 1278 patients in Alonzo *et al.*[82]

Six studies stated a statistically significant difference in DFS between treatment groups in favour of allogeneic BMT (Alonzo *et al.*,[82] Woods *et al.*,[83] Amadori *et al.*,[76] Nesbit *et al.*[72] and Lie *et al.*[86]) and three studies found a significant difference in OS (Woods *et al.*,[83] Nesbit *et al.*[72] and Perel *et al.*[85]).

Evidence from studies not included in previous reviews

Our search of RCTs and DvND studies identified two published papers (Kardos *et al.*[205] and Gibson *et al.*[206]) and two conference abstracts (Creutzig *et al.*[207] and Stine *et al.*[208]) not included in previous reviews.

The paper by Kardos *et al.*[205] reported three non-randomised single-arm studies (DCOG AML 82, 87, 92/94). In DCOG AML-82, patients with a matched sibling donor received allogeneic SCT whereas patients without a matched sibling donor received maintenance chemotherapy. In DCOG AML-87, only children with high-risk AML [according to the BFM (Berlin–Frankfurt–Münster) criteria] and with a matched sibling donor received allogeneic SCT. DvND comparison would have been possible in these two studies but results for such comparison were not reported. DCOG AML 92/94 allocated patients either to allogeneic SCT (for those with a matched sibling donor) or autologous SCT (for those without a matched sibling donor) and thus the allogeneic versus autologous SCT comparison was possible. However, compliance with the protocol was not good and again the results were not presented in a way that allowed such comparisons.

Gibson *et al.*[206] reported on two studies (MRC AML 10 and 12). In MRC AML 10, patients received either allogeneic or autologous BMT, depending on donor availability, following four blocks of intensive chemotherapy. In MRC AML 12, a risk group stratification based on response to first course of chemotherapy derived from AML 10 was used to deliver risk-directed therapy: allogeneic BMT was limited to standard- and poor-risk patients and autologous BMT was not employed. Patients were then randomised into receiving either four or five blocks of treatment. The OS and DFS were 66% and 56% for MRC AML-12 and 58% and 53% for MRC AML-10.

Creutzig *et al.*[207] described results from AML-BFM-93, in which allogeneic SCT was reserved for children with a high risk defined by morphology. No significant difference was found for 5-year event-free interval between children who received allogeneic SCT ($n = 26$) and those who did not ($n = 217$) (RR 0.63, 95% CI 0.23 to 1.74, $p = 0.37$). As the information is only available as a conference abstract, it is not clear how the outcome was defined and whether the analysis was conducted on a DvND basis.

Stine *et al.*[208] reported that 3-year DFS was significantly better among patients receiving allogeneic SCT (67.3%, $n = 83$) than patients receiving chemotherapy (37.5%, $n = 418$) in the POG 9421 study, in which patients who achieved a complete remission, had a matched sibling donor and did not have Down syndrome were allocated to allogeneic SCT.

Ongoing trials

One study (NOPHO-AML 2004) recruiting 250 children with AML is due to be completed in 2014. SCT is reserved for high-risk patients defined by cytogenetics and response to chemotherapy in this study.

Overall findings and discussions

Existing evidence from three systematic reviews consistently demonstrated results in favour of allogeneic SCT over other treatment options. However, evidence included in meta-analyses of these reviews constitutes only a small proportion of all possible evidence (albeit perhaps the 'better' studies). The potential bias/impact is not clear. Only very limited evidence is available in relation to specific risk groups (e.g. high-risk patients).

Conclusion

Three systematic reviews consistently concluded that allogeneic SCT is superior to other treatment options. In addition, a further Cochrane review is ongoing. Further systematic reviews and primary studies may not be required, except for prospective trials and/or collaborative IPD meta-analyses that could provide further information on the risks and benefits of allogeneic SCT compared with chemotherapy in difference risk groups.

RCTs comparing autologous SCT with other post-remission treatment strategies

Evidence from existing reviews

Three systematic reviews addressed this comparison (*Table 5*). The latest review by Oliansky *et al.*[16] (2007) covered all trials included in the two previous reviews and an additional combined analysis of five CCG trials. No quantitative synthesis of evidence was provided in this review. Meta-analysis was conducted in Johnson *et al.*[7] but not in Bleakley *et al.*[23] The last authors considered the trials to be too heterogeneous to be pooled owing to differences between trials in terms of both interventions (use of purging or not, use of different conditioning regimens with or without total body irradiation) and comparators (chemotherapies with or without the use of high-dose cytarabine, no further therapy).

The two earlier reviews concluded that evidence was insufficient to determine whether autologous SCT or chemotherapy is superior when compared with each other. Oliansky *et al.*[16] suggested that autologous SCT and chemotherapy have equivalent survival outcomes. Similarly, they did not recommend one treatment option over another owing to a lack of data on other outcomes. Further details from each of the reviews are provided below.

Johnson 1998[7]

Four RCTs evaluating autologous BMT versus chemotherapy were identified: two were full publications (Amadori *et al.*[76] and Ravindranath *et al.*[77]), the other two were abstracts (Woods *et al.*[79] and Stevens *et al.*[204]). Three of the studies compared autologous transplantation with conventional chemotherapy (Amadori *et al.*,[76] Ravindranath *et al.*[77] and Woods *et al.*[79]), while in the fourth trial patients were randomised between autologous transplantation and 'no further therapy' (Stevens *et al.*[204]). The studies were conducted between 1987 and 1995 and a total of 712 patients were randomised across the trials.

Whereas the CCG trial reported preliminary results that were significantly better in the chemotherapy arm (Woods *et al.*[79]), the POG 8821 and MRC AML 10 trials found no evidence of a difference between the two treatments for survival (Ravindranath *et al.*[77] and Stevens *et al.*[204]). However, combining the calculated 3- and 4-year ORs for the POG 8821 and CCG 2861 trials (Ravindranath *et al.*[77] and Woods *et al.*[79]) gave an overall OR of 1.43 (95% CI 1.02 to 2.01), suggesting an absolute survival benefit of approximately 8% (95% CI 0% to 16%) in favour of conventional chemotherapy.

With regard to PFS, none of the studies reported any statistical difference between the two treatment arms; the pooled ORs at 2, 3 and 4 years were again, at all three time points, in favour of chemotherapy.

Bleakley 2002[23]

Bleakley *et al.* identified four RCTs on AML in children (from six publications) that compared autologous BMT with other treatments (Amadori *et al.*,[76] Woods *et al.*,[78,79] Stevens *et al.*[80]/Burnett *et al.*[59] and Ravindranath *et al.*[77]). Three trials were randomised between autologous BMT and

TABLE 5 *RCTs of autologous stem cell transplantation versus chemotherapy or no further therapy among children with AML in CR1: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Bleakley 2002[23]	Oliansky 2007[16]
AIEOP LAM 87	Amadori 1993[76]		×	×
CCG 213, 251, 2861, 2891, 2941	Alonzo 2005[82]			×
CCG 2891	Woods 1996a,[78] 1996b,[79] 2001[83]	×	×	×
MRC AML 10	Stevens 1995,[204] 1998[80]	×	×	×
POG 8821	Ravindranath 1996[77]	×	×	×

chemotherapy (AEIOP LAM 87, CCG 2891, POG 8821) and one trial compared autologous BMT with no further therapy (MRC AML 10). Marrow was purged before transplantation in two of the trials (CCG 2891 and POG 8821). Between 50% and 73% of the eligible patients were randomised and between 54% and 100% of randomised patients received their allocated treatment. Patients were recruited between 1985 and 2000 across all trials.

Pooled estimates were not presented in this review because of qualitative heterogeneity between studies, with or without quantitatively significant heterogeneity, for each outcome of interest. The study by Ravindranath *et al.*[77] showed that the risk of relapse was lower in the autologous BMT group than in the control group (RR 0.70, 95% CI 0.53 to 0.93). The MRC AML 10 study (Stevens *et al.*[80]/ Burnett *et al.*[59]), which, unlike the other three trials, compared autologous BMT with no further therapy, was the only trial showing a significantly reduced risk of relapse or death in the autologous BMT group (RR 0.59, 95% CI 0.37 to 0.96 and HR 0.49, 95% CI 0.27 to 0.89).

Also, whereas no significant difference in the risk of death was reported in the POG 8821 and MRC AML 10 trials between autologous BMT and controls groups, the OS was significantly lower in patients randomised to autologous BMT in the CCG 2891 trial (RR 1.34, 95% CI 1.06 to 1.70; HR 1.43, 95% CI 1.04 to 1.97). Finally, TRM was < 6% and did not differ significantly between autologous BMT and control groups in the AEIOP LAM 87 (Amadori *et al.*[76]) and MRC AML 10 trials (Stevens *et al.*[80]/Burnett *et al.*[59]). However, in the Ravindranath *et al.*[78] study, where purged marrow was used, TRM was significantly higher in the autologous BMT group compared with the chemotherapy controls (RR 3.73, 95% CI 1.07 to 13.03). TRM was not reported in the studies by Woods *et al.*[78,79]

Oliansky 2007[23]
This review identified six studies investigating autologous transplantation versus chemotherapy in children with AML in CR1. These comprised four RCTs, one study of cumulative outcomes of five CCG trials and one retrospective study (Pession *et al.*[84]). Three of the RCTs randomised between autologous BMT and chemotherapy, while the fourth compared autologous BMT with no further therapy. The age limit for inclusion in the trials was 21 years (Alonzo *et al.*,[82] Woods *et al.*[78,79] and Ravindranath *et al.*[77]) or 15 years (Stevens *et al.*,[80] Amadori *et al.*[76] and Pession *et al.*[84]). The number of participants in the studies ranged from 72 (Amadori *et al.*[76]) to 905 patients (Alonzo *et al.*[82]). Median follow-up was stated for only one trial. Risk groups were also not stated for most studies.

None of the studies found a statistically significant difference in DFS between the two treatment groups except for the MRC AML 10 trial which reported a 7-year DFS of 68% in the autologous BMT group compared with 46% in the no therapy group ($p = 0.02$).

Evidence from primary studies not included in existing reviews
Our search for primary studies did not identify additional RCTs not included in existing reviews.

Ongoing trials
No ongoing trial was identified.

Overall findings and discussions
The three systematic reviews consistently concluded that there was no difference between autologous SCT and chemotherapy in children with AML in CR1.

Conclusion
Conclusions from the three systematic reviews suggest that neither autologous SCT nor chemotherapy is superior to the other. However, no new primary studies or ongoing studies were identified, which also suggests that the reviews covered the available evidence. Given the level of evidence available, no further primary studies may be required and decisions can be based on the findings from these reviews.

DP4: AML in children in CR2+ or with refractory disease

Evidence from existing reviews

Only the 2007 review by Oliansky *et al.*[16] covered this decision problem and identified one study by Wells *et al.*[90] that was classified as level 2 evidence. That study presented outcomes of allogeneic BMT versus chemotherapy only, for 101 children with refractory or first relapse AML enrolled in the CCG 2951 trial. However, the Oliansky review[16] concluded that there was a lack of evidence comparing allogeneic SCT with chemotherapy in children with AML in CR2.

Evidence from primary studies not included in existing reviews

Our search of primary studies identified only one RCT that addressed the comparison between autologous SCT and other post-remission treatment strategies. Webb *et al.*[210] described the results from MRC AML 10 trial, in which patients who achieved CR1 received autologous BMT, a matched unrelated donor allograft, a family donor allograft or chemotherapy. However the study did not present the results of comparisons between the treatment options but rather between stages of remission (CR1 and CR2).

Ongoing trials

No ongoing trial was identified.

Overall findings and discussion

The authors of the only review addressing this decision problem stated that there is a lack of evidence comparing matched related donor allogeneic SCT with chemotherapy in CR2, and therefore based their recommendations on the views of the expert panel, which favours the use of matched related donor allogeneic SCT, if available, over both chemotherapy and autologous SCT. Furthermore, the results of the identified primary study do not improve our existing knowledge, which is likely to remain the same as no ongoing trials were identified.

Conclusion

There is no good evidence from systematic reviews or primary studies with regard to this decision problem, nor is there a prospect for much information to emerge in the near future as no ongoing trials were identified. Given the limited evidence available, further primary studies may be required to inform an evidence-based decision on the role of SCT for AML in children in CR2 or beyond.

DP5: ALL in adults in CR1

Trials comparing allogeneic SCT with other therapeutic options

Evidence from systematic reviews and meta-analyses

The comparison was addressed by four existing systematic reviews (Johnson *et al.*,[7] Hahn *et al.*,[14] Yanada *et al.*[19] and Orsi *et al.*[26]). A total of 10 DvND studies were covered in these reviews but none of the individual reviews covered more than six DvND studies (see Table 6a). The review by Yanada *et al.*[19] appears to be the most comprehensive among the three more recent reviews, but it did not include four of the older DvND studies included in Johnson *et al.*[7] The reviews by Johnson *et al.*,[7] Yanada *et al.*[19] and Orsi *et al.*[26] included only DvND studies. This clear distinction was not made by Hahn *et al.*[14] and the review included both DvND studies and other non-randomised studies. We have attempted to include only DvND studies and remove other non-randomised studies in *Table 6*.

Overall, despite the fact that the reporting of results in some of DvND studies included in existing reviews was inadequate and none of the reviews provide comprehensive coverage of existing evidence, the three reviews with meta-analysis (Johnson *et al.*,[7] Yanada *et al.*[19] and Orsi *et al.*[26]) consistently showed that allogeneic SCT was associated with better survival compared with other treatment options. Some observations and/or consensus statements suggested a greater treatment effect for allogeneic SCT among high-risk groups compared with standard-risk groups, but none of these were based on appropriate subgroup analyses. Further details from each review are provided below.

Johnson 1998

This review included six studies (Sebban *et al.*,[96] Proctor *et al.*,[91] Forman *et al.*,[92] Fiere *et al.*[93] and Mrsic *et al.*[94,95]) that recruited 719 adult patients between 1982 and 1991. Five of the studies (Proctor *et al.*,[91] Forman *et al.*,[92] Fiere *et al.*[93] and Mrsic *et al.*[94,95]) compared allogeneic BMT with conventional chemotherapy in patients achieving complete remission after induction therapy, while the sixth (Sebban *et al.*[96]) compared allogeneic with autologous BMT or conventional chemotherapy. The authors pointed out that two of the studies (Mrsic *et al.*[94,95]) were likely to have reported on the same trial despite discrepancies in patient numbers between them. Outcomes were inconsistently reported in the trials and many of them reported only PFS.

There was no evidence of significant difference between allogeneic BMT and other treatment options in the two papers that reported overall survival: at 2 years, the calculated OR for allogeneic BMT compared with conventional chemotherapy was 0.81 (99% CI 0.50 to 1.30), according to data reported by Proctor *et al.*,[91] and 0.84 (99% CI 0.44 to 1.61) for allogeneic BMT

TABLE 6a *DvND studies comparing allogeneic stem cell transplant with other treatment options among adults with ALL in CR1: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Hahn 2006[14]	Yanada 2006[19]	Orsi 2007[26]
EORTC ALL-3	Labar 2004[117]			×	×
GOELAL02	Hunault 2004[116]			×	×
JALSG-ALL-93	Takeuchi 2002[112]		×	×	
LALA-87	Sebban 1994,[96] Fiere 1994[97]	×	×	×	
LALA-94	[a]Dombret 2002,[115] Thomas 2004[109]		×	×	×
PETHEMA ALL-93	Ribera 2005[118]			×	×
–	Fiere 1987[93]	×			
–	Forman 1991[92]	×			
–	[b]Gupta 2004[113]		×		
–	Mrsic 1992,[95] Mrsic 1993[94]	×			
–	Proctor 1988[91]	×			

a Philadelphia chromosome-positive patients only. The analysis reported in this paper included allogeneic SCTs from matched unrelated donors in the donor group and thus is not strictly a DvND comparison.
b The analysis reported in this paper included allogeneic SCTs from matched unrelated donors in the donor group and thus is not strictly a DvND comparison. Yanada 2006[19] also identified this paper but excluded it because the analysis was performed retrospectively.

TABLE 6b *DvND studies comparing allogeneic stem cell transplant with other treatment options among adults with ALL in CR1: trials not included in existing reviews*

Trial ID	Source and details
HOVON 18 and 37 ALL	Cornelissen 2009[211] (full paper), *n* = 257
UKALL XII/ECOG E2993	[a]Goldstone 2008[212] (full paper), *n* = 1031
Study 08/96	Bassan 2001[213] (full paper), *n* = 61
EORTC ALL-4	Labar 2007[214] (abstract), *n* = 325

a This is the most recent report of the trial; others are Rowe 2005,[216] Lazarus 2006.[217]

TABLE 6c *DvND studies comparing allogeneic stem cell transplant with other treatment options among adults with ALL in CR1: ongoing or recently concluded trials*

Trial ID	Details
GMALL 07/2003[215]	Recruiting; started April 2003; expected to complete December 2008; *n* = 1250

compared with autologous BMT or conventional chemotherapy, according to data reported by Sebban *et al.*[96] These data were not pooled owing to the difference in the control arms.

The combined 2-year OR of 0.38 (95% CI 0.22 to 0.65) from the studies by Forman *et al.*,[92] Fiere *et al.*[93] and Mrsic *et al.*,[94] however, suggested a benefit in PFS in favour of allogeneic BMT (risk reduction 23%, 95% CI 11% to 35%). Similarly, combining the calculated 3- and 4-year ORs from trials by Forman *et al.*[92] and Mrsic *et al.*[94] gave an OR of 0.23 (95% CI 0.10 to 0.51) and an absolute risk reduction of 35% (95% CI 15% to 51%) for PFS in favour of allogeneic BMT. The authors of the review concluded however that it was not possible to determine whether SCTs offer any benefit over conventional chemotherapy as these pooled analyses did not include information from all trials.

Hahn 2006[14]

This review identified nine studies (11 papers: Sebban *et al.*,[96] Thomas *et al.*, [109] Zhang *et al.*,[99] Horowitz *et al.*,[110] Messerer *et al.*,[100,101] Oh *et al.*,[111] Takeuchi *et al.*,[112] Gupta *et al.*,[113] Ueda *et al.*[114] and Tamura *et al.*[102]) investigating allogeneic BMT with other methods in adult ALL in CR1. Four of the studies (JALSG-ALL-93, LALA-87, LALA-94, Gupta *et al.*[113]) appear to be DvND studies but Gupta *et al.*[113] included patients who received allogeneic BMT from matched unrelated donors in the donor group. This study was therefore not a DvND comparison.

As with other ASBMT reviews, no meta-analysis was performed and the results of the trials were individually described/tabulated. None of the three individual DvND studies reported a significant difference in overall survival between allogeneic BMT and other treatment options. There was also no significant difference in DFS in all the studies except in LALA-94 where the 3-year DFS was 47% in the donor group compared with 34% in the no-donor group ($p = 0.007$). The conclusion of the review, based on recommendations made by an expert panel, suggested that SCT yields outcomes similar to chemotherapy and would not be recommended as first-choice therapy in standard-risk patients. The expert panel indicated that there are no direct comparisons for high-risk patients, but some data suggest an advantage for SCT compared with chemotherapy.

Yanada 2006[19]

Seven studies (Sebban *et al.*,[96] Takeuchi *et al.*,[112] Dombret *et al.*,[115] Thomas *et al.*,[109] Hunault *et al.*,[116] Labar *et al.*[117] and Ribera *et al.*[118]) dealing with DvND in adults with ALL in CR1 were included. Patients in the studies were recruited between 1986 and 2002 and the lower age limit was 15 years. All studies were from Europe except Takeuchi *et al.*,[112] which was from Japan. Two of the studies (Dombret *et al.*[115] and Thomas *et al.*[109]) reported on the same trial (LALA-94), which used a risk-adapted strategy for post-remission treatment and divided patients into four risk groups. Dombret *et al.*[115] reported results from one of the risk groups (Ph+ve ALL) whereas Thomas *et al.*[109] (2004) reported results from all four groups. The review authors appear to have requested data from Thomas *et al.*[109] and used results for two other high-risk groups in the meta-analysis, hence there is no double-counting of patients from this trial.

Despite the fact that the authors of the review attempted to use rigorous criteria to select studies that used DvND comparisons and adopted ITT analysis, one of the included studies (Dombret *et al.*[115]) appears to have included patients who received allogeneic SCT from matched unrelated donors in the donor group in their analysis, and thus is not a genuine DvND comparison. Pooling results from all seven studies (duration of follow-up not specified), the summary HR for overall survival was 1.29 (95% CI 1.02 to 1.63, $p = 0.037$), suggesting a significant survival advantage in favour of the donor group. A greater benefit was observed for allogeneic haematopoietic SCT when the analysis was restricted to high-risk patients (HR 1.42, 95% CI 1.06 to 1.90; $p = 0.019$).

Orsi 2007[26]

This review included four DvND studies (GOELAL02, EORTC ALL-3, PETHEMA ALL-93 and LALA-94), all of which were included in the review by Yanada *et al.*[19] Orsi *et al.*[26] recognised the problems of including matched unrelated donor allogeneic SCT in the donor group in Dombret *et al.*[115] and Gupta *et al.*[113] mentioned earlier, and excluded these two studies. Other studies published before 2000 were not included, possibly because the authors only searched electronic databases from 2000 onwards. However it was not clear why JALSG-ALL-93 (Takeuchi *et al.*[112]) was not included.

In the survival analysis using IPD reconstructed according to published information or obtained from trial authors, the OS was better in the donor group than in the no-donor group with a mean EFS time of 5.88 years in the donor group and 4.88 years in the no-donor group (survival times truncated at 12 years). The survival rates (± SE) between the donor group and no-donor group were 63.5% (± 2.8%) versus 60.7% (± 2.2%), 50.3% (± 2.9%) versus 47.9 (± 2.3%) and 44.2% (± 2.9%) versus 31.6% (± 2.2%) at 1 year, 2 years and 7 years respectively (log-rank test $p = 0.011$). The relative risk of an event occurring calculated by Cox regression was also statistically significant in favour of the donor group (RR 0.79, 95% CI 0.66 to 0.96; $p = 0.017$).

Evidence from studies not included in previous reviews

Our search of RCTs and DvND studies identified three published papers (Bassan *et al.*,[213] Goldstone *et al.*[212] and Cornelissen *et al.*[211]) and one conference abstract (Labar *et al.*[214]) not included in previous reviews. The donor group in all studies was allocated allogeneic SCT. The no-donor group was allocated to autologous SCT in HOVON

18 and 37 (Cornelissen *et al.*[211]); randomised to either autologous SCT or standard chemotherapy in MRC UKALL XII/ECOG E2993 (Goldstone *et al.*[212]); and allocated to chemotherapy and/or autologous SCT in EORTC ALL-4 (Labar *et al.*[214]) and Study 08/96 (Bassan *et al.*[213]).

Bassan *et al.*[213] reported the outcome for study 08/96, which adopted risk-oriented post-remission strategies in a cohort of previously untreated, unselected adult with ALL. High-risk patients achieving CR1 were allocated to allogeneic SCT if a related family donor was available and were allocated to alternative treatments (chemotherapy with/without autologous SCT depending on B or T lineages) if a related donor was not available. No significant difference in median DFS (1.5 years vs 1.9 years) and 3-year DFS (38% vs 43%, *p*-value not stated) between the donor and no-donor groups was found. It was not clear why this study was not included in the three more recent reviews.

Labar *et al.*[214] described the results of EORTC ALL-4, in which patients younger than 50 years with family donors received allogeneic SCT while those without donors received either autologous SCT or chemotherapy. No significant difference was found between the donor group and no-donor group for 5-year DFS (41% vs 36%, $p = 0.38$) and overall survival (42% vs 38%, *p*-value not stated). The relapse incidence was significantly lower in the donor group (38% vs 58%, $p < 0.05$) than the non-donor group, but this was annulled by a significantly higher treatment related mortality in the donor group (22% vs 3%, $p < 0.05$).

Goldstone *et al.*[212] reported on the results of UKALL XII/ECOG E2993 study, the preliminary results of which were previously reported by Rowe *et al.*[216] In this trial all patients under 50 years of age (or under 55 years of age from 2003 onwards) who had an HLA-matched sibling donor and achieved CR1 were allocated to allogeneic SCT. Those who did not have a matched sibling donor or who were older than 50 years (55 years from 2003 onwards) were randomised to receive a single autologous SCT or consolidation/maintenance chemotherapy. As patients with Philadelphia chromosome (Ph) who did not have a matched sibling donor could receive allogeneic SCT from a matched unrelated donor in this trial, only Philadelphia chromosome-negative (Ph–ve) patients were included in the DvND comparison. The 5-year OS for Ph–ve patients was significantly better ($p = 0.01$) in the donor group ($n = 443$) (53%, 95% CI 48% to 58%) than the no-donor group ($n = 588$) (45%, 95% CI 40% to 49%). Analysis stratified by risk groups did not show a significant difference in treatment benefit between standard-risk and high-risk groups (test for interaction, $p = 0.4$). In both risk groups, the relapse rate was significantly lower (at 10 years, $p < 0.0005$ in both risk groups) and the non-relapse rate was higher (at 2 years, *p* values not given) in the donor group compared with the no-donor group.

Cornelissen *et al.*[211] reported results from the HOVON-18 ALL and HOVON-37 ALL studies, in which patients in the donor group ($n = 96$) were allocated allogeneic SCT whereas patients in the no-donor group ($n = 161$) were allocated autologous SCT. At 5 years, the donor group had better OS (61% vs 47%, $p = 0.08$; HR 0.70, 95% CI 0.46 to 1.05) and DFS (60% vs 42%, $p = 0.01$; HR 0.60, 95% CI 0.41 to 0.89) compared with the no-donor group. The 5-year relapse rate was significantly lower in the donor group than in the no-donor group (24% vs 55%, $p < 0.001$; HR 0.37, 95% CI 0.23 to 0.60) while the non-relapse mortality was significantly higher in the donor group (16% vs 3%, $p = 0.002$; HR 4.84, 95% CI 1.60 to 14.6). No significant difference in treatment benefit between standard-risk and high-risk groups was found (test for interaction, $p > 0.10$).

Ongoing trials

One study (GMALL 07/03) with an estimated enrolment of 1250 in adults with ALL started in April 2003 and final data collection for the primary outcome was expected to be completed by December 2008.[215] SCT was reserved for high-risk patients and those with a high risk of relapse.

Overall findings and discussions

Four existing systematic reviews addressed this comparison. The earliest (Johnson *et al.*[7]) showed favourable outcomes for allogeneic SCT compared with other treatment options but could not draw a firm conclusion owing to the incompleteness of data that could be included in meta-analyses. More recent reviews covered largely different (more recent) evidence. With the exception of Hahn *et al.*[14] in which no meta-analysis was performed, the reviews similarly found that allogeneic SCT from a matched sibling donor was more effective than chemotherapy and/or autologous SCT. Trials published subsequently have further confirmed this conclusion.

While the effectiveness of allogeneic SCT in adults with ALL in CR1 appears to have been established, whether a specific subgroup (risk

group) of patients can benefit more from this procedure remains uncertain. One of the existing reviews (Yanada *et al.*[19]) and some expert opinion (Hahn *et al.*[14]) have suggested that allogeneic SCT may be more effective in high-risk groups than in standard risk groups. However, results from two subsequent large RCTs do not support this and indeed have shown an opposite trend (the results were numerically more favourable in standard-risk groups than in high-risk groups but the differences between the standard-risk and high-risk groups were not statistically significant). These findings demonstrated the importance of drawing firm conclusions based only on prospectively planned and appropriately conducted subgroup analyses.

Given the uncertainty of the role of risk stratification and the large volume of emerging evidence, an updated systematic review seems warranted. As risk stratification was conducted using different sets of criteria in different trials and none of the existing sets of criteria appears to be predictive of the relative benefit of allogeneic SCT compared with other treatment options, IPD meta-analysis would be needed to allow the exploration of different criteria for risk stratification. Existing studies have shown that allogeneic SCT has significantly better anti-leukaemic effects compared with other treatment options in this patient population, but the benefit was offset by TRM. It has therefore been suggested that risk stratification for the purpose of informing decisions on allogeneic SCT needs not only to reflect the risk of relapse but also to allow better prediction of the risk of TRM.

Conclusion

Despite some discrepancies in the conclusions of individual systematic reviews and trials, the overall evidence appears consistent in suggesting that allogeneic SCT is superior to chemotherapy and/or autologous SCT. Existing risk stratifications, which have been used to guide treatment decisions regarding allogeneic SCT for adults with ALL in CR1, do not appear adequate for selecting patients who could benefit from this procedure most. Further systematic review (preferably using IPD) and primary studies may be required to optimise the selection of patients to receive allogeneic SCT.

RCTs comparing autologous SCT with other post-remission treatment strategies

Evidence from systematic reviews and meta-analyses

This comparison was addressed by two existing systematic reviews (Hahn *et al.*[14] and Johnson *et al.*[7]) already discussed in the comparison between allogeneic SCT and other treatment options (*Table 7*). The reviews identified a total of four RCTs, but neither performed a meta-analysis. The HTA report by Johnson *et al.*[7] covered all but one trial included in the later review by Hahn *et al.*[14] Johnson *et al.*[7] found no difference in OS and DFS between autologous SCT and other treatment options but cautioned that individual trials were insufficiently powered. Hahn *et al.*[14] concluded that SCT yields outcomes similar to chemotherapy in standard-risk patients, and some data suggest an advantage for SCT in high-risk patients, although

TABLE 7a *Autologous SCT versus chemotherapy/no further therapy among adults with ALL in CR1: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Hahn 2006[14]
LALA-85	Fiere 1990[103]	×	
LALA-87	Fiere 1993,[120] Fiere 1994,[97] Sebban 1994[96]	×	×
LALA-94	Thomas 2004[109]		×
–	Bernasconi 1992[105]	×	

TABLE 7b *Autologous SCT versus chemotherapy/no further therapy among adults with ALL in CR1: trials not included in existing reviews*

Trial ID	Source and details
EORTC ALL-3	Labar 2004[117] (full paper) ($n = 45$)
PETHEMA ALL-93	Ribera 2005[118] (full paper) ($n = 98$)
UKALL XII/ECOG E2993	Goldstone 2008[212] (full paper) ($n = 456$)

there are no direct comparisons. They did not however draw any specific conclusion regarding the comparison of autologous SCT versus chemotherapy.

Johnson 1998[7]
Three RCTs (LALA-85, LALA-87 and Bernasconi *et al.*[105]) that randomised a total of 213 patients between 1985 and 1991 and compared autologous BMT with conventional chemotherapy were identified. Meta-analysis was not performed because the information available only allowed the calculation of ORs for survival and PFS in one trial each.

None of the trials found a significant difference in survival and PFS between the two treatment arms. However, the review authors commented that each of the trials was small and thus was able to detect reliably only large differences in efficacy.

Hahn 2006[14]
The authors identified two RCTs (LALA-87 and LALA-94) that included a total of 320 patients randomised to receive either autologous BMT or chemotherapy in the consolidation of CR1. LALA-87 compared autologous BMT with chemotherapy while LALA-94 compared chemotherapy and autologous PBSCT. The lower age limit was 15 years for the two trials and the median follow-up period was 38 months (LALA-87) and 62 months (LALA-94). It is worth noting that the reference cited in this review for LALA-87 (Fiere *et al.*[120]) was not cited/included in the above review by Johnson *et al.*,[7] and there are discrepancies in the reported number of patients related to this trial/comparison between the two reviews ($n = 117$ in Johnson *et al.*[7]; $n = 191$ in Hahn *et al.*[14]).

No meta-analysis was performed and results of the trials were individually described/tabulated. The overall 3-year survival for autologous BMT/autologous PBSCT compared with chemotherapy was 49% versus 42% (not significant) in LALA-87 and 44% versus 35% in LALA-94 (statistical significance not stated). Corresponding figures for 3-year DFS were 39% versus 32% in LALA-87 (not significant) and 39% versus 24% in LALA-94 (not significant).

Evidence from studies not included in previous reviews
We identified three RCTs (EORTC ALL-3, PETHEMA ALL-93 and MRC UKALL XII/ECOG E2993) not included in existing reviews. All three RCTs reported DvND comparisons for allogeneic SCT versus other treatment options and the results were covered in the previous section. Patients who had no matched sibling donor but were eligible for autologous SCT in these trials were randomly allocated to either autologous SCT or chemotherapy. The results of these randomised comparisons are briefly described below.

The EORTC ALL-3 trial (Labar *et al.*[117]) recruited patients aged 15–60 years with de novo ALL (88%) and lymphoblastic non-Hodgkin lymphoma (12%). All patients without a matched sibling donor and younger than 51 years of age were randomised to receive either autologous BMT ($n = 24$) or maintenance chemotherapy ($n = 21$). DFS was very similar for both groups throughout the trial (median follow-up 9.5 for the whole trial) with an estimated HR of 1.06 (95% CI 0.50 to 2.23) for autologous BMT versus chemotherapy.

The Spanish PETHEMA ALL-93 trial (Ribera *et al.*[118]) recruited adult patients ≤ 50 years of age with high-risk ALL. Patients who achieved complete remission without a matched sibling donor were randomised to receive either autologous SCT ($n = 50$) or delayed intensification followed by conventional maintenance chemotherapy ($n = 48$) until 2 years after achievement of complete remission. The probability for OS at 5 years was 37% (95% CI 25% to 49%) in the autologous SCT group compared with 50% (95% CI 38% to 65%) in the chemotherapy group ($p = 0.17$).

In the UKALL XII/ECOG E2993 study (Goldstone *et al.*[212]), 456 patients (including 16 Ph+ve patients) in the no-donor group were randomised to either autologous SCT or chemotherapy. Patients randomised to the chemotherapy group had a significantly improved 5-year EFS (41% vs 32%; $p = 0.02$) and OS [46% (95% CI 39% to 53%) vs 37% (95% CI 31% to 44%); $p = 0.03$] than those in the autologous SCT group. There was no significant difference in the survival benefit between standard- and high-risk groups (test for interaction $p = 0.8$). No difference in the non-relapse mortality between autologous SCT and chemotherapy was found.

Ongoing trials
No additional ongoing study was identified that compared autologous SCT with chemotherapy.

Overall findings and discussions
Neither existing reviews found a significant difference between autologous SCT and chemotherapy in adults with ALL in CR1. The

reviews, however, had discrepancies in the evidence reviewed/reported, did not quantitatively synthesise results across trials and did not include a substantial volume of evidence from recently published RCTs. An updated review is therefore warranted. Overall the evidence suggests that autologous SCT may produce similar or inferior outcomes as chemotherapy.

Conclusion

Given the limitation of existing reviews and the new evidence from three recent trials, an updated systematic review is required. An ongoing Cochrane review (Naumann *et al.*[11]) should fill in this gap. Existing evidence does not favour the use of autologous SCT in this population, hence the scope of further primary studies may be limited.

DP6: ALL in adults in CR2+ or with refractory disease

Evidence from existing reviews

No DvND studies or RCTs of adults with ALL in CR2 were found in any of the identified reviews. Hahn *et al.*,[14] however, recommended SCT over chemotherapy, based on non-analytical studies with no direct comparative data, in which a sizeable fraction of patients achieved extended leukaemia-free survival compared with chemotherapy alone.

Evidence from primary studies

No RCTs or DvND studies addressing this decision problem were identified in our search of primary studies. One cohort study by Tavernier *et al.*[218] was identified. It examined the outcome of 421 adult patients who entered the LALA-94 trial and subsequently experienced relapse. 181 patients achieved CR2 and genoidentical allogeneic SCT was performed in 55 patients and three patients received donor lymphocyte infusions. Forty-four transplantations were performed from an unrelated donor (of which four were cord blood). The authors concluded that most adult patients with recurring ALL could not be rescued using currently available therapies, although allogeneic SCT remains the best therapeutic option.

Ongoing or recently closed trials

No ongoing/recently completed trials were identified.

Overall findings and discussion

No RCTs or CCTs were identified from the search of existing reviews. Although studies comparing allogeneic and autologous SCT were presented in one review, they were of very small sample sizes, from lower down the evidence hierarchy and arrived at conflicting conclusions. Therefore, the recommendation favouring SCT over chemotherapy by the authors of that review was based on non-analytical studies with no direct comparative data, in which a sizeable fraction of patients achieved extended leukaemia-free survival compared with chemotherapy alone. The conclusion of the primary study identified by us is in consonance with their stance.

Conclusion

It is apparent that robust evidence about the role of SCT in the management of adults with ALL in CR2 or relapse is lacking. In this regard, the importance of well-designed and adequately powered trials that will help to inform decision-making cannot be overemphasised.

DP7: ALL in children in CR1

Trials comparing allogeneic SCT with other therapeutic options

Evidence from systematic reviews and meta-analyses

Donor versus no-donor comparison of ALL in children in CR1 was addressed by two reviews: the 1998 HTA report of Johnson *et al.*[7] and the 2005 review by Hahn *et al.*[13] (*Table 8*). Two trials were identified by the more recent Hahn review,[13] one of which was also identified by the HTA report.[7]

Johnson 1998[7]

This review presented the results of the MRC ALL X trial, which accrued a total of 111 patients between 1985 and 1990. The authors of the trial reported no evidence of a difference in OS, although no data were presented in their paper to support this statement. A PFS curve was presented and an OR of 0.8 (95% CI 0.43 to 1.14) was given, indicating that there was no significant difference between the two treatments. The authors of the review concluded that it was not possible to comment with any certainty on the true efficacy of allogeneic SCT compared with chemotherapy for this group of patients.

TABLE 8a *DvND studies comparing allogeneic SCT with other treatment options among children with ALL in CR1: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Hahn 2005[13]
MRC UKALL X and XI	Wheeler 2000[124]		×
MRC UKALL X	Chessells 1992[121]	×	×

TABLE 8b *DvND studies comparing allogeneic SCT with other treatment options among children with ALL in CR1: trials not included in existing reviews*

Trial ID	Source and details
ALL-BFM 90 and 95	Schrauder 2006[219] (full paper) ($n = 83$)
EBMT/I-BFM SG	Balduzzi 2005[220] (full paper) ($n = 357$)
PETHEMA ALL-93	Ribera 2007[221] (full paper) ($n = 100$)

TABLE 8c *DvND studies comparing allogeneic SCT with other treatment options among children with ALL in CR1: currently ongoing trials*

Trial ID	Details
DCOG-INTERFANT-06[222]	Recruiting; trial started June 2007; expected completion date 1 January 2012

Hahn 2005[13]

As with the other ASBMT reviews, this review summarises evidence from all types of studies (i.e. not just RCTs and DvND studies) and describes treatment recommendations made by an expert panel. No clear distinction was made between DvND studies and other observational studies. The review presented six studies comparing allogeneic SCT with chemotherapy, only two of which were DvND studies (MRC UKALL X and XI). Combined results for very high-risk patients from the two trials did not reach statistical significance (10-year EFS, 39.7% for the donor group vs 50.4% for the no-donor group; difference –10.7%, 95% CI –24% to 2.6%; log-rank test $p > 0.1$). The expert panel concluded that a benefit was demonstrated only for matched related allogeneic SCT in very high-risk (Ph+ve only) ALL and therefore did not recommend allogeneic SCT over chemotherapy for standard- or other high-risk patients, except in the context of clinical trials.

Evidence from studies not included in previous reviews

Three DvND studies were identified. Schrauder *et al.*[219] reported on the results of ALL-BFM 90 and 95 studies which were aimed at determining the role of haematopoietic SCT in CR1 for children with very high-risk ALL. Out of the initial 191 high-risk T-ALL patients, 179 achieved CR1 (96 patients from ALL-BMF 90 and 83 patients from ALL-BFM 95). As information on donor availability was not available for patients on the ALL-BFM90 trial, DvND comparison was made only for patients on the ALL-BFM 95 trial. Five-year DFS was 72% ± 11% in the donor group and 48% ± 6% for the no-donor group ($p = 0.07$).

Balduzzi *et al.*[220] described the results of very high-risk chlidren with ALL (< 18 years old) in a co-operative prospective study. A total of 357 patients across seven countries were allocated to either chemotherapy (280 patients) or allogeneic SCT (77 patients), according to the availability of a HLA-compatible related donor. Patients allocated to allogeneic SCT had a better 5-year DFS compared with patients in the chemotherapy group (56.7% vs 40.6%, HR 0.67 95% CI 0.46 to 0.99; $p = 0.02$). The difference in 5-year survival between donor and no-donor groups was not statistically significant (50.1% vs 56.4%, HR 0.73, 95% CI 0.49 to 1.09, $p = 0.12$).

The paper by Ribera *et al.*[221] reported on the PETHEMA ALL-93 trial in which three options of post-remission therapy were compared among 100 very high-risk patients who achieved complete remission. Those with an HLA-identical family donor were assigned to allogeneic SCT (24 children) while the remainder were randomly assigned to autologous SCT (38 children) or to chemotherapy (38 children). No significant

difference was observed in 5-year DFS [45% (95% CI 27% to 65%) vs 45% (95% CI 37% to 55%)] and OS [48% (95% CI 30% to 67%) vs 51% (95% CI 43% to 61%)] between the donor and no-donor groups. Further subgroup analysis did not produce a statistically significant difference between the two groups.

Ongoing trials

One trial (DCOG-INTERFANT-06) which started in 2007 is ongoing at the moment. It is due to be complete in 2012.[222]

Comment on overall evidence

Because chemotherapy is relatively effective in childhood ALL, allogeneic SCT has been tested mainly among patients with a very high risk of relapse. The two reviews addressing this decision problem were relatively outdated, as evidence from three DvND studies has since become available. Findings from existing DvND studies appear inconsistent and there is still some uncertainty about the benefit of allogeneic SCT over chemotherapy in this group of patients.

Conclusion

In view of the number of new primary studies with inconsistent findings, a new systematic review incorporating meta-analysis could prove to be very useful. Even more useful would be a collaborative IPD meta-analysis that would include the data from all of these studies as well as from the ongoing DCOG trial.

RCTs comparing autologous SCT with other post-remission treatment strategies

No RCTs comparing autologous SCT with other post-remission treatments were identified in either of the reviews. Our search for primary studies identified one RCT (the PETHEMA ALL-93 trial, described earlier), in which very high-risk patients without a matched sibling donor were randomly allocated to autologous SCT or chemotherapy. No significant difference was found between autologous SCT and chemotherapy groups in 5-year DFS [44% (95% CI,29% to 60%) vs 46% (95% CI 32% to 62%)] and OS [45% (95% CI 31% to 612%) vs 57% (95% CI 43% to 73%)]. Given the very limited volume of evidence from RCTs, no systematic review is currently needed. Evidence from the only RCT identified does not favour the use of autologous SCT, hence the scope for further primary studies may be limited.

DP8: ALL in children in CR2+ or with refractory disease

Trials comparing allogeneic SCT with other therapeutic options

Evidence from systematic reviews and meta-analyses

The comparison of allogeneic SCT with other treatment options among children in CR2 or beyond was investigated by two systematic reviews (*Table 9*). The 1998 HTA report by Johnson *et al.*[7] identified only one study (Johnson *et al.* 1981[128]) which might be a CCT or a prospective cohort study. The exact study design was not clear owing to the inadequate information provided in the original paper. The 2005 review by Hahn *et al.*[14] included 15 studies of various design, only three of which were potentially DvND studies (including the study also identified by Johnson *et al.*[7]).

Johnson 1998[7]

The only potential CCT identified in this review accrued 45 patients between 1976 and 1980. The review authors stated that the original paper made no statistical comment on its findings and was too poorly reported to allow for any data synthesis, and therefore concluded that it was not possible to comment with any certainty on the true efficacy of allogeneic SCT compared with chemotherapy for this group of patients.

Hahn 2005[14]

Fifteen studies of various designs concerning childhood ALL in CR2 were identified in this review. Only three of these were potentially DvND studies (Johnson *et al.*,[128] Torres *et al.*[132] and Harrison *et al.*[142]). Results of the studies were described/tabulated individually. No quantitative synthesis of evidence was performed. In contrast to the statement in the 1998 HTA report by Johnson *et al.*,[7] numerical results for the 1981 study by Johnson *et al.*[128] were presented in that review (possibly using crude numbers, not Kaplan–Meier survival analysis). In that study DFS (length of follow-up not described) was significantly better in the related allogeneic BMT group ($n = 24$) compared with the chemotherapy group ($n = 21$) (38% vs 5%, $p = 0.002$). OS (length of follow-up not described) also appeared favourable in the related allogeneic BMT group (46% vs 10%, p-value not stated).

TABLE 9a *Potential DvND studies comparing allogeneic SCT with other treatment options among children with ALL in CR2: trials included in existing reviews*

Trial ID	Source	Johnson 1998[7]	Hahn 2005[14]
MRC UK ALL R1	Harrison 2000[142]		×
–	Johnson 1981[128]	×	×
–	[a]Torres 1989[132]		×

a Johnson 1998[7] also identified this study but classified it as a cohort study.

TABLE 9b *Potential DvND studies comparing allogeneic SCT with other treatment options among children with ALL in CR1: trials not included in existing reviews*

Trial ID	Source and details
CCG 1941	Gaynon 2006[223] (full paper), *n* = 214
–	[a]Torres 1999[224] (full paper), *n* = 76

a This is a longer-term follow-up of Torres 1989,[132] which is included in the Hahn 2005 review.[14]

TABLE 9c *Potential DvND studies comparing allogeneic SCT with other treatment options among children with ALL in CR1: ongoing or recently closed trials*

Trial ID	Details
ALL-REZ BFM 2002[225]	Recruiting; started 01/01/2002; expected completion date 31 July 2012; *n* = 338

Torres *et al.*[132] reported on 76 children (under 17 years at diagnosis) with ALL in CR2 after bone marrow relapse treated in four Spanish centres. Patients with a related HLA-matched donor ($n = 15$) received allogeneic BMT whereas the other 55 patients were treated with conventional chemotherapy. DFS (adjusted for time-to-transplantation bias; timing not specified in the review) was significantly higher in the allogeneic BMT group compared with the chemotherapy group (47.1% vs 9%, $p < 0.025$). This study was classified as a cohort study in the HTA report by Johnson *et al.*[7]

Harrison *et al.*[142] reported the results for children (under 15 years at diagnosis) with ALL in CR2 from the MRC UKALL R1 trial. Most patients had previously been treated on the MRC UKALL X and XI trials but none had received a BMT in CR1. Based on donor ($n = 67$) versus no-donor ($n = 139$) comparison, the EFS was not significantly different between the donor and no-donor groups (5 years, unadjusted 45% vs 45%, $p > 0.10$; 8 years, adjusted for prognostic factors 45% vs 37%, $p > 0.10$).

Based on all evidence included in the review by Hahn *et al.*,[14] the expert panel of ASBMT recommended matched related allogeneic SCT over chemotherapy, but noted that the recommendation was tempered because one prospective trial (i.e. Harrison *et al.*[142]) did not demonstrate a benefit for transplantation on a DvND basis.

Evidence from studies not included in previous reviews

Two full text publications were retrieved. Torres *et al.*[224] presented an update of an earlier Spanish trial reported in 1989 (mentioned previously) that compared allogeneic BMT with chemotherapy in 76 children with relapsed ALL. Twenty-one of the patients had an HLA-identical sibling donor and were accepted for allogeneic BMT, while the other 55 patients were treated with conventional chemotherapy (the authors, however, excluded 15 of these patients from analysis because they relapsed within 3 months of achieving CR2). Ten years on, the probability of DFS was 42.8 ± 10.8% versus 10.0 ± 4.74% ($p = 0.001$) and probability of relapse was 40.2 ± 11.7% versus 87.5 ± 5.2% ($p = 0.0004$) for the allogeneic BMT group compared with the chemotherapy group. The authors concluded that the results strongly reflect those at the initial analysis and confirm a key role of allogeneic BMT in the management of ALL in CR2. It is not clear why this paper was not mentioned in either of the previous reviews.

Gaynon *et al.*[223] presented the findings of the CCG study CCG-1941. Two-hundred and fourteen patients with ALL and early marrow relapse began induction therapy, and 163 patients who achieved CR2 were allocated by donor availability: 50 patients with sibling donors were allocated to matched related allogeneic BMT; 72 patients were randomly allocated between alternative BMT (with the hierarchy of stem cell sources being matched unrelated donor, haplo-identical related donor, and purged autologous marrow) and chemotherapy; while 41 patients refused allocation. Results showed that, overall, 3-year EFS from entry was 19% ± 3% and more than 50% of patients died, failed reinduction or relapsed again before 3 months after CR2. The DFS for patients allocated to sibling donor BMT, alternative donor BMT and chemotherapy was 29% ± 7%, 21% ± 7% and 27% ± 8% respectively at 3 years and 29% ± 7%, 21% ± 7% and 20% ± 7% respectively at 5 years (not significant; exact *p*-value not reported).

Intention-to-treat pair-wise comparison of sibling donor BMT versus alternative donor BMT, sibling donor BMT versus chemotherapy, and alternative donor BMT versus chemotherapy showed no significant differences ($p = 0.36$, 0.80 and 0.56 respectively). The authors concluded that outcomes remain similar and poor for children with ALL and early marrow relapse and that BMT is not a complete answer.

Ongoing trials

ALL-REZ BFM 2002 has been ongoing since 2002. It is expected to recruit 338 participants and has a tentative completion date of 31 July 2012.[225]

Comment on overall evidence

The HTA report by Johnson *et al.*[7] found little evidence from DvND studies and concluded that it was not possible to comment with any certainty on the true efficacy of allogeneic SCT compared with chemotherapy for this group of patients. Based on evidence from studies of various designs, the review by Hahn *et al.*[14] suggested a tempered recommendation for matched allogeneic SCT over chemotherapy. Further evidence from primary studies not included in these reviews is conflicting, with Torres *et al.*[224] showing significant benefit for allogeneic SCT over chemotherapy but Gaynon *et al.*[223] concluding that outcomes between these treatment options remain similar and poor for children with ALL in CR2. An evidence-based role for allogeneic SCT with regard to ALL in children in CR2 or beyond remains unclear.

It is worth noting that the two studies (Johnson *et al.*,[128] Torres *et al.*[132,224]) demonstrating significant benefit for allogeneic SCT over chemotherapy were conducted in the 1970s and 1980s with very poor treatment outcomes for the chemotherapy groups. There were also doubts with regard to whether they were truly DvND studies. By contrast, the two more recent, larger prospective trials that clearly adopted DvND comparison (plus randomisation) failed to demonstrate significant advantage of allogeneic SCT (either matched related or matched unrelated) over chemotherapy.

Conclusion

In the presence of evidence from new primary studies that appears inconsistent with the findings of previous studies/reviews, an updated systematic review (with meta-analysis where appropriate) could prove very useful. Recent studies have failed to demonstrate the effectiveness of allogeneic SCT compared with chemotherapy. The scope for further primary studies may be limited and may be influenced by the results from the ongoing ALL-REZ BFM 2002 trial.

RCTs comparing autologous SCT with other post-remission treatment strategies

No RCTs comparing autologous SCT with other post-remission treatments in children with ALL in CR2 or relapse were identified in any of the reviews. Our search for primary studies and ongoing trials identified one study (MRC UKALL R1, mentioned earlier) in which patients with ALL in CR2 without a matched sibling donor were to be randomised to either autologous SCT or chemotherapy. However, the planned randomisation failed (only 9% of those eligible were actually randomised), highlighting the difficulties of running RCTs with patients who have relapsed from a previous trial.[226]

DP9: comparison between sources of stem cells

PBSCT vs BMT

Evidence from existing reviews

This comparison was addressed by two systematic reviews (Oliansky *et al.*[16] and Hahn *et al.*[14]) (*Table 10*). There was no overlap between the primary studies covered by the two reviews, however the studies covered by the latest review (Oliansky *et al.*[16]) were recent compared with those in Hahn *et al.*[14]

A comparable result was available only for AML in children and the results available were not consistent. One of the studies (Matsuzaki *et al.*[155]) suggested that there was no difference in EFS between PBSCT and BMT, while Anak *et al.*[156] suggested that the 5-year DFS was in favour of PBSCT.

Hahn 2006[14]

Three studies (Powles *et al.*,[157] Tiley *et al.*[158] and Mehta *et al.*[159]) reported on the same trial, which was conducted between 1984 and 1994. Fifty adults (≥ 15 years) with ALL in CR1 at a single UK centre were included with a median follow-up period of 40 months.

The trial investigated BMT with PBSCT in adults and considered patients with unpurged autologous BMT with unmanipulated autologous PBSCT, with all patients being offered only autologous PBSCT towards the end of the study.

The 4-year OS and DFS were 56.2% and 53.2% respectively. There was no comparable arm as autologous PBSCT was the only treatment offered towards the end of the study.

Oliansky 2007[16]

This review identified two primary studies (Matsuzaki *et al.*[155] and Anak *et al.*[156]), previously described under autologous versus allogeneic SCT,

TABLE 10a *Studies comparing PBSCT with BMT among adults and children with ALL/AML in CR1 or beyond or with refractory disease in CR1: trials included in existing reviews*

Trial ID	Source	Hahn 2006[14]	Oliansky 2007[16]
CCSG ANLL93	Matsuzaki 2000[155]		×
–	Powles 1995,[157] Tiley 1993,[158] Mehta 1996[159]	×	
–	Anak 2005[156]		×

TABLE 10b *Studies comparing PBSCT with BMT among adults and children with ALL/AML in CR1 or beyond or with refractory disease in CR1: trials not included in existing reviews*

Trial ID	Source and details
–	Blaise 2000[227] (full paper), *n* = 111
–	Cornelissen 2003[228] (full paper), *n* = 120
–	Mahmoud 1999[229] (full paper), *n* = 30
–	Schmitz 2006[230] (full paper), *n* = 606
–	Skodlar 1997[231] (full paper), *n* = 30
–	Remberger 2007[232] (full paper), *n* = 74
EORTC/GIMEMA AML-10	[a]De Witte 2003[233] (abstract), *n* = 292
–	Friedrichs 2008[234] (abstract), *n* = 105
–	Russell 1999[235] (abstract), *n* = 87

a This is the most recent report of the trial; others are Keating 1997[239] (abstract).

TABLE 10c *Studies comparing PBSCT with BMT among adults and children with ALL/AML in CR1 or beyond or with refractory disease in CR1: ongoing or recently completed trials*

Trial ID	Details
CBMTG-0601[236]	Recruitment started March 2007; *n* = 230
BMTCTN-0201[237]	Recruitment started January 2004; expected completion date April 2012; *n* = 550
COG-ASCT0631[238]	Recruitment started December 2007; expected completion date May 2010; *n* = 425

investigating outcomes from autologous BMT with autologous PBSCT in children with AML. Matsuzaki *et al.*[155] was a multicentre trial involving 23 sites in Japan, while Anak *et al.*[156] was a single-centre study conducted in Turkey. The studies were conducted between 1992 and 2002. The number of patients in both arms of the studies (autologous BMT vs autologous PBSCT) were 17 (Matsuzaki *et al.*[155]) and 36 (Anak *et al.*[156]). The age limits for inclusion were 17 years and 18 years for Matsuzaki *et al.*[155] and Anak *et al.*[156] respectively.

There was no statistically significant difference between the two arms in the study by Matsuzaki *et al.*[155] for EFS. On the other hand, 5-year DFS in the study by Anak *et al.*[156] favoured autologous PBSCT with a DFS of 75% when compared with 50% in autologous BMT; $p = 0.046$. The OS was not reported for the two studies.

Evidence from primary studies not in existing reviews

Nine new primary studies were found. Seven of them (Blaise *et al.*,[227] Cornelissen *et al.*,[228] Friedrichs *et al.*,[234] Mahmoud *et al.*,[229] Schmitz *et al.*,[230] Remberger *et al.*[232] and Russell *et al.*[235]) were studies involving allogeneic transplantation while the two remaining studies considered autologous transplantation. Of the seven studies on allogeneic transplantation, results were available for only six of the studies. Five of these (Blaise *et al.*,[227] Cornelissen *et al.*,[228] Mahmoud *et al.*,[229] Schmitz *et al.*[230] and Remberger *et al.*[232]) were studies incorporating both AML and ALL. They were conducted in adults, except for Remberger *et al.*[232] which was conducted in children.

In the studies by Blaise *et al.*[227] and Schmitz *et al.*[230] there was no difference between PBSCT and BMT with regard to leukaemia-free survival. For Remberger *et al.*,[232] children with ALL/AML were studied, and RFS, TRM and relapse were equal in the two treatment groups. On the other hand, the study by Mahmoud *et al.*[229] suggests that treatment-related toxicity was lower in PBSCT than in BMT, while that of Cornelissen *et al.*[228] suggested that OS was better with BMT than PBSCT.

Skodlar *et al.*,[231] De Witte *et al.*[233] and Keating *et al.*[239] reported on autologous PBSCT and BMT, with the publications by Keating *et al.*[239] and De Witte *et al.*[233] reporting on the same trial (EORTC LG & GIMEMA AML-10 trial). The study included adult patients with AML, and DFS and relapse was the same in the two intervention groups.

Ongoing studies

There are currently three ongoing trials (CBMTG-0601, BMTCTN-0201 and COG-ASCT0631) comparing allogeneic BMT with PBSCT. CBMTG-0601 started in March 2007, including only adults with AML, with estimated enrolment of 230 patients. BMTCTN-0201 started in January 2004 and is expected to include 550 patients under 60 years of age with AML and ALL until completion in April 2012. The last trial (COG-ASCT0631) started in December 2007 but was suspended before the expected completion date.

Overall findings and discussion

The two reviews that provided evidence for this decision problem covered two patient groups and each of the reviews addressed one patient group, though the findings from Hahn *et al.*,[14] which addressed ALL in adults, were not considered because it was not a comparable study. However, the evidence included in these systematic reviews constituted only a proportion of all the possible evidence, as other identified evidence was from studies of mixed populations and it is difficult to draw conclusions from the findings in such populations. The evidence so far is inconclusive and it is still too early to suggest that autologous PBSCT is better than autologous BMT in children with AML.

Conclusion

Nine additional primary studies not already covered by the existing systematic reviews were identified from the search of primary studies. Most of the new primary studies identified were RCTs and they represent a higher level of evidence when compared to the primary studies incorporated within the systematic reviews addressing the decision problem under study. More so, the new primary studies identified combined different patient groups (vis-à-vis leukaemia and ALL/AML) and age groups (adults and children) and the results presented were for the combined groups.

In order to make a sound judgement and to identify which treatment modality is better (BMT or PBSCT), a new systematic review synthesising data from the identified primary studies might be required. However, considering the mixed populations in the studies identified, an IPD analysis may be required in order to get an explicit result for each population group.

CBSCT vs BMT

Evidence from existing reviews

None of the identified reviews included any trials comparing BMT with CBSCT.

Evidence from primary studies

Takahashi *et al.*[240] was the only primary study (non-RCT) that compared PBSCT/BMT with CBSCT. The results of the study suggest that there is no difference between the two treatment group with regard to TRM, relapse and DFS.

Ongoing trials

No ongoing study was identified that compared BMT with CBSCT among adults and children with ALL/AML.

Overall findings

There is no evidence addressing the comparison between BMT and CBSCT.

Conclusion

Considering the lack of evidence on the comparison between BMT and CBSCT, well-conducted new primary studies may be required that will inform decisions on the best treatment option between BMT and CBSCT in adults and children with AML/ALL.

DP10: comparison between conditioning regimens

Comparison of two or more myeloablative regimens

Evidence from systematic reviews and meta-analyses

Two reviews (Hahn *et al.*[14] and Oliansky *et al.*[17]) addressed comparisons between different myeloablative conditioning regimens (*Table 11*).

Hahn 2006[15]

This review included five studies that compared conditioning regimens in allogeneic SCT among children with ALL. Only one of these studies (Bunin *et al.*[171]) was an RCT in which 43 patients were randomised to receive busulfan + VP-16 (etoposide) + cyclophosphamide or TBI + VP-16 + cyclophosphamide as a conditioning regimen. At a median follow-up of 43.3 months, the 3-year EFS was significantly better in the TBI group (58% vs 29%, $p = 0.03$). There was no significant difference in the 3-year OS for the two groups (TBI group 67% vs busulfan group 47%, $p = 0.09$). Overall, the review concluded that TBI regimens have better outcomes than non-TBI regimens.

TABLE 11a *Studies comparing two or more myeloablative regimens in patients with acute leukaemias: trials included in existing reviews*

Trial ID	Source	Hahn 2006[14]	Oliansky 2008[17]
GEGMO	Blaise 1992[162]		×
–	Bunin 2003[171]	×	
–	Ringdén 1999[241]		×

TABLE 11b *Studies comparing two or more myeloablative regimens in patients with acute leukaemias: trials not included in existing reviews*

Trial ID	Source and details
GEGMO	[a]Blaise 1999[242] (abstract)
a This is a longer term follow-up of Blaise 1992,[162] which is included in the Oliansky 2008 review.[17]	

TABLE 11c *Studies comparing two or more myeloablative regimens in patients with acute leukaemias: currently ongoing trials*

Trial ID	Details
RPCI-I-72806[243]	Recruiting; started June 2006; expected completion date April 2024; $n = 530$

Oliansky 2008[17]

Two studies in this review compared conditioning regimens in autologous SCT. Neither was a randomised study. Eight studies compared myeloablative conditioning regimens in allogeneic SCT, of which two were RCTs (Blaise *et al.*[162] and Ringdén *et al.*[241]). In the GEGMO study (Blaise *et al.*[162]), a total of 101 adult patients with AML in CR1 were conditioned prior to an HLA-matched sibling donor allogeneic SCT with either busulfan + cyclophosphamide ($n = 51$) or cyclophosphamide + TBI ($n = 50$). At 2-year follow-up patients allocated to cyclophosphamide + TBI had significantly better DFS (73% vs 49%, $p = 0.01$) and OS (75% vs 51%, $p = 0.02$) compared with patients allocated to busulfan + cyclophosphamide. The study by Ringdén *et al.*[241] also compared busulfan + cyclophosphamide with cyclophosphamide + TBI and included patients with mixed haematological malignancy (41% of whom had AML). There was no significant difference in EFS at 2 years but there appeared to be higher TRM for the busulfan + cyclophosphamide group compared with the cyclophosphamide + TBI group at 7 years (34% vs 14%, *p*-value not stated). The overall conclusion of the review was that there was no significant survival advantage with any one myeloablative conditioning regimen but that studies of late effects might change this conclusion.

Results from primary studies

Our search of primary studies did not identify any additional RCTs. The results of a longer follow-up (mean 111 months) of the aforementioned GEGMO study were described in a conference abstract (Blaise *et al.*[242]). Consistent with the 2-year results reported previously, the cyclophosphamide + TBI group had better OS (62% vs 46%, $p < 0.08$) and DFS (58% vs 39%, $p < 0.03$) compared with the busulfan + cyclophosphamide group.

Ongoing studies

One long-term RCT was identified which compared TBI-containing regimens with non-TBI regimens. It started in June 2006, is expected to accrue a total of 530 patients and is not due to complete until April 2024.

Overall findings and conclusion

There is not enough good-quality evidence to really be able to make a recommendation among the conditioning regimens. In light of this, there is an urgent need to address this issue in the form of well-conducted RCTs.

RIC regimen vs myeloablative conditioning regimen

Evidence from systematic reviews and meta-analyses

Only one review (Oliansky *et al.*[17]) addressed the comparison between RIC and myeloablative conditioning. However, none of the four studies included was an RCT. The review authors' conclusion was that there are insufficient data to make a recommendation and the use of RIC is dependent on patient characteristics such as age, comorbidities and cytogenetic risk.

Results from primary studies

Our search of primary studies did not identify any RCT addressing this comparison.

Ongoing studies

Five ongoing/recently closed trials were identified. Details of their start and expected completion dates, as well the estimated/expected numbers of participants are given in *Table 12*.

Overall findings and conclusion

No published RCT was found in existing reviews or our search of primary studies. However five ongoing/recently completed trials were identified.

TABLE 12 *RCTs comparing RIC with myeloablative conditioning regimens: ongoing or recently completed trials*

Trial ID	Details
AOM04088[244]	Recruiting; started July 2005; expected completion date July 2009; $n = 100$
FHCRC-1992.00[245]	Recruiting; started January 2006; expected completion date January 2010; $n = 280$
MC-FludT.14/L[246]	Recruiting; started November 2008; expected completion date September 2013; $n = 545$
NILG-AML 02/06[247]	Recruiting; started November 2006; expected completion date November 2011; $n = 500$
RPCI-I-72806[243]	Recruiting; started June 2006; expected completion date April 2024; $n = 530$

Thus, more evidence should become available in the next few years, when it may be most appropriate to embark on a systematic review.

DP11: comparison of autologous SCT with and without purging

Evidence from systematic reviews and meta-analyses

Two existing systematic reviews (Hahn *et al.*[14] and Oliansky *et al.*[17]) covered this decision problem but neither of these identified any CCT or RCT that addressed the decision problem's subquestions

However, the review by Hahn *et al.*[15] identified a retrospective study reported both by Granena *et al.*[182] and Garcia *et al.*[183] that addressed the comparison between autologous SCT with purged and unpurged stem cells. The study presented the result of 52 patients on purged or 23 patients on unpurged autologous BMT in CR1, CR2 and CR3 between 1987 and 1993. There was no statistically significant difference between the two groups with a 3-year DFS of 46.8% and 25.6% in the purged and unpurged groups, respectively ($p = 0.13$). There was an improvement in DFS in the purged groups for patients over 15 years old following multivariate analysis.

The review by Oliansky *et al.*[18] also reported on three retrospective studies (Miller *et al.*,[179] Gorin *et al.*[180] and Chao *et al.*[181]) that compared autologous SCT with purging with autologous SCT without purging. The studies were carried out between 1982 and 1993 and included patients ranging from 50 (Chao *et al.*[181]) to 294 (Miller *et al.*[179]). The age limits for inclusion were 47 years (Gorin *et al.*[180]) and 60 years (Miller *et al.*[179] and Chao *et al.*[181]).

The OS for all the included studies was not stated except for the study by Miller *et al.*,[179] in which the 3-year OS was 63% in the purged BMT compared with 40% in the unpurged BMT, though the *p*-value was not stated. Similarly, the leukaemia-free survival was longer in the purged BMT than the unpurged BMT in the same study, with the *p*-value not stated either. However, there was no difference between the two intervention arms for leukaemia-free survival in the studies by Gorin *et al.*[180] and Chao *et al.*[181]

Evidence from studies not included in previous reviews

Our search of primary studies did not yield any study that addressed this question.

Ongoing trials

No ongoing trial was identified among this group of patients.

Overall findings and discussion

Only retrospective studies identified from the two reviews provided evidence on the comparison between autologous purged and unpurged SCT; these are evidence of a lower level.[7] Neither Oliansky *et al.*[17] nor Hahn *et al.*[14] made any recommendations due to the poor quality of the available data.

Conclusion

There is a lack of evidence for this decision problem. The number of autologous SCTs carried out in patients with acute leukaemia has decreased substantially in recent years (see *Figure 1* in Chapter 1). The lack of a current role for autologous SCTs concords with the findings of previous sections (Chapter I, Decision problems), which indicate that in general autologous SCTs offer no advantage over other treatment options in the management of acute leukaemia. Further studies of purging methods in autologous SCT is therefore not a priority.

DP12: T-cell depleted compared with T-cell replete allogeneic SCT

Evidence from systematic reviews and meta-analyses

Only one review (Oliansky *et al.*[17]) focused on this decision problem. Three studies were identified and one of them was an RCT. Wagner *et al.*[184] presented the outcomes of 101 adult patients with AML randomised to undergo an unrelated allogeneic BMT with either T-cell depleted marrow and ciclosporin or a T-cell replete BMT with methotrexate and ciclosporin. The follow-up period was 4.2 years. There was no difference between the two groups in terms of DFS; OS was not stated.

Evidence from primary studies

Our search for primary studies did not yield any additional papers.

Ongoing/recently closed trials

No ongoing trials comparing T-cell depleted with T-cell replete allogeneic SCT were identified.

Overall findings and discussion

Using results from the only RCT identified, Oliansky *et al.*[17] concluded that there was no evidence of a survival advantage with T-cell depleted grafts.

No additional publications were retrieved from our search of primary studies and no ongoing/recently completed trials were identified.

Conclusion

There is a palpable lack of evidence for this decision problem. More primary research in the form of well-designed and adequately powered RCTs is required.

Chapter 5

Cost-effectiveness review

Objective

To identify and summarise the published economic literature on the cost and cost-effectiveness of SCT for acute leukaemias with particular respect to the decision problems defined for the effectiveness review.

In brief these are:

- DP1 relates to transplantation in adults in CR1 with AML
- DP2 relates to transplantation in adults in CR2+ with AML
- DP3 relates to transplantation in children in CR1 with AML
- DP4 relates to transplantation in children in CR2+ with AML
- DP5 relates to transplantation in adults in CR1 with ALL
- DP6 relates to transplantation in adults in CR2+ with ALL
- DP7 relates to transplantation in children in CR1 with ALL
- DP8 relates to transplantation in children in CR2+ with ALL
- DP9 relates to different sources of stem cells in transplantation in any acute leukaemia or age group
- DP10 relates to different conditioning regimens in transplantation in any acute leukaemia or age group
- DP11 relates to use of purging in transplantation in any acute leukaemia or age group
- DP12 relates to T-cell depletion in transplantation in any acute leukaemia or age group.

In the systematic review of economic evaluations DPs 1 and 2, DPs 3 and 4, DPs 5 and 6, and DPs 7 and 8 were considered jointly because economic evaluations rarely considered patients with CR1 and CR2 separately. Although done for convenience, the fact that such separation was not possible may have implications for future economic evaluation, an issue returned to in the discussion.

Results of searches and volume of evidence

The methods for conducting the cost-effectiveness review are described in Chapter 2. This section describes the results of the literature searches and provides an overview of the volume of evidence.

Six hundred and twenty-one hits were identified in the database searches; 561 of these were immediately excluded on the basis of general relevance assessed on the title and abstract.

Of the 60 provisionally included citations from the database searches, 44 hard copies were retrieved for detailed assessment. The remaining 16 hits were duplicates.

A further 15 additional hard copies were requested from the reference lists of two included reviews. Unfortunately, one could not be retrieved because the web address was no longer active and a further two required translation, which could not be done in the time available. In total there were thus 56 studies that could potentially be included. Nineteen were finally included. How each contributed to each of the decision problems is summarised in *Table 13*.

In general terms there was less economic evidence on ALL than AML, and little information on children as opposed to adults. Concerning type of economic evidence, studies providing cost data predominated, with far fewer cost-effectiveness evaluations and just one full economic model.

Thirty-seven studies were excluded. The reasons for exclusion are given in *Table 14*. Only the first reason encountered is recorded; the order of reasons in the table is the order in which the reasons for exclusion were considered in the review.

The relevance of the population was a major limiting factor contributing to exclusion, often because the nature of the population was not clearly stated. Relevance of the population

TABLE 13 *Mapping of included studies to decision problem*

	Costs		Cost-effectiveness		Economic model	
DP	**No. studies**	**References**	**No. studies**	**References**	**No. studies**	**References**
DPs 1 and 2	15	Johnson 1998,[7] Redaelli 2004,[248] Ngamkiatphaisan 2007,[249] Yu 2007,[250] Cordonnier 2005,[251] van Agthoven 2002,[252] Uyl-de Groot 2001,[253] Schwarzenbach 2000,[254] Barr 1996,[255] Dufoir 1992,[256] Welch 1989,[257] Viens-Bitker 1989,[258] Kay 1980,[259] Uyl-de Groot 1995,[260] Armitage 1984[261]	6	Johnson 1998,[7] Redaelli 2004,[248] Yu 2007,[250] Barr 1996,[255] Dufoir 1992,[256] Welch 1989[257]	0	
DPs 3 and 4	2[a]	Johnson 1998,[7] Redaelli 2004[248]	2[a]	Johnson 1998,[7] Redaelli 2004[248]	0	
DPs 5 and 6	2	Johnson 1998,[7] Barr 1996[255]	3	Johnson 1998,[7] Orsi 2007,[26] Barr 1996[255]	0	
DPs 7 and 8	2[b]	Johnson 1998,[28] Madero 2000[262]	1[b]	Johnson 1998[7]	0	
DP9	7	Johnson 1998,[7] Redaelli 2004,[248] Costa 2007,[263] van Agthoven 2002,[252] Uyl-de Groot 2001,[253] Madero 2000,[262] Faucher 1998[264]	3[a]	Johnson 1998,[7] Redaelli 2004,[248] Costa 2001[263]	1	Costa 2001[263]
DP10	2[b]	Johnson 1998,[7] Cordonnier 2005[251]	1[b]	Johnson 1998[7]	0	
DP11	1[b]	Johnson 1998[7]	1[b]	Johnson 1998[7]	0	
DP12	1[b]	Johnson 1998[7]	1[b]	Johnson 1998[7]	0	

a Includes two reviews (Johnson 1998[7] and Redaelli 2004[248]) which, although appearing to cover the decision problem in question, do not have any included studies relevant to it.
b Includes review by Johnson which although appearing to cover the decision problem in question does not have any included studies relevant to it.

TABLE 14 *Reasons for exclusion of studies for the cost-effectiveness review*

Reason for exclusion	**Number of studies**
< 50% of participants have acute leukaemia	25
Does not directly address one of the eight decision problems (1 and 2, 3 and 4, 5 and 6, 7 and 8 were considered as a single problem in this context)	4
Not a costing study, cost-effectiveness study or full economic model	8
TOTAL (still awaiting eight references)	37

remained an issue for many of the included studies too, although in all these cases it was clear that the majority of the population matched the condition and age indicated in the particular decision problem.

The disposition of the included and excluded studies is summarised in the QUOROM-style flow diagram shown in *Figure 7*.

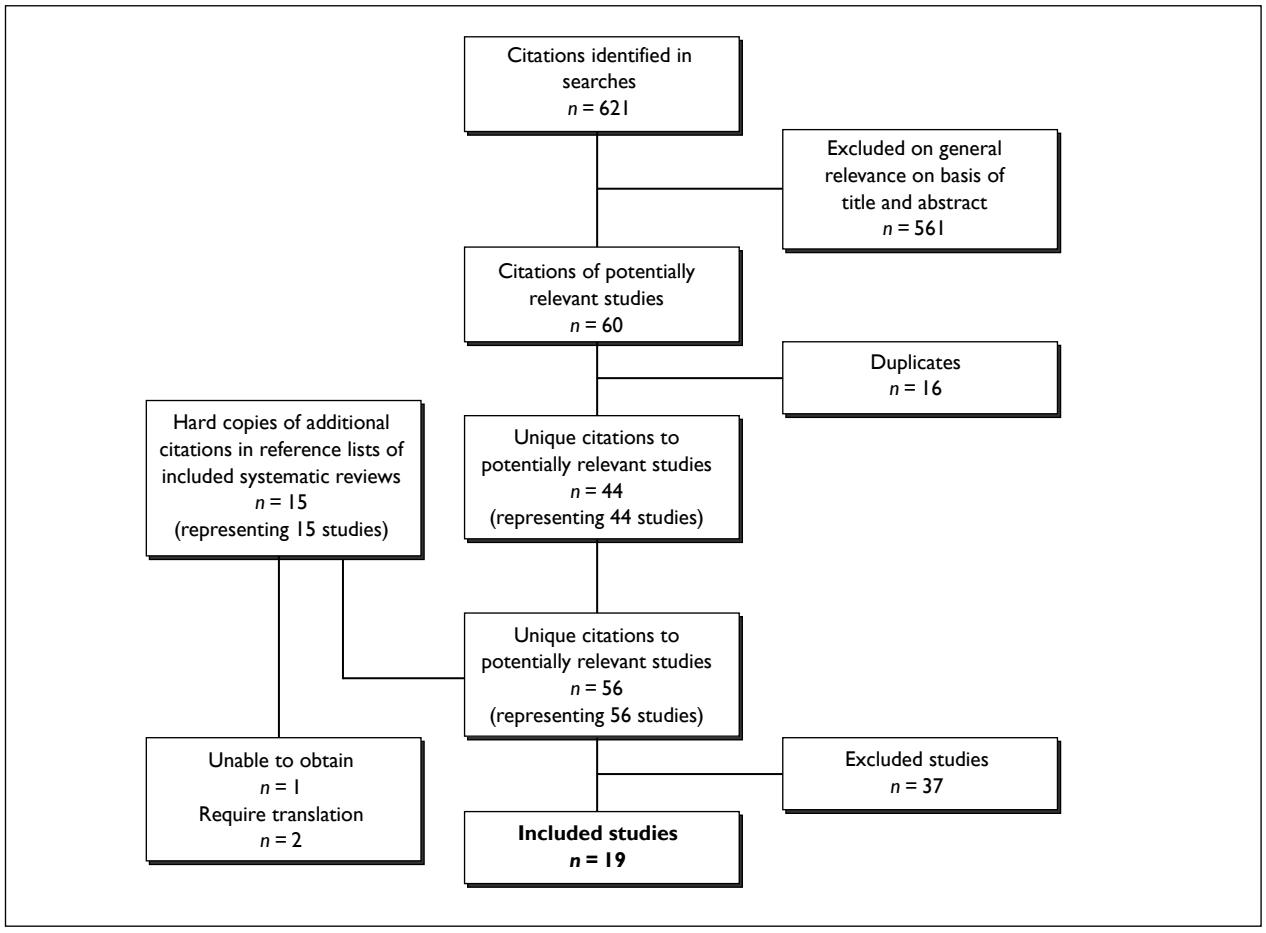

FIGURE 7 *Study selection process for the cost-effectiveness review.*

Results relating to DPs 1 and 2

Nature of decision problems

DP1

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy in the management of AML in adults of various risk groups in CR1?

DP2

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy in the management of AML in adults of various risk groups in CR2, and in adults with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

Number of included studies

There were 15 studies contributing information on costs, two of which were reviews[7,248] and 13 primary studies.[249–261] Six studies contributed information on cost-effectiveness, two of which were reviews[7,248] and four primary studies.[250,255–257] Finally, there were no economic models.

Costs – validity of included studies

Relevance

The review by Johnson *et al.*[7] was structured in the same manner as the decision problems targeted in this review. However, that structure was not used for the reporting of cost studies. Only a general conclusion was drawn across the different decision problems, thus all the included cost studies were examined to identify how generalisable the general conclusions were to DPs 1 and 2. This is

TABLE 15 *Applicability of cost studies apparently addressing acute leukaemia included in the review by Johnson* et al.[7]

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative)				Non-transplantation comparator	Relevance to decision problems
				Al/ Au	Donor	Source	*n*		1 2 / 3 4 / 5 6 / 7 8 / 9 / 10 / 11 / 12
Welch 1989[257]	'Acute non-lymphocytic leukaemia'	17–50 years	?CR1	Al	?Sib	?BM	17	Chemotherapy (*n* = 19)	✓ × × × × × × ×
Corker 1989[266]	AML	?	CR1	Al	Sib	? BM	?	Chemotherapy – 2 options (*n* = ?)	Abstract only No detail about how cost estimates were calculated
Dufoir 1992[256]	AML	Adult < 50 years	CR1	Al	Sib	?BM	14	Chemotherapy (*n* = 15)	✓ × × × × × × ×
				Au	N/A	?BM	11		
Masaoka 1994[267]	'Acute leukaemia'	Adult	CR1	?	?	?	16	Chemotherapy (*n* = 22)	Abstract only No detail about how cost estimates were calculated
Viens-Bitker 1986[265]	AML	?	?	?	?	?	?	?	Main text in French
Armitage 1984[261]	AML	Adult	CR1	Al	Sib	BM	13	Chemotherapy (*n* = 20)	✓ × × × × × × ×
Aulesa 1992[268]	AML	?	?	Mixed	?	?	?	Chemotheraphy (*n* = ?)	Main text in Spanish

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative)				Non-transplantation comparator	Relevance to decision problems							
				AI/Au	Donor	Source	*n*		1 2	3 4	5 6	7 8	9	10	11	12
Barr 1996[255]	Two subpopulations:							Control? Chemotheraphy (*n* = 2 and 6)	✓	×	✓	×	×	×	×	×
	AML	Adults	CR2+	AI	?Sib	?BM	5									
	ALL	Adults	CR1	AI	?Sib	?BM	5									
Rollinson 1982[269]	'Acute leukaemia'	Adult and child	?	?AI	?	?BM	2	Conventional treatment (*n* = 16)	×	×	×	×	×	×	×	×
	AML (12) and ALL (6) (only 2 received BMT; 1 adult with ALL and 1 with AML)															
Kay 1980[259]	AML	Adult (16); child (6)	CR1	?AI	?	BM	22	None	✓	×	×	×	×	×	×	×
Le Corroller 1997[270]	Non-leukaemic malignant disease	Mixed	?	Au	N/A	BM	65	None	×	×	×	×	×	×	×	v
				Au	N/A	PB	64									
de Arriba 1996[271]	Minority of patients leukaemias	Ad	?	Au	N/A	BM	8	None	×	×	×	×	×	×	×	×
				Au	N/A	PB	9									
Julia 1995[272]	Mostly non-Hodgkin lymphoma	Ad	?	Au	N/A	BM	10	None	×	×	×	×	×	×	×	×
				Au	N/A	PB	10									

AI, allogeneic transplantation; Au autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation.
Donor (only applies to allogeneic transplants): Sib, sibling.

summarised in *Table 15*. It shows that, although several of the included studies were applicable to DPs 1 and 2, a number were not. The table also shows that the information about the precise nature of the transplantation being evaluated was often lacking.

The review by Redaelli *et al.*[248] was specifically about AML, but did not differentiate between adults and children. Thus, once again the included cost studies were checked for relevance. This is summarised in *Table 16*. The majority were AML in adults and so relevant to DPs 1 and 2. However, many were not, and in some cases it was unclear on what grounds some studies[273–278] had been included by Redaelli *et al.*[248]

Concerning the primary studies included, most were studies of adult AML (*Table 17*). A minority were mixed populations in which it was clear that the majority of patients were adults with AML. Information on remission status was usually unclear. Most studies offered cost estimates of either allogeneic or autologous transplantation. However, in addition, the following comparisons were also provided by the named studies:

- Allogeneic transplantation from bone marrow or peripheral blood versus conventional therapy (chemotherapy): Dufoir *et al.*,[256] Barr *et al.*,[255] Welch and Larson,[257] Armitage *et al.*[261]
- Allogeneic transplantation from bone marrow or peripheral blood versus high-dose chemotherapy: Yu *et al.*[250]
- Autologous transplantation from bone marrow or peripheral blood versus conventional therapy (chemotherapy): Dufoir *et al.*,[256] Uyl-de Groot *et al.* 1996.[260]
- Autologous transplantation from bone marrow or peripheral blood versus allogeneic transplantation from bone marrow or peripheral blood: Dufoir *et al.*,[256] Ngamkiatphaisan *et al.*,[249] Uyl-de Groot *et al.* 2001.[253]
- Allogeneic transplantation from bone marrow from sibling versus allogeneic transplantation from bone marrow from matched unrelated donor: van Agthoven *et al.*[252]
- Autologous or allogeneic transplantation from bone marrow versus autologous or allogeneic transplantation from peripheral blood – these are considered in detail in DP9: van Agthoven *et al.*,[252] Uyl-de Groot *et al.* 2001.[253]
- Myeloablative versus non-myeloablative transplantation – these are considered in detail in DP10: Cordonnier *et al.*[251]

In many cases the value of the cost information was reduced by missing information about the precise nature of the transplantation procedure being offered.

Internal validity

The majority of the primary studies reporting cost estimates for DPs 1 and 2 appear to be of reasonably good quality.

All the studies estimated total costs from the perspective of the health-care system. Although it is commonly suggested that cost studies should be ideally carried out from a societal perspective, adopting a health-care system perspective is justified owing to the fact that the bulk of the costs in this disease area is expected to be incurred by the health-care system.

Similarly, all the included studies estimated total costs by using resource use estimates obtained from hospital records. Estimated costs were commonly related to outpatient services, inpatient stay, laboratory and diagnostic tests, procedures, and medications. Given that the majority of health services are expected to be provided in secondary care, hospital records provide a good source of cost data.

Most of the assessed studies adopted a 1-year time horizon. It is not clear whether such a short time horizon would be adequate to capture the resource use and costs related to the assessed treatments. Only three of the studies reporting cost results (van Agthoven *et al.*[252] and Uyl-de Groot *et al.* 1995[260] and 2001[253]) considered a 2-year follow-up, while all the studies reporting both cost and cost-effectiveness results (Barr *et al.*,[255] Welch and Larson[257] and Yu *et al.*[250]) used longer time horizons (see *Table 18*). Sensitivity analysis related to cost estimates was performed in the Cordonnier *et al.* 2005[251] and Uyl-de Groot *et al.* 2001[253] studies, where the authors considered the impact of different assumptions on length of hospitalisation and different protocols of care respectively.

Overall, the assessed studies appear to be of reasonable quality and in some agreement with current methodological guidelines [National Institute for Health and Clinical Excellence (NICE) 2008].[279] However, it is not clear whether the results of these studies could be used in the UK setting, mostly owing to the fact that costs are based on unit cost estimates and patterns of care that might not be relevant to current UK practice.

DOI: 10.3310/hta14540

TABLE 16 *Applicability of cost studies apparently addressing acute leukaemia included in the review by Redaelli* et al.[248]

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative) Al/Au	Donor	Source	*n*	Non-transplantation comparator	Relevance to decision problems 1 2	3 4	5 6	7 8	9	10	11	12
Tennvall 1994[273]	AML	?	?	Al/Au	?	?BM	?	None	Not an economic evaluation							
Uyl-de Groot 2001[253]	AML	?Adult	?CR1	Al	?	BM	84 in total	None	✓	×	×	×	✓	×	×	×
				Al	?	PB										
				Au	N/A	BM										
				Au	N/A	PB										
Stalfelt 1994[274]	AML	Adult	Mixed	Unclear that any transplantation used				Chemotherapy (*n* = 15)	×	×	×	×	×	×	×	×
Uyl-de Groot 1995[260]	AML	?	Mixed	Au	N/A	?	20	Conventional (*n* = 10)	×	×	×	×	×	×	×	
Dufoir 1992[256]	AML	Adult <50 years	CR1	Al	Sib	?BM	14	Chemotherapy (*n* = 15)	✓	×	×	×	×	×	×	×
				Au	N/A	?BM	11									
Barr 1996[255]	Two subpopulations:							Control? chemotherapy (*n* = 2 and 6)	✓	×	✓	×	×	×	×	×
	AML	Adults	CR2+	Al	?Sib	?BM	5									
	ALL	Adults	CR1	Al	?Sib	?BM	5									
NCI (web)	Unable to obtain from website															
Lee 2000[275]	Only 60/236 acute leukaemia	?	?	Au and Al	?	BM and PB	236	None	×	×	×	×	×	×	×	×
Wagner 1998[276]	Minimal information on costs															
Bennett 1999[277]	<50% acute leukaemia	Adults	?	Al	?	BM	13	None	×	×	×	×	×	×	×	×
				Al	?	PB	21									
Viens-Bitker 1989[258]	AML	Adults	CR1	Al	?	?BM	N/A	None	✓	×	×	×	×	×	×	×
Beard 1991[278]	?Majority acute leukaemias	?	?	?	?	?BM	41	None	×	×	×	×	×	×	×	×
van Agthoven 2002[252]	Very mixed AML(66)/ALL(31)	Most adults	?	Al	Sib	BM	47	None	✓	×	×	×	✓	×	×	×
				Al	MUD	?	29									
				Al	Sib	PB	21									

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation.
Donor (only applies to allogeneic transplants): MUD, matched unrelated donor; Sib, sibling.

TABLE 17 *Applicability of included cost studies to DPs 1 and 2*

					Nature of transplantation (one row for each alternative)				
Study	**Study type**	**AML**	**Adult**	**CR1/CR2**	**AI/Au**	**Donor**	**Source**	***n***	**Non-transplantation comparator**
Johnson 1998[7]	Review	Thirteen studies contribute to conclusions on cost? Majority relate to AML and so overall conclusions on cost are mostly applicable to DPs 1 and 2							
Redaelli 2004[248]	Review	Thirteen studies contribute to conclusions on cost. Many are relevant to DPs 1 and 2. However there are also a number of studies that are clearly not, and indeed it is unclear why they were included in the review at all							
[a]Kay 1980[259]	Primary	✓	✓ Mixed adults 16/22	CR1	?AI	?	BM	22	None
[b]Viens-Bitker 1989[258]	Primary	✓	✓	CR1	AI	?	?BM	N/A	None
[a,b]Dufoir 1992[256]	Primary	✓	✓	CR1	AI	Sib	?BM	14	Chemotherapy ($n = 15$)
					Au	N/A	?BM	11	
[b]Uyl-de Groot 1995[260]	Primary	✓	?	?	Au	N/A	?	?	None
Schwarzenbach 2000[254]	Primary	✓	✓ Mixed adults 9/10	CR1	AI	?	?BM	10	None
[b]van Agthoven 2002[252]	Primary	✓ Mixed AML 66/97	✓	?	AI	Sib	BM	47	None
					AI	MUD	?	29	
					AI	Sib	PB	21	
Cordonnier 2005[251]	Primary	✓	✓	Mixed	AI (MA)	?	Mixed (9 BM: 3 PB)	12	None
					AI (NMA)	?	PB	11	

Study	Study type	AML	Adult	CR1/CR2	Nature of transplantation (one row for each alternative)				Non-transplantation comparator
					Al/Au	Donor	Source	*n*	
Ngamkiatphaisan 2007[249]	Primary	✓	✓	?	Al	?	Mixed (4 BM: 47 PB)	51	None
					Au	N/A	PB	16	
[b]Uyl-de Groot 2001[253]	Primary	✓	?	?CR1	Al	?	BM	84 in total	None
					Al	?	PB		
					Au	N/A	BM		
					Au	N/A	PB		
[a,b]Barr 1996[255]	Primary	✓	✓	CR2+	Al	Sib	BM	5	Control? chemotherapy (*n* = 2)
[a]Welch 1989[257]	Primary	✓	✓	?CR1	Al	?Sib	?BM	17	Chemotherapy (*n* = 19)
Yu 2007[250]	Primary	✓ Mixed AML 49/54	✓	?CR1	Al	?	PB	21	Intensive chemotherapy (*n* = 33)
[a]Armitage 1984[261]	Primary	✓	✓ Mixed adults 32/33	CR1	Al	Sib	BM	13	Chemotherapy (*n* = 20)

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; MA, myeloablative; NMA, non-myeloablative PB, peripheral blood; source, source of cells for transplantation.

a The study was included in the review by Johnson *et al.*[7]

b The study was included in the review by Radaelli *et al.*[248]

Donor (only applies to allogeneic transplants): MUD, matched unrelated donor; Sib, sibling.

Costs – results of included studies

The results of included studies are summarised in *Table 18*. Concerning costs it is very difficult to disentangle the findings from the two previous systematic reviews beyond the obvious expense of SCT in acute leukaemias.

This review confirms that but offers some more specific information. First, the high cost applies irrespective of the type of transplantation. However, there is considerable variability from study to study, seen particularly for the costs of allogeneic transplantation. This is likely to be driven by many factors such as chance variation, country, year, costing method, precise procedures employed, aspects of transplantation included in the costs, and variation in the nature of the populations. For allogeneic transplantation, costs of 50,000–100,000 are typical, irrespective of whether they are expressed in euros or US dollars. For autologous transplantation, the available costs are generally < US$50,000. In both cases it is notable that there are few estimates based on recent data, offering the possibility of considerable inaccuracy in the published estimates, either through the influence of inflation or improved efficiency through greater proficiency with the SCT techniques.

Given the variability, it is possible that studies offering internal comparisons may provide more robust cost estimates. On this basis it seems clear that both allogeneic and autologous SCT costs considerably more than conventional care, even when that conventional care involves high-dose chemotherapy. Comparing the costs of allogeneic with autologous transplantation in adult AML offers little certainty with mixed results across the four studies addressing this question. This is in marked contrast to the general level of costs for allogeneic and autologous transplants in individual studies, which suggests a very clear difference with autologous transplantation being less expensive. The discrepancy between the two sources of estimate on the relative cost of autologous and allogeneic transplantation suggests that this issue deserves further and closer investigation.

Finally, one study indicates greater costs associated with allogeneic transplantation using matched unrelated donors from those using matched siblings as donors.

Cost-effectiveness – validity of included studies

Relevance

The applicability of included cost-effectiveness studies to DPs 1 and 2 is summarised in *Table 19*.

The conclusions on cost-effectiveness in the two reviews by Johnson *et al.*[7] and Redaelli *et al.*[248] appear to be applicable to DPs 1 and 2. The relevance of the four primary cost-effectiveness studies is also confirmed in *Table 19*. It should be noted that three of these studies, Dufoir *et al.*,[256] Barr *et al.*[255] and Welch and Larson[257] have already been considered in either the review by Johnson *et al.*[7] or Redaelli *et al.*[248] and so it is only the study by Yu *et al.*[250] that presents new information. Further, this study considers only the comparison between SCT and high-dose chemotherapy.

Internal validity

The included studies appear to be of reasonable quality. However, in some cases there are substantial discrepancies between the methods used and the methods for economic evaluation currently suggested in the UK.[279] This is mostly owing to the age of the included cost-effectiveness studies and the fact that most of them were conducted outside the UK.

All the included studies derive effectiveness estimates (in terms of survival) from single clinical studies as opposed to synthesis of evidence from multiple studies. Treatment effectiveness is measured in terms of survival in all the studies, while Barr *et al.*[255] attempts to present effectiveness outcomes in terms of health-related quality of life.

Similarly, all the studies use cost estimates calculated according to health services utilisation rates obtained from patients' medical records. Three of the studies report analyses based on time horizons > 1 year. Barr *et al.*,[255] Dufoir *et al.*[256] and Welch and Larson[257] adopt a 5-year horizon, while Yu *et al.*[250] analyses costs and benefits for 4 years after treatment. Nonetheless, discounting to express costs and benefits in present values was carried out in only two studies (Welch and Larson[257] discounted costs at 5% and Barr *et al.*[255] discounted benefits at 5%).

On the other hand, incremental analysis of cost-effectiveness was attempted in all the included studies. However, Yu *et al.*[250] calculated the

DOI: 10.3310/hta14540

TABLE 18 *Costs results of included studies for DPs 1 and 2*

Study	Years	BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Sensitivity analysis and comments
General										
Johnson 1998[7]	Key points made by review: In acute leukaemia (mostly AML) the cost of transplantation (mostly allogeneic from BM) was 1–2 times that of conventional care All analyses were based on mean costs from small patient cohorts which were not from randomised or pseudo-randomised trials. It is therefore possible that these data are not representative of the cost of either treatment modality The use of BM for transplantation was found to be 1–1.7 times the cost of PB. Unfortunately few if any of the included studies underpinning this conclusion appeared to have populations with acute leukaemia									
Redaelli 2004[248]	Key points made by review: Transplantation is the most expensive medical procedure for the treatment of AML Costs range from €24,887 in New Zealand to €144,508 in the USA (both adjusted to 2001 prices) Cost of autologous transplantation was equal to or lower than the cost of allogeneic transplantation Transplantation from PB reduces resource utilisation									
Allogeneic transplantation costs										
[a]Welch 1989[257]	1978–82	No further details	**	Retrospective Global cost model over 5 years	17	CCT Genetic allocation	1989 5 years	US$	193,000	
[a,b]Dufoir 1992[256]	1984–9	Sib Source not stated	***	Retrospective Actual usage	14	CCT Genetic allocation	1991 5 years	FF	424,696	Cost also calculated without relapse
[a]Armitage 1984[261]	1973–81	Sib BM	**	Retrospective Actual usage	13	Case series	1981 1 year	US$	84,102	
[a]Kay 1980[259]	1978–79	No further details	**	Retrospective Actual usage	22	Case series	1978/9 1 year	GB£	11,564	
[a,b]Barr 1996[255]	1986–90	Sib BM	***	Retrospective Actual usage	5	Case series	1992 5 years	Can$	100,600	
[b]Viens-Bitker 1989[258]	1986	No further Details	Unclear	Unclear	?	?	1986 1 year	FF	250,465	Cost also calculated with complications
Schwarzenbach 2000[254]	1995–6	No further details	**	Retrospective Actual usage	10	Case series	1999 1 year	Euros and US$	111,454 118,459	

continued

TABLE 18 *Costs results of included studies for DPs 1 and 2 (continued)*

Study	Years	BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Sensitivity analysis and comments
[b]van Agthoven 2002[252]	1994–9	Sib BM	***	Retrospective Actual usage	47	Case series	1998 2 years	Euros	98,334	
[b]van Agthoven 2002[252]	1994–9	MUD BM	***	Retrospective Actual usage	29	Case series	1998 2 years	Euros	151,754	
[b]van Agthoven 2002[252]	1994–9	Sib PB	***	Retrospective Actual usage	21	Case series	1998 2 years	Euros	98,977	
Cordonnier 2005[251]	1998–2003	MA Most BM Sib	**	Retrospective Actual usage	12	Case series	2001 1 year	Euros	74,900	
Cordonnier 2005[251]	1998–2003	NMA PB Sib	**	Retrospective Actual usage	11	Case series	2001 1 year	Euros	78,700	
Ngamkiatphaisan 2007 [249]	1994–2005	Donor? Most PB	**	Retrospective Actual usage	51	Case series	2006 1 year	US$	22,593	Thailand
[b]Uyl-de Groot 2001[253]	1994–5	Donor? BM	**	Retrospective Actual usage	? All types 84	Case series	1995 2 years	US$	53,846	
[b]Uyl-de Groot 2001[253]	1994–5	Donor? PB	**	Retrospective Actual usage	? All types 84	Case series	1995 2 years	US$	34,033	
Yu 2007[250]	1994–2002	Donor? PB	**	Retrospective Actual usage	21	Case series	2003 *c.* 4 years	US$	76,423	Taiwan
Autologous transplantation costs										
[a,b]Dufoir 1992[256]	1984–9	Source?	***	Retrospective Actual usage	11	RCT Random allocation	1991 5 years	FF	505,364	Cost also calculated without relapse
[b]Uyl-de Groot 1995[260]	1992	Source?	**	Retrospective Actual usage	20	Case series	1992 2 years	US$	55,440	

Study	Years	BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Sensitivity analysis and comments
Ngamkiatphaisan 2007[249]	1994–2005	PB	**	Retrospective Actual usage	16	Case series	2006 1 year	US$	24,171	Thailand
[b]Uyl-de Groot 2001[253]	1994–5	Donor? BM	**	Retrospective Actual usage	? All types 84	Case series	1995 2 years	US$	44,887	
[b]Uyl-de Groot 2001[253]	1994–5	Donor? PB	**	Retrospective Actual usage	? All types 84	Case series	1995 2 years	US$	24,427 or 31,495	Depends on treatment protocol used
Allogeneic transplantation vs conventional costs										
[a]Welch 1989[257]	1978–2	No further details	**	Retrospective Global cost model over 5 years	17; 19	RCT Genetic selection	1989 5 years	US$	+57,000	
[a,b]Dufoir 1992[256]	1984–9	Sib Source?	***	Retrospective Actual usage	14; 15	CCT Genetic allocation	1991 5 years	FF	+119,450	Cost also calculated without relapse
[a]Armitage 1984[261]	1973–81	Sib BM	**	Retrospective Actual usage	13; 20	Case series	1981 1 year	US$	+67,301	
[a,b]Barr 1996[255]	1986–90	Sib BM	***	Retrospective Actual usage	5; 2	Case series	1992 5 years	Can$	+48,800	
Allogeneic vs high-dose chemotherapy										
Yu 2007[250]	1994–2002	Donor? PB	**	Retrospective Actual usage	21; 33	Case series	2003 *c.* 4 years	US$	+24,733 $p = 0.001$ (AI more expensive)	Taiwan
Autologous transplantation vs conventional										
[a,b]Dufoir 1992[256]	1984–9	Source?	***	Retrospective Actual usage	11; 15	RCT Random allocation	1991 5 years	FF	+200,518	Cost also calculated without relapse
[b]Uyl-de Groot 1995[260]	11992	Source?	**	Retrospective Actual usage	20; 10	Case series	1992 2 years	US$	+44,440	

continued

TABLE 18 *Costs results of included studies for DPs 1 and 2 (continued)*

Study	Years	BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Sensitivity analysis and comments
Autologous transplantation vs AI										
[a,b]Dufoir 1992[256]	1984–9	N/A or Sib Source?	***	Retrospective Actual usage	11; 15	RCT Random allocation	1991 5 years	FF	+80,668 (Au more expensive)	Cost also calculated without relapse
Ngamkiatphaisan 2007[249]	1994–2005	N/A or donor? Most PB	**	Retrospective Actual usage	16; 51	Case series	2006 1 year	US$	+1578 (Au more expensive)	Thailand
[b]Uyl-de Groot 2001[253]	1994–5	Donor? BM	**	Retrospective Actual usage	? All types 84	Case series	1995 2 years	US$	–8959 (Au less expensive)	
[b]Uyl-de Groot 2001[253]	1994–5	Donor? PB	**	Retrospective Actual usage	? All types 84	Case series	1995 2 years	US$	–9606 or –2538 (Au less expensive)	Depends on treatment protocol used
Allogeneic transplantation (Sib) vs AI (MUD)										
[b]van Agthoven 2002[252]	1994–9	Sib/MUD BM	***	Retrospective Actual usage	47; 29	Case series	1998 2 years	Euros	–53,420 (Sib less expensive)	

AI, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; MA, myeloablative; PB, peripheral blood; source, source of cells for transplantation.
a The study was included in the review by Johnson *et al.*[7]
b The study was included in the review by Redaelli *et al.*[248]
Donor (only applies to allogeneic transplants): MUD, matched unrelated donor; Sib, sibling.
Costs included: *procedure costs only; **procedure + subsequent therapy; ***procedure + subsequent therapy + set-up costs.

TABLE 19 *Applicability of included cost-effectiveness studies to DPs 1 and 2*

Study	Study type	AML	Adult	CR1/CR2	Nature of transplantation (one row for each alternative)				Non-transplantation comparator
					Al/Au	Donor	Source	*n*	
Johnson 1998[7]	Review	Three studies contribute to conclusions on cost-effectiveness in acute leukaemia. All relate to AML and are applicable to DPs 1 and 2							
Redaelli 2004[248]	Review	Three studies contribute to conclusions on cost-effectiveness in acute leukaemia. All relate to AML and are applicable to DPs 1 and 2							
[a,b]Dufoir 1992[256]	Primary	✓	✓	CR1	Al	Sib	?BM	14	Chemotherapy (*n* = 15)
					Au	N/A	?BM	11	
[b]Barr 1996[255]	Primary	✓	✓	CR2	Al	Sib	BM	5	Control? chemotherapy (*n* = 2)
[a]Welch 1989[257]	Primary	✓	✓	?CR1	Al	?Sib	?BM	17	Chemotherapy (*n* = 19)
Yu 2007[250]	Primary	✓ Mixed AML 49/54	✓	?CR1	Al	?	PB	21	Intensive chemotherapy (*n* = 33)

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation.
a The study was included in the review by Johnson *et al.*[7]
b The study was included in the review by Redaelli *et al.*[248]
Donor (only applies to allogeneic transplants): Sib, sibling.

incremental cost-effectiveness ratio (ICER) incorrectly, comparing ratios of cost per life-year gained against each other.

Sensitivity analysis was conducted and reported in two of the studies. Barr *et al.*[255] assessed the impact of the length of hospitalisation and survival on the final results, while Welch and Larson[257] varied discount rates and the relative effectiveness of the compared therapies.

In summary, while all the studies attempted to answer the decision problem in a systematic way, it is not clear whether the reported results can be considered as robust indications of the treatments' cost-effectiveness and it is unlikely that evidence from the specific studies could inform current UK practice.

Cost-effectiveness – results of included studies

The results of included studies are summarised in *Table 20*.

Previous reviews have offered few specific conclusions about the cost-effectiveness of SCT. However even in this they are contradictory in that Johnson *et al.*[7] feels cost-effectiveness is driven by cost alone, in which case the high cost of transplantation mitigates against cost-effectiveness. In contrast Redaelli *et al.*[248] indicates that cost-effectiveness of allogeneic transplantation has been demonstrated.

In this review, although there is only one additional primary study not considered in the two previous reviews, more detailed assessment of the studies does reveal some additional insights. First, the quality of the assessments is noteworthy. All are based on extremely small numbers of patients. Further, all are extremely simple in approach, consistent with the standard of economic evaluation prevailing in health care at the time the studies were reported, but it is debatable whether such approaches could be considered adequate estimates of current cost-effectiveness. The date of the costings, mentioned in the previous section, alone indicates that this is likely to be a problem. It should also be noted that there is a methodological flaw in the methods used by Yu *et al.*[250] to estimate the incremental cost-effectiveness of the assessed interventions. While cost-effectiveness analysis should determine the additional cost for an additional unit of outcome (e.g. life-year), Yu *et al.*[250] divided the total mean cost associated with the treatment by the median years of survival resulting from this treatment. Correcting this error reveals that high-dose chemotherapy (HDC) appears to be dominant (both cheaper and more effective) against allogeneic transplantation. In the study by Barr *et al.*[255] when the ICER is expressed as cost per life-year saved (LYS) the cost-effectiveness looks acceptable, but when expressed as cost per quality-adjusted life-year (QALY) (with the arithmetical error corrected) SCT is unlikely to be considered cost-effective using current commonly used thresholds. Given the above, the unequivocal statement by Redaelli *et al.*[248] that the cost-effectiveness of SCT has been demonstrated is difficult to sustain in the face of the available data, even if there is widespread belief in its validity.

Finally, both previous reviews commented only on the cost-effectiveness of allogeneic transplantation. It should be noted that Barr *et al.*[255] also provide some information on the cost-effectiveness of autologous transplantation. With the same provisos indicated above, this suggests that the cost-effectiveness of autologous transplantation may be inferior to that of allogeneic transplantation. This may also need further investigation given the uncertainty noted about the relative costs of allogeneic and autologous transplantation for AML noted in the section on costs.

Economic models – validity and results

There were no economic models relating to DPs 1 and 2.

Summary for DPs 1 and 2

Ostensibly there appears to be a wealth of information on the costs and some information on cost-effectiveness of allogeneic transplantation in adults with AML. Unfortunately the age and quality of the studies mean that there is considerably more uncertainty than there might at first appear. The expense of allogeneic transplantation does seem to be confirmed, but what drives the observed marked variation and whether the figures fairly represent current costs is debatable. Previous statements about the proven cost-effectiveness of allogeneic transplantation appear to deserve careful re-examination using up-to-date methods and more credible sample sizes. Much less is known about the costs and cost-effectiveness of autologous transplantation and, again, past statements about the relative cost of

DOI: 10.3310/hta14540

TABLE 20 *Cost-effectiveness results of included studies*

Study	Years	Comparison	Method	Source and no. patients	Cost year and duration	Currency	Costs	Effects	ICER	Sensitivity analysis and comments
Systematic review conclusions on cost-effectiveness										
Johnson 1998[7]	Included studies addressing cost-effectiveness in AML: Welch 1989,[257] Corker 1989,[266] Dufoir 1992[256] Key points made by review: If efficacy cannot be considered significantly different, then the only changing variable in a cost-effectiveness analysis will be cost. Therefore only cost data are considered further									
Redaelli 2004[248]	Included studies addressing cost-effectiveness in AML: Welch 1989,[257] Dufoir 1992,[256] Barr 1996[255] Key points made by review: Just comments on cost-effectiveness of allogeneic transplantation vs chemotherapy. In general studies have found that transplantation was cost-effective because, despite the higher overall costs, allogeneic transplantation resulted in longer quality-adjusted survival									
Primary study cost-effectiveness results										
[a,b]Welch 1989[257]	1978–82	Al (?donor?source) vs chemotherapy	Retrospective Global cost model over 5 years Simple ICER	CCT Genetic allocation 17; 19	1989 5 years	US$	Al 193,000 Chemotherapy 136,000	Al 3.32 years Chemotherapy 2.24 years	59,300/LYS (5% discount rate)	Extending time horizon greatly improves ICER – 10,000/LYS
[a,b]Dufoir 1992[256]	1984–9	Al (Sib?source) vs Au (?source vs chemotherapy	Retrospective Actual usage Effectiveness from whole trial population Simple ICER	CCT Genetic allocation and RCT 14; 11; 15	1991 5 years	FF	Al 425,000 Au 505,000 Chemotherapy 305,000	Al 3.78 years Au 3.58 years Chemotherapy 2.84 years	Al/ chemotherapy 122,000/LYS Au/ chemotherapy 282,000/LYS	No discounting or sensitivity analyses. Paper concludes that Al is most cost-effective
[b]Barr 1996[255]	1986–90	Al (Sib; BM; CR2) vs control	Retrospective Actual usage Simple ICER (note arithmetical error in paper)	Case series 5; 2	1992 5 years	Can$	Al 101,000 Control 52,000	Al 2.24 years Control 0.57 years	29,000/LYS 108,000/QALY (assuming utility of 0.26 or 5)	Estimate sensitive to plausible changes in parameters
Yu 2007[250]	1994–2002	Al (?donor; PB) vs high-dose chemotherapy (some had transplantation too)	Retrospective Actual usage Simple ICER	Case series 21; 33	2003 *c.* 4 years	US$	Al 76,000 HDC 52,000	Al 1.92 HDC 4.36	HDC dominates Al (according to corrected cost-effectiveness analysis)	Taiwan

Al, allogeneic transplantation; Au, autologous transplantation; HDC, high-dose chemotherapy; LYS, life-year saved; QALY, quality-adjusted life-year.
a The study was included in the review by Johnson *et al.*[7]
b The study was included in the review by Redaelli *et al.*[248]
Doner (only applies to allogeneic transplants): Sib, sibling.

allogeneic and autologous transplantation deserve re-examination.

Results relating to DPs 3 and 4

Nature of decision problems

DP3

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy or with no further therapy in the management of AML in children of various risk groups in CR1?

DP4

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy, or with no further therapy in the management of AML in children of various risk groups in CR2+ and in children with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

Number of included studies

There were two studies claiming to contribute information on costs, both of which were reviews.[7,248] The same two studies[7,249] also claimed to contribute information on cost-effectiveness. There were no economic models.

Relevance, validity and results of included studies

Closer examination of the scope of the included studies in each of the reviews by Johnson *et al.*[7] and Redaelli *et al.*[248] (see *Tables 15* and *16* in previous section) makes it clear that any general conclusions made in the reviews about costs and cost-effectiveness in acute leukaemias or AML are not generalisable to children as many included studies are clearly restricted to adults who would have been treated with different protocols and required different doses of drugs compared with children. Although a few of the included studies have mixed populations, children are always in the minority. We identified no new studies addressing costs or cost-effectiveness of transplantation in AML in children.

Summary for DPs 3 and 4

There are currently no published estimates of costs or cost-effectiveness relevant to this decision problem. Given the low frequency of AML in children the absence of specific information on costs and cost-effectiveness of transplantation may not be problematic. However, it does seem likely that both costs and cost-effectiveness may differ in important ways from adults.

Results relating to DPs 5 and 6

Nature of decision problems

DP5

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy or with no further therapy in the management of ALL in adults of various risk groups in CR1?

DP6

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy or with no further therapy in the management of ALL in adults of various risk groups in CR2+ and in adults with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

Number of included studies

There were two studies contributing information on costs, one of which was a review[7] and one a primary study.[255] Three studies contributed information on cost-effectiveness, one of which was a review[7] and two primary studies.[26,255] There were no economic models.

Costs – validity of included studies

Relevance

As shown in *Table 15* (repeated here for the reader's convenience), only two studies included in the review by Johnson *et al.*[7] clearly had participants with ALL, and in one further study the nature of the leukaemias was not clear. One of these studies by Rollinson *et al.*[269] had only a single transplant in a patient with ALL and was not considered as an included study, and even the study by Barr *et al.*[255] only had five patients with ALL. Given the paucity of evidence derived from studies with participants with ALL, none of the general conclusions made by Johnson *et al.*[7] on the costs incurred in acute leukaemia were felt to be generalisable to DPs 5 and 6. The review made no specific conclusions about costs in ALL.

TABLE 15 *Applicability of cost studies apparently addressing acute leukaemia included in the review by Johnson* et al.[7]

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative)				Non-transplantation comparator	Relevance to decision problems							
				Al/ Au	Donor	Source	*n*		1 2	3 4	5 6	7 8	9	10	11	12
Welch 1989[257]	'Acute non-lymphocytic leukaemia'	17–50 years	?CR1	Al	?Sib	?BM	17	Chemotherapy (*n* = 19)	✓	×	×	×	×	×	×	×
Corker 1989[266]	AML	?	CR1	Al	Sib	? BM	?	Chemotherapy – 2 options (*n* = ?)	Abstract only No detail about how cost estimates were calculated							
Dufoir 1992[256]	AML	Adult < 50 years	CR1	Al	Sib	?BM	14	Chemotherapy (*n* = 15)	✓	×	×	×	×	×	×	×
				Au	N/A	?BM	11									
Masaoka 1994[267]	'Acute leukaemia'	Adult	CR1	?	?	?	16	Chemotherapy (*n* = 22)	Abstract only No detail about how cost estimates were calculated							
Viens-Bitker 1986[265]	AML	?	?	?	?	?	?	?	Main text in French							
Armitage 1984[261]	AML	Adult	CR1	Al	Sib	BM	13	Chemotherapy (*n* = 20)	✓	×	×	×	×	×	×	×
Aulesa 1992[268]	AML	?	?	Mixed	?	?	?	Chemotheraphy (*n* = ?)	Main text in Spanish							

continued

TABLE 15 *Applicability of cost studies apparently addressing acute leukaemia included in the review by Johnson* et al.[7] *(continued)*

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative)				Non-transplantation comparator	Relevance to decision problems							
				AI/Au	Donor	Source	*n*		1 2	3 4	5 6	7 8	9	10	11	12
Barr 1996[255]	Two subpopulations:							Control? Chemotheraphy (*n* = 2 and 6)	✓	×	✓	×	×	×	×	×
	AML	Adults	CR2+	AI	?Sib	?BM	5									
	ALL	Adults	CR1	AI	?Sib	?BM	5									
Rollinson 1982[269]	'Acute leukaemia'	Adult and child	?	?AI	?	?BM	2	Conventional treatment (*n* = 16)	×	×	×	×	×	×	×	×
	AML (12) and ALL (6) (only 2 received BMT; 1 adult with ALL and 1 with AML)															
Kay 1980[259]	AML	Adult (16); child (6)	CR1	?AI	?	BM	22	None	✓	×	×	×	×	×	×	×
Le Corroller 1997[270]	Non-leukaemic malignant disease	Mixed	?	Au	N/A	BM	65	None	×	×	×	×	×	×	×	×
				Au	N/A	PB	64									
de Arriba 1996[271]	Minority of patients leukaemias	Ad	?	Au	N/A	BM	8	None	×	×	×	×	×	×	×	×
				Au	N/A	PB	9									
Julia 1995[272]	Mostly non-Hodgkin lymphoma	Ad	?	Au	N/A	BM	10	None	×	×	×	×	×	×	×	×
				Au	N/A	PB	10									

AI, allogeneic transplantation; Au autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation.
Donor (only applies to allogeneic transplants): Sib, sibling.

TABLE 21 *Applicability of included cost studies to DPs 5 and 6*

Study	Study type	ALL	Adult	CR1/ CR2+	Nature of transplantation (one row for each alternative)				Non-transplantation comparator
					Al/Au	Donor	Source	*n*	
Johnson 1998[7]	Review	Thirteen studies contribute to conclusions on cost? The majority relate to AML and so overall conclusions on cost are not applicable to DPs 5 and 6							
[a]Barr 1996[255]	Primary	✓	✓	CR1	Al	Sib	BM	5	Control? chemotherapy (*n* = 6)

Al, allogeneic transplantation; Au autologous transplantation; BM, bone marrow; source, source of cells for transplantation.
a The study was included in the review by Johnson *et al.*[7]
Donor (only applies to allogeneic transplants): Sib, sibling.

Table 21 confirms that the single primary study identified was relevant to DPs 5 and 6.

Internal validity

The included study appears to be of good internal validity. It is conducted from the perspective of the Canadian health-care service and includes a comprehensive list of costs related to the treatments under assessment. The study allows for a relatively long follow-up period of 5 years. It should be mentioned that costs in this study are reported undiscounted but the authors' justification, on the basis that the bulk of the costs are incurred in the first year of the follow-up period, appears reasonable. Nonetheless, it is uncertain whether the results reported in this study can be considered as good estimates of the likely costs of the treatment in the UK setting.

Costs – results of included studies

The results of included studies are summarised in *Table 22*.

Based on the very limited information provided by this study, it appears that allogeneic transplantation in ALL in adults is as expensive as transplantation in AML, but control treatments may be more expensive. This leads to the cost saving associated with transplantation observed in the study by Barr *et al.*[255] The very small scale of this study must however be re-emphasised.

Cost-effectiveness – validity of included studies

For reasons analogous to cost, none of the general conclusions made by Johnson *et al.*[7] on cost-effectiveness in acute leukaemia were felt to be generalisable to DPs 5 and 6. The review made no specific conclusions about cost-effectiveness in ALL.

The relevance of the two included primary studies is confirmed in *Table 23*. The study by Orsi *et al.*[26] considered much greater numbers of participants than other cost-effectiveness studies by meta-analysing data from existing trials. In this respect it is more akin to an economic model than a primary evaluation of cost-effectiveness. It did not, however, use a computer-based model to integrate the data and so is considered in the cost-effectiveness section. A problem associated with the approach used by Orsi *et al.*,[26] is that the chemotherapy and autologous transplantation participants in the control arms of the meta-analysed trials could not be separated, so the comparator is distinct from those encountered in other economic evaluations in this review.

Internal validity

The internal validity of the Barr *et al.*[255] study is discussed in the previous section. In brief, that study followed sound techniques to estimate costs and benefits and assessed the robustness of the reported results by conducting sensitivity analysis. Unlike Barr *et al.*, [255] who obtained total cost estimates from medical records, Orsi *et al.*[26] calculated total costs by synthesising available estimates from published studies identified through a systematic literature search. However, the validity of the approach used by Orsi *et al.*[26] is questionable as it appears that the pooled cost estimates used in the analysis come from studies conducted in different periods and settings, which are also based on different protocols of care.

TABLE 22 *Results of included cost studies related to DPs 5 and 6*

Study	Years	BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Sensitivity analysis and comments
Allogeneic transplantation costs										
[a]Barr 1996[255]	1986–1990	Sib BM	***	Retrospective Actual usage	5	Case series	1992 5 years	Can$	92,000	
Allogeneic transplantation vs control costs										
[a]Barr 1996[255]	1986–1990	Sib BM	***	Retrospective Actual usage	5; 6	Case series	1992 5 years	Can$	–10,800 (Al less expensive)	

BM, bone marrow.
a The study was included in the review by Johnson *et al.*[7]
Donor (only applies to allogeneic transplants): Sib, sibling.
Costs included: ***procedure + subsequent therapy + set-up costs.
There were no studies for autologous transplantation.

TABLE 23 *Applicability of included cost-effectiveness studies to DPs 5 and 6*

					Nature of transplantation (one row for each alternative)				
Study	Study type	ALL	Adult	CR1/ CR2+	Al/Au	Donor	Source	*n*	Non-transplantation comparator
[a]Barr 1996[255]	Primary	✓	✓	CR1	Al	Sib	BM	5	Control? chemotherapy (*n* = 6)
Orsi 2007[26]	Primary	✓	✓	CR1	Al	?	?	293	Chemotherapy (*n* = 241)
					Au	N/A	?	238	Chemotherapy and Au groups considered in combination

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; source, source of cells for transplantation.
a The study was included in the review by Redaelli *et al.*[248]
Donor (only applies to allogeneic transplants): Sib, sibling.

Cost-effectiveness – results of included studies

The results of the two primary studies are tabulated in *Table 24*.

The study by Barr *et al.*[255] indicates that, in adult ALL, allogeneic transplantation was considerably more cost-effective than the control treatment, which is not further specified but presumed to be chemotherapy. Specifically, allogeneic transplantation dominated control, which means that it was more effective at reduced cost. No indication is given about the uncertainty around results owing to small numbers of observations. However, the sensitivity analyses, which explore the effect of variation in several inputs such as use of discounting, extending the time horizon, increasing costs and changing the estimates of effect on survival, suggest that the results are sensitive to changes contrary to claims in the paper.

In the study by Orsi *et al.*[26] allogeneic transplantation appeared to improve survival but at increased cost. The ICER of €45,000 per LYS is broadly comparable to the cost-effectiveness thresholds of cost per additional QALY as they appear in the NICE *Guide to the methods of technology appraisal*.[279] This estimate indicates that allogeneic transplantation is less cost-effective than in the study by Barr *et al.*,[255] but that may be accounted for by the fact that the comparison group in Barr *et al.*[255] is chemotherapy and in Orsi *et al.*[26] control or autologous transplantation. Unfortunately, Orsi's estimate of cost-effectiveness is undermined by uncertainty, the key sources of which are that the cost studies used to calculate the cost-effectiveness did not consider patients with ALL and that the results are highly sensitive to the variation in a single variable, the effect of which the investigators examined. An advantage of the study was a much greater number of participants on which estimates of effect on survival were based, afforded by meta-analysis of existing trials.

Economic models – validity and results

With the exception of the study by Orsi *et al.*,[26] discussed in the previous section, which might be considered by some as more akin to an economic model than a primary evaluation of cost-effectiveness, there were no economic models addressing DPs 5 and 6.

Summary for DPs 5 and 6

There is very limited evidence on the costs and cost-effectiveness of transplantation in ALL. This supports the unsurprising observation that, like transplantation in AML, allogeneic transplantation in ALL comes at a high cost. There is, however, also a suggestion that the high cost is justified by the level of additional clinical benefit in terms of improved survival, particularly relative to chemotherapy. However, the limited number of studies, the small size of one and the observed limitations of the other strongly suggest that this conclusion deserves further investigation. There is no information on the cost and cost-effectiveness of autologous transplantation.

Results relating to DPs 7 and 8

Nature of decision problems

DP7

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy or with no further therapy in the management of ALL in children of various risk groups in CR1?

DP8

What is the cost-effectiveness of different forms and techniques of SCT compared with further chemotherapy or with no further therapy in the management of ALL in children of various risk groups in CR2+ and in children with refractory disease, i.e. those who did not achieve complete remission following induction(s)?

Number of included studies

There were two studies claiming to contribute information on costs, one of which was a review[7] one a primary study.[262] One review[7] also claimed to contribute information on cost-effectiveness. There were no economic models.

Costs – validity of included studies

Relevance

The analysis of the included studies in the review by Johnson *et al.*[7] in the preceding decision problem also makes it clear that there are no included studies considering cost of transplantation in ALL in children. It thus does not contribute to DPs 7 and 8, which is not clear on initial reading.

TABLE 24 *Cost-effectiveness results of primary studies for DPs 5 and 6*

Study	Years	Comparison	Method	Source and no. patients	Cost year and duration	Currency	Costs	Effects	ICER	Sensitivity analysis and comments
Primary study cost-effectiveness results for DPs 5 and 6										
[a]Barr 1996[255]	1986–90	Al (Sib; BM; CR1) vs control	Retrospective Actual usage Simple ICER	Case series 5; 6	1992 5 years	Can$	Al 92,000 Control 103,000	Al 3.69 years Control 3.32 years	–29,000/LYS –90,000/QALY (assuming utility of 0.6) Al dominates[b]	Estimate sensitive to plausible changes in parameters
Orsi 2007[26]	2004[c]	Al (?donor?source; CR1) vs Au or chemotherapy	Data based on published trials and cost studies Cost studies are not on ALL patients	CCT Genetic allocation and case series	?Cost year or duration	Euros	Al 94,000 Au/chemotherapy not given Difference 45,000	Al 5.88 years Au/conventional 4.88 years	45,000/LYS	Sensitivity to one variable examined. Estimate sensitive to Au transplant cost

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; CCT, clinical controlled trial.
a The study was included in the review by Redaelli *et al.*[248]
b Dominates indicates that the option improves outcome at lower cost.
c Publication dates of included trials.
Donor (only applies to allogeneic transplants): Sib, sibling.

TABLE 25 *Applicability of included cost studies to DPs 7 and 8*

Study	Study type	ALL	Children	CR1/CR2+	Nature of transplantation (one row for each alternative)				Non-transplantation comparator
					Al/Au	Donor	Source	*n*	
Madero 2000 [262]	Primary	✓	✓	Mixed CR1/CR2+	Al	?Sib	BM	12	None
					Al	Sib	PB	13	

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation.
Donor (only applies to allogeneic transplants): Sib, sibling.

We identified one new primary study by Madero *et al.*[262] The details are summarised in *Table 25* and confirm the study's relevance. What the study reports about the costs of allogeneic transplantation is included in this section. The study also provides information comparing the costs of transplantation using bone marrow and peripheral blood as sources. These results are reported in DP9. There were no studies on the costs of autologous transplantation relevant to DPs 7 and 8.

Internal validity

The only identified primary study relevant to this decision problem was published in 2000 by Madero *et al.*[262] The study estimates costs from the Spanish health-care system perspective and derives estimates from hospital records. The study reports results at different time points (100 days, 1 and 2 years) and includes costs for a number of treatment-related services (hospitalisation, conditioning, harvesting, supportive care and drugs). However, the analysis would benefit from discounting for the 2-year time point. Some sensitivity analysis could have been performed.

Costs – results of included studies

The results of the single included cost study by Madero *et al.*[262] are summarised in *Table 26*. The most notable feature is that the absolute level of costs (US$14,000–20,000) is considerably lower than the costs encountered for the other decision problems. Whether this is because of the patients being children, the condition being ALL, the country in which health care was provided or the costing method employed is unknown.

Cost-effectiveness and economic models – validity and results of included studies

The only study that appears to contribute information on cost-effectiveness is the review by Johnson *et al.*[7] However, as before on closer inspection there are actually no studies included that are relevant to the cost-effectiveness of transplantation in children with ALL. There are thus effectively no studies contributing to the assessment of cost-effectiveness for DPs 7 and 8.

Summary for DPs 7 and 8

There is little information on the costs and cost-effectiveness of transplantation for ALL in children. The single small study available suggests that allogeneic transplantation costs are much lower. This observation, however, requires verification.

Results relating to DP9

Nature of decision problem

What is the cost-effectiveness of BMT versus PBSCT versus CBSCT in the management of acute leukaemia. The need to separate evidence by given types of leukaemia (AML/ALL), populations (age/risk) and disease stage stipulated for clinical effectiveness was relaxed for cost-effectiveness.

Number of included studies

There were seven studies contributing information on costs, two of which were reviews[7,248] and five primary studies.[252,253,262–264] Three studies claimed

TABLE 26 *Results of included cost studies relating to DPs 7 and 8*

Studies	Years	BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Sensitivity analysis and comments
Allogeneic transplantation costs										
Madero 2000[262]	1990–9	?Sib BM CR1 or 2	**	Retrospective Actual usage	12	Case series	Cost year not given 100 days	US$	19,840	Spain
Madero 2000[262]	1990–9	Sib PB CR1 or 2	**	Retrospective Actual usage	13	Case series	Cost year not given 100 days	US$	14,046	Spain

BM, bone marrow; PB, peripheral blood.
Donor (only applies to allergeneic transplants): Sib, sibling.
Costs included: ** = procedure + subsequent therapy.
There were no studies for autologous transplantation.

to contribute information on cost-effectiveness, two of which were reviews[7,248] and one a primary study.[263] Finally, there was one full economic model.[263]

Costs – validity of included studies

Relevance

The claimed relevance of the review by Johnson *et al.*[7] to DP9 was re-examined by scrutinising the characteristics of the included studies that might have been relevant. This exercise is summarised in *Table 15* (repeated here for the readers convenience). This table does not contain studies included in the Johnson *et al.*[7] review where it was clear that the study population was not patients with acute leukaemia.

This makes it clear that there were no included studies comparing bone marrow with peripheral blood or other stem cell sources in acute leukaemia. The conclusions made by Johnson *et al.*[7] concerning relative cost of bone marrow and peripheral blood as stem cell sources are thus not applicable.

A similar exercise was undertaken for the review by Redaelli *et al.*,[248] recorded in *Table 27*. Studies cited by Redaelli *et al.*[248] to support conclusions on the relative costs of different approaches to transplantation were highlighted in the shaded areas in *Table 27*. Only two of these, Uyl-de Groot *et al.* 2001[253] and van Agthoven *et al.*[252] appear to be directly relevant and both of these are included in this review as primary studies. Some caution is required in generalising any conclusions reached by Redaelli *et al.*[248] to answer DP9. The claims made concerning the relative cost of bone marrow or peripheral blood as sources of stem cells in transplantation in acute leukaemia are, however, very limited.

Information confirming the relevance of the five included primary studies are summarised in *Table 28*. Four of the included studies provide cost comparisons of bone marrow with peripheral blood as sources of stem cells in a variety of acute leukaemias. In one case, Faucher *et al.*,[264] the inclusion might be considered borderline as only just over 50% of patients in the costing study had acute leukaemia. One modelling study, Costa *et al.*,[263] assesses the cost-effectiveness of cord blood as a source of stem cells relative to bone marrow or peripheral blood. This study is discussed in more detail in the next section, but is also mentioned briefly here as cost data were collected as part of the assessment of cost-effectiveness.

Internal validity

The quality of the van Agthoven *et al.*,[252] Uyl-de Groot *et al.* 2001[253] and Madero *et al.* 2000 [262] studies has been assessed and described in previous sections. The study by Faucher *et al.* 1998[264] was carried out in France and aimed to report total costs related to BMT and PBSCT incurred by the French health-care system. The study measures and reports a comprehensive list of costs related to the compared treatments (outpatient services, inpatient 'hotel' costs, and costs related to tests, procedures and drugs). Also, the robustness of the results of the study is explored by varying estimates on the hospital room costs and number of outpatient visits. Overall, the Faucher *et al.* 1998[264] study appears to be of sound internal validity, but it is doubtful whether the estimates reported here can be used to inform policy in the UK.

Costs – results of included studies

The table of comparative costs (*Table 29*) suggests reasonably consistently that using bone marrow as the source of stem cells increases the costs of transplantation by approximately US$5000–20,000 relative to peripheral blood. van Agthoven *et al.*[252] is the exception to this, showing no difference between bone marrow and peripheral blood. It is not clear what this difference might be due to, but inclusion or not of follow-up costs does not seem to be an explanation as all estimates included this to some degree. Despite the general consistency, the small size of the studies does require a note of caution to be added to the interpretation too. There is no information to gauge whether the observed differences could have been explained by chance alone.

There was only one study providing comparative costs on cord blood, which showed that cord blood also adds to the cost of transplantation relative to bone marrow or peripheral blood as sources of stem cells for transplantation. The limited amount of data on which the study is based again needs to be remembered.

TABLE 15 *Applicability of cost studies apparently addressing acute leukaemia included in the review by Johnson* et al.[7]

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative)				Non-transplantation comparator	Relevance to decision problems
				Al/ Au	Donor	Source	*n*		1 2 / 3 4 / 5 6 / 7 8 / 9 / 10 / 11 / 12
Welch 1989[257]	'Acute non-lymphocytic leukaemia'	17–50 years	?CR1	Al	?Sib	?BM	17	Chemotherapy (*n* = 19)	✓ × × × × × × ×
Corker 1989[266]	AML	?	CR1	Al	Sib	? BM	?	Chemotherapy – 2 options (*n* = ?)	Abstract only No detail about how cost estimates were calculated
Dufoir 1992[256]	AML	Adult < 50 years	CR1	Al	Sib	?BM	14	Chemotherapy (*n* = 15)	✓ × × × × × × ×
				Au	N/A	?BM	11		
Masaoka 1994[267]	'Acute leukaemia'	Adult	CR1	?	?	?	16	Chemotherapy (*n* = 22)	Abstract only No detail about how cost estimates were calculated
Viens-Bitker 1986[265]	AML	?	?	?	?	?	?	?	Main text in French
Armitage 1984[261]	AML	Adult	CR1	Al	Sib	BM	13	Chemotherapy (*n* = 20)	✓ × × × × × × ×
Aulesa 1992[268]	AML	?	?	Mixed	?	?	?	Chemotheraphy (*n* = ?)	Main text in Spanish

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative)				Non-transplantation comparator	Relevance to decision problems							
				AI/Au	Donor	Source	*n*		1 2	3 4	5 6	7 8	9	10	11	12
Barr 1996[255]	Two subpopulations:							Control? Chemotheraphy (*n* = 2 and 6)	✓	×	✓	×	×	×	×	×
	AML	Adults	CR2+	AI	?Sib	?BM	5									
	ALL	Adults	CR1	AI	?Sib	?BM	5									
Rollinson 1982[269]	'Acute leukaemia' AML (12) and ALL (6) (only 2 received BMT; 1 adult with ALL and 1 with AML)	Adult and child	?	?AI	?	?BM	2	Conventional treatment (*n* = 16)	×	×	×	×	×	×	×	×
Kay 1980[259]	AML	Adult (16); child (6)	CR1	?AI	?	BM	22	None	✓	×	×	×	×	×	×	×
Le Corroller 1997[270]	Non-leukaemic malignant disease	Mixed	?	Au	N/A	BM	65	None	×	×	×	×	×	×	×	v
				Au	N/A	PB	64									
de Arriba 1996[271]	Minority of patients leukaemias	Ad	?	Au	N/A	BM	8	None	×	×	×	×	×	×	×	×
				Au	N/A	PB	9									
Julia 1995[272]	Mostly non-Hodgkin lymphoma	Ad	?	Au	N/A	BM	10	None	×	×	×	×	×	×	×	×
				Au	N/A	PB	10									

AI, allogeneic transplantation; Au autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation.
Donor (only applies to allogeneic transplants): Sib, sibling.

TABLE 27 *Applicability of cost studies apparently addressing acute leukaemia included in the review by Redaelli* et al.[248]

Study	Condition, age and remission status			Nature of transplantation (one row for each alternative)				Non-transplantation comparator	Relevance to decision problems							
				Al/Au	Donor	Source	*n*		1 2	3 4	5 6	7 8	9	10	11	12
Tennvall 1994[273]	AML	?	?	Al/Au	?	?BM	?	None	Not an economic evaluation							
Uyl-de Groot 2001[253]	AML	? Ad	?CR1	Al	?	BM	84 in total	None	✓	×	×	×	✓	×	×	×
				Al	?	PB										
				Au	N/A	BM										
				Au	N/A	PB										
Stalfelt 1994[274]	AML	Adult	Mixed	Unclear that any transplantation used				Chemotherapy (*n* = 15)	×	×	×	×	×	×	×	×
Uyl-de Groot 1995[260]	AML	?	Mixed	Au	N/A	?	20	Convention-al (*n* = 10)	×	×	×	×	×	×	×	
Dufoir 1992[256]	AML	Adult <50 years	CR1	Al	Sib	?BM	14	Chemotherapy (*n* = 15)	✓	×	×	×	×	×	×	×
				Au	N/A	?BM	11									
Barr 1996[255]	Two subpopulations:							Control? chemotherapy (*n* = 2 and 6)	✓	×	✓	×	×	×	×	×
	AML		CR2	Al	?Sib	?BM	5									
	ALL		CR1	Al	?Sib	?BM	5									
NCI (web)	Unable to obtain from website															
Lee 2000[275]	Only 60/236 acute leukaemia	?	?	Au and Al	?	BM and PB	236	None	×	×	×	×	×	×	×	×
Wagner 1998[276]	Minimal information on costs															
Bennett 1999[277]	<50% acute leukaemia	Adults	?	Al	?	BM	13	None	×	×	×	×	×	×	×	×
				Al	?	PB	21									
Viens-Bitker 1989[258]	AML	Adults	CR1	Al	?	?BM	N/A	None	✓	×	×	×	×	×	×	×
Beard 1991[278]	?Majority acute leukaemias	?	?	?	?	?BM	41	None	×	×	×	×	×	×	×	×
van Agthoven 2002[252]	Very mixed AML (66)/ ALL (31)	Most adults	?	Al	Sib	BM	47	None	✓	×	×	×	✓	×	×	×
				Al	MUD	?	29									
				Al	Sib	PB	21									

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation; MUD, matched unrelated donor.
a The study was included in the review by Redaelli *et al.*[248]
Donor (only applies to allogeneic transplants): MUD, matched unrelated donor; Sib, sibling.

DOI: 10.3310/hta14540

TABLE 28 *Applicability of included cost studies to DP9*

Study	Study type	Condition (AML or ALL)	Adult/ children	CR1/CR2	Nature of transplantation (one row for each alternative)				Non-transplantation comparator
					Al/Au	Donor	Source	*n*	
Comparing BM and PB as stem cell sources									
[a]van Agthoven 2002[252]	Primary	✓ Mixed	Mainly adult	?	Al	Sib	BM	47	None
		AML (66)/ALL (31)			Al	MUD	?	29	
					Al	Sib	PB	21	
[a]Uyl-de Groot 2001[253]	Primary	✓ All AML	?	?CR1	Al	?	BM	84 in total	None
					Al	?	PB		
					Au	N/A	BM		
					Au	N/A	PB		
Madero 2000[262]	Primary	✓ All ALL	All children	Mixed CR1/CR2+	Al	?Sib	BM	12	None
					Al	Sib	PB	13	
Faucher 1998[264]	Primary	✓ Majority acute leukaemia	All adult	Most CR1	Al	?	BM	17	None
					Al	?	PB	17	
		AML 10							
		ALL 8							
		CML 16							
Comparing cord blood with other sources stem cells									
Costa 2007[263]	Model	Targets 'adults with acute leukaemia'		?CR1	Al	MUD	BM or PB	N/A	'No transplantation'
					Al	MUD	Cord	N/A	

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; PB, peripheral blood; source, source of cells for transplantation; MUD, matched unrelated donor.

a The study was included in the review by Redaelli *et al.*[248]

Donor (only applies to allogeneic transplants): Sib, sibling.

TABLE 29 *Results of included cost studies relating to DP9*

Study	Years	Condition and BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Cost difference	Sensitivity analysis and comments
Bone marrow vs PB as stem cell source											
[a]van Agthoven 2002[252]	1994–9	Adult AML/ ALL Al Sib	***	Retrospective Actual usage	47; 21	Case series	1998 2 years	Euros	BM 98,334 PB 98,977	–643 (BM less expensive)	
[a]Uyl-de Groot 2001[253]	1994–5	Age? AML Au	**	Retrospective Actual usage	? All types 84	Case series	1995 2 years	US$	BM 44,846 PB 24,427 or 31,495	+20,460 or +13,392	Depends on treatment protocol used (HOVON or EORTC)
[a]Uyl-de Groot 2001[253]	1994–5	Age? AML Al Donor?	**	Retrospective Actual usage	? All types 84	Case-series	1995 2 years	US$	BM 53,846 PB 34,033	+19,813	
Madero 2000[262]	1990–9	Children ALL Al Sib	**	Retrospective Actual usage	12; 13	Case series	Cost year not given 100 days	US$	BM 19,840 PB 14,046	+5794	Spain
Faucher 1998[264]	1995–7	Adult AML/ALL Al Donor?	**	Retrospective Actual usage	17; 17	Case series	1996 100 days	US$	BM 56,527 PB 40,123	+16,134	
Comparing cord blood with other sources of stem cells											
Costa 2007[263]	1998[b]	Adult AML/ALL Al Unrelated donors	**	Hospital finance dept and published estimates	Not stated	Case series	2004 100 days	US$	Cord 88,822 BM/PB 64,978	+23,844	

Al, allogeneic transplantation; Au, autologous transplantation; BM, bone marrow; PB, peripheral blood.
a The study was included in the review by Redaelli *et al.*[248]
b Publication date of study used in cost estimate.
Donor (only applies to allergenic transplants): Sib, sibling.
Costs included: **procedure + subsequent therapy; ***procedure + subsequent therapy + set-up costs.

Cost-effectiveness and economic models – validity and results of included studies

For reasons analogous to costs, the suggestion that the reviews by Johnson *et al.*[7] and Redaelli *et al.*[248] might contribute useful evidence on cost-effectiveness for DP9 was rejected. This left just one piece of original research by Costa *et al.*[263] to be considered. This was also an economic model, the only one to be encountered during the course of the review. The applicability of this study to DP9 can be seen from information in *Table 28*. However, it needs to be clearly noted that Costa *et al.*[263] provides estimates of cost-effectiveness for cord blood as source of stem cells for transplantation relative to bone marrow or peripheral blood. It does not deal with the more commonly encountered question of the incremental cost-effectiveness of bone marrow relative to peripheral blood as a source of stem cells in transplantation.

The only model-based study identified in this review was carried out by Costa *et al.*[263] The study was conducted in Canada from the perspective of the regional health-care system. The methodological validity of the study is appraised below.

Model structure

For the purposes of the study, Costa *et al.*[263] constructed a Markov model with five distinctive health states. To be specific, at the end of each 1-year cycle, patients in the model could survive without complications, survive with complications (chronic GvHD, leukaemia relapse, infection) or die. The model follows patients for 20 years.

The choice of a Markov type model is justified as such a model appears to be suitable for representing the underlying biological and clinical process of the considered disease (Barton *et al.*).[280] Similarly, the choice of a 20-year time horizon is considered adequate for the population and disease in question. However, it is unclear whether the cycle length of 1 year is short enough to capture expected changes in disease progression. A shorter cycle might have been more appropriate for the specific decision problem.

Data

Data on treatment effectiveness were obtained from a review of the available literature. Relevant data were survival at different time intervals and complication rates. Supplementary data necessary for the analysis, such as estimates of life expectancy, was obtained from regional (Quebec, Canada) life-expectancy tables.

The systematic review appears to have been conducted in a systematic manner. Costa *et al.*[263] searched a number of major electronic bibliographic databases and followed widely accepted criteria to ensure compliance with 'good practice' in meta-analysis of observational studies.[281]

Costa *et al.*[263] also made specific assumptions (GvHD and disease relapse were assumed to occur in year 1 if the timing was not specified in the original studies; no mortality was attributable to disease or transplantation procedure after year 5) which were justified on the grounds of available evidence from the literature. In the absence of data, they further assumed that the long-term survival of the patients followed that of the general population but was only 50% of the population estimate. The assumptions appear reasonable, but alternatives were explored by sensitivity analysis. Additionally, it is not clear whether benefits (life-years) were undiscounted to reflect their present value.

Cost input for the model was obtained from the host hospital's financial department and from existing Canadian studies on BMT/ PBSCT. Relevant costs included direct medical costs of hospitalisation, inpatient and outpatient medications and costs related to nursing and physicians' input. All costs estimates were discounted annually at 3%. Costa *et al.*[263] considered a comprehensive list of cost categories related to the disease and treatments in question. However, it is not clear whether the cost of identifying the unrelated donor is included.

Cost-effectiveness results and sensitivity analysis

The cost-effectiveness results of the analysis are reported in terms of ICERs (cord blood transplantation vs no transplantation; BMT/ PBSCT vs no transplantation). ICER estimates were accompanied by 95% confidence intervals. In addition, the Costa *et al.*[263] presented graphs depicting alternative point estimate ICERs resulting from univariate sensitivity analysis and cost-effectiveness acceptability curves (CEACs) from probabilistic sensitivity analysis (PSA).

TABLE 30 *Cost-effectiveness results for DP9*

Study	Years	Comparison	Method	Source and no. patients	Cost year and duration	Currency	Costs	Effects	ICER	Sensitivity analysis and comments
Cost-effectiveness model results for DP9										
Costa 2007[263]	1998–2005[a]	Cord blood vs BM or PB as stem cell sources In adults with AML/ALL receiving AI transplants from unrelated donors Each compared with no transplantation	Markov model Univariate and multivariate PSAs Effectiveness data from systematic review of trials Cost data from local hospital and published cost estimates	Not given	2004 10 years (costs over 100 days)	US$	Cord 72,000 BM/PB 50,000	Cord 2.1 life-years BM/PB 3.04 life-years	Cord 34,000/LYS (95% CI 23,000 to 89,000) BM/PB 16,000/LYS (95% CI 9000 to 38,000)	Limited reporting of sensitivity analyses. ICER sensitive to assumptions about life-years without transplantation For PSA virtually all simulations were <50,000 for BM/PB and 66% for cord blood

AI, allogeneic transplantation; BM, bone marrow; PB, peripheral blood.
a Publication dates of studies used to obtain effectiveness and cost data.
There were no primary studies for cost-effectiveness for DP9.

To assess the impact of uncertainty, Costa *et al.*[263] carried out univariate sensitivity analysis on survival (10 years survival for transplantation group, 3 years for no transplantation) and cost (250% increase), as well as PSA on survival, complication rates and costs.

The methods employed for dealing with uncertainty in this study appear sound. Carrying out both deterministic (univariate) analysis and PSA allows a better representation of the uncertainty surrounding the model parameters and the effect of these parameters on the study results.[282] In addition, the probability distributions assigned to parameters subject to PSA (survival, complication rates, beta distribution) is consistent with current recommendations, although the use of the triangular distribution for costs may not represent the most appropriate choice.[283]

However, sensitivity analysis in this study appears to concentrate on parameter uncertainty, although structural assumptions, such as allowing for only two states for patients without transplantation, and methodological assumptions, e.g. different discount rates for benefits, could have a significant impact on the study results and, thus, should have been explored in further sensitivity analyses.

At this point it is worth mentioning that Costa *et al.*[263] did not attempt to estimate outcomes that combine life expectancy with health-related quality of life, e.g. QALYs. According to the authors, this was owing to the absence of quality of life estimates in the literature.

As a general conclusion, the Costa *et al.*[263] study appears to be of sound internal validity. The methods used in the study are in broad agreement with suggested 'good practice' and with the NICE *Guide to the methods for technology appraisal*.[279] In addition, the review of the Costa *et al.*[263] model reveals that the main structure of the presented model can be used to assess different decision questions related to SCT. In brief, this would require: (1) modifying (or possibly adding) health states to facilitate relevant treatment comparisons; (2) reducing the cycle length to ensure that all the transitions between health states are captured; and (3) identifying relevant evidence in terms of treatment effectiveness, baseline patient progression, costs, etc. and populating the model with appropriate distributions representing the available evidence and the uncertainty surrounding that evidence. Once such evidence becomes available, adapting the Costa model, or constructing a similar structure, will be relatively straightforward. The results of the study by Costa *et al.*[263] are summarised in *Table 30*.

Notwithstanding the limitations of the model identified, many of which reside in the limitations of the data used for estimates of effectiveness and cost, it appears that both cord blood and bone marrow or peripheral blood are cost-effective as sources of stem cells in allogeneic transplantation of acute leukaemias, relative to no transplantation. The costs used in this model are, however, low relative to the costs of allogeneic transplantation identified earlier in the chapter, and it is debatable whether the 'no transplantation' option really represents the costs and outcomes that would be expected in the absence of SCT. Different assumptions about longevity in the no transplantation arm are considered in a univariate sensitivity analysis and small increases from the base case of 0.75 in the life-years assumed with no transplantation bring about a marked deterioration in the cost-effectiveness ratios.

The study by Costa *et al.*[263] relates only to allogeneic transplantation, so the cost-effectiveness of different stem cell sources in autologous transplantation does not appear to have been addressed.

Summary for DP9

There is limited information about the costs and cost-effectiveness of different sources of stem cells in transplantation for acute leukaemias.

For arguably the most important comparison between bone marrow and peripheral blood, the costs of bone marrow appear to be greater than (or at worst the same as) peripheral blood. There are no assessments of cost-effectiveness.

Comparing cord blood with bone marrow or peripheral blood suggests in one study that the cost of cord blood is greater and that all options appear to be cost-effective. There is, however, considerable uncertainty about this finding and the study relates only to allogeneic transplantation.

Results relating to DP10

Nature of decision problem

What is the cost-effectiveness of various conditioning regimens, including standard myeloablative regimens and RIC regimens (mini-

SCT)? The need to separate evidence by given types of leukaemia (AML/ALL), populations (age/risk) and disease stage stipulated for clinical effectiveness was relaxed for cost-effectiveness.

Number of included studies

There were two studies claiming to contribute information on costs, one of which was a review[7] and one a primary study.[251] One review[7] also claimed to contribute information on cost-effectiveness. There were no economic models.

However, there are no included studies in the review by Johnson *et al.*,[7] in which the costs and cost-effectiveness of myeloablative transplantation are compared with non-myeloablative (mini-SCT), so effectively the only published information to inform this decision problem is the primary study on costs by Cordonnier *et al.*[251]

Costs – validity of included studies

Relevance

The relevance of the study by Cordonnier *et al.*[251] is confirmed in *Table 31*.

Internal validity

The study by Cordonnier *et al.*[251] aimed to assess the cost of myeloablative and non-myeloablative allogeneic SCT to the French health-care system. To do so, the authors obtained treatment-related resource use and cost estimates from accounting systems in a number of participating hospitals. Costs were recorded over a 12-month follow-up period, and thus discounting was not required. The study appears to be of good quality and accounts for different number of days of hospitalisation; however, owing to a limited follow-up period and sample size, it cannot provide safe and generalisable results.

Costs – results of included studies

As indicated in *Table 32*, the study by Cordonnier *et al.*[251] indicates that costs for myeloablative and non-myeloablative transplantation are similar. Early excess costs for myeloablative therapy were offset by excess costs for non-myeloablative regimens in the second 6 months owing to late complications and re-admissions. It needs to be noted that groups compared differ not only by whether the regimen was myeloablative but also by source of stem cells. The probable reduced cost of transplants using peripheral blood as a stem cell source, discussed in the previous section, suggests that this alone should have led to reduced costs in the group receiving the non-myeloblative regimen. Further caution is required in interpretation, given that this is a single study with a small number of participants.

Cost-effectiveness and economic models – validity and results of included studies

As already indicated, because the review by Johnson *et al.*[7] does not actually include any cost-effectiveness studies relevant to this decision problem, there is effectively no information on cost-effectiveness.

Summary for DP10

There is very limited information.

Tentatively, there is some evidence that myeloablative and non-myeloablative regimens have similarly high costs in allogeneic transplantation in AML. However, given the causes of uncertainty noted, this finding requires replication.

There is no evidence on the cost of myeloablative regimen in ALL or autologous transplantation, and a complete absence of any evidence at all on cost-effectiveness.

Results relating to DP11

Nature of decision problem

What is the cost-effectiveness of autologous SCT with purging compared with autologous SCT without purging? The need to separate evidence by given types of leukaemia (AML/ALL), populations (age/risk) and disease stage stipulated for clinical effectiveness was relaxed for cost-effectiveness.

Number of included studies

There was one study, a review,[7] claiming to contribute information on costs. The same review[7] also claimed to contribute information on cost-effectiveness. There were no economic models.

However, there are no included studies in the review by Johnson *et al.*[7] in which the costs and cost-effectiveness of purging are compared with

DOI: 10.3310/hta14540

TABLE 31 *Applicability of included cost studies to DP10: comparing bone marrow and peripheral blood as stem cell sources*

Study	Study type	Condition (AML or ALL)	Adult/children	CR1/ CR2+	Nature of transplantation (one row for each alternative)				Non-transplantation comparator
					Al/Au	Donor	Source	*n*	
Cordonnier 2005[251]	Primary	✓	✓	Mixed	Al (MA)	?	Mixed (9 BM/3 PB)	12	None
					Al (NMA)	?	PB	11	

Al, allogeneic transplantation; Au autologous transplantation; BM, bone marrow; MA, myeloablative; NMA, non-myeloablative; PB, peripheral blood; source, source of cells for transplantation.

TABLE 32 *Results of included cost studies relating to DP10: allogeneic (myeloablative) vs allogeneic (non-myeloablative) in AML*

Study	Years	BMT detail	Costs included	Method	No. patients	Source of patients	Cost year and duration	Currency	Costs	Cost difference	Sensitivity analysis and comments
Cordonnier 2005[251]	1998–2003	MA (Al; most BM; Sib) vs NMA (Al; PB; Sib)	**	Retrospective Actual usage	12; 11	Case series	2001 1 year	Euros	MA 74,900 NMA 78,700	–3800 (MA less expensive)	

Al, allogeneic transplantation; BM, bone marrow; MA, myeloablative; NMA, non-myeloablative; PB, peripheral blood; Sib, sibling.
Costs included: **procedure + subsequent therapy.

no purging, so effectively there is no published information to inform this decision problem.

Results relating to DP12

Nature of decision problem

What is the clinical effectiveness and cost-effectiveness of T-cell-depleted allogeneic SCT compared with T-cell-replete allogeneic SCT? The need to separate evidence by given types of leukaemia (AML/ALL), populations (age/risk) and disease stage stipulated for clinical effectiveness was relaxed for cost-effectiveness.

Number of included studies

There was one study, a review,[7] claiming to contribute information on costs. The same review[7] also claimed to contribute information on cost-effectiveness. There were no economic models.

However, there are no included studies in the review by Johnson *et al.*[7] in which the costs and cost-effectiveness of T-cell depletion are compared with no T-cell depletion, so effectively there is no published information to inform this decision problem.

Discussion and conclusions

Main findings

This review revealed a significant paucity of evidence on most of the considered decision problems. While there exists a wealth of information regarding the costs and some information on cost-effectiveness of allogeneic transplantation in adults with AML (DPs 1 and 2), there is very limited evidence on the relative costs and cost-effectiveness of different techniques of SCT against further chemotherapy for AML in children (DPs 3 and 4) and for ALL in adults and children (DPs 5 and 6 and DPs 7 and 8 respectively).

Similarly, there is little evidence on the costs and cost-effectiveness of BMT versus PBSCT versus CBSCT in the management of leukaemia in general (DP9), with indications that the costs of BMT may be greater than those for PBSCT.

There is also very limited information relating to the cost and cost-effectiveness of various conditioning regimens, including standard myeloablative regimens and RIC regimens (DP10). Results from the only relevant study (Cordonnier *et al.*[251]) suggest that myeloablative and non-myeloablative regimens have similarly high costs in allogeneic transplantation in AML; however, such a conclusion is subject to considerable uncertainty and requires replication.

Finally, no studies providing evidence on the cost-effectiveness of autologous SCT with purging compared with autologous SCT without purging (DP11) or the cost-effectiveness of T-cell-depleted allogeneic SCT compared with T-cell-replete allogeneic SCT (DP12) were identified, thus there is virtually no published information to inform these decision problems.

At this point, it must be pointed out that, when evidence exists, it is surrounded by considerable uncertainty. This is mostly owing to (1) the age of the included studies; (2) methods used in studies not necessarily according with widely accepted methods for conducting economic evaluations in the UK;[279] and (3) likely differences in patterns of care and use of health-care services across different countries (UK, Netherlands, Spain, Canada, France, Taiwan).

Limitations of primary data

With regards to the primary data used in the reviewed cost and cost-effectiveness papers, it must be noted that, in the majority of the studies, evidence on costs and treatment effectiveness came from clinical studies with a small number of participants and, in most cases, a limited time horizon. Such limitations have a negative impact on the robustness of the reported results and contribute to uncertainty in the reported cost-effectiveness estimates.

It is also worth mentioning that there is a paucity of evidence on health-related quality of life associated with relevant health states. Only one of the reviewed studies attempted to express treatment effectiveness in terms of outcomes that take into account quality of life (QALYs). This is an important limitation as the use of QALYs facilitates decision-making on the use of available resources across different clinical areas and is suggested as the outcome of choice by existing guidelines (NICE 2008).[279]

Conclusions in light of limitations

Bearing in mind the limitations in the available evidence, safe conclusions on what treatment is or is not cost-effective cannot be made. While allogeneic SCT appears to be effective compared with chemotherapy in adults and children with AML and adults and children with ALL with high and very high risk of relapse, whether this strategy is also cost-effective is debatable.

Suggestions for practice

The evidence in this review is not sufficient to allow any recommendations for practice to be made without further research.

Recommendations for research

Primary research is needed to provide more precise evidence on treatment effectiveness and impact on health-related quality of life, as well as up-to-date information on health service use and costs associated with transplantation from the perspective of the UK NHS. Decision-analytical models should be then constructed, possibly in the form of Markov models, to synthesise such information and provide evidence to inform the relevant decision problems.

Chapter 6
Discussion

Strengths and limitations of the report

This report provides an overview of published systematic reviews, meta-analyses and economic literature concerning the use of SCT in the treatment of acute leukaemia. In addition, we have attempted to identify RCTs/DvND studies not covered in existing systematic reviews/meta-analyses and trials that are ongoing or have been completed but not yet published. The strength of this report includes:

- comprehensive searches of electronic databases for systematic reviews, meta-analyses, ongoing trials and economic literature, complemented by contact with experts in the subject area
- critical appraisal of existing reviews/meta-analyses and economic literature
- systematically mapping evidence from RCTs/DvND studies covered in existing reviews/meta-analyses to predefined decision problems
- an attempt to consider treatment pathway and clinical priority alongside research evidence.

The main purpose of this report is to produce a reasonably accurate inventory of existing evidence to inform decisions on whether further research is required and, in particular, whether that research should be new trials or reviews.

Given the time and resources available for compiling the report, there are some limitations that readers should bear in mind:

- We presented evidence from published systematic reviews and meta-analyses and highlighted its strengths, weaknesses and consistency. However, given available time and resources, we were unable to critically assess the primary studies on which these reviews/meta-analyses were based, nor could we provide an updated quantitative synthesis of evidence.
- Similarly, while an attempt was made to briefly summarise findings from the identified RCTs/DvND studies not included in existing systematic reviews/meta-analyses, we did not critically appraise these primary studies.
- It was not always possible to confirm whether an identified primary study was genuinely an RCT or DvND study, as information provided in published literature, particularly in conference abstracts, was sometimes limited.
- Records retrieved from searches for new and ongoing RCTs/DvND studies and for cost-effectiveness reviews were initially screened by only one reviewer. Although the initial screening was intentionally inclusive so that any potentially relevant records would be passed on to the next stage for further checking, there remains a possibility that a small number of potentially relevant studies may have been missed.
- SCT (when used) constitutes only part of the management of acute leukaemia, which involves complex interventions including chemotherapy and/or radiotherapy among others. Although we have assessed a few aspects of SCT (i.e. source of stem cells, conditioning regimens, purging, T-cell depletion), other interventions that could potentially influence the effectiveness/safety of SCT, such as the type, course and intensity of chemotherapy administered prior to SCT, the use of G-CSF to increase the number of stem cells in the blood of the donor or to accelerate recovery of the patients after SCT and various measures to control or prevent infections and GvHD, are not covered in this report.
- Ongoing advances in chemotherapy and improved risk stratification of patients according to cytogenetic and other factors may alter the applicability of evidence summarised in this report.
- This report focuses on evidence from RCTs and DvND studies. Such evidence is often lacking for patients with acute leukaemia beyond CR1 and for patients receiving unrelated donor transplants or cord blood transplants, owing partly to the difficulties in designing and conducting large clinical trials in these patient groups. Evidence from studies of other designs was not reviewed. These studies are unlikely to provide robust evidence regarding the effectiveness of SCT, although they may include valuable information regarding long-term/late effects of SCTs.

- As stated in the protocol of this report, we had intended to model a key clinical pathway/decision problem. Despite the large number of potentially relevant economic studies identified in our cost-effectiveness review, we found little quality of life data and paucity of cost information that is applicable to current practice in the NHS. Because of the lack of these required data, it has not been feasible to carry out economic modelling within the given time frame for this study. Nevertheless, based on the review of clinical effectiveness evidence, we did identify a few key clinical areas (allogeneic SCT for adult AML except good-risk patients in CR1; childhood AML in CR1 and adult ALL in CR1) to be the priority for future economic evaluations (see Chapter 7).

Synthesis of evidence on the use of SCT in acute leukaemia

There are several challenges in the synthesis of evidence on the use of SCT in acute leukaemia. A major finding from our evidence-mapping exercise is that many existing systematic reviews and meta-analyses seem to have covered only part of the potentially available evidence. In addition to issues related to literature searching and non-publication or inadequate reporting of study results, difficulties in identifying and confirming DvND studies and access to the required data may have contributed to the incompleteness of evidence included in the reviews/meta-analyses. This could potentially affect both the direction and the precision of estimated treatment effects. Inclusion of different studies among reviews/meta-analysis of the same topic could be the result of selection bias related to study results. This does not appear to be the case as most reviews/meta-analyses on the same topic reached a similar conclusion despite being based on different data. The omission of evidence in some of the systematic reviews/meta-analyses is therefore more likely to have resulted in reduced sample size, hence statistical power, of the pooled estimates. Attempts to cover as much as possible the totality of available evidence in future meta-analyses may help to address some of the areas in which a moderate benefit or harm cannot be ruled out according to current reviews/meta-analyses.

The systematic reviews and meta-analyses included in this report adopted different approaches regarding the inclusion of trials conducted at different times. Both chemotherapy and the techniques of SCT have evolved over the past few decades, and it could be argued that evidence from older trials no longer reflects current practice. Nevertheless, the change in practice over time is gradual and it is difficult to draw a clear cut-off date before which evidence should be discarded.

Evolving practice in the management of acute leukaemia also has implications for how evidence is reported and synthesised. For example, in recent years patients with ALL between the ages of 16 years and 25 years have been increasingly treated with protocols for children rather than adults. Evidence for this subgroup of young adults may need to be synthesised separately in the future.

Acute leukaemia comprises heterogeneous diseases and the patient population is diverse. For a quantitative synthesis of the evidence, a broad review might combine the results from studies with very different patient populations, which actually compromises the applicability of the findings. On the other hand, the number of potential subgroups and comparisons increases rapidly as a review divides the evidence to answer very specific research questions. This may result in a large number of analyses that lack statistical power, and it is often difficult to obtain data with sufficient detail from published literature. The evolving risk stratification of patients using patient age, WBC count at presentation, early chemotherapy response, cytogenetic analysis, detection of minimal residual disease by different techniques and new molecular factors, e.g. *FLT3* gene abnormalities, further complicates the issue. The contribution of systematic reviews and meta-analyses based solely on published literature may therefore be limited. Collaborative IPD meta-analysis may overcome some of these problems, but the time and resources required to undertake this type of analysis should not be underestimated.

Potential biases and limitations of DvND comparisons

Although the number of RCTs concerning the use of SCT in the treatment of acute leukaemia has been increasing, conducting RCTs is still difficult in some situations and data from DvND comparisons remain the best alternative source of evidence for evaluating the effectiveness of matched sibling allogeneic SCT. The rationale and use of DvND comparisons were described

in Chapter 2 and evidence derived from such comparisons has been presented throughout this report. Readers should, however, be aware of potential biases and limitations relating to this type of comparison. These are discussed below.

Potential biases

The probability of finding a matched sibling donor is related to the patient's age (availability of siblings for donation) and family size (number of siblings). There may be differences in these aspects between donor and no-donor groups, and results may be confounded if these factors are not adjusted for.

Another potential bias may occur during enrolment of patients into trials if patients and/or physicians already have knowledge of the availability of a matched sibling donor prior to enrolment. For example, patients who are at high risk of relapse may be more likely to participate in a trial if they have a donor and less likely to be enrolled if they do not because of the perceived benefit of allogeneic SCT and perceived lack of efficacy of alternative treatments. Conversely, patients with a good prognosis may be less likely to participate in a trial if they do have a matched sibling donor owing to the risk associated with allogeneic SCT. To reduce such enrolment bias, it is important that patients are enrolled into trials before the results of HLA typing are known to the patient and physician.

During the preparation of this report, it became apparent that determining whether an analysis reported in a research paper is based on a DvND comparison can be difficult owing to inadequate description of methods. Many studies that could have contributed data for DvND comparisons were (justifiably) excluded from existing reviews because reported analyses were based on actual treatments received. It is not clear whether the lack of reporting of results based on DvND comparisons in these studies was because of incomplete typing, lack of awareness of this method or selective reporting of more 'statistically significant' results. The last raises concern of potential publication bias, which does not appear to be a problem in a recent review published during the preparation of this report[197] but should be carefully examined in future systematic reviews.

We also found several cases in the literature in which DvND comparison was clearly intended but the analyses actually performed did not strictly follow the principle of genetic randomisation. Examples were the inclusion of allogeneic SCT from matched unrelated donors in the donor group,[113,115] inclusion of all patients without a sibling in the no-donor group, and classifying patients with a matched sibling who refused or was unable to donate stem cells in the no-donor group.[22,211] The actual impact of the potential bias that could be introduced is unclear. Practical issues relating to DvND comparison have been discussed elsewhere.[284]

Limitations

Not all patients with a matched sibling donor actually receive allogeneic SCT. The statistical power for DvND comparison to detect a difference in the effectiveness between allogeneic SCT and other treatment options decreases as the proportion of patients who have a matched sibling donor but do not actually receive allogeneic SCT increases. DvND comparison therefore almost always underestimates the difference in effectiveness (if it exists) between allogeneic SCT from a matched sibling donor and other treatment options. In addition, treatments received in the 'no-donor' group varied between studies depending on the study protocols. Therefore the DvND comparisons may not be directly comparable between studies. The clinical application of such evidence may also be limited because of the varied and sometimes not well defined treatment option received by the 'no-donor' group.

Chapter 7
Conclusions

Evidence on clinical effectiveness

Many systematic reviews and meta-analyses have been published to address the clinical effectiveness of SCT for the treatment of acute leukaemia. A significant volume of new and ongoing primary research has also been identified. This study aimed to provide an overview of the best available evidence found in previous systematic reviews/meta-analyses and an inventory of new and ongoing primary research not yet covered by earlier reviews/meta-analyses.

We found that many systematic reviews and meta-analyses included only part of the potentially available evidence (taking into account the time of their publication), although their conclusions are generally consistent. The use of SCT in AML in adults in CR1 was covered by more than half of the fifteen reviews/meta-analyses included in this report, whereas each of the other methods of treatment for acute leukaemia was addressed in only a small number of reviews.

Overall, these reviews confirmed the benefit of allogeneic SCT from a matched sibling donor compared with chemotherapy in adults with AML in CR1 (except those with good-risk cytogenetics), and suggested favourable results for allogeneic SCT in children with AML in CR1, adults with ALL in CR1 with a high risk of relapse, and children with ALL in CR1 with a very high risk of relapse. Either there is a lack of good-quality evidence or existing evidence does not suggest significant benefit from the use of allogeneic SCT for other patients with acute leukaemia or for the use of autologous SCT in the treatment of acute leukaemia as a whole. A significant volume of evidence from RCTs is being accumulated to address the use of RIC regimens and the comparison between BMT and PBSCT.

Evidence on cost-effectiveness

The aim of the cost-effectiveness review was to identify and summarise the available evidence relating to the explored decision problems. The review has revealed a scarcity of evidence for most of the considered decision problems.

While there exists a wealth of information regarding the costs and some information on cost-effectiveness of allogeneic transplantation in adults with AML, there is very limited evidence relating to transplantation in children with AML and adults and children with ALL. Similarly, little information exists on the cost-effectiveness of different sources of stem cells and different conditioning regimens while, at the same time, no evidence was retrieved on the cost-effectiveness of purging or T-cell depletion for patients acute leukaemia in any age group.

Even when evidence exists, it comes from relatively old studies of small sample size conducted outside the UK. Furthermore, most of the identified and reviewed studies do not comply with reference case methods for conducting economic evaluations in the UK. For these reasons, it is highly uncertain whether the results from the reviewed studies represent evidence that can be used to inform clinical practice in the UK.

Recommendations for future research

Based on the findings of this report, in *Table 33* we offer some suggestions for priorities for future research on clinical effectiveness. The suggestions take into account both available evidence and the volume of ongoing studies identified. Therefore it is worth emphasising that where new trials or evidence synthesis is not indicated as a priority, it does *not* suggest that the area is not important. In some cases it in fact indicates that the area is the focus of currently ongoing trials and reviews, hence *additional* trials or reviews may not be a priority. Researchers should also be strongly encouraged to accompany any new data from trials with an updated evidence synthesis, which in turn could inform the priority for and design of new trials. Wider consultation on clinical priority for each of the areas will be needed to formulate exact research recommendations. In addition to the research recommendations related to

TABLE 33 *Recommendations for future research*

Decision problem	Treatment	New trials	Evidence synthesis	Comments (January 2010)
DP1 (adult AML CR1)	Al vs other	×	×	Evidence from existing reviews and more recent trials consistently shows that allogeneic SCT confers overall survival benefit for intermediate- and poor-risk AML compared with other treatments. Large-scale RCTs are ongoing and updated evidence synthesis will be required when new data become available
	Au vs chemotherapy	×	×	Evidence from existing reviews and more recent trials consistently demonstrates that autologous SCT may reduce relapse but does not improve overall survival compared with chemotherapy. Scope for further research is limited
DP2 (adult AML CR2+)	Al vs other	✓	×	Evidence is lacking. New trials are needed although practicality may be an issue
	Au vs chemotherapy	✓	×	Evidence is lacking. New trials are needed although practicality may be an issue
DP3 (childhood AML CR1)	Al vs other	×	×	Evidence supports the effectiveness of allogeneic SCT over other treatments. Further systematic reviews and trials may not be required, except for prospective trials and/or collaborative IPD meta-analysis which can provide further information on the risk and benefit of allogeneic SCT compared with chemotherapy in difference risk groups
	Au vs chemotherapy	×	×	Evidence from existing reviews does not favour autologous SCT over other treatment. No recent or ongoing trials were found
DP4 (childhood AML CR2+)	Al vs other	✓	×	Evidence is lacking. New trials are needed
	Au vs chemotherapy	✓	×	Evidence is lacking. New trials are needed
DP5 (adult ALL CR1)	Al vs other	×	✓	Evidence supports the effectiveness of allogeneic SCT over other treatments. However, new trial evidence suggests existing risk stratifications may not be adequate for selecting patients for allogeneic SCT. A new systematic review possibly using IPD is needed
	Au vs chemotherapy	×	×	Existing reviews covered limited evidence. Data from more recent trials are available and shall be included in an ongoing Cochrane review. Existing evidence does not favour the use of autologous SCT in this population, hence the scope for further trials may be limited

Decision problem	Treatment	New trials	Evidence synthesis	Comments (January 2010)
DP6 (adult ALL CR2+)	Al vs other	✓	×	Evidence is lacking. New trials are needed
	Au vs chemotherapy	✓	×	Evidence is lacking. New trials are needed
DP7 (childhood ALL CR1)	Al vs other	×	✓	Use of allogeneic SCT is restricted to very high-risk groups given that chemotherapy is highly effective. Findings from new RCTs were inconsistent. A systematic review is warranted
	Au vs chemotherapy	×	×	Limited evidence does not favour autologous SCT over chemotherapy. Scope for further research is limited
DP8 (childhood ALL CR2+)	Al vs other	×	✓	There were discordant findings between new trial data and previous studies/reviews. A systematic review is warranted
	Au vs chemotherapy	✓	×	Evidence is lacking. New RCTs are needed although practicality may be an issue
DP9 (BMT vs PBSCT vs CBT)	BMT vs PBSCT	×	✓	Data from several recent RCTs warrant a systematic review
	BMT vs CBT	✓	×	Evidence is lacking. Further RCTs are needed
DP10 (conditioning regimens)	Myeloablative	✓	×	Evidence is limited. Further RCTs are needed although practicality may be an issue
	RIC vs MAC	×	✓	Evidence is currently lacking but several RCTs are ongoing. Synthesis of evidence from these RCTs will be needed
DP11 (purging in autologous SCT)		×	×	Evidence is lacking. However, given current general lack of role and utility of autologous SCT in the management of acute leukaemia, further research on methods of purging is not a priority
DP12 (T-cell depletion)		✓	×	Only one RCT (n = 101) was found. Further RCTs are needed

Al, allogeneic transplantation; Au, autologous transplantation; CBT, cord blood transplantation; MAC, myeloablative conditioning regimen.
✓, areas considered as current priority; ×, areas not considered as current priority

specific decision problems, studies that evaluate the effectiveness of matched unrelated donor allogeneic SCT are required. Further research, possibly from long-term follow-up of RCTs/DvND studies on late effects of SCT in acute leukaemia, is also needed as these late effects contribute significantly to mortality, morbidity and quality of life.

On the basis of the results from the cost-effectiveness review, we suggest that further research should be directed towards (1) primary research to provide high-quality estimates of the cost and clinical effectiveness resulting from the assessed treatments; (2) research on the health-related quality of life associated with these treatments; and (3) economic analyses that use up-to-date decision-analytical modelling techniques to synthesise evidence in order to provide meaningful results to inform decision-making (e.g. cost per QALY). Areas in which sufficient clinical evidence supports the use of SCT should be the priority for future economic evaluations, such as allogeneic SCT for AML in adults (except good-risk patients) in CR1, AML in children in CR1 and ALL in adults in CR1. The continuous development of new methods for selecting patients (e.g. risk stratification) and new techniques for carrying out SCT, as well as the advent of new chemotherapeutic agents, pose many challenges for conducting an economic evaluation that reflects current practice. Consideration should be given to building in an economic evaluation in future RCTs.

Acknowledgements

We are grateful to Dr Sue Richards, Professor Keith Wheatley and Professor Charles Craddock for their invaluable advice on methodological and clinical issues and input during the preparation of the protocol and report; CTSU Leukaemia Overviews Secretariat, University of Oxford, for help with cross-checking trial lists and eligibility; Dr Phil Darbyshire and Dr Olalekan Uthman for their input during the preparation of the protocol; and Natalie Rowles, Karen Biddle, Linda Briscoe, Ann Massey and Shelley Smith for their administrative support. We thank anonymous external peer reviewers for their helpful comments on the draft of this report.

Contribution of authors

Khalid Ashfaq selected and reviewed the clinical effectiveness evidence, drafted the clinical effectiveness sections and compiled lists of relevant trials. Ismail Yahaya selected and reviewed clinical effectiveness evidence and drafted the clinical effectiveness sections. Chris Hyde selected and reviewed the cost-effectiveness evidence, drafted the main body of the cost-effectiveness review, commented on draft protocols and reports, and provided senior support to the project. Lazaros Andronis critiqued the validity of included cost-effectiveness evidence and drafted various parts of the cost-effectiveness review. Pelham Barton helped design the review protocol and provided senior support for the review of cost-effectiveness. Sue Bayliss conducted literature searches and drafted the methods section. Yen-Fu Chen compiled the review protocol, co-ordinated the overall running of the project, reviewed the clinical effectiveness evidence, and drafted various sections and revised some parts of the report.

About Home Unit

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively undertake research synthesis to produce health technology assessments. Most of our members are based in the Unit of Public Health, Epidemiology and Biostatistics, University of Birmingham; however, other members are drawn from a wide field of expertise including economists and mathematical modellers from the Unit of Health Economics, University of Birmingham.

WMHTAC produces systematic reviews, health technology assessments and economic evaluations for the NIHR HTA programme, NICE, and for the health service in the West Midlands. WMHTAC also undertakes methodological research on research synthesis and provides training in systematic reviews and health technology assessment.

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Appendix 1
Search strategies

Scoping searches

Database: Cochrane Library (Wiley) 2008 Issue 2 (CDSR, DARE, HTA, EED)

#1 stem next cell*
#2 bone next marrow
#3 hemapoietic
#4 autologous
#5 allogeneic
#6 allograft
#7 homologous
#8 MeSH descriptor Hematopoietic Stem Cell Transplantation explode all trees
#9 MeSH descriptor Stem Cell Transplantation explode all trees
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 ALL
#12 AML
#13 acute near leukaemia
#14 acute near leukemia
#15 MeSH descriptor Leukemia, Myeloid explode all trees
#16 MeSH descriptor Leukemia, Lymphoid explode all trees
#17 (#11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 (#10 AND #17)

Database: MEDLINE (Ovid) 1950 to April week 3, 2008

1. (stem adj cell$).mp.
2. Bone Marrow Transplantation/
3. bone marrow transplant$.mp.
4. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
5. Hematopoietic Stem Cell Transplantation/
6. (haematopoietic adj3 cell$).mp.
7. (autologous adj transplant$).mp.
8. allogeneic transplant$.mp.
9. allograft.mp. or exp Transplantation, Homologous/
10. Peripheral Blood Stem Cell Transplantation/
11. Transplantation, Autologous/
12. SCT.mp.
13. or/1–12
14. exp Leukemia, Myeloid/or exp Leukemia, Lymphoid/or leukaemia.mp. or exp Leukemia, Myeloid, Acute/
15. AML.mp.
16. ALL.tw.
17. (acute adj2 leukaemia).mp.
18. (acute adj2 leukemia).mp.
19. or/17–18
20. 13 and 19
21. limit 20 to "reviews (specificity)"

Database: EMBASE (Ovid) 1980 to week 16, 2008

1. (stem adj cell$).mp.
2. (haematopoietic adj3 cell$).mp.
3. (autologous adj transplant$).mp.
4. allogeneic transplant$.mp.
5. allograft.mp.
6. homologous.tw.
7. (hemapoietic adj3 cell$).mp)
8. exp Bone Marrow Transplantation/
9. SCT.mp.
10. or/1–10
11. acute leukemia/or lymphatic leukemia/or myeloid leukemia/
12. (acute adj2 (leukaemia or leukemia)).mp.
13. ALL.tw.
14. AML.tw.
15. or/12–15
16. 11 and 16
17. limit 17 to "reviews (1 term high specificity)"

Database: MEDLINE In-Process & Other Non-Indexed Citations (Ovid) as at 24 April 2008

1. (stem adj cell$).mp.
2. bone marrow transplant$.mp.
3. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
4. (haematopoietic adj3 cell$).mp.
5. (autologous adj transplant$).mp.
6. allogeneic transplant$.mp.
7. allograft.mp.
8. homologous.tw.
9. or/1–8
10. ALL.tw.
11. AML.tw.
12. acute myeloid leukemia.mp. or exp Leukemia, Myeloid, Acute/
13. acute lymphocytic leukemia.mp.
14. (acute adj2 leukaemia).mp.
15. or/10–14
16. 9 and 15

17. limit 16 to "reviews (specificity)"
18. limit 16 to "therapy (specificity)"
19. 17 or 18

Database: MEDLINE (Ovid) 1950 to April week 3, 2008

1. (stem adj cell$).mp.
2. Bone Marrow Transplantation/
3. bone marrow transplant$.mp.
4. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
5. Hematopoietic Stem Cell Transplantation/
6. (haematopoietic adj3 cell$).mp.
7. (autologous adj transplant$).mp.
8. allogeneic transplant$.mp.
9. allograft.mp. or exp Transplantation, Homologous/
10. Peripheral Blood Stem Cell Transplantation/
11. Transplantation, Autologous/
12. SCT.mp.
13. or/1–12
14. exp Leukemia, Myeloid/or exp Leukemia, Lymphoid/or leukaemia.mp. or exp Leukemia, Myeloid, Acute/
15. AML.mp.
16. ALL.tw.
17. (acute adj2 leukaemia).mp.
18. (acute adj2 leukemia).mp.
19. or/17–18
20. 13 and 19
21. limit 20 to "therapy (specificity)"

Systematic review searches

Database: MEDLINE In-Process & Other Non-Indexed Citations (Ovid) as at 30 December 2008

1. (stem adj cell$).mp.
2. bone marrow transplant$.mp.
3. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
4. (haematopoietic adj3 cell$).mp.
5. (autologous adj transplant$).mp.
6. allogeneic transplant$.mp.
7. allograft.mp.
8. homologous.tw.
9. or/1–8
10. ALL.tw.
11. AML.tw.
12. acute myeloid leukemia.mp. or exp Leukemia, Myeloid, Acute/
13. acute lymphocytic leukemia.mp.
14. (acute adj2 leukaemia).mp.
15. or/10–14
16. 9 and 15
17. limit 16 to "reviews (specificity)"
18. limit 17 to yr = "2008 – 2009"

Database: MEDLINE (Ovid) 1950 to April week 3, 2008

1. (stem adj cell$).mp.
2. Bone Marrow Transplantation/
3. bone marrow transplant$.mp.
4. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
5. Hematopoietic Stem Cell Transplantation/
6. (haematopoietic adj3 cell$).mp.
7. (autologous adj transplant$).mp.
8. allogeneic transplant$.mp.
9. allograft.mp. or exp Transplantation, Homologous/
10. Peripheral Blood Stem Cell Transplantation/
11. Transplantation, Autologous/
12. SCT.mp.
13. or/1–12
14. exp Leukemia, Myeloid/or exp Leukemia, Lymphoid/or leukaemia.mp. or exp Leukemia, Myeloid, Acute/
15. AML.mp.
16. ALL.tw.
17. (acute adj2 leukaemia).mp.
18. (acute adj2 leukemia).mp.
19. or/17–18
20. 13 and 19
21. limit 20 to "reviews (specificity)"
22. limit 21 to yr = "1997 – 2009"

Database: EMBASE (Ovid) 1980 to week 52, 2008

1. (stem adj cell$).mp.
2. bone marrow transplant$.mp.
3. (haematopoietic adj3 cell$).mp.
4. (autologous adj transplant$).mp.
5. allogeneic transplant$.mp.
6. allograft.mp.
7. homologous.tw.
8. (hemapoietic adj3 cell$).mp.
9. exp Bone Marrow Transplantation/
10. SCT.mp.
11. or/1–10
12. acute leukemia/or lymphatic leukemia/or myeloid leukemia/
13. (acute adj2 (leukaemia or leukemia)).mp.
14. ALL.tw.
15. AML.tw.
16. or/12–15
17. 11 and 16
18. limit 17 to "reviews (1 term high specificity)"
19. limit 18 to yr = "1997 – 2009"

Database: Cochrane Library (Wiley) 2008 Issue 2 (CDSR, DARE, HTA, EED)

#1 stem next cell*
#2 bone next marrow
#3 hemapoietic
#4 autologous
#5 allogeneic
#6 allograft
#7 homologous
#8 MeSH descriptor Hematopoietic Stem Cell Transplantation explode all trees
#9 MeSH descriptor Stem Cell Transplantation explode all trees
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 ALL
#12 AML
#13 acute near leukaemia
#14 acute near leukemia
#15 MeSH descriptor Leukemia, Myeloid explode all trees
#16 MeSH descriptor Leukemia, Lymphoid explode all trees
#17 (#11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 (#10 AND #17)

Effectiveness searches

Database: Cochrane Library (Wiley) 2009 Issue 1 (CENTRAL)

#1 stem next cell*
#2 bone next marrow
#3 hemapoietic
#4 autologous
#5 allogeneic
#6 allograft
#7 homologous
#8 MeSH descriptor Hematopoietic Stem Cell Transplantation explode all trees
#9 MeSH descriptor Stem Cell Transplantation explode all trees
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 ALL
#12 AML
#13 acute near leukaemia
#14 acute near leukemia
#15 MeSH descriptor Leukemia, Myeloid explode all trees
#16 MeSH descriptor Leukemia, Lymphoid explode all trees
#17 (#11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 (#10 AND #17)
#19 limit #18 to 1997–2009

Database: MEDLINE In-Process & Other Non-Indexed Citations (Ovid) as at 30 March 2009

1. (stem adj cell$).mp.
2. bone marrow transplant$.mp.
3. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
4. (haematopoietic adj3 cell$).mp.
5. (autologous adj transplant$).mp.
6. allogeneic transplant$.mp.
7. allograft.mp.
8. homologous.tw.
9. or/1–8
10. ALL.tw.
11. AML.tw.
12. acute myeloid leukemia.mp. or exp Leukemia, Myeloid, Acute/
13. acute lymphocytic leukemia.mp.
14. (acute adj2 leukaemia).mp.
15. or/10–14
16. 9 and 15
17. genetic$randomi$.tw.
18. natural$randomi$.tw.
19. mendelian randomi$.tw.
20. (donor adj2 no donor).tw.
21. (donor and intent$to treat$).tw.
22. or/17–21
23. 22 and 16
24. limit 16 to "therapy (specificity)"
25. 24 or 23

Database: MEDLINE (Ovid) 1950 to March week 3, 2009

1. (stem adj cell$).mp.
2. Bone Marrow Transplantation/
3. bone marrow transplant$.mp.
4. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
5. Hematopoietic Stem Cell Transplantation/
6. (haematopoietic adj3 cell$).mp.
7. (autologous adj transplant$).mp.
8. allogeneic transplant$.mp.
9. allograft.mp. or exp Transplantation, Homologous/
10. Peripheral Blood Stem Cell Transplantation/
11. Transplantation, Autologous/
12. SCT.mp.
13. or/1–12
14. exp Leukemia, Myeloid/or exp Leukemia, Lymphoid/or leukaemia.mp. or exp Leukemia, Myeloid, Acute/
15. AML.mp.
16. ALL.tw.
17. (acute adj2 leukaemia).mp.
18. (acute adj2 leukemia).mp.
19. or/14–18

20. genetic$randomi$.tw.
21. natural randomi$.tw.
22. mendelian randomi$.tw.
23. (donor adj2 no donor).tw.
24. (donor and intent$to treat$).tw.
25. or/20–24
26. 25 and 19 and 13
27. 19 and 13
28. limit 27 to "therapy (specificity)"
29. 28 or 26
30. limit 29 to yr = "1997 – 2009"

Database: EMBASE (Ovid) 1980 to week 13, 2009

1. (stem adj cell$).mp.
2. bone marrow transplant$.mp.
3. (haematopoietic adj3 cell$).mp.
4. (autologous adj transplant$).mp.
5. allogeneic transplant$.mp.
6. allograft.mp.
7. homologous.tw.
8. (hemapoietic adj3 cell$).mp.
9. exp Bone Marrow Transplantation/
10. SCT.mp.
11. or/1–10
12. acute leukemia/or lymphatic leukemia/or myeloid leukemia/
13. (acute adj2 (leukaemia or leukemia)).mp.
14. ALL.tw.
15. AML.tw.
16. or/12–15
17. 11 and 16
18. limit 17 to "treatment (1 term high specificity)"
19. genetic$randomi$.tw.
20. natural randomi$.tw.
21. mendelian randomi$.tw.
22. (donor adj2 no donor).tw.
23. (donor and intent$to treat$).tw.
24. or/19–23
25. 17 and 24
26. 25 or 18
27. limit 26 to yr = "1997 – 2009"

Database: Science Citation Index Expanded (Web of Science) as at 31 March 2009

Topic = ("stem cell" or "bone marrow") AND
Topic = ("leukaemia" or "leukemia") AND
Topic = ("randomi*")
Timespan = 1997–2009. Databases = SCI-EXPANDED.

Cost-effectiveness searches

Database: MEDLINE (Ovid) 1950 to January week 1, 2009

1. (stem adj cell$).mp.
2. Bone Marrow Transplantation/
3. bone marrow transplant$.mp.
4. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
5. Hematopoietic Stem Cell Transplantation/
6. (haematopoietic adj3 cell$).mp.
7. (autologous adj transplant$).mp.
8. allogeneic transplant$.mp.
9. allograft.mp. or exp Transplantation, Homologous/
10. Peripheral Blood Stem Cell Transplantation/
11. Transplantation, Autologous/
12. SCT.mp.
13. or/1–12
14. exp Leukemia, Myeloid/or exp Leukemia, Lymphoid/or leukaemia.mp. or exp Leukemia, Myeloid, Acute/
15. AML.mp.
16. ALL.tw.
17. (acute adj2 leukaemia).mp.
18. (acute adj2 leukemia).mp.
19. or/17–18
20. 13 and 19
21. economics/
22. exp "costs and cost analysis"/
23. cost of illness/
24. exp health care costs/
25. economic value of life/
26. exp economics medical/
27. exp economics hospital/
28. economics pharmaceutical/
29. exp "fees and charges"/
30. (econom$or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
31. (expenditure$not energy).tw.
32. (value adj1 money).tw.
33. budget$.tw.
34. or/21–33
35. 34 and 20

Database: EMBASE (Ovid) 1980 to week 3, 2009

1. (stem adj cell$).mp.
2. bone marrow transplant$.mp.
3. (haematopoietic adj3 cell$).mp.
4. (autologous adj transplant$).mp.
5. allogeneic transplant$.mp.
6. allograft.mp.
7. homologous.tw.
8. (hemapoietic adj3 cell$).mp.

9. exp Bone Marrow Transplantation/
10. SCT.mp.
11. or/1–10
12. acute leukemia/or lymphatic leukemia/or myeloid leukemia/
13. (acute adj2 (leukaemia or leukemia)).mp.
14. ALL.tw.
15. AML.tw.
16. or/12–15
17. 11 and 16
18. cost benefit analysis/
19. cost effectiveness analysis/
20. cost minimization analysis/
21. cost utility analysis/
22. economic evaluation/
23. or/18–22
24. 23 and 17

Database: Cochrane Library (Wiley) 2008 Issue 4 (DARE, EED)

#1 stem next cell*
#2 bone next marrow
#3 hemapoietic
#4 autologous
#5 allogeneic
#6 allograft
#7 homologous
#8 MeSH descriptor Hematopoietic Stem Cell Transplantation explode all trees
#9 MeSH descriptor Stem Cell Transplantation explode all trees
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 ALL
#12 AML
#13 acute near leukaemia
#14 acute near leukemia
#15 MeSH descriptor Leukemia, Myeloid explode all trees
#16 MeSH descriptor Leukemia, Lymphoid explode all trees
#17 (#11 OR #12 OR #13 OR #14 OR #15 OR #16)
#18 (#10 AND #17)

Database: MEDLINE (Ovid) 1950 to January week 1, 2009

Population and intervention

1. (stem adj cell$).mp.
2. Bone Marrow Transplantation/
3. bone marrow transplant$.mp.
4. hematopoietic stem cell$.mp. or exp Hematopoietic Stem Cells/
5. Hematopoietic Stem Cell Transplantation/
6. (haematopoietic adj3 cell$).mp.
7. (autologous adj transplant$).mp.
8. allogeneic transplant$.mp.
9. allograft.mp. or exp Transplantation, Homologous/
10. Peripheral Blood Stem Cell Transplantation/
11. Transplantation, Autologous/
12. SCT.mp.
13. or/1–12
14. exp Leukemia, Myeloid/or exp Leukemia, Lymphoid/or leukaemia.mp. or exp Leukemia, Myeloid, Acute/
15. AML.mp.
16. ALL.tw.
17. (acute adj2 leukaemia).mp.
18. (acute adj2 leukemia).mp.
19. or/17–18
20. 13 and 19
21. decision support techniques/
22. markov.mp.
23. exp models economic/
24. decision analysis.mp.
25. cost benefit analysis/
26. or/21–25
27. 26 and 20

Database: MEDLINE (Ovid) 1950 to January week 1, 2009

Population

1. exp Leukemia, Myeloid/or exp Leukemia, Lymphoid/or leukaemia.mp. or exp Leukemia, Myeloid, Acute/
2. AML.mp.
3. ALL.tw.
4. (acute adj2 leukaemia).mp.
5. (acute adj2 leukemia).mp.
6. or/4–5
7. decision support techniques/
8. markov.mp.
9. exp models economic/
10. decision analysis.mp.
11. cost benefit analysis/
12. or/7–11
13. 6 and 12

Appendix 2

Studies comparing allogeneic with autologous SCT

In addition to the comparison between transplantation and chemotherapy (which was presented in the main text in Chapter 4), existing reviews have also compared the two transplantation techniques, i.e. autologous SCT versus allogeneic SCT. However, as previously explained, such comparisons do not reflect the actual clinical decisions needing to be made, especially for patients who are fit enough and have a matched sibling donor – allogeneic SCT is the preferred option in most cases. In addition, trials comparing allogeneic SCT with autologous SCT are unlikely to contain comparable patients (see Chapter 1, Decision problems). Therefore, this appendix is included in this report only to reflect the comparisons in existing reviews rather than with a view to making any conclusions or recommendations in this respect. Readers should be aware that many studies listed or mentioned in this appendix are likely to be observational studies rather than RCTs and DvND studies.

DPI

Evidence from existing reviews

Three studies presented a review of comparisons between autologous and allogeneic SCT among adults with AML in CR1 (*Table 34*). One review found some evidence of a better DFS for allogeneic SCT but none of found a difference in OS between the two transplantation techniques. The overall inclination in this regard tends to be that if a matched related donor is available, allogeneic SCT is to be preferred over autologous SCT. Further details of each review are given below.

Schlenk 2004[48]

This IPD meta-analysis of 392 adults with CBF AML has been previously described. Among other results, ITT analysis revealed that there was no difference in RFS and OS between chemotherapy, autologous transplantation and allogeneic transplantation in the inv(16) group ($p = 0.22$).

Visani 2006[15]

One of the end points of this review was to establish whether allogeneic SCT was superior to other therapeutic options in improving DFS and/or OS in adults with AML. Since no studies effectively compared allogeneic SCT and intensive chemotherapy, we mainly focused our analysis on the comparison between allogeneic and autologous SCT, and, as this was based on genetic randomisation, it has also been included in the DvND subsection. Nine studies addressed the question and none of them was able to demonstrate any difference for OS between allogeneic and autologous SCT; five of the studies could not show any statistical differences for DFS while, in four studies, allogeneic SCT obtained a significant benefit concerning DFS and relapse risk.

Oliansky 2008[17]

The comparison of autologous and allogeneic SCT in the consolidation of CR1 in adults with AML was addressed in this review by a total of 11 studies: six prospective trials and five retrospective studies. The EORTC/GIMEMA AML-10 trial recruited the most participants ($n = 734$), with 293 in the donor group and 441 in the no-donor group; the trial with the smallest sample size was ECOG P-C 486 ($n = 58$). Of the clinical trials, only one found a significant difference in DFS and none a difference in OS. Across the six trials 1516 patients were accrued.

The conclusion of the authors was that, based on the data within the studies and expert opinion, an HLA matched related donor allogeneic SCT is recommended over autologous SCT, if such a donor is available. For matched unrelated donor allogeneic versus autologous SCT, there were insufficient data. As all of the trials were conducted at least 10 years ago, it is our view that these studies do not reflect modern techniques in supportive care, stem cell source, or the use of molecular HLA typing, especially for the matched unrelated donor studies.

Evidence from primary studies not included in existing reviews

Four additional trials not included in previous reviews were identified by our search for primary studies. All of these trials are also included in the section on DvND comparison.

TABLE 34a *Studies of allogeneic SCT versus autologous SCT among adults with AML in CR1: trials included in existing reviews*

Trial ID	Source	Schlenk 2004[48]	Visani 2006[15]	Oliansky 2008[17]
AMLCG 92	Buchner 2003[49]	×		
AMLCG 99/2000	Buchner 2002[50]	×		
AMLSG Ulm AML HD93	Schlenk 2003[47]	×		
AMLSG Ulm AML HD98-A	Schlenk 2004[48]	×		
BGMT 84	Reiffers 1989[56]		×	
BGMT 87	Reiffers 1996[51]		×	
CETLAM 88	Sierra 1996[285]			×
DSIL Dresden AML 96	Schaich 2001[46]	×		
ECOG P-C 486	Cassileth 1993[286]			×
ECOG/SWOG/CALGB	Cassileth 1998[58]		×	×
EORTC/GIMEMA	Zittoun 1995[41]		×	×
EORTC/GIMEMA AML-10	Suciu 2003[55]		×	×
GOELAM	Harousseau 1997[57]		×	
Hellenic CG AML-8	Tsimberidou 2003[60]		×	
MRC AML 10	Burnett 1994[39]		×	
OSHO (#33) AML 96	Schlenk 2004,[25] Schaich 2007[24]	×		
SHG AML 1/99	Schlenk 2004,[25] Schaich 2007[24]	×		
SHG AML 2/95	Heil 2004[45]	×		
–	Ferrant 1991[56]		×	
–	Mitus 1995[287]			×

TABLE 34b *Studies of allogeneic SCT versus autologous SCT among adults with AML in CR1: trials not included in existing reviews*

Trial ID	Source and details
CETLAM 94	Brunet 2004[188] (full text), *n* = 2000
EORTC/GIMEMA AML-12	Willemze 2005[189] (abstract), *n* = 355
GOELAMS AML 2001	Lioure 2006[190,191] (abstract), *n* = 550
–	[a]Ganser 2005[193] (abstract), *n* = 484

a This is the most recent report of the trial; others are Ganser 2004[198] (abstract), Heil 2004[199] (abstract).

Ongoing trials

No currently ongoing trials were identified focusing on the comparison between autologous and allogeneic SCT in adult AML in CR1.

DP2

No trials comparing autologous with allogeneic SCT were identified in any of the reviews, or in our search for primary studies and ongoing trials.

DP3

Evidence from existing reviews

Only Oliansky *et al.*[16] included studies comparing autologous with allogeneic SCT among children with AML in CR1 (*Table 35*). The conclusion of the authors was that matched related donor allogeneic SCT has superior survival outcomes compared with autologous SCT in CR1, although additional prospective data regarding risk subgroups may alter this stance.

Eleven studies were included addressing this comparison, four of which were retrospective studies (Gorin *et al.*,[292] Matsuyama *et al.*,[293] Pession *et al.*[294] and Anak *et al.*[154]). The upper age limit for inclusion in the studies was 21 years. The total number of study participants in both arms range from 48 (Ortega *et al.*[288]) to 1278 (Alonzo *et al.*[82]).

Overall, DFS was better in allogeneic BMT than for autologous BMT, with a statistically significant difference between the study arms in only two studies (Woods *et al.*[83] and Ravindranath *et al.*[77]).

Evidence from primary studies not included in existing reviews

Two full papers were retrieved, both of which have been discussed under the DvND subsection of this decision problem.

Ongoing trials

No ongoing trials were identified

DP4

The review also identified three articles comparing autologous with allogeneic SCT, two of which were retrospective studies (Gorin *et al.*,[292] Pession *et al.*[294]) while the third paper by Aladjidi *et al.*[295] presented the findings of the French prospective LAME 89/91 protocol. The median duration of CR1 was 10 months and of the patients that attained CR2, 12 were allocated to the matched allogeneic BMT group, 16 to unrelated allogeneic BMT and 25 to autologous BMT. Results showed that there was no statistical significant difference in 5-year DFS between the three study arms.

DP5

Evidence from systematic reviews and meta-analyses

Only Hahn *et al.*[14] addressed the comparison between allogeneic and autologous SCT (*Table 36*).

The conclusion from the review was that OS and DFS were better for allogeneic than autologous SCT. The results from the studies identified in the reviews were not pooled together and there was no evidence in relation to specific risk group.

Hahn 2006[14]

Seven of the included studies within this review (Dombret et al.,[115] Hunault *et al.*,[116] Attal *et al.*,[298] Sotomayor *et al.*,[300] Annaloro *et al.*,[297] Blaise *et al.*,[299] Ifrah *et al.*[296]) addressed the comparison between autologous and allogeneic BMT. The studies were conducted between 1981 and 2002 with a median follow-up period ranging from 25 months to 158 months.

Three studies (Dombret *et al.*,[115] Hunault *et al.*[116] and Sotomayor *et al.*[300]) found a significant difference in OS between the treatment groups in favour of the donor group with an OS of 75% versus 39%, 37% versus 12% and 48% versus 12% respectively. Similarly, three studies (Hunault *et al.*,[116] Attal *et al.*[298] and Sotomayor *et al.*[300]) found a significant difference in DFS in favour of the donor group. No quantitative synthesis of evidence was provided in this review.

Evidence from studies not included in previous reviews

The search of primary studies identified one published paper (Cornelissen *et al.*[211]) and three conference abstracts (Lee *et al*.,[302] Mrsic *et al.*[303] and Arnold *et al.*[301]) not included in previous reviews. Arnold *et al.*[301] and Cornelissen *et al.*[211] were already discussed in the DvND comparison,

TABLE 35a *Trials of allogeneic SCT versus autologous SCT among children with AML in CR1: trials included in existing reviews*

Trial ID	Source	Oliansky 2007[16]
AML 88	Ortega 2003[288]	×
ANZCCSG AML1 & AML2	O'Brien 2002[289]	×
CCG 213, 251, 2861, 2891, 2941	Alonzo 2005[82]	×
CCG 2861	Woods 1993[290]	×
CCG 2891	Woods 2001[83]	×
K-Y CCSG ANLL 93	Matsuzaki 2000[155]	×
POG 8821	Ravindranath 1996[77]	×

TABLE 35b *Trials of allogeneic SCT versus autologous SCT among children with AML in CR1: trials not included in existing reviews*

Trial ID	Source and details
AIEOP LAM 92P/Modified protocol	Berger 2005[291] (full paper), *n* = 16
DCOG AML 92/94	Kardos 2005[205] (full paper), *n* = 209

TABLE 36a *Allogeneic SCT versus autologous SCT among adults with ALL in CR1: trials included in existing reviews*

Trial ID	Source	Hahn 2006[14]
GOELAL02	Hunault 2004[116]	×
GOELAMS	Ifrah 1999[296]	×
LALA 94	Dombert 2002[115]	×
–	Annolaro 2004[297]	×
–	Attal 1995[298]	×
–	Blaise 1990[299]	×
–	Sotomayor 2002[300]	×

TABLE 36b *Allogeneic SCT versus autologous SCT among adults with ALL in CR1: trials not included in existing reviews*

Trial ID	Source and details
HO-18 ALL and HO-37 ALL	Cornelissen 2009[211] (full paper)
GMALL 06/99 & 07/03	Arnold 2008[301] (abstract)
–	Lee 2000[302] (abstract)
–	Mrsic 2000[303] (abstract)

where the donor group were allocated to allogeneic BMT while the no-donor group were allocated to autologous BMT.

Mrsic *et al.*[303] evaluated the efficacy of SCT and chemotherapy in 148 patients with ALL. Patients were divided into three groups (chemotherapy, allogeneic BMT and autologous BMT) according to the type of consolidation therapy. Patients in the allogeneic BMT group had a higher TRM and higher 5-year DFS than patients in the autologous BMT group, although the *p*-value available is applicable only to the comparison among allogeneic BMT, autologous BMT and chemotherapy.

Lee *et al.*[302] identified adult patients with high-risk ALL in which allogeneic BMT was compared with autologous PBSCT using the result of the HLA typing as a random allocation. Allogeneic BMT had a lower relapse (32.3% vs 57.1%, $p = 0.06$) and better DFS (69% vs 42%, $p = 0.09$) than autologous PBSCT. The prognosis of Ph+ve patients with ALL was significantly poorer than the other patient group ($p < 0.01$).

Ongoing trials

No additional ongoing study was identified that compared autologous with allogeneic SCT.

DP6

The review identified six studies comparing autologous with allogeneic SCT; two of these (Kroger *et al.*,[304] Stockschlader *et al.*[305]) were retrospective studies. The other four are described below.

Soiffer *et al.*[306] treated 22 adult patients with B-lineage ALL with purged autologous BMT. No patients with autologous BMT had HLA-identical sibling donors. All patients except one underwent transplantation in CR2+. These patients with autologous BMT were compared with a concurrent cohort of 14 adult patients with ALL treated in CR2 or CR3 with T-cell-depleted HLA-identical related allogeneic BMT. Patients with allogeneic BMT were treated with the same conditioning regimen as the autologous group and met similar eligibility criteria. There was no significant difference between the autologous and allogeneic BMT groups with respect to DFS or OS (survival and *p*-value not stated in original article). In the autologous BMT group, only age was a prognostic factor, whereby patients younger than 28 years at the time of BMT had a longer DFS than those who were older than 28 years (45% vs 0%; *p*-value not stated).

Martino *et al.* (1998,[307] 1999[308]) described the results of 22 consecutive adult patients with ALL treated with an autologous ($n = 9$, eight of which were purged) or an HLA matched related donor allogeneic ($n = 14$) BMT at a single Spanish centre from 1988 to 1997. All patients with autologous BMT and nine patients with allogeneic BMT were in CR2+ at time of BMT; five with allogeneic BMT were in second or greater relapse. At a

TABLE 37a *Trials of allogeneic SCT versus autologous SCT among adults with ALL in CR2+: trials included in existing reviews*

Trial ID	Source	Hahn 2005[13]
ALL R-87	Giona 1997[311]	×
UK ALL R1	Lawson 2000[226]	×
–	Woods 1990[310]	×

TABLE 37b *Trials of allogeneic SCT versus autologous SCT among adults with ALL in CR2+: trials not included in existing reviews*

Trial ID	Source and details
–	Sandler 2006[313] (full paper)

median follow-up of 44 months, the median OS was 15.4 months for autologous BMT and was not yet reached for patients receiving allogeneic BMT ($p = 0.2$).

Dunlop *et al.*[309] reported the results of 19 patients with Ph+ve ALL who were treated with 20 transplantation procedures (9 autologous or 11 matched related donor allogeneic BMT) in CR1 ($n = 12$), CR2 ($n = 3$), or relapse ($n = 5$) between 1986 and 1995 at one UK centre. No patients received purged or T-cell-depleted grafts. There was no significant difference in DFS between the autologous and allogeneic BMT groups. OS for the whole cohort was 37.5% at 3 years and was not specified for the two BMT groups.

DP7

No trials comparing autologous with allogeneic SCT were identified in any of the reviews, or in our search for primary studies and ongoing trials.

DP8

Evidence from systematic reviews and meta-analyses

Eight studies comparing autologous with allogeneic SCT in children with ALL in CR2 were included in the review by Hahn *et al.*[13] (*Table 37*). Three of these studies were clinical trials, with one of these trials consisting of < 70% patients (Woods *et al.*[310]). All three trials reported similar rates of TRM for allogeneic SCT (between 10% and 13%); one study (Giona *et al.*[311]) achieved a statistical level of significance for DFS. The overall conclusion was that the outcomes of autologous versus allogeneic SCT for ALL in children in CR2 have not been adequately studied, thus no recommendation was made.

Evidence from studies not included in previous reviews

One full text publication by Sandler *et al.*[312] was identified and has been described in the DvND subsection.

Ongoing trials

No ongoing trials with regard to this subsection were identified.

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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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ISSN 1366-5278